mbi

Mathematical Biosciences Institute

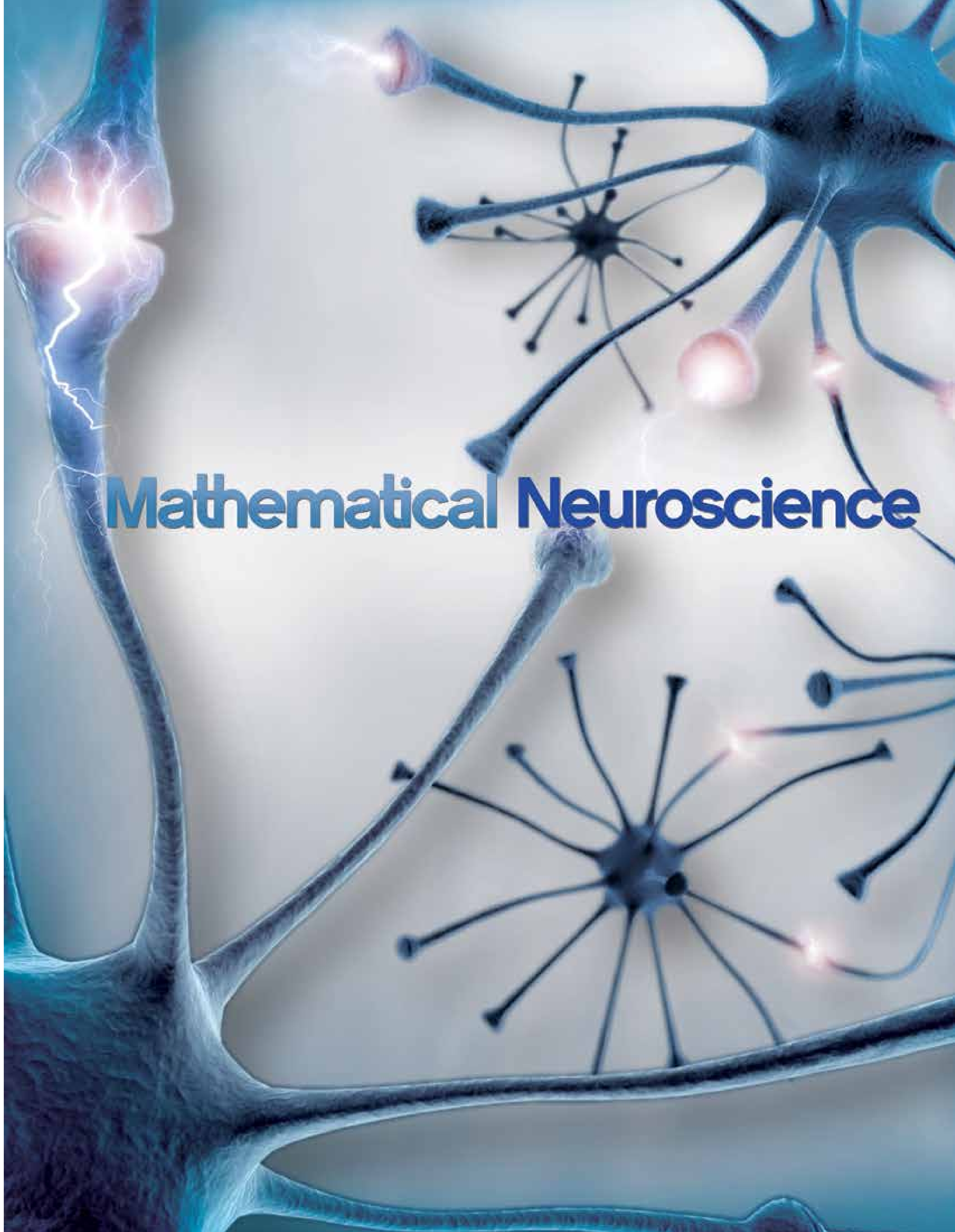
2012-2013 ANNUAL REPORT

Mathematical Neuroscience

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

The Ohio State University

Mathematical Neuroscience



Mathematical Biosciences Institute

www.mbi.osu.edu | The Ohio State University | Jennings Hall 3rd Floor, 1735 Neil Ave. | Columbus, OH 43210 | 614-292-3648

Message from the Director

In 2012-13 MBI returned to the topic of its first annual program: Mathematical Neuroscience. The program emphasized progress that had been made in the past few years and was a great success, mainly due to the efforts of the program organizers: Carmen Canavier, John Rinzel, Steven J. Schiff, Eric Shea-Brown, and Murray Sherman.

MBI's missions include Math to Bio and Bio to Math. The first mission emphasizes the many ways that the mathematical sciences are used to clarify issues in the life sciences and the second emphasizes the ways that questions in biology are pushing developments in the mathematical sciences. The six MBI Current Topic Workshops that were held this year illustrated both of these missions with special emphasis on Bio to Math. There were two workshops on mathematical challenges spawned by models in different fields (bio-fluid dynamics and visualization) and one on statistical challenges (Statistics of Time Warping and Phase Variation). This year also saw MBI produce two milestone meetings: the MBI Tenth Anniversary Meeting (Math Biology: Looking at the Future) and The Keyfitz Centennial Symposium on Mathematical Demography. I want to point especially to the eleven spectacular talks at the tenth anniversary meeting, which can be viewed on our website.

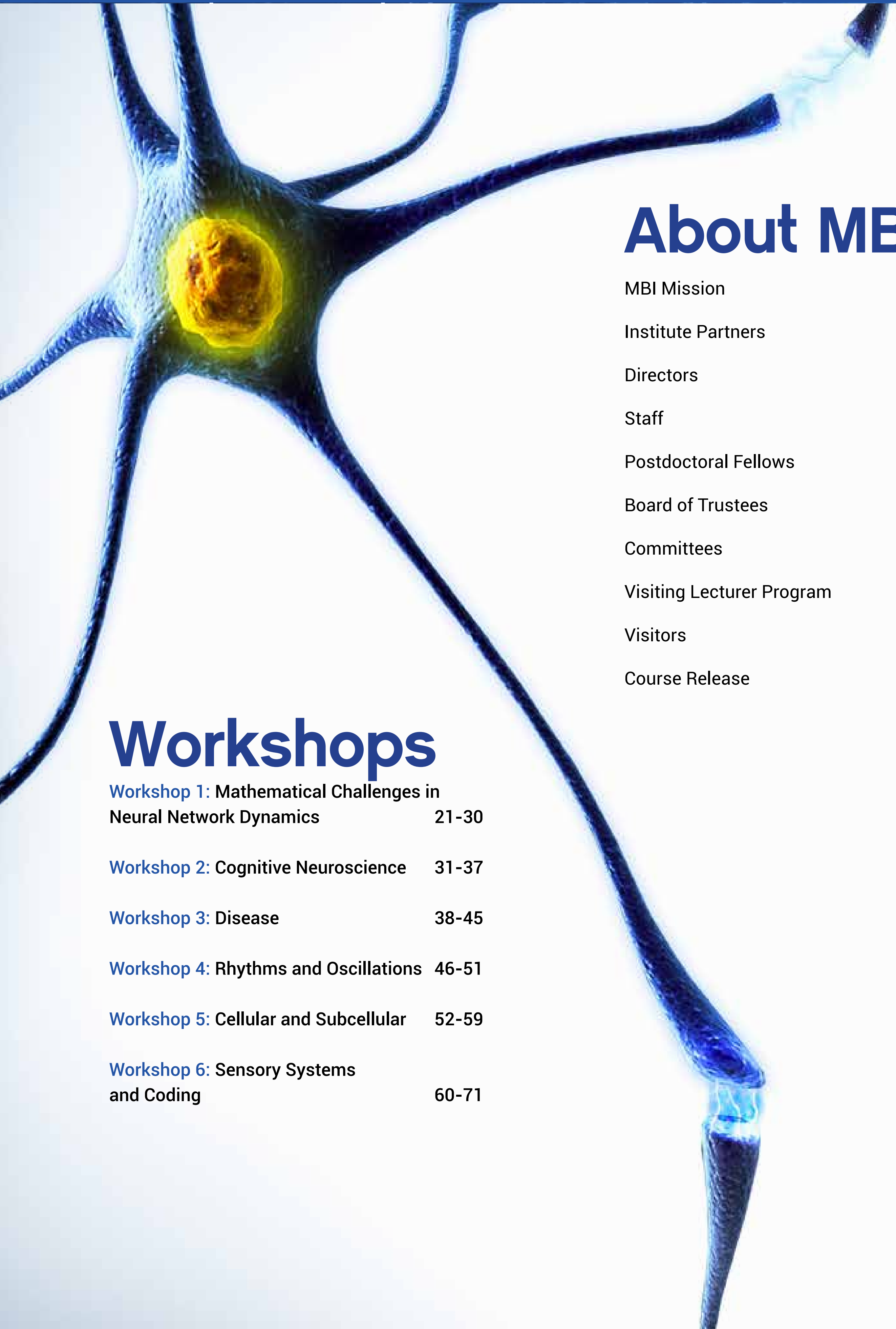
In addition, MBI organized successful three-part undergraduate research programs in summer 2012 and summer 2013. This innovative program begins with a two-week summer school for the 15 selected students. It is followed by an eight-week distributed REU, where the students divide into small groups and travel to six of our institute partners for mentoring. The program ends with a one-week Capstone Conference at MBI. At the Capstone Conference, 30-40 students who participated in math biology REU type summer programs around the country join our MBI REU students for a week of talks, posters, and special events (including a very popular grad school fair).

In summer 2013, MBI continued its summer graduate program in cooperation with CAMBAM and NIMBioS. This year's program was on Connecting Biological Data with Mathematical Models and was held at NIMBioS.

MBI is about people: from our excellent staff members who make the institute work to the participants who attend our events. This year, MBI supported 18 postdoctoral fellows who were mentored by 30-40 researchers, many at our institute partners (MBI now has more than 50 IPs). During the past few years MBI has developed several innovative programs to enable more people to take advantage of MBI programming. Specifically I want to point to MBI Early Career Awards (which enable untenured tenure-track faculty to spend 3-9 months at MBI) and the MBI Conference Awards (which are best presentation prizes that provide support for each winner to attend one MBI workshop of his or her choice and are offered at conferences with a large number of women or underrepresented minority participants). MBI granted five Early Career Awards and four Conference Awards this year.

Many wonder who generates MBI programs. Some are suggested by the MBI Directors, but almost all are not. The MBI Board of Trustees, the MBI Scientific Advisory Committee, the MBI Local Scientific Advisory Committee, and attendees at the annual MBI Institute Partner Meeting are all involved in program selection. The community also suggests topics for many of our workshops, and we are delighted to receive these suggestions. If you have an idea for a meeting or indeed some different way that MBI can help stimulate research at the interface between the mathematical and life sciences, please let us know.

Marty Golubitsky - Director



About MBI

Workshops

Current Topic Workshops

Summer Programs

Mission

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

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

To engage mathematical and biological scientists in these pursuits; and

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

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.

IP Mentoring Program

Researchers from both the mathematical and biological sciences (broadly defined) at IP institutions can join the pool of approved scientific mentors of MBI postdoctoral fellows.

Reasonable costs for off-site mentoring are borne by MBI, and IP mentors can be similarly funded to visit MBI.

MBI Supported IP Meetings

University of Nottingham
MBI Institute Partner conference Multiscale Modelling in Medicine and Biology - September 3-5, 2012

University of Miami
Everything Disperses to Miami: The Role of Movement and Dispersal in Ecology, Epidemiology and Environmental Science - December 14-16, 2012

Arizona State University
SMB Annual Meeting: 2013 Travel Grant for young researchers - June 10-13, 2013

Current Institute Partners

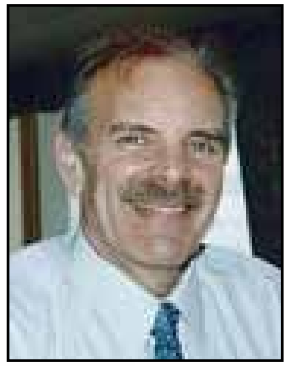
Arizona State University
Battelle
Boston University
Case Western Reserve University
Cornell University
Drexel University
Duke University
Florida State University
Howard University
IBM
Indiana University-Purdue University Indianapolis
Instituto Gulbenkian de Ciencia
Iowa State University
Konkuk University
McGill University
Michigan State University
Mississippi State University
National Tsing Hua University
New Jersey Institute of Technology
The Ohio State University
Ohio University
Penn State University
Princeton University
Texas Tech University
Trinity University
Tulane University
University of California at Davis
University of California at Irvine
University California at Los Angeles
University of California at San Diego
University of Cincinnati
University of Exeter
University of Georgia
University of Glasgow
University of Houston
University of Iowa
University of KwaZulu-Natal
University of Maryland at Baltimore County
University of Miami
University of Michigan
University of Minnesota
Universidad Nacional Autónoma de México
University of Notre Dame
University of Nottingham - CMMB
University of Oxford
University of Pittsburgh
University of Southern California
University of Twente
University of Utah
University of Washington
University of Waterloo
University of Wyoming
Vanderbilt University
Virginia Tech

Directors

Marty Golubitsky

Director

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



Michael Reed

Senior Scientific Advisor

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

Helen Chamberlin

Associate Director

Works with the director on diversity issues.

Yuan Lou

Associate Director

Responsible for the summer graduate program.

Tony Nance

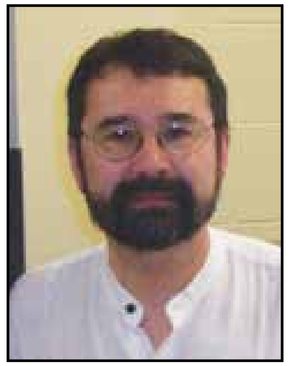
Deputy Director

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

Grzegorz Rempala

Deputy Director

Greg Rempala provides scientific advice and support to the Director and also serves as liaison with workshop organizing committees.



Andrej Rotter

Associate Director

Andrej Rotter chairs the MBI Colloquium Committee.

Laura S. Kubatko

Associate Director

Laura Kubatko is responsible for MBI education programs.

Staff

Nikki Betts

Financial and HR Manager

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

Michael Siroskey

Systems Manager

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

Matt Thompson

Program Coordinator

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

April J. Shelton

Visual Communications Specialist

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

Casey Jacobs

Program Assistant

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

Jason Bray

Systems Specialist

Provides support to users of MBI computer and presentation facilities.

Carter Schoenfeld

Systems Specialist

Provides critical support and development of MBI web and database projects.

Sarah Hancock

Program Assistant

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

Rebecca Martin

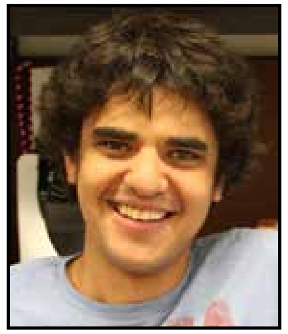
Office Admin. Associate

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.

Amanda Siroskey

Student Worker

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



Chris Reilly

Student Worker

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

Ryan Knighton

Student Worker

Assists IT unit on web programming and development projects.

Noelle G. Beckman

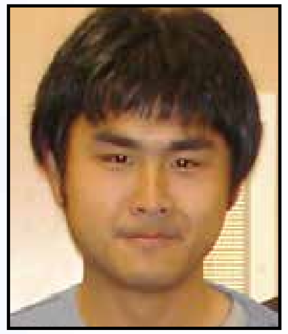
Ph.D. Ecology, Evolution, Behavior, University of Minnesota

My research contributes to long-standing questions concerning species coexistence and investigates the consequences of anthropogenic pressures on the mechanisms that maintain plant diversity, which ultimately influence ecosystem processes. Towards this goal, I combine ecological theory, statistical modeling, and empirical field and laboratory studies to enhance our knowledge of the mechanisms that limit populations and maintain species diversity in natural and modified environments.

Arjun Beri

Applied Mathematics, University of Houston

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



Josh Chang

Biomathematics, University of California, Los Angeles

From 2008-2012, I was a graduate student in the UCLA Department of Biomathematics (Department of Mathematical and Computational Biology), an applied mathematics program with emphasis on biological applications. I work primarily on inverse problems in statistical physics and imaging. I also work on modeling of neurophysiology using partial differential equations.

Duan Chen

Applied Mathematics, Michigan State

My research is partial differential equations (PDE) based modeling, computation and analysis of problems in structural biology and cancer research. My current research interests include :

(1)Multi-scale and multi-physics modeling of ion channels;

(2)Solid tumor growth under complicated cell-cytokines interaction pathways;

(3)Modeling and computation of industrial nano-transistors such as MOSFETs;

(4)Numerical algorithms of PDE system;

(5)Analysis of free boundary problem and its applications.

Casey Diekman

Engineering and Bioinformatics, Michigan

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

Franziska Hinkelmann

Mathematics, Virginia Tech

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

Paul Hurtado

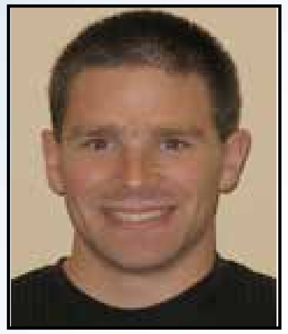
Applied Mathematics, Cornell University

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

Hye-Won Kang

Mathematics, Wisconsin-Madison

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

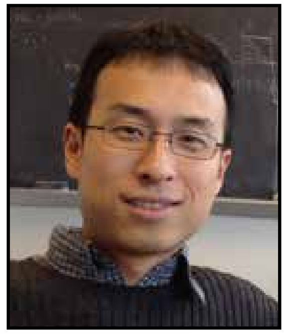


David Koslicki

Applied Mathematics, The Pennsylvania State University

My research focuses on establishing a principled mathematical approach to answering questions such as: How do genes work? How do genes and genomes mutate and evolve? What is the relationship between epigenetics, gene expression, and phenotype? How can inherent randomness in nucleotide composition be properly considered when analyzing DNA sequences? Why is there redundancy in the genetic code?

To answer such questions, I develop finite implementations of techniques utilized in symbolic dynamics and ergodic theory and apply them to DNA sequences. So my research blends a number of general, as well as specialized areas of mathematics (such as thermodynamic formalism and substitutive dynamical systems) and with judicious use of high-performance computing, applies techniques from these fields to pertinent problems in the study of DNA sequences and Genomic analysis in general.



Adrian Lam

Mathematics, University of Minnesota

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

Rachel Leander

Mathematics, University of Tennessee

My long-term research goals are to combine ecological theory and empirical studies to enhance our knowledge of the mechanisms that limit populations and maintain plant community diversity, which in turn influence ecosystem processes, and to determine the impact of anthropogenic pressures on these processes. My current research specifically addresses the role of animals and microbes in plant recruitment, the influence of plant traits on these interactions, and how environmental change alters plant-animal and -microbe interactions, thus ultimately affecting plant communities.

Kang-Ling Liao

Applied Mathematics, National Chiao Tung University, Taiwan

My research interests are in differential equations, delayed differential equations, and bifurcation theory. I have been working on many interesting mathematical biological problems, such as somitogenesis, modeling in cancer immunoediting, and evolution in ecology.

Somitogenesis is the process that vertebrate embryos develop somites. This process depends on gene expressions which have the interesting phenomena: synchronous oscillation with period around 30 minutes in the tail bud, traveling wave pattern, oscillation-arrested in the anterior of presomitic mesoderm. In order to investigate these phenomena, we used sequential-contracting technique to derive conditions for oscillation-arrested and applied delay Hopf bifurcation theorem, center manifold theory, and the normal form method to analyze the existence of the stable synchronous/asynchronous oscillation in the tail bud. We also used numerical simulation to find some suitable gradient for degradation rates of cells to generate normal traveling wave pattern.

Jon Lo

Mathematics, University of California, Irvine

My area of research is mathematical and computational biology. I have worked in collaboration with other faculty from different departments, for example, Mathematics, Pathology, Surgery, Molecular Genetics, etc. I apply ODE, PDE and stochastic equation to describe models, and compare the computational simulation and analytic results with actual data in order to validate the model so that it can be useful for making new hypotheses in biology. The main focus of my studies is robust cell polarization and pattern formation of biological systems. I am also interested in studying inflammatory diseases and cancer modeling.

Jay Newby

Mathematics, University of Utah

Often we hear claims that stochastic effect are significant, particularly in models of biological phenomena. But how are they significant? What does the stochastic model tell us that a deterministic model cannot? The intricate machinery of a living cell must function even when subjected to thermal fluctuations. These thermal fluctuations are well described by a stochastic process, called noise, which can take many different forms. While noise can be detrimental, it is also possible that a cell sometimes uses noise to its benefit. One example is using Brownian motion, or diffusion, to transport small molecules throughout the cell. The central motivation of my research is to discover how cells take advantage of noise to do things they could not do otherwise.

Leopold Matamba Messi

Applied Mathematics, University of Georgia

I am a postdoctoral fellow here at the Mathematical Biosciences Institute. Originally from The Republic of Cameroon in Central Africa, I earned a doctorate degree from the University of Georgia in the summer of 2012 and joined the MBI thereafter. I am interested in mathematical neuroscience, dynamical systems and computational mathematics. Specifically, I am interested in investigating neurological disorders using dynamical systems and PDE modeling, stochastic modeling, and imaging techniques. My dissertation was in variational image analysis. I proved the convergence of the Rayleigh-Ritz method for the Hilbertian total variation model of image denoising.

Jincheol Park

Statistics, Texas A & M University

I am a Postdoctoral Fellow both of Department of Statistics with Shili Lin and of the Mathematical Bioscience Institute (MBI).

Currently, I am working on statistical models for long-range epigenetic controls in regulating distant transcription factor binding sites (TFBSs).

The other ongoing research is developing Bacterium and virus analysis of Orthologous Groups (BOG) which is a package for identifying differentially regulated genes in the light of gene functions. BOG can be useful in transcriptional profiling of virulent pathogens having potential to be used as biological weapons.

Michael A. Schwemmer

Applied Mathematics, University of California, Davis

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

Lucy Spardy

Mathematics, University of Pittsburgh

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

Michal Seweryn

Biostatistics, University of Lodz

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

Board of Trustees

The Board consists of individuals with leadership experience in the public and private sectors, and of recognized scientists in fields related to the MBI activities. The Board meets annually to review the institute management and programs and to advise and approve the strategic priorities of the institute. More details at http://mbi.osu.edu/about/committees/board-of-trustees

Scientific Advisory Committee

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

Alexander R. A. Anderson
H. Lee Moffitt Cancer Center
January, 2011 - December, 2013

Paul Bressloff
University of Utah
January, 2011 - December, 2013

Thomas Chou
University of California, Los Angeles
January, 2012 - December, 2014

Chris Cosner
University of Miami
January, 2011 - December, 2013

Thomas Daniel
University of Washington
January, 2010 - December, 2012

Domitilla Del Vecchio
Massachusetts Institute of Technology
January, 2013 - December, 2015

Nina Fefferman
Rutgers University
January, 2013 - December, 2015

Gerda deVries
University of Alberta
January, 2011 - December, 2013

Tim Elston
University of North Carolina, Chapel Hill
January, 2011 - December, 2013

Greg Forest
University of North Carolina, Chapel Hill
January, 2011 - December, 2013

James Glazier
Indiana University
January, 2013 - December, 2015

Abba Gumel
University of Manitoba
January, 2013 - December, 2015

Shandelle M. Henson
Andrews University
January, 2012 - December, 2012

Trachette Jackson
University of Michigan
January, 2012 - December, 2014

Nan Laird
Harvard University
January, 2012 - December, 2014

Reinhard Laubenbacher
University of Connecticut Health Center
January, 2011 - December, 2013

Naomi Leonard
Princeton University
January, 2009 - December, 2012

Andre Longtin
University of Ottawa, Canada
January, 2010 - December, 2012

Sharon Lubkin
North Carolina State University
January, 2011 - December, 2013

Michael Mackey (Chair)
McGill University
January, 2011 - December, 2014

L. Mahadevan
Harvard University
January, 2010 - December, 2012

Qing Nie
University of California
January, 2010 - December, 2012

Jonathan Rubin
University of Pittsburgh
January, 2010 - December, 2012

Jack Tuszynski
University of Alberta
January, 2012 - December, 2014

Local Scientific Advisory Committee

The Local Scientific Advisory Committee consists of members of The Ohio State University community. It helps identify current topics workshops, suggest ideas for future emphasis programs and organizers, and potential mentors for postdoctoral fellows. More details at http://www.mbi.osu.edu/committees/local.html

Irina Artsimovitch
Microbiology / July, 2011 - June, 2014

Janet Best
Mathematics /July, 2011 - June, 2014

Ralf Bundschuh
Physics /July, 2010 - June, 2013

James Cogdell
Mathematics /July, 2010 - June, 2013

Meg Daly
Evolution, Ecology, and Organismal Biology
July, 2009 - June, 2012

Andrea Doseff
Heart and Lung Research Institute, Molecular Genetics, and Internal Medicine /July, 2011 - June, 2014

Martin Feinberg
Chemical Engineering /July, 2010 - June, 2013

Avner Friedman
Mathematics /July, 2009 - June, 2015

Erich Grotewold
Plant Biology / July, 2010 - June, 2013

Richard Hart
Biomedical Engineering / July, 2009 - June, 2012

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

Kay Huebner
Molecular Virology, Immunology and Medical Genetics
July, 2011 - June, 2014

Daniel Janies
Biomedical Informatics / July, 2010 - May, 2012

Doug Kniss
Obstetrics and Gynecology / July, 2011 - June, 2014

Stanley Lemeshow
Dean College of Public Health / July, 2009 - June, 2012

Gustavo Leone
Molecular Virology, Immunology, and Medical Genetics
July, 2009 - June, 2012

Shili Lin
Statistics / July, 2010 - June, 2013

Thomas J. Magliery
Chemistry / July, 2010 - June, 2013

Stuart Mangel
Neuroscience / July, 2010 - June, 2013

Elizabeth Marschall
Evolution, Ecology, and Organismal Biology
July, 2010 - June, 2013

Deborah Parris
Molecular Virology / July, 2010 - July, 2013

Roger Ratcliff
Psychology / July, 2010 - June, 2013

Wolfgang Sadee
Pharmacology / July, 2009 - June, 2012

Larry S. Schlesinger
Infectious Diseases, Microbial Interface Biology
July, 2009 - June, 2012

Chandan Sen
Surgery /July, 2009 - June, 2012

Amanda Simcox
Molecular Genetics / July, 2009 - June, 2015

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

Don Stredney
Research Dept./ July, 2009 - June, 2015

Joe Travers
Neuroscience / July, 2011 - June, 2014

MBI Diversity Committee

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

Current Members

Erika Camacho
Arizona State University
May, 2012 - December, 2015

Ricardo Cortez
Tulane University
January, 2013 - December, 2015

Helen Chamberlin (Chair)
The Ohio State University
January, 2011 - December, 2014

Holly D. Gaff
Old Dominion University
January, 2013 - December, 2015

Maeve McCarthy
Murray State University
January, 2011 - December, 2013

Kim Weems
North Carolina State University
January, 2013 - December, 2015

Aziz Yakubu
Howard University
January, 2011 - December, 2014

Past Members

Carlos Castillo-Chavez
Arizona State University (2009-2012)

Joan Herbers
The Ohio State University (2009-2012)

Trachette Jackson
University of Michigan (2009-2011)

Yi Li
Wright State University (2009-2011)

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.

To view a list of visiting lecturers go to www.mbi.osu.edu/about/vlprogram.html

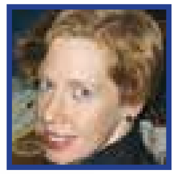
Visiting Lecturer Program


Marty Golubitsky
Ohio State


Jonathan Mattingly
Duke University


Janet Best
Ohio State


Erika Camacho
Arizona State


Christine Heitsch
Georgia Tech


Fabio Milner
Arizona State University


Emery Brown - MIT


Carlos Castillo Chavez
Arizona State


Fern Hunt
Howard and NIST


Asamoah Nkwanta
Morgan State


Ricardo Cortez
Tulane University


Trachette Jackson
University of Michigan


Michael Reed
Duke University


Isabel Darcy
University of Iowa

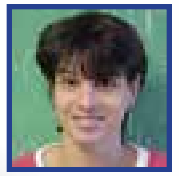

James Keener
University of Utah


Miranda I. Teboh-Ewungkem
Lafayette College


Lisette de Pillis
Harvey Mudd


Nancy Kopell
Boston University


Talitha Washington
Howard University


Lisa Fauci
Tulane University


Reinhard
Laubenbacher
University of
Connecticut Health
Cntr.


Abdul-Aziz Yakubu
Howard University

Visitors

2012-2013

Peter Ashwin
Mathematics, University of Exeter: February 14 - March 31, 2013

Andrea Barreiro
Mathematics, SMU: January 15 - May 15, 2013

Yibeltal Bayleyegn
African Institute for Mathematical Science(AIMS)
August 26 - September 22, 2012

Sze-Bi Hsu
National Tsing-Hua University: July 11 - 24, 2012

Vince Billock
Neuroscience, Wright Patterson: March 11 - May 31, 2013

Zhe Chen
Washington University in St. Louis: January 2 - April 2, 2013

Markus Dahlem
Humboldt University Berlin:
September 30 - December 15, 2012
Otto-von-Guericke University Magdeburg:
February 1 - March 25, 2013

Patrick Tchepmo Djomegni
University of KwaZulu-Natal:
August 26 - September 22, 2012

Alessio Franci
University of Liege: March 17 - April 14, 2013

Atarsaikhan Ganbat
Kyoto University, Graduate School of Science
November 21 - December 22, 2012

Gemma Huguet
Mathematics, Catalunya University:
March 10, 2013 - May 25, 2013

Martin Krupa
INRIA Paris-Rocquencourt: December 2012

Tim Lewis
Mathematics, UC Davis:
January 27- February 9/ March 10 - 23, 2013

Yoram Louzoun
Mathematics, Bar Ilan University: July 2 - 30, 2012

Edward Lungu
University of Botswana: April 30 - August 15, 2013

Michael Ngouma
Kwa-Zulu Natal University: September 30 - October 19, 2012

Mike Reed
Mathematics, Duke University: April 1 - 30, 2013

Greg Rempala
Georgia Health Sciences: October 17 - 24, 2012

John Rinzel
Mathematics, Courant, NYU: April 1 - May 11, 2013

Bob Rink
Amsterdam University: May 15 - 18, 2013

Joaquin Rivera-Cruz
Puerto Rico: September 1 - December 31, 2012

Jon Rubin
Mathematics, University of Pittsburgh
September 16 - October 13, 2012

Steve Schiff
Engineering Science & Mechanics, Penn State:
September 12, 2012 - July 01, 2013

Eric Shea-Brown
Applied Mathematics, University of Washington
September 29 - October 5, 2012

LieJune Shiau
Mathematics, UHCC: February 15 - May 11, 2013

Nourridine Siewe
Howard University: July 15 - 29, 2013

Ian Stewart
University of Warwick: September 17 - October 9, 2012

Yi Sun
Mathematics, Neuroscience, University of South Carolina
4 months

Ghanim Ullah
Engineering Science & Mechanics, LANL
August 1, 2012 - May 31, 2013

Stephan Van Gils
Mathematics University of Twente: February 2013

Martin Wechselberger
University of Sydney: March 11 - 24, 2013

Yina Wei
Penn State University: September 20 - 29, 2012

Aziz Yakubu
Howard University: July 15 - 29, 2013

Najat Yakubu
Howard University: July 15 - 29, 2013

Wenjun Ying
Mathematics, Shanghai Jiao: June 30 - July 3, 2012

Visitors

2013-2014

Afassinou Komi
Kwa-Zulu Natal: Aug 26 - Sept 22, 2013

Lee Altenberg
University of Hawaii: Sept 1- Nov 30, 2013

Reinhard Burger
University of Vienna: Sept 11- Oct 12, 2013

Steve Cantrell
Miami University: Sept 8 - Oct 11, 2013

Obiora Collins
Kwa-Zulu Natal: Aug 25 - Sept 22, 2013

Chris Cosner
Miami University: Sept 7 - Oct 10, 2013

Leah Johnson
University of Chicago: Aug 15- Dec 15, 2013

Eddy Kimba
Kwa-Zulu Natal: Aug 25 - Sept 22, 2013

Vlastimil Krivan
Czech Republic: Aug 18 - Nov 2, 2013

Maria Leite
University of Toledo: Aug 1 - Dec 21, 2013

Jinhuo Luo
Shanghai Ocean University: Jan 26 - Dec 31, 2013

Richard Rebarber
University of Nebraska-Lincoln: Oct 31 - Nov 23, 2013

Hao Wang
Edmonton University: Aug 23 - Dec 31, 2013

Jin Wang
Old Dominion University: Sept 15 - Oct 26, 2013
Jan 1 - June 30, 2014

Bruce Gluckman
Engineering, Pennsylvania State University
Mid March- Mid May, 2014

Farai Nyabadza
Mathematics, Stellenbosch University: April-July, 2014

Course Release

Department of Mathematics

- Janet Best
- Ching-Shan Chou (fall semester)
- Adriana Dawes
- Avner Friedman (fall semester)
- Yuan Lou (spring semester)
- Joe Tien (fall semester)
- Chuan Xue (fall semester)

Department of Computer Science & Engineering

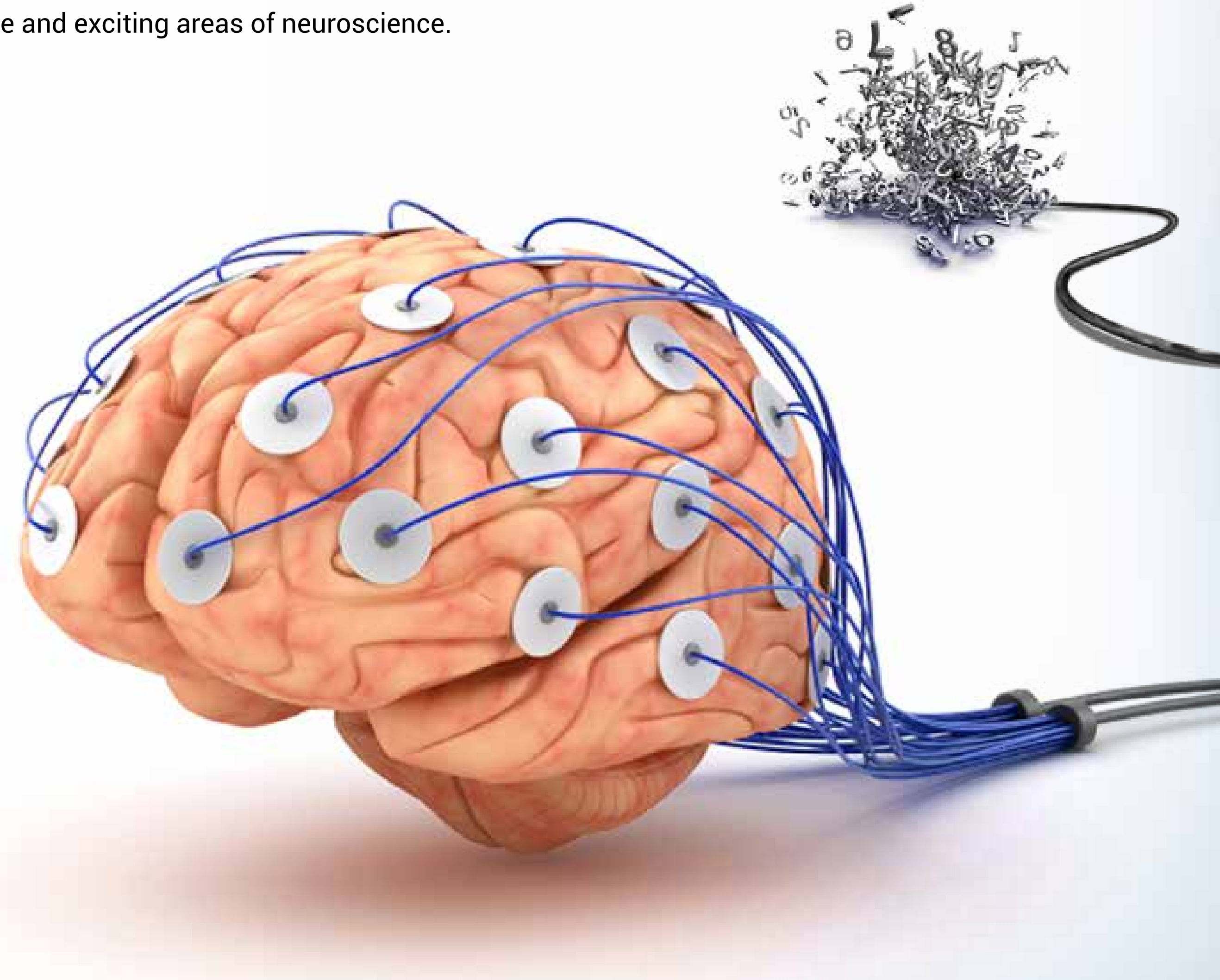
- Raghu Machiraju (spring semester)

Department of Statistics

- Radu Herbei
- Laura Kubatko
- Shili Lin (spring semester)

Mathematical Neuroscience

In 2012-13 MBI returned 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 opened the emphasis year with a workshop focusing on such parallels, in the form of general challenges posed by dynamics of nonlinear, spiking networks, and organized a series of workshops to follow that highlighted mathematical impact and possibilities in the most active and exciting areas of neuroscience.



Workshop 1

Mathematical Challenges in Neural Network Dynamics
October, 1-5, 2012

Organizers: Nicolas Brunel, Eric Shea-Brown, John Rinzel, and Sara Solla

Report by: King-Yeung Lam, Leopold Matamba Messi, and Michael Schwemmer

We will focus on dynamics and information processing in large, nonlinear networks. The aim is to highlight a set of mathematical questions that recur across neuroscience, and to discuss both recent progress and outstanding problems. The final day will feature a series of retrospective talks on the interplay of mathematics and neuroscience, leading into moderated discussions of future prospects. These sessions will align with the major themes of the workshop, which are proposed to be as follows:

Linking large-scale network structure and dynamics. The heterogeneous components and vast scale and connectivity of neural systems make for an overwhelming range of possible networks. However, network architectures are constrained by key principles - for example, each cell produces connections of only one sign, leading to non-normal connectivity matrices (Murphy and Miller). What are the consequences of such features for general properties of network dynamics? We will focus on this and other systematic departures from random connectivity, including small-world structures, localized connection "neighborhoods," feedforward inhibition circuits, and the impact of highly recurrent, and hence bistable, network components. In addition, we will cover the latest results on how basic assumptions about single-neuron properties do and do not impact network-wide dynamics.

Bridging scales -- mean field models. What mathematical tools can bridge scales from networks of spiking cells to averaged statistical variables that usefully summarize the activity of large networks? Mean-field techniques have yielded major advances in mathematical neuroscience for decades, but many developments remain to be realized, especially for networks with nonsparse connections and hence partial synchrony among spikes.

Information and coding in large spiking networks. Information-theoretic studies have shown that certain patterns of correlated, or partially synchronized, spiking across large networks enhances the fidelity with which they can transmit information. But what network dynamics lead to such patterns? We will highlight general mathematical results that connect architecture and information processing.

Plasticity and learning in network connections. Perhaps the most fascinating aspect of neural dynamics is how network activity drives network architecture to evolve over time. We will focus on mathematical tools for understanding the consequences of such rules, both in terms of the general connectivity structures that they produce and in terms of network function - e.g., encoding and releasing "memories" of past inputs. A related theme is robustness and variability in neural circuits - for example, how widely can connection strengths and intrinsic properties vary while preserving basic features of a network's dynamics?

MONDAY, October 1, 2012

Reliable and Unreliable Spike Times in Simple Neural Networks

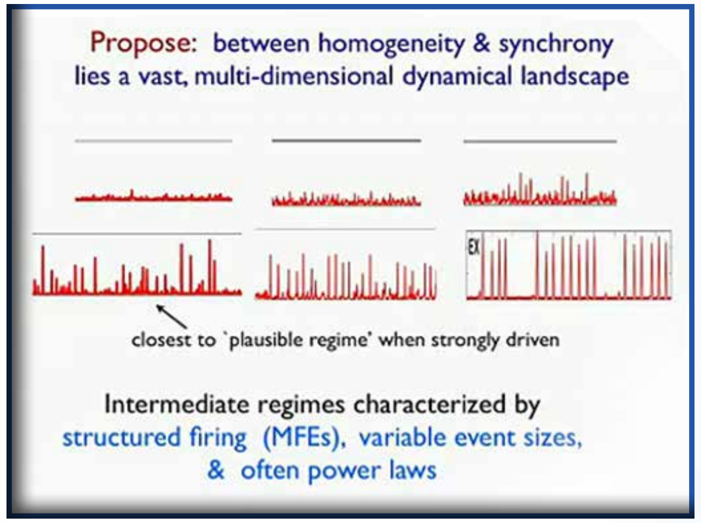
Eric Shea-Brown (University of Washington)

Dr. Shea-Brown spoke about recent attempts to explain the question of reliability in spiking neural networks. There is increasing evidence that precise repeatable spike timing seems to occur in biological systems; the question of interest to Dr. Shea-Brown in this talk was: Do trial-to-trial differences in initial conditions place limits on repeatability? He reviewed some results from the literature that partially answered this question using Lyapunov theory and gave two examples of two-cell networks of theta neuron models illustrating asymptotic reliability and the existence of random strange attractors. Dr. Shea-Brown noted that acyclic feedforward networks and one-cell networks of one-dimensional neurons are never unreliable as evidenced by the sign of the maximum Lyapunov exponent in such networks not being positive. He concluded the talk by examining the dependence of reliability on input parameters. Using a large random, sparse and balanced network of excitatory and inhibitory cells, he produced evidence that: (i) reliability increases with input mean and fluctuations and decreases with input correlation (ii) Feedback can produce unreliability and chaos, however, even in the chaotic regime, intermittent periods of highly reliable spiking often coexist with unreliable activity. Dr. Shea-Brown argued that the sustained coexistence of chaos and reliable spike events is due to the interaction of global state space expansion and dynamics local to individual cells.

Emergent Dynamics in a Model of Visual Cortex

Lai-Sang Young (New York University)

Dr. Young reported on a computational model of layer 2/3 of the mammalian visual cortex. Her goal in building such model was to construct a model with constrainable parameters that is coherent with multiple experimental observations and then analyze its emergent dynamics. The proposed model is a network of integrate-and-fire neurons from eight V1 hypercolumns, that are maximal tuned to three input orientations, with excitatory long-range connections, and sparse excitatory and inhibitory local connections. The model was then calibrated to reproduce qualitative features of phenomena observed in the visual cortex, including orientation tuning, gamma-band oscillations and surround suppression. The main finding of Dr. Young and colleague modeling efforts is that, in biological plausible regimes, networks dynamics of the mammalian visual cortex area neither homogeneous nor synchronous but highly structured and strongly shaped by temporally localized multiple firing events (MFEs) with characteristics signatures. Dr. Young proposed that the emergent dynamics of their model might be indicative of how the real mammalian visual cortex operates including the existence of MFEs but this has yet to be tested. If so is the case, she asked what might be the implications on pharmacological manipulations? Dr. Young also suggested that in the event that MFEs are real, current rate models or population dynamics models might be inadequate for capturing the underlying phenomena and may need to be supplemented for that purpose.



Propose: between homogeneity & synchrony
lies a vast, multi-dimensional dynamical landscape

closest to `plausible regime' when strongly driven

Intermediate regimes characterized by
structured firing (MFEs), variable event sizes,
& often power laws

Complexity without chaos: Plasticity within random recurrent networks generates locally stable neural trajectories

Dean Buonomano (University of California, Los-Angeles)

In this talk, Dr. Buonomano presented a new method by which a neural network can be entrained to stable coding of information. The question of interest was how do we build a time keeping device with neurons? He reviewed some of the literature that have established that sensory timing can rely primarily of hidden states of the network. However, there is a consensus that motor timing must rely on active states but encoding time in these states is complicated by chaos. Using firing rate models with random recurrent networks, he showed that one could suppress chaos through controlled feedback. He demonstrated that random recurrent networks that initially exhibit self-perpetuating and chaotic dynamics could be tuned through a supervised learning rule (innate training through recurrent plasticity learning) to generate locally stable neural patterns of activity; thus overcoming chaos. But the question of whether and hoe biological systems do it remain open. Through supervised learning and control feedback, Dr. Buonomano and colleagues have unearthed a novel dynamic regime in which the same network could behave chaotically, but locally stable for some trajectories. They posited that this local stability is computationally powerful and may be exploited for motor timing.

The stabilized supralinear network: A unifying circuit motif underlying multi-input integration in sensory cortex

Ken Miller (Columbia University)

Dr. Miller spoke about his efforts with several collaborators to build a unified model that explains how the sensory cortex integrates multi-inputs. He first reviewed a linear rate model of surround suppression in which they established that surround suppression is balanced de-amplification, not inhibition. The latter model was extended to a spatially self-consistent model of V1 incorporating both center and surround cells. The first finding is that, when the model is driven by a linear input/output function, only the inhibition stabilized network regimes can generate spatially periodic inhibitory activity in the absence of periodic connectivity. When the model incorporates periodicity in center and surround structures, they found that the preferred contrast modulated orientation is independent of the preferred luminance. A plausible mechanism for this observation is that contrast modulation tuning is done via intracortical interactions while the luminance tuning is via feedforward input. Finally to model the nonlinear behavior of contrast dependence, cells in the spatial model above are given an expansive power-law input/output function, identical for all cells. They observed that spatially periodic activity emerges at high contrast and a shift in dynamic regime causes contrast dependent changes in surround effects. To study normalization and suppression of correlated variability, they used a ring model of excitatory and inhibitory cells. The model predicts a transition from supralinear to sublinear summation with increasing stimulus contrast, and a winner-take-all-effect in sublinear regimes; thus explaining the reduction in shared variability with stimulus onset. Dr. Miller outlined the following principle as the underlining mechanisms of integration of multi-inputs by the sensory cortex: The supralinear input/output function quite generally creates a transition from supralinear response summation for weak stimuli to sublinear summation for stronger stimuli, as the subnetwork of excitatory neurons becomes increasingly unstable for stronger stimuli but is dynamically stabilized by feedback inhibition.

Neural field model of binocular rivalry waves in primary visual cortex

Paul C. Bressloff (University of Utah)

In this talk Dr. Bressloff aimed at explaining, using the example of binocular rivalry waves, how one can use neural field continuum model to study the nature of the waves and associated mechanisms from an analytical point of view. He described a competitive network model with synaptic depression which under a Heaviside firing rate function exhibits three possible steady states: the off state, the fusion state, and the winner-take-all state. Then, he focused on the spatially extended 1D competitive network model with synaptic depression from which he derived the neural field (integro-differential) 1D model of rivalry waves (left eye and right eye) as the continuum limit of the discrete spatial model. Assuming that the system is initially in a right-eye dominated winner-take-all state and using adiabatic approximation, he established the existence and uniqueness of a traveling front with slow adaptation, which imposes a symmetry breaking in the crossing conditions for computing the speed of the wave and the waves separation. He also showed that the speed of the wave covaries with switching frequencies of spontaneous oscillations and depends on the phase stimulus onset. In the presence of noise, the model exhibits a breakdown of mode locking with increase noise strength. Moreover, traveling waves persist if the input function is switched to a sigmoidal function.

Dr. Bressloff in joint effort with a joint effort with one of his student has also proposed a stochastic rivalry network assuming adiabatic approximation. Under the assumption of moderate noise, the stochastic model exhibits a separation of time scale with a diffusive like displacement of wave at long time scales and fast fluctuations at short time scales. They showed using perturbation theory that the wiggling of the front undergoes a Brownian motion and derived an analytical expression for the variance of the associated Brownian process.

TUESDAY, October 2, 2012

Wandering bumps in stochastic neural fields: robust memory through heterogeneity

Bard Ermentrout (University of Pittsburgh)

Dr. Ermentrout spoke about the effects of noise on stationary solutions in spatially extended neural fields. The dynamics of a neural field is described by an integrodifferential equation that models the firing rates of neurons at different spatial locations and whose integral term characterizes synaptic interactions between neurons at different spatial locations in the network. Before proving the existence of stationary solutions, or bumps, in the neural field model, Dr. Ermentrout noted that bumps have been observed in various models of working memory. In these models, the bumps generally represent neural activity during a working memory task where subjects are asked to remember the position of a brief visual stimulus flashed on a screen. In particular, the center of the bump is thought to encode the spatial position of the stimulus. However, these solutions are susceptible to noise, which affects the ability of the network to reliably decode the position of the visual stimulus. In the context of a neural field model, Dr. Ermentrout derived an expression for how white noise affects the position of the bump. In particular, the noise causes the bump to wander diffusively around the domain. Dr. Ermentrout then goes on to show that adding heterogeneity (spatially heterogeneous synaptic weights) can help to stabilize the position of the bump, which would allow for more robust decoding of the position of the visual stimulus. However, there is a tradeoff between robustness of reliable position encoding and the stability of the position of bump solution. As the modulation frequency of heterogeneity increases, the effective diffusion of bumps in the network approaches that of the network with spatially homogeneous synaptic weights. Lastly, Dr. Ermentrout showed that simulations with spiking neural networks have qualitatively similar behavior to that of the neural field model.

Beyond mean field theory for neural networks

Carson Chow (Laboratory of Biological Modeling, NIDDK, NIH)

Dr. Chow spoke about an approach to study fluctuations in neuronal networks that are due to finite system size induced correlations. These effects are normally ignored in mean field descriptions of networks, and are apparent when the network is of moderate size. Using phase oscillators as the model of neurons in the network, Dr. Chow uses techniques from kinetic theory of plasmas and gases and statistical field theory to construct a hierarchy for the moments of the density of oscillators, which describes the macroscopic behavior of the network. This framework allows one to capture the fluctuations and correlations of the network model that would be missing in the mean field description. Dr. Chow then discussed how this formalism can be generalized to any high dimensional dynamical system.

Slow dynamics and high variability in balanced cortical networks with clustered excitatory connections

Brent Doiron (University of Pittsburgh)

In this talk, Dr. Doiron spoke about how clustering of excitatory connections in balanced neural networks affects the network behavior. Anatomical studies show that excitatory connections in cortex are not uniformly distributed across a network but instead exhibit clustering into groups of highly connected neurons. There is no evidence of inhibitory clustering in the cortex. The implications of clustering of excitatory connections for cortical activity are unclear. In particular, Dr. Doiron wanted to explore whether these clustered connections can explain the variability in spike times in spontaneous firing, and how this variability is reduced when the network is stimulated. First, he showed that although the balanced network with uniformly distributed connections has firing rates that look similar to the clustered network, they differ dramatically in their distribution of Fano factors. Dr. Doiron then showed that even modest clustering substantially changes the behavior of these clustered networks, introducing slow dynamics where clusters of neurons transiently increase or decrease their firing rate. Consequently, neurons exhibit both short timescale spiking variability and long timescale firing rate fluctuations. Using a simplified model of binary (McCulloch-Pitts) neurons, Dr. Doiron showed that stimuli bias networks toward particular activity states, suppressing the mechanisms underlying slow timescale dynamics. This thereby reduces firing rate variability in evoked compared to spontaneous states, as observed experimentally in many cortical systems. However, these results were all with fixed cluster sizes. It is more likely cluster size is variable in the cortex. Dr. Doiron then showed that in a balanced network with variable cluster sizes, spontaneous network behavior is not highly variable. However, Dr. Doiron then showed that if inhibitory spike timing dependent plasticity is added, the network begins to exhibit behavior similar to that of the balanced network with fixed cluster sizes.

Orientation selectivity without orientation map

Carl van Vreeswijk (Universite Paris Descartes)

Dr. Van Vreeswijk talked about how orientation selectivity can occur in the primary visual cortex (V1) of animals that do not have orientation maps. Orientation selectivity (OS) in V1 has been studied extensively in cats and monkeys. In these animals, anatomically close V1 neurons have similar preferred orientations (PO), giving rise to orientation maps. Current theories of OS assume that, as a correlate of orientation maps, neurons with similar POs have a higher probability of connection. However, sharp selectivity is also observed in species (e.g., rat, mouse, or squirrel) whose V1 has no orientation map and neurons with very different POs are intermixed. Thus, the mechanism underlying orientation selectivity in V1 with such an intermixed organization is unknown; it is unclear whether a connectivity that depends on feature similarity is required, or a random connectivity suffices. Using a conductance-based network model, Dr. Van Vreeswijk showed that when the network operates in a regime where excitatory and inhibitory inputs are balanced, the neurons can be sharply selective even if the connectivity is random.

Spatially structured networks from sequences

Carina Curto (University of Nebraska-Lincoln)

The purpose of Dr. Curto's talk was to investigate how the synaptic organization of the hippocampus can be organized such that it supports bump solutions of neural firing activity. In particular, she examined how these bump solutions can arise in a two-dimensional model of a hippocampal network that does not a priori have a topographic network structure. Dr. Curto demonstrated how recurring short temporal sequences (similar to short wave ripples observed in the hippocampus) in the presence of a simple plasticity rule leads to the formation of spatially structured networks that exhibit robust bump attractor dynamics. Dr. Curto showed that these dynamics persist even if you force the network to have a sparse connection matrix. Using a simplified model, she was able to derive the minimum level of sparsity that still supported bump solutions for a given network size. Dr. Curto then showed simulations of the full network model to verify that the analytical result qualitatively carried over to the more complicated network model. Thus, spatially structured networks can emerge from short temporal sequences in the presence of a simple plasticity rule. Furthermore, these networks can support bumps that persist even in a sparse connectivity regime.

Amplification of high frequency oscillations by cell morphology and input segregation

Srdjan Ostojic (Ecole Normale Superieure de Paris)

In this talk, Dr. Ostojic showed that the individual features of a neuron in a network are vital to the output behavior of the network. In mean field models, for analytical tractability, the dynamics of single neurons are usually simplified. Dr. Ostojic attempted to construct such a mean field model of the Purkinje cell network, which is a network of inhibitory neurons in the cerebellum. The point of deriving the mean field model was to understand the mechanism of the self-sustained high frequency oscillations that are experimentally observed in the Purkinje cell network. Using the mean field model, one can analytically derive conditions for these self-sustained oscillations to occur. Dr. Ostojic first attempted to construct a mean field model using a simplified description of a single neuron (specifically, a exponential integrate and fire neuron with a sodium-like conductance). However, the resulting mean field model was unable to support high frequency oscillations. Dr. Ostojic then utilized a detailed conductance-based model of a Purkinje cell that takes into account morphology. The resulting mean field model in this case was able to support the high frequency self-sustained oscillations. In examining the cellular properties, Dr. Ostojic showed that the two models had very different rate response functions (i.e., the response of the firing frequency to different frequency sinusoidal input). However, experimentally recorded rate response functions of Purkinje cells look very similar to those of the detailed conductance-based model. That is, the firing frequency was selectively boosted at high frequencies (around 200Hz). Analysis using simplified and detailed models indicated that the boosting reflected a new amplification mechanism for high-frequency inputs. This novel mechanism selectively boosts high-frequency inhibitory synaptic input, contributing to the high-frequency oscillations of the Purkinje cell network in vivo.

WEDNESDAY, October 3, 2012

Balanced spiking networks can implement dynamical systems with predictive coding
Predictive coding in balanced spiking networks

Sophie Denéve (Laboratoire de Neurosciences Cognitives, ENS-INSERM)

Dr. Denéve spoke about how the dynamics of spiking neural networks can be related to the coding properties of the network. In particular, she derived a spiking neural network starting from the assumption that the network performs optimal spike-based computations. Dr. Denéve showed how this optimal computation can be done efficiently if spikes communicate "prediction errors" between neurons. Dr. Denéve then showed how her model naturally accounts for two puzzling aspects of cortex. First, it provides a rationale for the tight balance and correlations between excitation and inhibition. Second, it predicts asynchronous and irregular firing as a consequence of predictive population coding, even in the limit of vanishing noise. That is, optimal spike based computations lead to variable spike trains and balanced networks, and sensory information being represented by large neural populations. Lastly, Dr. Denéve showed that her spiking networks have error-correcting properties that make them far more accurate and robust than comparable rate models. The approach of Dr. Denéve suggests that spike times do matter when considering how the brain computes, and that the reliability of cortical representations could have been strongly under-estimated.

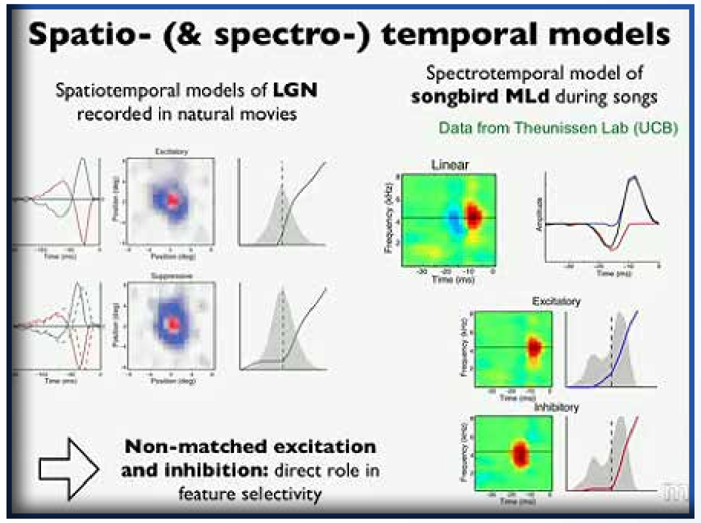
Detecting the many roles of inhibition in shaping sensory processing

Dan Butts (University of Maryland)

Dr. Butts proposed a method a nonlinear modeling framework that describes how a single neuron cell processes various feed-in signals as well as feedback signals from its outputs. Although nonlinear models are able to capture different features of the neural network more efficiently than linear models, one inherent problem is the large number of parameters involved. By considering the physiological-based description of neural computation, Dr. Butts and his collaborators hypothesized that the nonlinear computation is dominated by a discrete set of components, i.e. it is not arbitrarily complex. Their framework is able to infer the presence and stimulus tuning of inhibition using extracellular and intracellular recordings. By using the Maximum Likelihood Optimization, the parameters of their model is chosen and is tested on various spatially structured and natural stimulus signals. Different forms of inferred inhibition (subtractive and multiplicative) are also described, and the multiple roles in sensory processing are suggested. One of their future directions is to study the diversity of computation present in the retinal ganglion cells.

A mathematical theory of semantic development

Surya Ganguli (Stanford University)



Spatio- (& spectro-) temporal models

Spatiotemporal models of **LGN** recorded in natural movies

Spectrotemporal model of **songbird MLd** during songs

Data from Theunissen Lab (UCB)

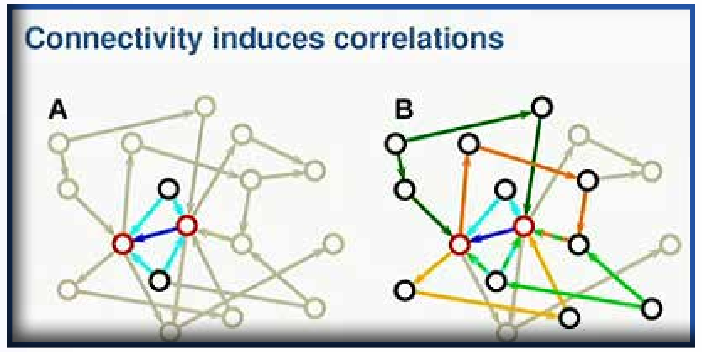
Non-matched excitation and inhibition: direct role in feature selectivity

In Dr. Ganguli's talk, a problem of understanding experimental data in semantic cognition is posed. More precisely, the goal is to understand the remarkable regularities in the developmental time course of infant semantic cognition, and the disparities in the learning time-scales of various categorial concepts. Dr. Ganguli developed a phenomenological, mathematical theory of the learning process through an analysis of the learning dynamics of multiplayer networks exposed to hierarchically structured data. Special exact solutions to the nonlinear dynamics are constructed, which decouples the deep, 3 layer networks. These solutions reveal that networks learn input-output covariation structure on a time scale that is inversely proportional to their statistical strength. Namely, concepts with more coherent categorial inferences are learned more rapidly comparing to less coherent ones. From this observation, a hierarchy of time-scales over which such modes are learned is generated by a hierarchy of those modes, which is related to the covariance structure of the data.

Spike Train Correlations Derived from Anatomical Microstructure

Stefan Rotter (University of Freiburg)

Spike train correlations reflect the structure of the network. Correlations are caused, for instance, by direct synaptic interaction and by shared input. Dr. Rotter's group proposed a mathematical model using Hawkes processes to relate rates and correlations of spike trains to the fine-scale anatomical structure of the network. Specifically, different modes of higher order neural connectivity can be described. The model is suitable in modeling irregularly spiky neurons, and has the advantage of being mathematically tractable: dynamical properties can be inferred analytically using linear algebra techniques. Based on the model, predictions of the influence of multi-synaptic pathways on activity dynamics are made and the network configurations that are significant to spike train correlations are identified. For instance, apart from the lower order connections, motifs of higher but uneven order are found to be contributing negatively to neural activities. Finally, an inverse problem of inferring connectivity from correlations is described and its ill-posedness is explained: Often different connectivities can lead to the same correlations in activities. A method based on the minimization of L^1vv norm of the coupling matrix is proposed to determine the simplest connectivity of the network, giving an approximate solution to the problem.



Managing heterogeneity in the study of neural oscillator dynamics

Carlo Laing (Massey University)

Dr. Carlo Laing considered a coupled heterogeneous population of relaxation oscillators, based on a network of Hodgkin-Huxley type neural models. Here the heterogeneity refers to certain parameter(s) having a probability distribution, rather than being fixed. The chief idea is to apply the fairly recent theory in uncertainty quantification in choosing specific values of the parameter used to describe the heterogeneity, sampled from the probability distribution. He argued that in this way, the effects of heterogeneity can be studied in a computationally efficient manner. However, he also commented that one main requirement of his approach is the smooth dependence of state on parameters. He then showed how the method can be generalized to the situation when more than one parameter is heterogeneous, where full or sparse tensor grids are used to select appropriate parameter values. In answer to a question raised by one of the audience, he commented that the spectral method adopted in his approach is optimal as far as one has the freedom to choose the underlying grid.

Balanced cortical microcircuitry for maintaining short-term memory

Sukbin Lim (University of California, Davis)

Dr. Lim proposed a new principle for short-term memory based on negative derivative feedback control. More specifically, it is demonstrated that the inhibitory and excitatory microcircuitry of neocortical memory-storing regions is sufficient to implement a corrective feedback mechanism that enables persistent activity to be maintained stably for prolonged duration. More precisely, when recurrent excitatory and inhibitory inputs to memory neurons are balanced in their amplitudes, but are temporally offset, drifts in activity trigger a corrective signal that counteracts memory decay. Circuits containing this mechanism have the advantages of being able to temporally integrate their inputs, to generate the irregular neural firing observed during persistent activity, and, more importantly, are robust against common perturbations. An example is given in the maintenance of spatially localized patterns of activity, e.g. in the visual cortex. Based on this approach, short-range excitation and long-range inhibition are no longer required for maintaining spatially localized patterns of activity. Moreover, the mechanism can encode the location as well as amplitude of stimulus. In response to a question raised, she also stated that a main assumption is that the strength of the negative feedback being proportion to the overall synaptic strength.

THURSDAY, October 4, 2012

Capturing effective neuronal dynamics in random networks with complex topologies

Duane Nykamp (University of Minnesota)

Dr. Nykamp spoke about understanding how the structure of a neuronal network influences its dynamics. In particular, he introduced a random network model in which one can prescribe the frequency of second order edge motifs. That is, the edges are random variables and one can increase number of motifs by increasing the covariance of certain motifs. Dr. Nykamp showed how to derive effective (mean field) equations for the activity of spiking neuron models coupled via such networks using an ad-hoc approach as well as a Field theoretical approach. A key consequence of the motif-induced edge correlations is that one cannot derive closed equations for average activity of the nodes (the average firing rate neurons) as is the case for the Wilson-Cowan equations, but instead must develop the equations in terms of the average activity of the edges (the synaptic drives). As a result, the network topology increases the dimension of the effective dynamics and allows for a larger repertoire of behavior. Lastly, Dr. Nykamp demonstrated this behavior through simulations of spiking neuronal networks.

The healing power of depression: synaptic transmission failure as a therapeutic mechanism in deep brain stimulation for Parkinson's disease

Jonathan Rubin (University of Pittsburgh)

One of the symptoms of Parkinson's Disease (PD) is an increase in the power of beta oscillations (10-15 Hz) in the globus pallidus (GP). It is believed that if you can reduce the power of these beta oscillations, you can reduce the motor pathologies of PD. Deep brain stimulation (DBS) of the substantia nigra (STN) reduces beta oscillations in GP, but not in STN. Suppression of beta oscillations in GP is correlated with alleviation of Parkinsonian symptoms. DBS also decreases STN somatic spiking. It is unknown how DBS reduces beta oscillations in GP but not in STN. Dr. Rubin spoke about how synaptic depression can help explain this puzzling finding. The idea is that DBS activates STN axonal spiking and this in turn affects the synaptic transmission between STN and GP. That is, DBS induces short-term depression in STN-GP projections. It is known that synapses in the rodent STN-GP pathway exhibit short-term depression. Furthermore, in primates, a gradual weakening of downstream response with sustained STN-DBS has also been observed. Dr. Rubin showed how adding short-term synaptic depression to the STN-GP synapses in a conductance based model of the basal ganglia in which DBS affects STN axons results in reduced power of beta oscillations in GP but not in STN. Thus, DBS-induced synaptic depression suppresses the transfer of low frequency oscillations between STN and GP.

Asymptotic Phase for Stochastic Limit Cycles

Peter Thomas (Case Western Reserve University)

Dr. Thomas spoke about a way to define a notion of asymptotic phase for stochastic neural models that display nearly periodic spiking behavior. In deterministic dynamics, a stable limit cycle is a closed, isolated periodic orbit that attracts nearby trajectories. Points in its basin of attraction may be disambiguated by their asymptotic phase. In stochastic systems with approximately periodic trajectories, asymptotic phase is no longer well defined, because all initial densities typically converge to the same stationary measure. Dr. Thomas explored circumstances under which one may nevertheless define an analog of the "asymptotic phase". In particular, Dr. Thomas considered jump Markov process models incorporating ion channel noise, and studied a stochastic version of the classical Morris-Lecar system in this framework. Dr. Thomas showed that his notion of stochastic asymptotic phase works well for systems perturbed by Gaussian noise, and also works well in systems with stochastic jump process ion channels when there are a large number of channels. Lastly, Dr. Thomas also showed that the stochastic asymptotic phase can be defined even for some systems in which no underlying deterministic limit cycle exists, such as an attracting heteroclinic cycle.

Wilson's rivalry networks and derived patterns

Marty Golubitsky (Ohio State University)

Dr. Golubitsky's talk focused on the analysis of the dynamics of binocular rivalry. The simplest rivalry models for two units exhibit three states: fusion between learned patterns, winner-take-all which is total dominance of a single learned pattern, and rivalry corresponding to periodic dominance of each of the learned patterns. In this talk, Dr. Golubitsky presented recent work with collaborators Casey Diekman, Tyler McMillen, and Yunjiao Wang on an attempt to explain rivalry states, other than learned patterns, in the context of a general class of coupled dynamical systems proposed by Hugh Wilson to study generalized rivalry. First, he showed how Wilson's general model with two learned patterns has an invariant subspace whose dynamics are equivalent to the simplest two-unit model. Second, Dr. Golubitsky explained how the states of Wilson networks transverse to the previously mentioned invariant subspace correspond to derived patterns. Moreover, he showed how the surprising results in a classic rivalry experiment of Kovacs et al. could be understood through rivalry between derived patterns. Dr. Golubitsky concluded the talk by constructing Wilson networks for a second experiment on binocular rivalry from the literature and proposed an experimental protocol for another Wilson network that could lead to unexpected rivalry between derived patterns.

Interplay between excitation, inhibition and calcium dynamics in a working memory model

David Terman (Ohio State University)

Dr. Terman reported on a recent effort of his and collaborators to construct a model of working memory. Their motivation in this modeling effort was to construct a model that could account for novel stimuli and elucidates how the persistent activity depends on context, previous experience, etc. The result was a network model of excitatory (E-cells) and inhibitory (I-cells) Hodgkin-Huxley type neurons, with random connections without excitatory-excitatory connections, in which Calcium modulates excitatory cells excitability and all E-cells are modulated by an h-current. The model also incorporates nonselective Calcium sensitive cation channels and SK-type Calcium dependent Potassium channels. To establish learning and study dependence to context, they incorporated E-E connections by assuming that E-cells are made of two compartments (Soma and Dendrite) modeled separately. The interaction between the two compartments is through Calcium diffusion and the E-E current is delivered to the dendrites. Dr. Terman provided numerical evidence that their model, though complicated, displays numerous properties of working memory. In particular, the model maintains persistent activity that is robust to noise and distractors and is also robust to heterogeneities. The model is able to maintain persistent activity consistent with context and only E-cells in the learned pattern maintain persistent activity.

A novel mechanism for sparse and reliable stimulus coding in sensory systems

Farzad Farkhooi (Free University of Berlin)

Dr. Farkhooi talk focused on the emergent properties of spike frequency adaptation on the reliability and sparseness of stimulus representation. To illustrate the idea, he used a mean-field model of a three-populations network with feedforward architecture and a temporally adapted input/output function, under the assumption of Poisson spike trains. Although the resulting model exhibits suppression to steady states with sequential adaptation, the reliability of single cell is not clear. Moreover, the Poisson process assumption is not appropriate, as the neurons are known to be non-renewal. To overcome the Poisson assumption and examine reliability, Dr. Farkhooi proposed a new paradigm, that he christened adaptive ensemble theory, in which the adaptation dynamics in the initial model are enhanced to a non-renewal process with known master equation. He concluded the talk with numerical evidences from an olfactory sensory model that incorporates his adaptive ensemble theory and is capable of sparseness and reliability of stimulus representation. The upshot of his talk was that the spike frequency adaptation is a natural and reliable framework for modeling sparse coding of dense and fluctuating stimuli.

FRIDAY, October 5, 2012

Mathematical challenges in the dynamics of balanced networks

Fred Wolf (Max-Planck-Institute for Dynamics and Self-Organization)

Dr. Wolf's talk focused on the statistically observed subtle interactions in the temporally irregularity observed in spike trains. By simulation and drawing from ergodic theory, the notion of Lyapunov exponents is used to study the evolution, or stretching, of each spike, as well as to quantify the information loss about initial condition of the system. The first part of the work focused on balanced theta networks, which are purely inhibitory. The positive Lyapunov spectrum is measured numerically and it is shown that spikes with different firing rates have different information decay rates. By manipulating the single spike instability by changing the spike profile, it is found that chaos reduces as the number of neurons increase in the model, to the contrary of common expectation. It is concluded that (i) balanced chaos are sensitive to single neuron properties and (ii) high absolute rates of entropy production are possible. The second part of the talk studies extensive stable chaos by looking at the effect of suppressing a single spike. A critical perturbation size is found, below which the system returns to its original state, but above which the system diverges and follows a completely different trajectory. It is concluded that (i) there is coexistence of stability and exponential separation (or decorrelation) in stable balanced chaos; (ii) there is an edge of chaos, beyond which the system decorrelates; and that (iii) the order of limit is important to discover such large system, small perturbative phenomena.

Cerebellar learning - A model of vestibulo-ocular reflex adaptation

Claudia Clopath (CNRS, Universite Paris Descartes)

Dr. Clopath covered two complementary approaches to study progressive phase learning experimental results. The experiment is performed in which wild-type and knocked-out-type (possessing only dysfunctional Purkinje cells) mice are placed on a rotating platform and are exposed to a rotating visual stimulus. The adaptation rates of the subjects are being recorded on a daily basis. The first (phenomenological) approach is the Vestibulo-ocular Reflex adaptation. It is concluded from this first approach that (i) delay in climbing fibre facilitates progressive phase learning; (ii) the lack of feedforward inhibition causes the knock-out-type to unlearn during the night. The second approach is to model input and target output using Markov chains. Here Dr. Clopath argues that the amount of bistability in the system promotes memory capacity. The maximal memory capacity is calculated by combining the analytical Replica method with numerical simulation. It is interpreted that as the correlation of output is positive, a large bistable range in the model maximizes the memory capacity. It is concluded that (i) the weight distribution of granule cells to Purkinje cells in the model enhances the robustness across different approaches of the ratio of silent synapses, in agreement with experiments; (ii) the role of bistability is to enhance memory capacity; (iii) the learning algorithm in this approach is in agreement with plasticity experiments. This is joint work with Nicolas Brunel, Jean-Pierre Nadal, Chris de Zeeuw and Aleksandra Badura.

Computations with population spikes during different cortical states

Misha Tsodyks (Weizmann Institute of Science)

It is observed experimentally that engaged animals react according to incoming sensory information, e.g., visual stimuli, while consolidation of the learned information takes place during their relaxed and sleeping states, with the different states being characterized by various forms of cortical activity levels. Dr. Tsokyks and his group study a possible neuronal mechanism for generating the diverse dynamics and give predictions about their possible functional significance. A realistic network with clustered architecture is being considered in this project. It is shown that certain network parameters are able to control the level of synchronization in neural activity smoothly. The network shifts from asynchronous activity to a regime in which clusters synchronized separately, then, the synchronization between the clusters increases gradually to fully synchronized state. By examining the effects of different synchrony levels on the transmission of information by the network, it is found that the regime of intermediate synchronization is preferential for the flow of information between sparsely connected areas. Based on these results, it is suggested that the regime of intermediate synchronization corresponds to engaged behavioral state of the animal, while global synchronization is exhibited during relaxed and sleeping states. Finally, an experiment performed by Buzsaki G., published in 1989 in Neuroscience is quoted to argue for the phenomenon observed numerically.

Workshop 2

Cognitive Neuroscience
December 10-14, 2012

Organizers: **Peter Dayan, Michael Shadlen, Eric Shea-Brown and Murray Sherman**

Report by: Leopold Matamba Messi, Jay Newby, and Michael Schwemmer

Cognitive neuroscience 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 experimentalists and theorists working on different levels, a workshop will move the field closer to a long-held goal of understanding and predicting behavior in increasingly rich cognitive tasks.

Each day will feature a different theme, as described in more detail below, and will emphasize both work at the level of algorithms and phenomena, and at the level of implementation by circuits of spiking cells.

The organizing committee suggests that this workshop include a select group of students and post-docs as participants. Time could be made available each day for brief student/post-doc presentations (short talks and/or poster sessions), and the day capped by evening sessions that encourage interactions among the students and post-docs. In addition, a student or postdoc will be chosen to be a "reporter" for each day to summarize the day's events and highlights. These will then be assembled into an overall workshop report that could be published by pre-arrangement with an appropriate journal.

Attention. Where are attentional effects "generated," how are they coordinated across multiple brain areas, how is attention fed back to earlier levels of sensory processing, and what are the underlying mechanisms at the level of circuits of spiking cells?

Decision making. How are diverse sensory and task cues integrated over time and combined into a "single" decision signal, how are decision rules applied to this signal, and what is the role of dopamine and other modulators in this process?

Coordination of neural circuits. Under different behavioral constraints, different brain areas form cooperative units. What is the role of thalamocortical and basal ganglia circuitry here? Nascent physiological work is in need of a theoretical counterpart, both to reveal how signals are gated and amplified, and to compare the performance and efficiency of different possible mechanisms and network architectures.

Reinforcement learning. Complex tasks require learning and updating of rules that relate reward to action in changing environments. What algorithms can perform this updating optimally, in the face of uncertainty about rewards and sensory cues? What neural circuitry can implement these algorithms?

MONDAY, December 10, 2012

Thalamus Plays a Central Role in Cortical Functioning

Murray Sherman (University of Chicago)

In this talk, Dr. Sherman focused on the interactions between the thalamus and the cortex. His goal was to explain why the conventional scheme of thalamocortical circuitry is wrong and suggest a more comprehensive scheme that accounts for the two categories of glutamatergic inputs into these areas of the brain. The current strategy to analyze thalamocortical circuitry assumes that all glutamatergic inputs are "drivers" that represent the main information, and other inputs are "modulators" affecting how driver input is processed. But most glutamatergic inputs are modulators and defining the actual subpopulation of drivers is critical. He argued that following the logic that identifying driver pathways in thalamus and cortex permit insights into information processing leads to two types of thalamic relay: first order nuclei that receive input from subcortical sources and higher order nuclei that relay driver input between cortical areas. To support his point, he presented a paradigm that may be used in classifying glutamatergic pathways into drivers and modulators. The latter classification of glutamatergic pathways leads to a different way of looking at circuit properties and information transfer. Dr. Sherman speculated that most of the thalamus consists of high order relays and provided experimental evidence that many, if not all, direct cortico-cortical connections are paralleled by indirect transthalamic driver routes involving higher order thalamic relays. He ended the talk with questions about the information content of each o the two parallel pathways and why is one processed through thalamus?

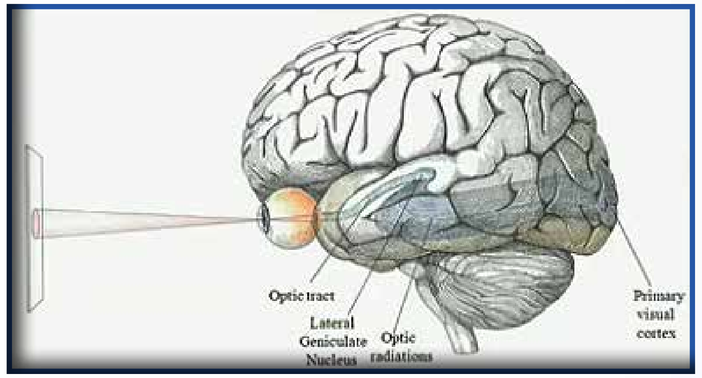
Most of the Messages Thalamus Sends to Cortex Contribute to "Forward Models"

Ray Guillery (University of Oxford)

Dr. Guillery spoke about the detailed communication mechanisms between the cortical areas, the thalamus and the motor centers. He examined in details the components that are involved for example in the spinal reflex and pointed out that the messages that go up to the thalamus have already branched out to motor centers. Specifically, cortex receives information from sensory receptors about the body and the world and about subcortical activity from first order thalamic relays and about cortical processing of those inputs from higher order relays. In addition cortex also receives from all of these inputs copies of instructions for upcoming actions (efference copies) that are on their way to execution in the motor branches. Dr. Guillery argued that efference copies produce a forward model about upcoming actions and thalamus, as a filter of information to the cortex, controls the generation of ubiquitous forward models; cortical areas are set up to monitor each other and the lower sensory inputs, all of which acts on the motor centers. The ubiquity of efference copies in thalamocortical circuits suggests that key problems of the self and of attention depend on readily identifiable thalamocortical pathways.

Visual Attention Modulates Thalamocortical Communication

Marty Usrey (University of California, Davis)



In this talk, Dr. Usrey reported on a study that sought to test the hypothesis that attention enhances bottom-up processing pathways across cortical areas. This test was based on investigating the influence of attention on the geniculocortical synapse. The experiment consisted in recording from cortical layer 4C neurons in monkeys that have been trained to attend to a drifting grating stimulus and report a contrast change. The connectivity was assessed from spike train data using a cross-correlation analysis and a collision test was applied to discern feedback vs. feedforward connection in corticogeniculate neurons. Dr. Usrey study revealed a significant influence of attention on geniculocortical communication. If retinal and geniculate receptive fields are very similar and overlap extensively, the cells will be strongly connected. However, as receptive fields begin to differ connection falls off rapidly and the strength weakens. Also attention reduces timing jitter of postsynaptic response in cortical neurons. This study demonstrated that attention could enhance neuronal communication in the very first synapse in the visual cortex.

Neural Basis of Visual Attention in the Primate Brain

Sabine Kastner (Princeton University)

In this talk, Dr. Kastner discussed functional magnetic resonance imaging (fMRI) and transcranial magnetic stimulation studies in humans that revealed the mechanisms underlying space-based control of selective attention. The fMRI study revealed that a dorsal fronto-parietal cortex controls spatial attention; multiple topographic areas of the network in the right and left hemisphere generate "attention weights" to control the left and right visual field, respectively, and these attentional weights predict and individual's spatial biases across the visual field as observed in the landmark task. Perturbations of the network using transcranial magnetic stimulation suggest that spatial attention control is accomplished through an inter-hemispheric competition process. She also reported on monkey physiology studies that suggest an important function of the pulvinar in controlling the routing of information through the visual cortex during spatial attention. The pulvinar regulates synchrony between cortical areas according to attentional demands by influencing cortex in the alpha band, in so doing pulvinar may control information flow between cortical areas. In view of these studies, Dr. Kastner suggested that pulvinar must be considered a subcortical component of the attention network in the brain and views of cognitive processing need to be expanded to incorporate the thalamus.

Choosing Valuable Objects Automatically – A Basal Ganglia Mechanism

Okihide Hikosaka (National Eye Institute, National Institutes of Health)

In this talk, Dr. Hikosaka spoke about the neural mechanism underlying object-reward association. The research hypothesis that tested in the study that he reported is that "the values of individual objects are stored in the brain as long term memories. He began by describing the task used to train the monkeys to associate values to objects and presented videos of primate performing the task. To test the hypothesis, they recorded from CDt and SNr neurons and observed that after several learning sessions across several days, these neurons showed differential responses to the objects. Many of the CDt neurons showed excitatory responses to high-valued objects more strongly than to low-valued objects whereas SNr neurons were inhibited by high-valued objects and excited by low-valued objects. Many of the SNr neurons projected to the Superior Colliculus (SC) suggesting that reward-dependent visual signals are used for controlling saccadic eye movements. Dr. Hikosaka posited that their study suggest that basal ganglia subsystem CDt-SNr-SC contribute to the acquisition of the object reward association skill thus enabling the animals to select and look at high-valued objects automatically.

TUESDAY, December 11, 2012

Linking levels of analysis in computational models of corticostriatal function

Michael Frank (Brown)

The speaker asked the question: what is the role of creating computational models, and how do we relate mind and brain? He discussed fronto-basal ganglia circuits, which are involved in motivation and cognition. He also talked about dopamine, which regulates striatal activity and learning, and is involved in Parkinson's disease. There are two main theories of striatal dopamine, implicating it in performance and learning. In the former, dopamine reports incentive salience, energizing motor actions. In the latter, notably in reinforcement learning, dopamine reports prediction errors. Two different dopamine receptors (D1 and D2) are associated with separate paths through the striatum, and different functions, namely go and no go. Dr. Frank then discussed a semi-realistic model, consisting of point conductance neurons, and showed how this model could be used to explore the effect of different genes and drug affects on performance and learning. He also talked briefly about his work on the effects of conflict about rewards on decisions.

"I see what to do!" Some parallels between action selection and perception

Matthew Botvinick, (Princeton)

One common way of viewing perception is as inference about the contents of the world according to how likely they make the sensory evidence. Dr. Botvinick talked about doing the same formal operations, but where inference determines which actions make reward likely, treating the latter as notional or fictive observations of a random variable whose statistics are determined by the probability of getting a payoff. He showed the power of this approach in a number of contexts.

The orbitofrontal cortex as a state space for reinforcement learning

Yael Niv, (Psychology, Princeton University)

Classical or Pavlovian conditioning is often treated as a form of prediction learning. However, what exactly are animals learning? The simplest idea is that they learn parameters associated with the prediction. A more complex, but richer, notion is that they also learn the structure of the possible predictions, i.e., latent causes just like those in the models of perception in Dr. Botvinick's talk. This leads to the creation of a state space for learning, one that Dr. Niv has suggested is associated with the orbitofrontal cortex. One account of structure learning involves a generative model of the environment with an infinite capacity prior, which is flexible enough to capture the complex structure of the environment, but constrained enough to allow learning. Bayesian inference using such a model leads from observations to the latent causes. Dr. Niv illustrated this sort of structural inference using a task in which subjects had to combine prior and likelihood information, but where different priors would come from different notions of structure. She showed that her model predicted human behaviour well.

WEDNESDAY, December 12, 2012

Scaling laws of associative retrieval from long-term memory

Misha Tsodyks (Weizmann Institute of Science)

In this talk, Dr. Tsodyks addressed the question of how information is retrieved from memory when there are no precise item-specific cues. Examples from real life are when a person tries to recall the names of their classmates, their favorite writers, or places to see in Rome. This differs from situations in which a person may be given an explicit cue to trigger the retrieval of a specific item from memory. Experimental data seems to suggest that the number of items that can be retrieved from memory with no precise item-specific cues is very limited. Dr. Tsodyks hypothesized that in these types of situations, retrieval occurs in an associative manner, i.e. each recalled item triggers the retrieval of a subsequent one. Using a Hopfield-like memory neural network, Dr. Tsodyks shows that the retrieval behavior of such a network depends crucially on the amount of overlap (or similarity) between the stored items. Dr. Tsodyks then goes on to show mathematically that the problem can be reduced to analysis of random graphs, and general results about the retrieval capacity of the recall can be derived analytically. The main conclusion of the analysis is that retrieval capacity is severely limited, such that only a small fraction of items can be recalled, with characteristic power-law scaling with the total number of items in memory. Dr. Tsodyks then compared his theoretical results to free recall experiments and showed that they are in surprisingly good agreement.

The importance of mixed selectivity in complex cognitive tasks

Stefano Fusi (Columbia University)

In this talk, Dr. Fusi explored whether neurons in the prefrontal cortex (PFC) that respond to multiple aspects of a cognitive task (i.e., neurons that have mixed selectivity) assist in the cognitive functions that are attributed to the PFC. Dr. Fusi addressed this question by analyzing the neural activity recorded in PFC during an object sequence memory task. The experimental results demonstrate that mixed selectivity neurons can be as informative as highly selective cells (i.e., cells that respond selectively to a single aspect of a given task). Each task-relevant aspect can be decoded from the population of recorded neurons even when the selectivity to that aspect is eliminated from individual cells. In fact, Dr. Fusi shows that the recorded mixed selectivity neurons actually offer a significant computational advantage over specialized cells in terms of the repertoire of input-output

functions that are implementable by readout neurons. The superior performance is due to the fact that the recorded mixed selectivity neurons respond to highly diverse non-linear mixtures of the task-relevant variables. This property of the responses is a signature of the high-dimensionality of the neural representations. Dr. Fusi also observed that this dimensionality is predictive of animal behavior; demonstrating that in error trials the measured dimensionality of the neural representations collapses. In summary, Dr. Fusi's findings suggest that research focus should be moved from neurons that exhibit easily interpretable response tuning to the widely observed, but rarely analyzed, mixed selectivity neurons.

Making decisions with spiking neurons

Sophie Denéve (École Normale Supérieure)

Sensory information is represented in the brain by the spiking output of neurons. The precision (or reliability) of these neural signals varies from trial to trial, and is not known in advance. Dr. Denéve's talk focused on how these seemingly unreliable neural signals can be used to make decisions. In particular, to make fast and accurate behavioral choices, one needs to integrate these noisy sensory inputs, take prior knowledge into account, and adjust decision criteria. It was shown previously that in two-alternative-forced-choice tasks, optimal decision making can be formalized in the framework of a sequential probability ratio test and is then equivalent to a diffusion model. However, in order to know how quickly one should integrate the sensory input and set the optimal decision threshold, the reliability of the sensory observations must be known in advance. Most of the time, this reliability cannot be known without first observing the decision outcome. In order to address this issue, Dr. Denéve considers a Bayesian decision model that simultaneously infers the probability of two different choices and at the same time estimates the reliability of the sensory information on which this choice is based. The resulting model is a non-linear diffusion to bound where the weight of the sensory inputs and the decision threshold are both dynamically changing over time. Dr. Denéve then showed that this model accounts for recent findings in a motion discrimination task that are not captured by simple diffusion models of decision-making. Lastly, Dr. Denéve illustrated that this Bayesian decision-making model can be implemented in a neural architecture using fast Hebbian learning.

Not noisy, just wrong (The computational and neural causes of behavioral variability)

Alexandre Pouget (University of Rochester)

In this talk, Dr. Pouget focused on understanding the causes of behavioral variability. More precisely, it is known that neurons in the brain display nearly Poisson variability in their spiking activity. Furthermore, behavioral responses of humans are also quite variable, i.e., response times during the same repeated task can be quite variable. Previous work has put forth the idea that behavioral variability stems from the variability of neural activity in the brain. However, Dr. Pouget suggests an alternative account of behavioral variability. Dr. Pouget hypothesizes that the brain is noisy, but that this neural variability does not greatly affect behavior. In Dr. Pouget's view, most of the behavioral variability comes from variability in "data" from the world and suboptimal inference on the part of the brain. That is, suboptimal filters lead to higher variability in neural responses. In order to perform optimal inference, one would need to know how the data was generated, i.e., the generative model, which is intractable for real world problems. Dr. Pouget then went on to analytically show that the information limiting correlations in neural populations are the ones proportional to the product of the derivatives of the tuning curves of the individual neurons. Dr. Pouget then hypothesized that suboptimal inference limits information transfer in neural populations primarily by affecting this specific correlation structure.

A diversity of timescales for cognitive computation and memory

Xiao-Jing Wang (Yale University)

The prefronto-parietal cortex (PPC) is known to be involved in a number of cognitive functions, such as decision-making, working memory, and task switching, to name a few. In this talk, Dr. Wang explored the microcircuit details that allow the PPC to perform such functions. In particular, Dr. Wang argued that it is the prevalence of slow time constants (on the order of seconds) in the PPC that allow it to perform all of these cognitive functions. Dr. Wang then explored the biological basis of these slow time constants in the PPC. More precisely, Dr. Wang wanted to examine what causes the PPC to get such a distribution of time constants when the membrane time constants of individual neurons are on the order of 10-20 milliseconds. In order to answer this question, Dr. Wang created a multi-area neuronal network model using experimentally estimated connectivity, and estimates of how the input varies among the different brain areas. Dr. Wang then showed that a broad range of time scales across the different areas naturally arises in this multi-area model, but that the time scales are fairly localized within the different areas. That is, the early visual areas in the model have a prevalence of fast time constants, while the higher cognitive areas have a prevalence of slower time constants. Dr. Wang then argued that local connectivity does not imply such localized time scales. Lastly, Dr. Wang discussed the types of network architecture that do give rise to localized time scales and showed that feedforward and feedback connections are necessary.

THURSDAY, December 13, 2012

Do we have Bayes' theorem hardwired in the cortico-basal-ganglia circuit?

Rafal Bogacz (University of Bristol)

In this talk, Dr. Bogacz put forth the idea that, during decision-making, the cortico-basal-ganglia circuit is used to compute probabilities that different considered alternatives are correct. These probabilities would then be used to perform Bayesian inference in order to decide between the considered alternatives. First off, Dr. Bogacz showed how one constructs a neural network model that implements Bayes theorem for calculating and inverting conditional probabilities associated with actions and rewards during decision-making tasks. Dr. Bogacz then went on to show how such a model is mapped onto the functional anatomy of a circuit involving the cortex, basal ganglia, and thalamus. Lastly, Dr. Bogacz showed predictions of the model regarding the activity of neurons in different regions of the cortico-basal-ganglia circuit, and a prediction regarding how deep-brain stimulation of the basal ganglia affects the ability of the model (and therefore the cortico-basal-ganglia circuit) to make accurate decisions.

The neural dynamics of decision-making: multiple scales and a range of models

Philip Holmes (Princeton University)

In this talk, Dr. Holmes described a variety of models ranging from cellular to cortical scales, which illuminate how individuals accumulate evidence and make simple decisions. First off, Dr. Holmes showed how a decision-making network composed of large numbers of individual spiking neurons can be simplified using methods of mean field and dynamical systems theory. Dr. Holmes then argued that the simplification of these high-dimensional stochastic differential equations approximates simple drift-diffusion (DD) processes like those used to fit behavioral data in cognitive psychology. These DD models are analytically tractable and coincide with optimal methods from statistical decision theory. Dr. Holmes then showed that when comparing subject performance to the predictions of the DD models, the subjects tend to be suboptimal in maximizing their overall reward rate. Thus, the predictions of the DD models prompted new experiments in order to uncover the real objective function that subjects are optimizing. Dr. Holmes, showed results from such experiments revealing that many subjects tend to weight accuracy higher than monetary rewards. Lastly, Dr. Holmes described work in progress on a multi-area model of attention and decision-making in order to discern the roles and interactions of different brain areas hypothesized to be involved perceptual decision-making and visual attention.

Integrating Information across Time and Sensory Modalities for Decision-Making

Anne Churchland (Cold Spring Harbor Laboratory)

In this talk, Dr. Churchland presented a new paradigm for the study of multisensory decision-making in humans and rats a preliminary neuronal recording data that aim at identifying the neural basis of such decisions. She argued that the same circumstances that lead animals to integrate information across time, ambiguous and uncertain stimuli, lead them to integrate information across sensory modalities. Using a rate discrimination task, she investigates the following three questions: (1) Do judgments about an abstract, time-varying quantity benefit from multisensory stimuli? (2) Do rats and humans take into account stimulus reliability when making such decisions? (3) Do rats and humans use time similarity for reliable and unreliable decisions? She reported that the experiments carried out in her lab point to an affirmative answer to all three inquests. Both species show improvements in accuracy that are close to optimal prediction; the subjects make use of time in a similar way

for unisensory and multisensory stimuli, and for reliable and unreliable stimuli. Dr. Churchland also argued that synchronous activation of multiple sensory circuitries (e.g. auditory and visual) likely does not drive the improvements in accuracy, since they observed comparable improvements with asynchronous multisensory stimuli. The findings reported by Dr. Churchland identifies a novel strategy, information integration across time and sensory modalities, that can help animals overcome sensory uncertainty to make better decisions. She also shared preliminary recording data that seek to identify the signature of developing decision in rat posterior parietal cortex.

Neural Integrators – What do we need and what can we get away with?

Eric Shea-Brown (University of Washington)

In this talk, Dr. Shea-Brown spoke about the question of integration of different types of signals over time in decision-making. At the heart of this discussion was the question of whether simple integration mechanisms are applicable: (1) without perfect tuning of circuit feedback; (2) without perfect knowledge of stimulus onset time; (3) for sensory populations with different structured correlations? Dr. Shea-Brown reported on a modeling effort aimed at elucidating the three questions above using an optimal neural integrator based on the spike rate mean field model. The performance of the model was evaluated the standard way using a speed/accuracy curve and shown to be very sensitive to circuit mistuning. They proposed to address the sensitivity of the optimal integrator by amending the spike rate model and filtering it input through a saturation function. The resulting "robust" integrator yields a tradeoff between accuracy and stability; recovers 35-75% of loss in mistuned circuits and causes minimal performance lost for perfectly tuned circuits. Robust integrators cope with tuning and some onset time problems while correlations may not require special treatment except for widespread correlation events; they impact sampling distributions of inputs but have little effect on decision making performance.

FRIDAY, December 10, 2012

The neuroeconomics of simple choice

Antonio Rangel, (Caltech)

The speaker sought to understand why consumers choose a product when faced with a choice. This is a very hard problem in general; but it is possible to study simpler, binary, choices between pairs of sufficiently similar alternatives. Dr. Rangel asked whether there a dedicated valuation system, what the properties of value signals are, how values are computed, and how they are compared? He discussed a number of experiments that investigated this question, using tools from experimental economics to get people to reveal their values. He found critical roles for the orbitofrontal cortex, and areas that interact with this region.

Pavlovian corruption of instrumental behavior

Peter Dayan (University College London)

The speaker discussed instrumental and Pavlovian learning mechanisms. Instrumental actions are chosen because they lead to the acquisition of rewards or the avoidance of punishments. Pavlovian actions are pre-determined by evolution, and are automatically attached to affectively-important outcomes (these are called consummatory Pavlovian actions) and predictions thereof (preparatory ones). Dr. Dayan discussed a series of experiments in which Pavlovian and instrumental actions either cooperate or compete, providing some insight into their interaction.

Consciousness as a decision to engage

Michael Shadlen (HHMI Columbia University)

Neuroscience has so far failed to explain consciousness. How can we go about solving this problem? The speaker's main idea was to present two characterizations of consciousness. From neurology we think that it concerns states of arousal. From philosophy, we think it concerns awareness, authorship narrative, subjectivity, etc. Both share a common framework: consciousness as a *decision to engage*. The speaker discussed a series of experiments in which he recorded the activity of neurons in the Lateral Interparietal area (LIP), whilst macaques accumulated sensory evidence that would enable them to make a choice that would lead to reward.

Workshop 3

Disease
February 4-8, 2013

Organizers: Victoria Booth, Liam Paninski, Jonathan Rubin, Steven J. Schiff, and Charles Wilson

Report by: Kang-Ling Liao, Wing-Cheong (Jon) Lo, and Michal Seweryn

Mathematical neuroscience is required to understand the normal functions of the computational brain. As a corollary, we can translate our fundamental understanding of the nervous system to better understand and treat disorders of the brain.

There are a variety of brain diseases that are considered dynamical - where the symptoms are consequences of pathological parameters of the underlying neuronal elements and network. Several dynamical diseases have steadily improving mechanistic understanding, embodied into computational models that increasingly reflect the dynamics of the disease symptoms. These include Parkinson's disease and epilepsy. We suspect that other more complex brain diseases are revealing a dynamical component, such as depression and schizophrenia. Along with the advent of improving with computational models, the technical ability to perform open or closed loop deep brain stimulation is now becoming increasingly applied to treat these dynamical diseases. Thus as we better understand dynamical disease, the ability to dynamically probe and control them is now at hand.

Another area of medical application of mathematical theory is in the area of brain interfaces. Here, measurement arrays (electrodes or optical) can be used to extract dynamics from ensembles of neurons, and functions are created to decode such information. Such decodings enable us to understand the neural code, and to drive robotic devices or encode information to stimulate the brain. In addition to devices that can adapt to the brain's activity, it is now clear that the brain co-adapts to such devices - learning to use them to accomplish tasks. The cutting edge of interfacing with decoding from and encoding information for the brain is an important cutting edge of mathematical biosciences.

Lastly, genomic variability is an inherent aspect of the robustness of species --- it is the plausibility of life itself. Yet the dynamical expression of genomic variability may remain within, or branch across species boundaries --- speciation requires a phenotypic dynamical expression. In neuronal circuits, there is substantial variation in the levels of active channel proteins, and computationally, there are wide varieties of building equivalent dynamics from available genetic protein products. In epilepsy, there is increasing evidence that the combinatorics of multiple channel protein variations may contribute to producing similar expression of the dynamics of epilepsy. In depression, the autoreceptors and reuptake transporters on dopaminergic and serotonergic neurons change their expression levels in response to long-term changes in extracellular concentrations of neurotransmitters. Thus understanding the mechanisms by which SSRIs work necessarily involves understanding gene regulation, biochemistry, and electrophysiology, and how they influence each other dynamically in neurons. We will explore the intersection of evolution, genetic variability, and dynamical disease.

MONDAY, February 4, 2013

Parkinson's Disease

Striatum as a potential source of exaggerated beta rhythms in Parkinson's disease

Michelle M. McCarthy (Boston University)

In this talk, Dr. McCarthy suggested that the prominent beta oscillations in Parkinson's disease are the result of an exaggeration of normal striatal network dynamics. At the beginning, she introduced the relationship between beta oscillations and Parkinson's disease and pointed out that Parkinson's patients have increased beta oscillations in the cortex and basal ganglia.

Although the mechanisms by which these beta oscillations arise is unknown, mathematical models inform us that robust beta frequency rhythms can emerge from inhibitory interactions between striatal medium spiny neurons (MSNs). Her MSN network modeling studies propose that the pathologic beta oscillations in Parkinson's disease may arise as an indirect effect of striatal dopamine loss on the striatal cholinergic system. Experimental testing in which the cholinergic agonist carbachol is infused into mouse striatum induced pronounced, reversible beta oscillations in the striatal local field potential. Finally, she demonstrated that the interaction between the GABAa and the M-current is critical to the creation of beta oscillations in MSN network model.

Modeling the neuroprotective role of enhanced astrocyte mitochondrial metabolism during stroke

David Terman (The Ohio State University)

Dr. Terman introduced a mathematical model that integrates the dynamics of cell membrane potential, ion homeostasis, cell volume, mitochondrial ATP production, mitochondrial and ER Ca2+ handling, IP3 production and GTP-binding protein coupled receptor signaling. Simulations with the model support that the permeability transition pore (PTP) plays an important role for making cell more vulnerable to stroke-like conditions. The model can then be simplified and analyzed in order to better understand the mathematical behavior of the equations. This approach helps determine how changes in IP3-mediated calcium release, under varying conditions of oxygen and the energy substrate pyruvate, affect mitochondrial ATP production.

Mathematical modelling of abnormal beta oscillations in Parkinson's disease

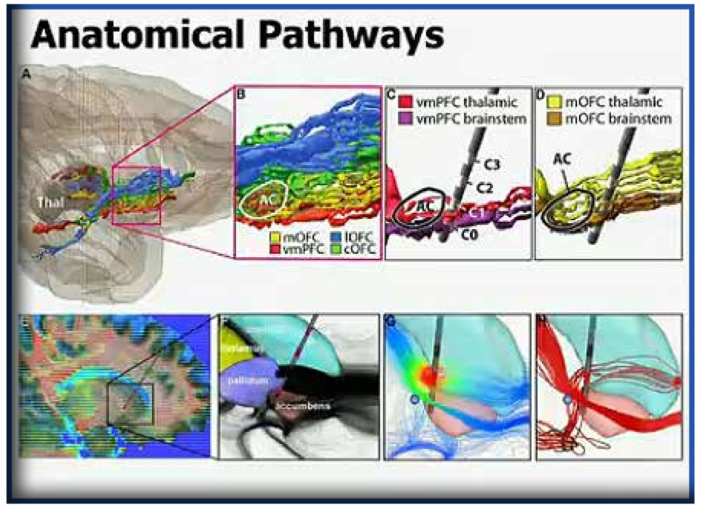
Rafal Bogacz (University of Bristol)

Dr. Bogacz pointed out the fact that among Parkinson's patients, increased power of beta oscillations in firing rate has been observed throughout the cortico-basal-ganglia circuit. Although there are many potential sources for generation of beta oscillations -- for example, STN-GPe -- it is difficult to determine where these oscillations are generated circuit on the basis of experimental data alone. A computational model of a subset of basal ganglia introduced in this talk is able to reproduce experimentally observed patterns of activity. The analysis of the model suggests that STN-GPe may be a source of beta oscillations and also determines the conditions for the generation of beta oscillations, which agree with recent experimental data.

Tractography-activation for deep brain stimulation

Cameron McIntyre (Case Western Reserve University)

In this talk, Dr. McIntyre was using the analysis of patient-specific computational models to identify the target for Deep Brain Stimulation (DBS) to improve the clinical implementation of DBS technology for patients with depression. DBS has emerged as an exciting new possibility for the treatment of neuropsychiatric disorders. Theoretical and experimental evidence suggest that when DBS is applied to neural tissue, it responds with the generation of action potentials in axons.



The speaker introduced a model that combines diffusion-tensor tractography, axonal stimulation predictions, and clinical outcome analyses. His results from patients with treatment refractory depression suggest that antidromic modulation of cortical pyramidal neurons appears to be a key factor in the therapeutic mechanisms of DBS and deciphering the cortical activity patterns induced by DBS represents an important next step for improving DBS technology.

A model of thalamocortical relay neuron and the parkinsonian network

Yixin Guo (Drexel University)

Dr. Guo first applied a data-driven model of a thalamo-cortical (TC) relay neuron to examine the TC relay responses to an excitatory input train, under inhibitory signals. Then she incorporated recording data as inhibitory signals to the TC model to investigate how the conventional deep brain stimulation (DBS) achieves its therapeutic effectiveness, for example, relieving motor symptoms for Parkinsonian patients, and explore other form of DBS that can overcome the downside of the conventional DBS. She explored the closed-loop stimulation paradigm using a Parkinsonian network model of the basal-ganglia thalamo-cortical circuit. Her computational results show that the type of stimulation, based on a filtered version of the local field potential, significantly improves the fidelity of TC relay. To further understand the different scenarios of TC relay responses, she analyzed the entrainment of the TC neuron to periodic signals that alternate between 'on' and 'off', respectively. By exploiting invariant sets of the system and their associated invariant fiber bundles that foliate the phase space, she applied map reduction to reduce the 3D TC model to a 2D map. Based on this reduced map, possible scenarios of TC relay responses observed in the data-driven model were obtained.

TUESDAY, February 5, 2013

Epilepsy, Parkinson's disease, and Methods

Neuronal and network dynamics in epilepsy

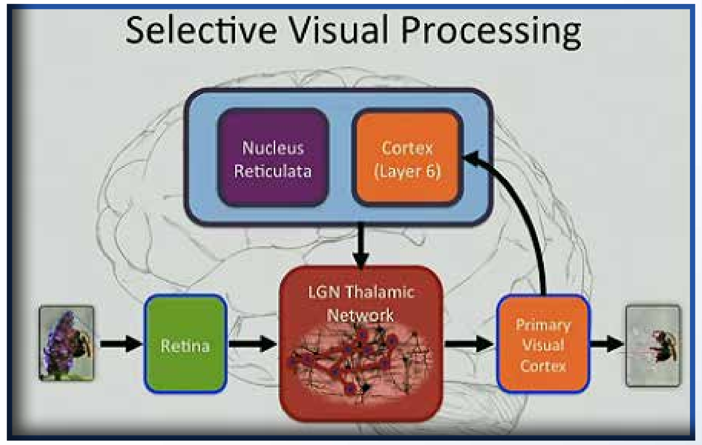
Tay Netoff (University of Minnesota)

The first talk of the day began with a brief introduction to modeling seizures in epilepsy, as well as statistics on epidemiology of this disease. It was underlined that it is a multi-scale disease and thus it should be modeled on the level of a single neuron and also on the level of a network of synchronized neurons with the ability to synchronize and desynchronize under certain conditions. The main focus was to propose models that allow for transition between the tonic and the clonic phase of seizures. As far as the dynamics of firing of a neuron is concerned, a version of the Hodgkin-Huxley model was considered. Then an analysis of this model was conducted based on the phase response curves. It was inferred that at the high firing rate the synchrony is less stable, and as the firing rate slows down, stable synchrony may be achieved. The next step was to determine how the structure of the network affects synchrony. A variety of different network topologies were considered – from the Erdos-Renyi random graph model, to more deterministic ones consisting of four different motifs (reciprocal, convergent, divergent and chain). Within that framework simulations were conducted. It was inferred that mainly the number of convergent connections influence synchrony. Also, it was noted, that the selection of an appropriate second order network topology (SONET) allows for the transition from asynchrony to synchrony with the change of the firing rate of neurons.

Therapeutic mechanism of deep brain stimulation in Parkinson's disease

Sridevi Sarma (Johns Hopkins University)

Dr. Sarma began her talk with a video that illustrated the process of selective processing. Then she explained in detail how selective processing works and its relation to Parkinson's disease (PD). She then outlined the role of deep brain stimulation (DBS) in PD and its influence on the input and output of the globus pallidus. Next Dr. Sarma presented a model of a (thalamic) relay neuron with two inputs (reference and modulating) and one output. An analytical tool was proposed for the analysis of the response 'relay reliability', which is the probability of a successful response (a spike) due to a reference pulse. Probabilistic bounds for relay reliability were presented. Point process models for spike train activity together with a generalized linear model (a log-linear model) for the intensity of the process was proposed with the parameters being estimated via the maximum likelihood method. The performance of reliability bounds was presented in the proposed models of a relay neuron.



A framework for statistical evaluation of neural synchrony

Robert E. Kass (Carnegie Mellon University)

The beginning of Dr. Kass talk was devoted to the introduction of binary time series framework for modeling spike trains in continuous and discrete time. The concept of instantaneous intensity was explained and a variety of modern regression models were presented. Next the issue of synchrony between two processes was addressed. It was noted that data does not support the independence hypothesis of two point processes, i.e. simultaneous events in two processes occur in different frequency in reality then under the independence hypothesis of the two processes. Moreover it was noted that an appropriate model of synchrony between two neurons ought to capture the sparsity of simultaneous spikes. An approach based on marked point processes was presented with a bivariate dependence structure between two processes. Afterwards the results of a statistical analysis for the parameters of a log-linear model for the intensity were presented. Dr. Kass also underlined the importance of incorporating the Bayesian control of false discoveries in the statistical analysis of large datasets.

Model of epilepsy

John Terry (University of Bristol)

In the introduction to his talk, Dr. Terry addressed various problems in modeling epilepsy from which he emphasized the multi-scale dynamics as one of the most challenging ones. He stressed that the underlying mechanism of focal and generalized seizures in epilepsy is poorly understood. H next discussed the problem of modeling epilepsy on different time scales, from dynamics of a single neuron, through oscillations in network dynamics to the dynamics of the disease itself. On the scale of a single neuron a mechanistic model was proposed whereas on the level network dynamics a phenomenological approach based on dynamical systems was suggested. Different approaches to modeling the initiation of seizures were discussed, among which a noise driven process in a bi-stable system was proposed. Since of interest is a model of seizure onset in the whole brain, the interplay between (cortico-thalamic) network topology (strongly and weakly connected networks) and the dynamics of oscillations was considered. Dr. Terry noted that the loss of a specific connection in the network might lead to seizure onset, thus resulting in the conclusion that the likelihood of seizures occurrence is related to the topology of the underlying network.

Multi-scale seizure dynamics

Mark Kramer (Boston University)

Dr. Kramer began his talk by presenting data on different rhythms observed during the onset and termination of seizures. He also discussed the spatial properties of a network of neurons and its relation to seizure propagation. Following this, a mean-field model of ODE's was proposed and simulation results were presented. The main aim was to determine the model characteristics at the end of seizure. Dr. Kramer inferred that seizure terminates at critical transition and as the system approaches this point critical slowing down of oscillations occur. What is more, it was noted that autocorrelation becomes larger and flickering (between high and low frequency seizures) takes place before the critical transition point. Moreover, such phenomena were presented on different time scales. Dr. Kramer also presented that status epilepticus (prolonged seizures) is a case when the system approaches repeatedly, but does not cross, the critical transition.

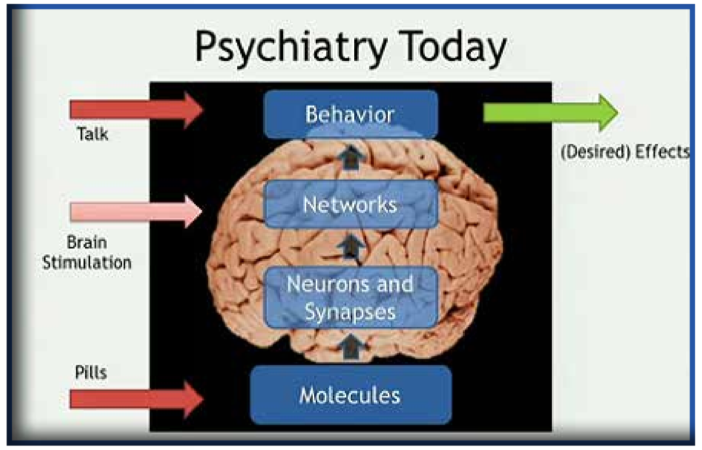
WEDNESDAY, February 6, 2013

Schizophrenia, Depression, Migraines

Understanding, treating, and cueing psychiatric illnesses

Flavio Frohlich (University of North Carolina)

In this talk, Dr. Frohlich focused on the treatment of psychiatric illnesses. The causes of schizophrenia could be defected genes or environmental factors. For the animal model of schizophrenia, there are three validities: face validity, construct validity, and predictive validity. Hence, pathologists use the animal model to investigate how to treat the schizophrenia and found that the effective of antidepressant is better than anxiolytics. On the other hand, pathologists also use vagal nerve stimulation to treat the schizophrenia.



Pathologists found that electroconvulsive therapy (ECT) is the most effective antidepressant intervention. However, there still have some disadvantages of ECT, such as the mechanism absolutely unclear, depletion of GABA followed by compensatory increase, monoamine neuromodulators, neurogenesis is unclear, the scenarios of hormonal and metabolism are not so clear. In fact, we still lack of convincing animal models to help us to understand the complex etiology and neurobiology of cognition. Moreover, even the brain stimulation work on cure the schizophrenia, we still do not know why and how this treatment works and the topology and dynamics of the complex circuitry. Accordingly, it is hard to appropriate understand that what are these experiments and treatments mean, so we still need to overcome these difficulties.

Serotonin and the mysteries of depression and SSRIs

Michael Reed (Duke University)

Parkinson's disease has been thought of as a dopaminergic disease. In Parkinson's disease, selective serotonin reuptake inhibitors (SSRIs) block the reuptake of serotonin and alleviate depression in some patients. Moreover, there is accumulating evidence that the serotonergic system in Parkinson's disease plays an important role in general and in physiological responses to levodopa therapy. However, it is not clear how or why this treatment works.

In this talk, Dr. Reed introduced some mathematical models to investigate the consequences of levodopa therapy on the serotonergic system and on the pulsatile release of dopamine (DA) from dopaminergic and serotonergic terminals in the striatum. These mathematical models assist in investigating the mechanism of serotonin synthesis, release, reuptake, the control mechanisms of the serotonin system, and suggest hypotheses about the action of SSRIs. At the end, the speaker presented two standard hypotheses: DDRIs raise e5HT in projection regions and 5HTIA autoreceptors desensitize over 4 weeks, and proposed an answer to the question of what serotonin is doing in the striatum in the first place.

Ionic dynamics mediate spontaneous termination of seizures and postictal depression state

Maxim Bazhenov (University of California, Riverside)

In epilepsy, K+ concentration increases and Ca2+ concentration decreases during paroxysmal activity in vivo. Hence, in epilepsy, ionic concentrations fluctuate significantly during seizures. These changes of the ionic concentrations trigger various homeostasis mechanisms. In this talk, Dr. Bazhenov focused on the ionic dynamics in epileptic treatment.

By using a computational model of in vivo epileptiform activity, they found that, in a range of elevated K+, the isolated pyramidal neuron generates bistability between tonic firing and bursting. In the network, synaptic coupling may stabilize the network in the bistable regime leading to slow periodic transitions between two oscillatory regimes in the absence of any external input. On the other hand, they also found that increase of Na+ over the course of seizure promotes bursting regime and termination of seizure. After seizure cessation, the potassium reduces such that post-ictal depression. In addition, increase of Na+ over the course of seizure in vivo activates hyperpolarization and termination of seizure. Accordingly, conventional antiepileptic drugs are designed to target various sodium channels in order to reduce their activity. Based on their results, these drugs would reduce likelihood of epileptic seizures, but may also prolong seizure duration.

Synchronized oscillations in cortico-basal ganglia circuits in Parkinson's disease

Leonid Rubchinsky (Indiana University - Purdue University)

In Parkinson's disease (PD), the symptoms have been related to the synchronized oscillatory activity in the cortico-basal ganglia-thalamic circuits. In this talk, Dr. Rubchinsky presented observations of the patterns of synchronized activity obtained in parkinsonian patients.

In the modeling basal ganglia activity, he discussed the temporal patterning of the observed synchronized patterning. They found that synchronization of beta oscillations in PD is intermittent and has specific temporal structure. This variability may be generated intrinsically without external inputs, noise or plasticity due to elevated synaptic strength, as is expected in PD. The intermittent synchrony may be a result of a propensity of BG circuits to be engaged in the brief synchronized episodes of activity needed for movement control. Low-dopaminc state may result in departure from very transient dynamics, favoring short desynchronization events and moving it closer to the synchronization domain. In addition, Parkinsonian brain is on the boundary between synchronized and nonsynchronized dynamics. They also found that delayed mean field feedback makes synchronous state unstable.

They do the stimulation of strongly and weakly synchronous dynamics. In these stimulations, they found that the only consistent improvement in desynchronization is in the region of strongly correlated activity.

Transient localized wave patterns and their application to migraine

Markus Dahlem (Humboldt - Universitat zu Berlin)

In this talk, Dr. Dahlem focused on four parts: macroscopic pattern in migraine, ion-based cellular models, cortical architecture, and pain pathways and modulation. In their work, they used a canonical reaction-diffusion model with mean-field inhibition to investigate statistical properties of transient cortical wave patterns with characteristic forms. They considered the following two kinds of systems: excitable element and excitable media. The patterns are formed by a ghost near a saddle-node bifurcation in which a stable traveling wave (node) collides with its critical nucleation mass (saddle). In migraine, similar patterns have been observed with fMRI. Their results advocate that waves of cortical spreading depression (SD) have a causal relationship with the headache phase in migraine. In addition, they suggest a consistence between the prevalence of two subtypes, MO and MA, and the statistical properties of the traveling waves. They also discussed model-based control and mentioned that neuromodulation techniques may affect pathways of pain formation.

THURSDAY, February 7, 2013

Statistical and Mathematical Methods

What network features have the strongest influence on synchrony?

Duane Nykamp (University of Minnesota)

The first talk of the day was devoted to analysis of structure of neuronal networks. Dr. Nykamp presented the concept of second order network topology (SONET) by adding structure, consisting of four motifs (reciprocal, convergent, divergent and chain), to the basic model of an Erdos-Renyi random graph. He discussed the influence of the structure of the network on distribution of the degree of nodes. The main aim was to investigate which types of connections have the strongest effect on synchrony. Results of simulations of synchrony in networks of excitatory neurons with various different SONET's were presented and it was inferred that synchrony is strongly related to the number of chain and convergent connections in the network. Moving on, Dr. Nykamp presented a way in which one can incorporate network structure into mean-field analysis and its relation to simultaneity of events in neuronal networks. A method of incorporating inhibitory parts of the network was also presented.

Tracking dynamic rhythms in the spiking of STN neurons using point process methods.

Uri Eden (Brown University)

Dr. Eden began his talk by giving some background on the types of oscillations of neurons in Parkinson's disease, its relation to deep brain stimulation, and presenting data collected from visually guided movement experiments. Characteristic features, such as dependence on the direction in which the movement is performed, dependence on past history of spikes and difference in firing rate during and post movement, of the dataset were outlined. Next, a point process model was proposed together with a log-linear model for the instantaneous intensity, which was based upon the general GLM modeling framework for exponential families of distributions. Dr. Eden noted that the dependence on the history of spikes in the model for neural intensity for the sub-thalamic nucleus varies between time scales, which might be either a result of a discrete change of state between movement and rest, or an outcome of a process that drives changes in oscillations.

Micro-dynamics of human focal seizures

Wilson Truccolo (Brown University)

The introductory part of Dr. Truccolo's talk was devoted to a detailed description of data that were collected by continuous microelectrode recordings of neuronal activity giving temporal as well as spatial patterns. Next, recordings from two patients were presented, first of which (patient A) had strong gamma oscillations at the onset of seizures whereas the second one (patient B) had an initial in beta wave and additionally high frequency oscillations. It was underlined that highly heterogeneous behavior takes place at the onset of seizures and then becomes more homogenous as it reaches termination. As a consequence, it was noted that the spiking process behaves in a non-stationary manner. Therefore a straightforward application of a GLM for the intensity of a point process is not possible, thus Dr. Truccolo proposed a conditional inference framework. He introduced the concept of temporal coarsening for which he established a maximum likelihood based statistical inference framework. Next, results of statistical analysis of data collected form patient A were presented. As to the data collected from patient B, it was shown that the high frequency oscillations are results of the spatial structure of the network. Therefore, the concept of spatial coarsening was introduced and the above described statistical inference procedures were adapted to the setting of temporal and spatial coarsening. It was also noted that such approach involves establishing and importance sampling Monte Carlo simulation algorithm.

How synaptic potentiation modulates in vitro neuronal network dynamics

Rhonda Dzakpasu (Georgetown University)

In this talk, Dr. Dzakpasu showed that after synaptic potentiation, a network of in vitro hippocampal neurons returns to a homeostatic state after widespread increases in firing. They attempt to answer the questions: (i) how does a synaptic perturbation that is thought to underlie the physiological basis of memory be characterized on the network level? (ii) how do these changes manifest over a long time scale? Their results show that chemical LTP does not cause the network to spiral into runaway excitation. There appears to be a conservation mechanism that restores the spike counts to the development curve. Also, chemical LTP modulates several network-level properties such as sharpens functional connections between nodes shortens characteristic path length. Moreover, these changes are stable and preferentially impacts weak connections. In addition, these functional changes relate to what has been measured electrophysiologically, and these functional analyses can connect small spatial scale effects with macroscopic, network effects.

Dynamics of healthy and pathological brain-from neuron excitability to network-wide activity and back

Michal Zochowski (University of Michigan)

In simulating networks, granule cells can appear randomly at any location in the network. They connect to neurons to which their neighbors connect in an activity-biased manner. In this talk, Dr. Zochowski focused on the dynamics of the simulating network. They used a computational model to investigate how the structural and functional outcomes of network reorganization, driven by addition of new cells during neurogenesis, depend on the original network structure. They found that there is a stable network topology that allows the network to incorporate new neurons in a manner that enhances activity of the persistently active region, but maintains global network properties. Networks may have other connectivity structures, and new cells can greatly alter the distribution of firing activity, possibly destroying the initial activity patterns. They thus found that new cells are able to provide focused enhancement of network only for small-world networks with sufficient inhibition. Moreover, by switching acetylcholine (Ach) levels during network dynamics, they found that sleep is necessary for renormalizing synapses.

FRIDAY, February 8, 2013

Observation and Control

Observability and controllability of neuronal networks

Steven J. Schiff (Penn State Center for Neural Engineering)

In the early 1960s, Rudolph Kalman introduced the notions of state space decomposition, controllability and observability. In 1964, Luenberger showed that the state vector of a linear system could be reconstructed from observations of its inputs and outputs. Dr. Schiff also discussed state observers for nonlinear systems, such as Fitzhugh-Nagumo equations. These discussions were summarized in his book, "Neural Control Engineering". Some newer studies, including non-Gaussian filters and variational/Monte Carlo Methods, were mentioned in the talk. One of the results discussed was observability in small (3 node) neuronal networks as a function of the connection topology and symmetry, the measured nodes, and the nodal dynamics (linear and nonlinear). His results show that typical observability metrics for 3 neuron motifs range over several orders of magnitude, depending upon topology, and for motifs containing symmetry the network observability decreases when observing from particularly confounded nodes.

An estimation framework for neural mass models

David Grayden (The University of Melbourne)

Dr. Grayden's work described a framework for creating patient-specific neural mass models using intracranial electroencephalogram (iEEG) recordings from patients with epilepsy. Neural mass models are used in epilepsy research to relate physiological parameters to iEEG in an attempt to generate hypotheses about the generation and termination of seizures. Dr. Grayden fused the data and the neural mass model to estimate parameters that specify the shape of post-synaptic potentials, connectivity strength between neural populations, and firing thresholds. A nonlinear version of the Kalman Filter was used with an augmented state-space model to solve the estimation problem. Results from artificial data and patient data showed that this is a promising framework.

Controlling populations of neurons

Jeff Moehlis (University of California, Santa Barbara)

Dr. Moehlis is interested in Deep Brain Stimulation (DBS) for the treatment in Parkinson's disease. After introducing reduction for phase model and phase response curve (PRC), he discussed how to apply the studies of PRC to figure out an optimal stimulation for specified time of neuron firing. The results can be applied to Hodgkin-Huxley models. Then, the studies were extended for making a real neuron fire at specified time with minimal energy, charge-balanced stimulus. Some evidence suggested that DBS works through chaotic desynchronization. Dr. Moehlis used his studies in phase models to determine optimal inputs for controlling neurons, including the desynchronization of neural populations. Finally, he concluded that optimal inputs require less energy to achieve objective than pulsatile stimuli.

Workshop 4

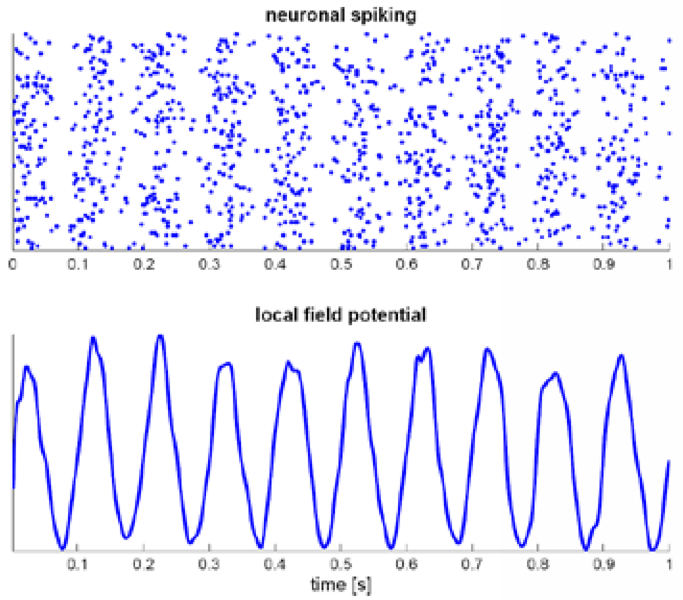
Rhythm and Oscillations
March 18-22, 2013

Organizers: Carmen Canavier, Bard Ermentrout, Pascal Fries, and Todd Troyer

Report by: Kang-Ling Liao, Jincheol Park, and Lucy Spardy

This workshop will focus on how mathematics can help us determine the functional roles that oscillations play in the nervous system. This workshop is timely in view of recent evidence that oscillations are critical for cognitive states and sensory processing. A broad range of oscillatory activity will be covered, including hippocampal and cortical oscillations, motor patterns, sensory processing and circadian rhythms. Competing theories will be presented on controversial issues, such as the role of gamma oscillations in binding of sensory information and the role of theta oscillations in hippocampal circuitry, with a view to how mathematics might help to resolve these controversies. We will try to draw parallels across different systems to see if central organizing principles emerge.

Recent theoretical advances in the understanding of several central pattern generators (CPGs) will be compared and contrasted, including the CPG for coordinating crawfish swimmerets, the CPG for respiratory pattern generation, the pyloric circuit, and spinal CPGs involved in human gaits. Circadian rhythms will be addressed at the level of the molecular clocks underlying the diurnal rhythm and at the level of the interaction of these clocks with the electrical activity of the suprachiasmatic nucleus. Sensory systems will be represented by theoretical and experimental studies on the role of oscillations in distinguishing odors. Theoretical results on the nonlinear dynamics of coupled oscillators in the presence of noise will be presented and integrated into the context of the specific examples presented for different systems.



MONDAY, March 18, 2013

Hippocampal Encoding Using Oscillations

The theta rhythm, spatial cognition and the hippocampus

Neil Burgess (University College London)

In this talk, the speaker Prof. Burgess described some experiments and computational mechanisms for the neural representations of spatial location and orientation, and the neural coding with respect to the theta rhythm of the local field potential. In their work, they used boundary vector cell firing to emphasize the roles of environmental boundaries in self-localization and used grid cell firing to investigate the temporal oscillations in the theta band in path integration. Next, they used a dual oscillator model of theta-phase precession in place cell firing to combine the information from boundary vector cell firing and grid cell firing. They also constructed some models of path integration and grid cell firing to investigate the phase difference as the time integral of frequency difference. Their results inform the study of human spatial memory. Self-location is calculated in the hippocampal formation as a compromise between environmental and movement-related information.

Computational understanding of neuronal representations in rodents allows for mechanistic models of human spatial memory and imagery, as well as episodic memory based on these concepts.

Oscillations and grid cells in entorhinal cortex

Michel E. Hasselmo (Boston University)

The mechanisms of memory in the entorhinal cortex and hippocampus are related to grid cells, place cells, and head direction cells. During the process, these cells generate oscillations and resonance. Dr. Hasselmo's talk focused on the functions of grid cells in the entorhinal cortex. In their results, they found that grid cell model predicts a frequency gradient on a dorsal to ventral axis. Oscillatory interference models can link grid cell spacing to the different intrinsic oscillation frequencies of entorhinal neurons. In their experiments, medial septum inactivation disrupts theta oscillations in the medial entorhinal cortex. They also found loss of grid cell periodicity during loss of theta rhythm. This result could underlie impairments of spatial memory behavior. They also indicated that spatial memory in rats is impaired by lesions or by inactivation of the entorhinal cortex, hippocampus or medial septum.

Mapping Euclidean space onto patterns of neural synchrony by septohippocampal microcircuits

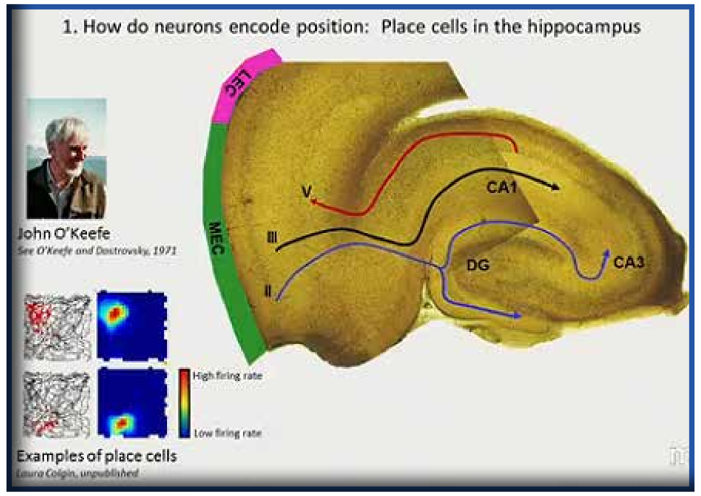
Tad Blair (University of California, Los Angeles)

The rodent spatial memory system contains two major classes of neurons: rhythm generators (RGs) and synchrony detectors (SDs). In this talk, the speaker provided a hypothetical model of a pattern generator circuit for producing velocity controlled oscillators (VCOs) to investigate how rodent performs path integration via RGs and SDs. First, they consider an oscillatory interference model to predict that the brain must contain rhythm generators. RGs correspond to 'theta cells' that burst rhythmically at velocity-dependent frequencies, whereas SDs correspond to spatially tuned neurons that burst selectively at locations where they detect synchrony among a preferred subset of RGs. The speaker also gave some evidence for linear modulation of theta oscillator frequencies by movement velocity in two dimensions. Their work indicates that VCOs may be generated by subcortical patterns generator circuits composed from theta cells; burst frequencies of theta cells appear to be modulated by movement velocity in two dimensions; synchrony of theta-rhythmic neurons may be modulated by position in two dimensions.

Mechanisms underlying medial entorhinal cortex topography

Lisa Giocomo (Stanford University)

Dr. Giocomo discussed how sensory inputs map to neural circuits and form functional cortical architectures. She described the long history of experiments indicating that rats have spatial memory, and discussed how medial entorhinal cortex neurons, called grid cells, fire when the animal is in a spatially specific location. To understand the mechanisms underlying the representation of space by these grid cells, she first considered which biophysical properties could contribute to encoding. She showed that temporal frequency changes correlate with spatial frequency changes along a dorsal-ventral line, indicating that multiple cellular properties show a dorsal/ventral organization. Next, she considered whether these biophysical changes relate to spatial changes, and showed that grid cells represent spatial encoding at different scales along the dorsal-ventral axis. Finally, she highlighted the presence of a topographic gradient in another functionally-defined medial entorhinal cell type; the head direction cell.



1. How do neurons encode position: Place cells in the hippocampus

John O'Keefe

See O'Keefe and Dostrovsky, 1971

Examples of place cells

Laura Colgin, unpublished

Slow and Fast Gamma Rhythms in the Hippocampal Network

Laura Colgin (University of Texas at Austin)

Brain rhythms reflect periodically synchronized electrical activity across groups of neurons and are thought to be important for neuronal communication across disparate brain regions. Dr. Colgin focused specifically on gamma rhythms, which occur throughout many regions of the brain and have been linked to functions such as attentional selection and memory. These oscillations vary in frequency (from ~25 Hz to ~ 100 Hz) from one brain region to another and also within a given brain region from one moment to the next. The exact frequency of oscillations is important for coherence, because different areas are hypothesized to communicate most effectively when their oscillatory timing is the same. In the hippocampus, a brain region critically involved in memory operations, two distinct subtypes of gamma oscillations, slow and fast gamma, occur at different times during the theta cycle. During slow gamma (~40 Hz), hippocampal subfield CA1 is coupled with neighboring subfield CA3, an area involved in memory retrieval. During fast gamma (~80 Hz), CA1 is coupled with the entorhinal cortex, a region transmitting information about the current environment.

Dr. Colgin presented new data supporting the hypothesis that slow and fast gamma rhythms serve different functions, namely that slow gamma facilitates memory retrieval and fast gamma promotes memory encoding, and that the separate frequencies may prevent interference between these prospective and retrospective modes.

TUESDAY, March 19, 2013

Mechanisms of gamma oscillations and gamma coherence over distance

Inter-network oscillatory synchronization: Mechanisms & consequences for information flow

Thomas Akam (Champalimaud Neuroscience Program)

In this talk, Dr. Akam began by introducing the response dynamics of gamma oscillating networks. Input to the CA3 network in a gamma oscillation state can either advance or delay the oscillation depending on the phase of stimulation. The response of the network can be understood by considering trajectories following stimulation in a two-dimensional space defined by excitatory and inhibitory activity levels. These dynamics allow the oscillation to entrain to periodic inputs over a wide frequency range and may support inter-regional synchronization. Next, the speaker presented the oscillatory multiplexing of population codes for selective communication. The speaker first introduced the convergent pathway model for studying oscillatory control of signal flow. Multiplexing by multiplicative modulation create multiple information channels in a single physical communication channel. Moreover, multiplicative modulation can in principle multiplex multiple firing rate population codes into orthogonal frequency components of spike activity. To exploit this for selective communication requires readout mechanisms that can selectively recover signals with specific modulations.

Toggling between gamma frequency activity and suppression of cell assemblies, and the type of the fast-spiking inhibitory cells

Christoph Borgers (Tufts University)

In this talk, Dr. Borgers introduced recent work about the oscillations generated by synaptic interaction of excitatory neurons (E-cell) and inhibitory neurons (I-cell). In earlier work, they suggested the transition from rhythmicity to suppression of the E-cells and suggested this transition could be exploited to allow the network to toggle between rhythmic activity and suppression. Recently, they assumed that gap junctions enforce synchronization of the I-cells. By using simulations and a one-dimensional map, they demonstrated that if gap junctions synchronize I-cells, then for a clean distinction between suppressed and active cell assemblies, inhibitory interneurons should have a type 2-phase response (excitation early in the phase retards them). Hence, the transition from rhythmicity to suppression is much more abrupt when the I-cells have a type 2 phase response than when they have a type 1 phase response (excitation always accelerates them).

State-dependent cortical rhythms

Jessica A Cardin (Yale University)

In this talk, Dr. Cardin introduced the investigation in the role of different sources of synapse inhibition in regular reaction in cortical network. In their local cortical circuits, they considered inhibitory interneuron and excitatory neuron. In this model, they focus on the normal and non-normal (i.e. disease) states that affect the dynamics of the network and try to find out the parameters space for inhibitory and excitatory neuron. First, the speaker described the cell type-specific manipulation and identification of cortical interneurons, and then introduced the mechanisms of gamma oscillation generation in their local cortical circuits. In addition, the speaker also discussed two different kinds of states: behavior state-dependent gamma activity and network consequences of long-term interneuron dysfunction.

Their experiments collectively indicate that: (i) parvalbumin (PV) but not somatostatin (SOM) positive interneurons play a critical role in generating cortical gamma oscillations; (ii) Cortical gamma activity is state-dependent; (iii) V1 gamma activity varies with walking behavioral state, increasing with locomotion; (iv) Shifts from quiescence to running are associated with entrainment of excitatory neurons to the gamma rhythm; (v) Global disruption of interneuron function by ErbB4 deletion causes a nonspecific increase in 20-80Hz activity, disrupting fine temporal relationships; and (vi) Effects of global ErbB4 deletion on gamma activity and overall firing patterns are replicated by targeted deletion from PV cells.

Collective oscillations in networks of spiking neurons: Mechanisms and input dependence

Nicolas Brunel (University of Chicago)

Dr. Brunel investigated the mechanisms for oscillations in recurrent networks of excitatory and inhibitory neurons under the presence of time-dependent inputs. He looked at properties of the networks under strong noise and characterized the region of stability of the "asynchronous state" (a state in which population activity is constant in time when external inputs are constant) in the space of parameters characterizing the connectivity of the network. He showed that oscillations can be classified by the numbers of synapses leading from peak to trough, which lead naturally to distinct frequency bands.

Gaining insight from theoretically-inspired biologically-based models

Frances Skinner (Toronto Western Research Institute)

Dr. Skinner illustrated how mathematical mechanisms can couple with a well-defined experimental context. She discussed gamma rhythm and mechanism. She presented work examining the generation of gamma rhythms in models of fast spiking inhibitory cell networks. To take theoretical mechanisms further, she suggested a framework to integrate theory and experiment. Based on this framework, she proposed the models for CA1 hippocampus based on an ING-type mechanism and on the experimental context of a whole hippocampus preparation exhibiting spontaneous population activities. She presented a key finding that a sharp transition in gamma coherence is found for small changes in excitatory drive, thus suggesting a potential design property underlying theta/gamma rhythms. At the end of talk, it was noted that without the experimental context and constraints, the key finding could not arise.

WEDNESDAY, March 20

Gamma frequency information chunking

Perceptual and attentional rhythms

Rufin VanRullen (Université de Toulouse, Université)

Neuronal communication between cortical areas is related to oscillatory, periodic mechanisms whose precise timing critically determines the flow of information. In order to investigate the perceptual and psychological consequences of such periodic neuronal dynamics at the rapid time scale of the oscillatory cycle, Dr. VanRullen showed several experimental examples of perceptual consequences in the visual domain. Alpha interacts with certain spatial patterns, causing illusory flicker at 10Hz. Visual perception and attention seem to wax and wane intermittently at frequencies in the theta (~7Hz) and alpha (~10Hz) range, possibly reflecting the underlying periodic neuronal processes. Based on spiking neural network simulations, the speaker indicated that similar perceptual cycles can also exist at higher frequencies (gamma range), and that perceptual experience may be the result of cross-frequency interactions between these different rhythms. In conclusion, brain rhythms serve a role in perception and the flip side of the coin is that oscillations must have perceptual consequences at the rapid time scale of the oscillatory cycle.

On the central role of theta in decoding speech

Oded Ghitza (Boston University)

It is postulated that decoding time is governed by a cascade of neuronal oscillators in the theta, beta, and gamma frequency bands that are crucial for speech intelligibility. Intelligibility is high, provided that the oscillations remain phase-locked to the auditory input rhythm. Dr. Ghitza presented a phenomenological model of speech perception, termed Tempo, which is capable of emulating psychophysical data on the intelligibility of speech sentences as a function of "packaging" rate. He concentrated on the role of theta and its importance in parsing an MEG signature, and proposed that the theta-syllable is an information unit defined by cortical function, an alternative to the conventional syllable.

Theta gamma coordination in setting of psychomimetics and other modulatory interventions

Bill Lytton (SUNY Downstate Medical Center)

Dr. Lytton began by discussing how difficult an organ the brain is to understand. The first topic he covered was the effect of simulated ketamine application on theta modulated gamma oscillations hippocampal region CA3. . By simulation, he showed that ketamine increases firing rates, alters phasic relationships and reduces responsivity to environment by acting at a particular subpopulation of interneurons, the OLM cells. The other topics of the talk were Ih modulation in hippocampal and neocortical activation patterns. With a variety of simulation and data, he discussed that activation patterns depend on laminar inputs and different sub-circuit activations would trigger different outputs.

Theta-gamma nested oscillations in speech perception

Alexander Hyafil (Laboratoire de Neurosciences Cognitives)

Dr. Hyafil discussed some of the main challenges for speech processing. Neural oscillations in related time scales have been observed and a possible role in parsing speech has been formulated in a nested oscillation model, with gamma oscillations nested within a theta cycle. In proposing speech-processing models, he discussed how to detect syllables boundaries and how the gamma processed fast phonemic information. He mentioned the key findings that gamma power reflects the degree of processing in sensory areas, and gamma could parse speech signal into discrete chunks. Based on key findings, he proposed the architecture of a full model. In the end, he demonstrated performance of the models.

Large-Scale Synchronous Beta Rhythms

Steve Bressler (Florida Atlantic University)

Dr. Bressler began by presenting the hypothesis that the long-range synchronization of beta frequency activity is a mechanism for behaviorally related large-scale network formation in the cerebral cortex. To test this hypothesis, he modeled the beta frequency synchronization with vector autoregressive model and discussed how to estimate spectral power, coherence and Granger causality. Using a vector autoregressive model, he discussed beta synchrony in Motor control, in working memory, and in visual expectations. He concluded that long-range synchronization of beta frequency activity supports large-scale network formation in the cerebral cortex. He also suggested that sophisticated coupled-oscillation models of beta synchronization would lead to better understanding of the neural basis of task-related set.

THURSDAY, March 21, 2013

The role of oscillatory entrainment in auditory attention

Peter Lakatos (Nathan Kline Institute)

Attending to a stimulus enhances neuronal representation, even at the level of primary sensory cortex. Cross-modal modulation can similarly enhance a neuronal representation, and this process can also operate at the primary cortical level. In his talk, Dr. Lakatos presented a series of attention-related results from recent lab studies. He considered the influence of attention on oscillatory phase reset in primary auditory and visual cortices of macaques performing an intermodal selective attention task. He showed both preferred and nonpreferred modality stimuli could "modulate" local cortical excitability by phase reset of ongoing oscillatory activity, and that this effect was linked to their being attended. These findings outline a supramodal mechanism by which attention can control neurophysiological context, thus determining the representation of specific sensory content in primary sensory cortex. In another study, Dr. Lakatos investigated whether entrainment was detectable in human scalp recordings. He showed that ongoing oscillations were entrained in an effort dependent manner, and that their main role was a predictive suppression of excitability in task irrelevant regions. He also presented preliminary results on two other topics, regarding entrainment across neuronal ensembles in A1 and entrainment by spectrotemporally complex stimuli.

Neural dynamics of cognitive control

Tim Buschman (Princeton University)

Cognitive control is the ability to direct behavior in a goal-directed manner. This ability lies at the core of intelligent behaviors, allowing us to focus our limited cognitive capacity on one task while still maintaining the flexibility to quickly switch to another task as the situation (or our goals) change. Dr. Buschman presented results on the role of frontal and parietal cortices in two forms of cognitive control: the control of attention and flexible rule use. By leveraging large-scale, multiple-region electrophysiology in non-human primates, he observed synchronization of neural activity within and between brain regions while animals perform these complex behaviors. He described results suggesting that synchrony supports cognitive behaviors, and that its dynamic nature may underlie cognitive flexibility.

Oscillations and neural coding

Paul H. Tiesinga (Donders Centre for Neuroscience)

Dr. Tiesinga presented on the topic of optogenetic interrogation. He started with an experimental result revealing resonance for interneuron stimulation but not for pyramidal cell stimulation. He modeled the experimental outcomes via the PING model, concluding that if the PING mechanism is responsible for oscillations, then there should be a low frequency resonance; also, blocking slow currents in E cells should facilitate high frequency resonance upon E cell stimulation. Then he covered the topics of neural code and oscillations and concluded that synchrony is established when frequency of receiving area is lower than sending area and high synchrony does not guarantee a high level of information transmission.

Brain Rhythms Facilitate Bottom-Up and Top-Down Processing

Nancy Kopell (Boston University)

It is well known that brains rhythms are associated with different cognitive states and tasks, but it is still mysterious how the rhythms take part in functions. In this talk, Dr. Kopell presented key findings in understanding functions of various brain rhythms. She demonstrated that two gamma rhythms of A1 help route signaling among layers, depending on saliency and direct plasticity among layers. Showing top-down beta and gamma flexibly gate inputs to Par2 changing bottom-up flow of signal, she summarized that layers matters to physiology and physiology matters to dynamics and dynamics matters to function.

Pascal Fries: Distinct top-down and bottom-up attention networks revealed through high-resolution electrocorticography

Pascal Fries, Director (Ernst Strüngmann Institute for Neuroscience in Cooperation with Max Planck Society)

Brain-wide networks operating at a millisecond timescale are thought to underlie our cognitive functions, but have never been observed directly. However, limitations of current recording methods have restricted our ability to detect and investigate these putative brain-wide synchronization networks. Dr. Fries presented data from large-scale, high-density electrocorticography grids, combining millisecond temporal and millimeter spatial resolution with coverage of large parts of one hemisphere. He showed that a given brain area may simultaneously participate in different networks that synchronize in distinct frequencies and mediate influences in counter-streams. A gamma-band (50 90 Hz) network synchronizes visual-occipital areas and parts of parietal cortex, and gamma-mediated inter-areal influences are bottom-up. A beta-band (peaking at 14-18 Hz) network synchronizes parietal and frontal areas and parts of visual cortex, and beta-mediated inter-areal influences are mostly top-down. Both networks subserve the cognitive function of attention: gamma- and beta-mediated inter-areal influences are enhanced when they mediate behaviorally relevant signals.

FRIDAY, March 22, 2013

Synthesis and wrap-up by organizers

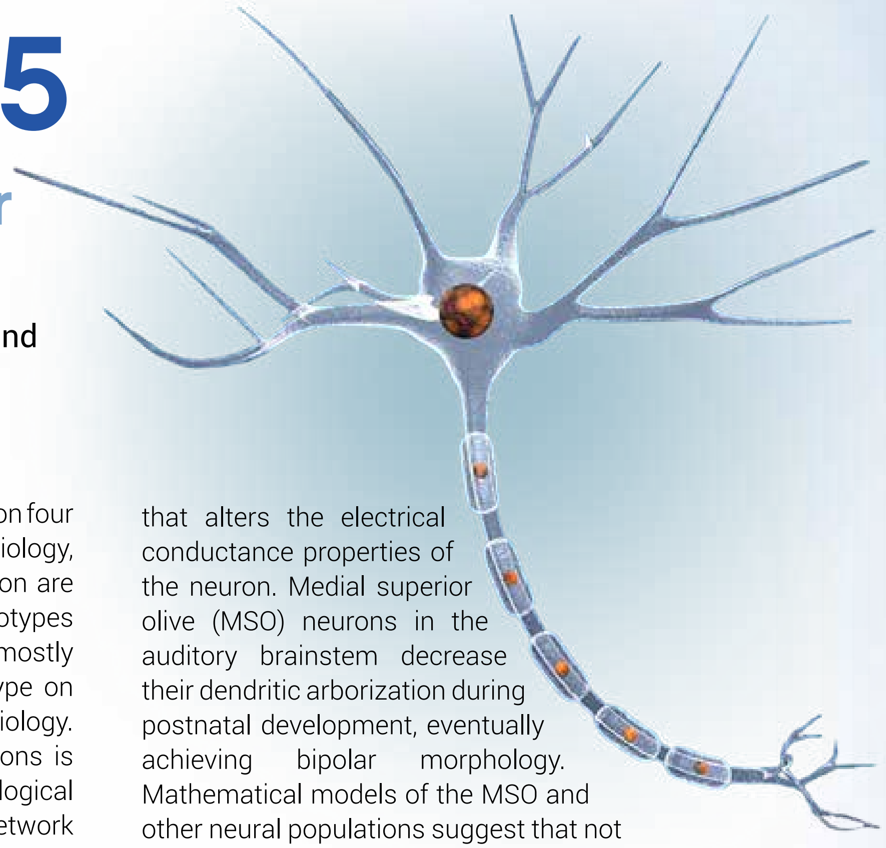
The organizers led an open discussion synthesizing the various topics presented throughout the week. Topics included a clarification of the roles of the oscillations at different frequency bands, classifying the different mechanisms for generating oscillations and how to analyze data to distinguish between these mechanisms, and understanding the different mechanisms of synchronization and how to design experiments to probe these mechanisms. Some of the major roles for oscillations include 1) providing a sampling rate to limit how fast representations of the environment can be updated (for example sampling the visual environment at alpha frequencies or attention switching at theta frequencies), 2) chunking information (into syllables by theta, for example) 3) providing a coding space to represent the environment (changes in frequency relative to a master oscillator for path integration in different directions) 4) synchrony detection to disambiguate position (convergent input from grid cells to place cells) 5) routing or gating of information so that inputs that arrive at the correct receptive time window in the oscillation will be selectively attended and transmitted (communication through coherence) and 6) provide a clock for stimulus prediction. Some of the major roles for oscillations include 1) providing a sampling rate to limit how fast representations of the environment can be updated (for example sampling the visual environment at alpha frequencies or attention switching at beta frequencies), 2) chunking information (into syllables by theta, for example) 3) providing a coding space to represent the environment (changes in frequency relative to a master oscillator for path integration in different directions) 4) synchrony detection to disambiguate position (convergent input from grid cells to place cells) 5) routing of gating of information so that inputs that arrive at the correct receptive time window in the oscillation will be selectively attended and transmitted (communication through coherence) and 6) provide a clock for stimulus prediction.

Workshop 5

Cellular and Subcellular
April 8-12, 2013

Organizers: Janet Best, Avrama Blackwell and Paul Bressloff

Report by: Arjun Beri, Casey Diekman, Lucy Spardy



It is natural to think about the brain and brain function on four different levels: genomics, biochemistry, electrophysiology, and behavior. Enormous amounts of new information are becoming available on associations between genotypes and behavior. The causal mechanisms, which are mostly unknown, necessarily involve the effects of genotype on development, cellular biochemistry, and electrophysiology. The cellular biochemistry and morphology of neurons is fundamental for understanding the electrophysiological properties of neurons and networks. And the network properties then give rise to the brain functions that we label with terms such as memory, mood, decision-making, motor control, and so forth. This simple characterization is misleading because the use of the word "level" suggests that there is bottom up control, the genes control the chemistry that controls the electrophysiology that controls behavior. The scientific issues are so difficult and interesting precisely because this is not true. Behavior affects gene expression levels, electrophysiology induces short and long term changes in cell biochemistry and morphology, which in turn influence the electrophysiology. On each of these levels, mathematicians and computational neuroscientists have created models to give conceptual understanding, to organize data, and to explore causal mechanisms. This workshop will focus on three particular areas. Morphology of neurons and electrophysiological processing. The great variety of dendritic morphologies suggest functional roles for different geometries and it is now understood that dendrites are often not passive conductors. Mathematical models have shown how the distribution of channels and receptor trafficking influence electrophysiological signaling. However, it is also known that electrophysiological signaling affects dendritic processing by affecting synapses and spines and other changes in morphology. For example, gonadotropin-releasing hormone cells of the hypothalamus drive the transition through puberty via changes in cellular- and population-level firing patterns. This change in electrical activity is accompanied by dendritic pruning that alters the electrical conductance properties of the neuron. Medial superior olive (MSO) neurons in the auditory brainstem decrease their dendritic arborization during postnatal development, eventually achieving bipolar morphology. Mathematical models of the MSO and other neural populations suggest that not only the morphology but also the distribution of different ion channels contributes to dendritic computation. Mathematical models that relate cellular properties to the electrophysiology of neurons often raise new questions in deterministic and stochastic dynamical systems. These include the origins of mixed mode oscillations and bursting behavior, as well as the interplay of stochasticity and synchony.

From signaling molecules to behavior. The brain can be in different states with different corresponding behaviors. Signaling molecules play an important role in modulating state, and behavior interacts with the signaling molecules. For instance, the extracellular concentration of the neuromodulator adenosine, which increases during wakefulness and decreases during sleep, appears to increase propensity to transition from waking to sleep by inhibiting wake-active cholinergic cells. In turn, cholinergic cells play a role in inducing REM sleep as well as mediating cognitive functions via signaling on multiple time scales, and acetylcholine has long been recognized as a slow-acting neuromodulator of arousal states. While awake, behavioral activity can provide positive feedback helping to sustain wakefulness in the face of accumulating adenosine. Molecular and electrical signals interact to develop the neuronal network underlying the interactions described above.

MONDAY, April 8, 2013

Molecular dynamic at neuronal synapses: from super-resolution to the physical chemistry of molecular interaction

Antoine Triller (IBENS Ecole Normale Superieure)

Dr. Triller discussed the variability of individual synaptic responses. He pointed out that the variability of the postsynaptic response following a single action potential arises from two sources: the neurotransmitter release being probabilistic, and the postsynaptic response to neurotransmitter release having variable timing and amplitude. He then discussed the role of interactions between the neurotransmitter receptors on the postsynaptic membrane and the scaffolding proteins, such as Gephyrin, in neural transmission. Using single particle tracking (SPT) technology, precise molecular mechanisms involved in regulation of neuronal activity can be studied. Dr. Triller pointed out that a combination of single particle tracking and super-resolution methods (such as PALM), provide access to molecular counting and the energy involved in receptor-scaffold interactions as well as on and off rate of molecular interactions. This facilitates the understanding of submicroscopic diffusion behavior of neurotransmitter receptors.

Microtubule transport of mRNA in dendrites

Jay Newby (MBI, The Ohio State University)

Dr. Newby presented a stochastic model for bidirectional microtubule transport which is ideal for the task of distribution and delivery of mRNA to synaptic sites in dendrites. He showed that if the branch topology of the dendrites is ignored, then a purely unidirectional transport mechanism results in the smallest conditional mean first-passage time for any level of delivery probability (or, hitting probability). However, given the branch topology of a dendritic tree, bidirectional motion becomes a requirement for optimal transport. He introduced a two-state stochastic model of directed intermittent search on a one-dimensional track, and then discussed an expansion of the study using a biophysical model of motor transport of mRNA delivery. This involves an ATP signal for enhancing stochastic transport of motor-driven delivery. In addition to ATP he shows that tau, a microtubule associated protein, also lead to dramatic improvements in capture probability.

Effects of subcellular dendritic structure on robustness and plasticity of synaptic function

Fidel Santamaria (University of Texas at San Antonio)

The cumulative effects of a wide range of heterogeneous components found in cells and networks at multiple scales could give rise to reaction-diffusion processes away from equilibrium. This complex behavior can result in the breakdown of classical laws of reaction-diffusion which could give rise to power-law distributions. Dr. Santamaria presented experimental and computational work that shows the breakdown of classic diffusion at multiple scales in single neurons. Dr. Santamaria showed that molecular crowding in the postsynaptic density causes anomalous diffusion of glutamate receptors. This process is able to explain the results from single particle tracking experiments and provides a low energy strategy to retain glutamate receptors in the synapse for long periods of time. At a spatial scale two orders of magnitude larger than a synapse, the presence of dendritic spines causes anomalous diffusion of soluble cytosolic signals. This type of anomalous diffusion affects the integration of second messengers involved in synaptic plasticity. Dr. Santamaria then presented generalization for the analysis of reaction-diffusion systems outside equilibrium by using fractional reaction diffusion equations.

Synaptic dynamics: modeling, analysis, stochastic simulations and extraction of features from superresolution data of live cell imaging

David Holcman (IBENS Ecole Normale Superieure)

Simultaneous tracking of many thousands of individual particles in living cells is possible with the availability of high-density superresolution imaging techniques. Dr. Holcman discussed AMPA receptor trafficking on neuronal cells. Organization of the receptors at the PSD is critical in shaping the synaptic response. He used stochastic descriptions at a molecular level to help determine the local biophysical properties underlying trafficking, such as the diffusion coefficient and the organization of receptor-membrane interactions. Narrow escape theory forms a useful tool to quantify time for receptor to reach a small hole in the domain. The massive superresolution dataset generated is modeled by an overdamped Langevin equation on the membrane. Also, superresolution data can be used to solve a reverse engineering problem and extract local physical properties that underlie trafficking.

Constructing a minimal molecular model of long-term memory

Harel Shouvel (University of Texas Health Center)

Dr. Shouvel presented a study of how synaptic plasticity is maintained in a synapse. Memories are encoded at the cellular level by varying synaptic efficacies that, in turn, are expressed by changes in the number of conformational states of synaptic proteins. Synaptic proteins have a lifetime that is shorter than long-term memory; therefore maintenance of long-term memories, in particular, the late-phase long-term potentiation (L-LTP), requires synthesis of new proteins. The protein kinase PKMζ is shown to be critical for maintaining long-term potentiation and long-term memory. Dr. Shouvel discussed presence of a synapse-specific, bistable translational switch that is based on a positive feedback loop between a memory protein (PKMζ) and a translation factor protein (PDK1).

TUESDAY, April 9, 2013

Modeling calcium influx and biochemical signalling controlled by the NMDA-type glutamate receptor in postsynaptic spines

Mary Kennedy (California Institute of Technology)

Dr. Kennedy in her study considers biochemical mechanisms in synaptic modulation for information processing occurring in the neuron cytosol. She provided an example that when long-term potentiation (LTP) is induced, more AMPA-type glutamate receptors are added to the postsynaptic membrane, coordinated with an expansion of the actin cytoskeleton structure, making the synapse stronger. Dr. Kennedy summarized a crucial physiological finding, in particular, if calcium is induced to rise to a level below a threshold then long-term depression (LTD) is induced, and LTP is induced if the rise is to a higher level. Moreover, high frequency stimulation induces LTP, and lower frequency stimulation induces LTD. She then described a simplified signalling pathway in the spine involving calcium- induced activation through NMDA-type glutamate receptor binding to small molecule (Calmodulin) connected to LTP. She introduced the structure of postsynaptic density describing the receptors on the postsynaptic membrane. Modeling the dynamics of this system faces the challenge that molecules in a test tube are well mixed and typical reaction-diffusion equations are applicable; however, in the spine, molecules are concentrated at various places and are not at equilibrium. Dr. Kennedy pointed out that the study has been motivated by a desire to understand regulatory biochemistry in a living spine by simulating reactions with minimal assumptions. She proposed the use of an agent-based modeling approach and exploits the MCell modeling environment. In this model the diffusing molecules are modeled as pseudo-random walks. Dr. Kennedy then summarized the numerical results and presented fascinating 3D plots of this system.

Propagation of CaMKII translocation waves in heterogeneous spiny dendrites

Paul Bressloff (University of Utah)

Dr. Bressloff presented a theory of wave propagation in heterogeneous environments applied to translocation of Calcium-calmodulin-dependent protein kinase II (CaMKII) in spiny dendrites. There is experimental evidence suggesting that CaMKII is an important signalling molecule involved in synaptic plasticity. A calcium elevation in dendrites leads not only to local translocation of CaMKII from the dendritic shaft to synaptic targets within spines, but also initiates a wave of CaMKII translocation that spreads distally along the dendrite with an average speed of order 1 micron/s. Dr. Bressloff presented a reaction-diffusion model of CaMKII translocation waves that can account for the observed wave speed and predicts wave propagation failure if the density of spines is too high. Moreover, the role of heterogeneities is studied in the model. These heterogeneities exist at two spatial scales, namely, the discrete spines that are joined to the dendritic branch through a thin spine neck which is of submicron radius, and a second source that occurs on a longer time scale, reflecting the experimental observation that there is a slow proximal to distal variation in the density of spines. Dr. Bressloff then presented the application of perturbation theory (homogenization) and Hamilton-Jacobi methods as relevant to this problem.

Synaptic integration in pyramidal neuron dendrites is balanced by distance-dependent synapse distributions and amplification by dendritic spines

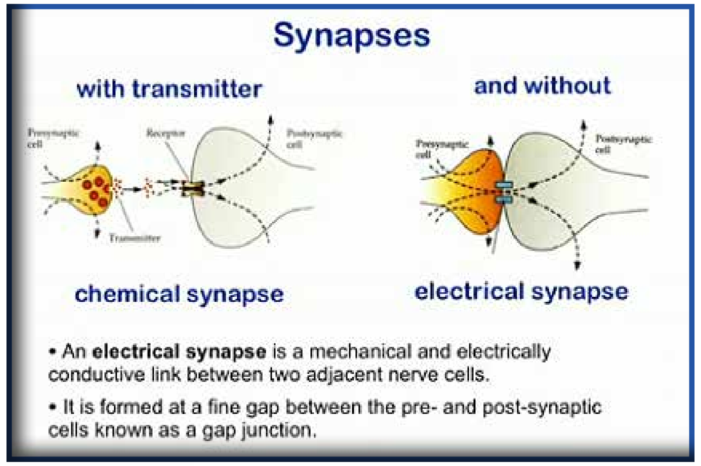
William Kath (McCormick School of Engineering, Northwestern University)

Dr. Kath discussed the capability of CA1 pyramidal neurons to integrate inputs and fire action potentials. Excitatory synapses in pyramidal neurons are distributed on spines spread over extensively arborized dendrites. These inputs are the sites of contact for a large fraction of the excitatory synapses in the mammalian brain, and as a result such dendritic inputs are the first step in the signaling between such inputs and a neuron's action potential output. Synaptic potentials attenuate dramatically, however, as they propagate along dendrites toward the soma. Dr. Kath presented a combined computational and experimental study of CA1 pyramidal neurons to demonstrate how spatially varying distributions of synapse number and size combine to influence somatic membrane potential and action potential initiation in the axon. He also demonstrated that spines provide a uniformly high impedance compartment across the dendritic arbor that amplifies local depolarization. This spine amplification increases nonlinear voltage-dependent conductance activation and promotes electrical interaction among coactive inputs, enhancing neuronal response.

Gap junctions, dendrites and resonances: a recipe for tuning network dynamics

Yulia Timofeeva (University of Warwick)

Dr. Timofeeva focused on the importance of gap junctions in mediating various brain rhythms in both normal and pathological states. Gap junction connections can form between the dendritic trees of individual cells, and many dendrites express membrane channels that confer on them a form of sub-threshold resonant dynamics. To obtain insight into the modulatory role of gap junctions in tuning networks of resonant dendritic trees, Dr. Timofeeva generalized the "sum-over-trips" formalism to treat networks of dendritic trees connected via dendro-dendritic gap junctions. Applying this framework to a two-cell network, she constructed compact closed form solutions for the network response function in the Laplace (frequency) domain and studied how a preferred frequency in each soma depends on the location and strength of the gap junction.



Synapses

with transmitter

and without

chemical synapse

electrical synapse

- An **electrical synapse** is a mechanical and electrically conductive link between two adjacent nerve cells.
- It is formed at a fine gap between the pre- and post-synaptic cells known as a gap junction.

Neuronal model reduction: cells, junctions, and circuits

Steve Cox (Rice University)

Dr. Cox discussed the use of Krylov subspace projection methods in constructing reduced models of quasi-active neurons. This method preserves both the spatial specificity of inputs and the biological interpretation as an RLC circuit. The spatial component of the input signal often carries information crucial to a neuron's function, but models that map synaptic inputs to transmembrane potential can be computationally expensive. Existing reduced models of the neuron either merge compartments, thereby sacrificing the spatial specificity of inputs, or apply model reduction techniques that sacrifice the biological interpretation of the model. Dr. Cox showed both numerically and theoretically that by using the suggested method, a reduced model could accurately compute the potential at the spike initiation zone given a much smaller dimension and simulation time. Additionally, the structure was preserved through the similarity in the circuit representations. Furthermore, the transformation from the full to the reduced system was straightforward and depended on the intrinsic properties of the dendrite. Thus the reduced models could be used not only to simulate morphologically accurate neurons but also to examine the underlying functions performed in dendrites.

WEDNESDAY, April 10, 2013

Mathematical analysis of depolarization block mediated by slow inactivation of the fast sodium channels that limits phasic signaling in midbrain dopamine neurons.

Carmen Canavier (Louisiana State University)

Dopamine neurons in freely moving rats often fire behaviorally-relevant high frequency bursts, but depolarization block limits the maximum steady firing rate of dopamine neurons in vitro. Dr. Canavier showed that in a reduced model, adding an additional slow component of sodium channel inactivation qualitatively changes how the model enters depolarization block in two different ways: first, the slow time course of inactivation allows multiple spikes with progressively increasing interspike intervals to be elicited during a strong depolarization prior to entry into depolarization block, which may be critical for the ability to burst in vivo. Second, depolarization block occurs much closer to spike threshold, because the additional slow component of inactivation negates the sodium window current. Significantly, the time constant of recovery from slow inactivation during the interspike interval limits the maximum steady firing rate observed prior to entry into depolarization block. These qualitative features of the entry into depolarization block can be reversed experimentally by replacing the native sodium conductance with a virtual one lacking the slow component of inactivation, and suggest that activation of NMDA receptors may contribute to circumventing the firing rate limitation during behaviorally relevant, high frequency bursts in vivo.

Calcium-based synaptic plasticity: from single synapses to networks

Nicolas Brunel (University of Chicago)

Calcium is known to play a fundamental role in synaptic plasticity. However, it is still unclear to what extent the dynamics of calcium concentration in post-synaptic spines alone can account for the phenomenology of plasticity. Dr. Brunel indicated that most synaptic plasticity models fit data using purely phenomenological models that are at odds with many experiments. He then presented a simplified, minimal calcium-based synaptic plasticity model and showed that it can reproduce quantitatively a large amount of experimental data which have diverse plasticity outcomes (in hippocampal cultures, hippocampal slices and cortical slices). Differences between these outcomes in such preparations are predicted to arise due to differences in parameters controlling calcium dynamics (such as the extracellular calcium concentration), which potentially reconciles conflicting studies.

The emerging role of forces in axonal elongation

Kyle Miller (Michigan State University)

Dr. Miller presented results on axon elongation, and focused on three questions: whether the mechanism of growth cone advance is conserved between vertebrate and invertebrate neurons; how growth cones advance in vivo; and what the role of myosin II force generation is in growth cone motility. He showed that the mechanism for growth cone motility is conserved and occurred in vivo, and found that axonal myosin II acted antagonistically against forces generated in the growth cone to modulate translocation of the growth cone. His results suggest that a molecular mechanical model should utilize the balance of myosin II along the growth cone and axon. This work could have important implications for the development of treatments for stroke, peripheral nerve damage, and spinal cord injury.

A Hybrid Approach for Understanding Cell Dynamics

Richard Bertram (Florida State University)

Dr. Bertram described techniques that he is using to integrate mathematical modeling into experimental studies in a way that addresses two important modeling challenges: the first being that models contain parameters that determine the behavior of the model, and the values of these parameters are often hard to determine from the available biological data. The second modeling challenge stems from the fact that many biological systems exhibit a great deal of heterogeneity in behavior, so even if the model parameters could be perfectly calibrated by pooling cell behaviors to produce an "average cell model", this model may not provide a good description of any single cell in the population. He studied endocrine pituitary cells, with the aim of developing an approach for modeling the behaviors of these cells with enough accuracy so that in spite of heterogeneity within the cell population, they can use the models to make, and subsequently test, predictions. His work focused on cell by cell calibration – fitting the model to an individual cell while patched to that cell.

Modeling localized calcium elevations and whole cell calcium responses: stochastic dynamics and bidirectional coupling

Gregory D. Smith (The College of William & Mary)

Localized Ca elevations can produce three modes of Ca release – fundamental (blips and quarks), elementary (puffs and sparks), or global (waves). These cellular signals arise from the cooperative activity of clusters of receptors clustered at Ca release sites on the surface of the endoplasmic reticulum or sarcoplasmic reticulum. Markov chain models provide insight into the relationship between single-channel kinetics and the statistics of puff/spark duration, and clarify the role of stochastic attrition, Ca inactivation, luminal depletion, and allosteric interactions in the dynamics of puff/spark termination. The stochastic dynamics of local Ca is an important aspect of excitation-contraction coupling in cardiac myocytes. Here sarcoplasmic reticulum Ca-induced Ca-release is locally controlled by trigger Ca influx via L-type channels of the plasma membrane. Dr. Smith utilized a whole cell modeling approach and avoided the computationally demanding task of resolving spatial aspects of global Ca signaling by using probability densities and associated moment equations to represent heterogeneous local Ca signals in a population of Ca release units. This new class of whole cell models of Ca handling facilitates simulation and analysis of the bidirectional coupling of localized calcium elevations and whole cell calcium responses in cardiac myocytes.

THURSDAY, April 11, 2013

Genesis of gamma bursts in neural local field potentials

Priscilla Greenwood (University of British Columbia)

Dr. Greenwood presented mathematical analysis and simulations of a stochastic model of the generation of gamma bursts in local field potential (LFP) recordings. Electrodes inserted into a certain region in the brain measure a local field potential. Data show bursts of activity at a number of frequencies, including the gamma region of 40-100Hz. By analyzing a simple linear model, which represents a large class of similar but more complicated models, Dr. Greenwood was able to proceed further with mathematical analysis than has been accomplished previously. She demonstrated that the simple stochastic model can be approximated in terms of a rotation multiplied by a two-dimensional Ornstein-Uhlenbeck (OU) process, and that gamma bursts arise in the model as excursions of the modulus of the OU process. Finally, she showed that there is a reciprocal relationship between the amplitude of the envelope of the gamma oscillation and the time derivative of phase that, among other properties of the approximation, is mirrored in LFP data simulated from the original model. The close relationship between the properties of the approximation and those of simulations of the original model suggests that the approximation is a valid representation for a wide class of models of oscillatory neural processes.

Mathematical modeling of sleep/wake behavior and the role of orexin/hypocretin

Cecilia Diniz Behn (Gettysburg College)

Dr. Diniz Behn's talk focused on the dynamics of sleep/wake. The neuropeptide orexin/hypocretin is essential for normal consolidation of sleep/wake behavior, and disruption of the orexin system is associated with the sleep disorder narcolepsy. Recent experimental work has characterized elements of orexin neuron electrophysiology and state-dependent behavior, however, many questions, particularly questions of dynamics, can be difficult to address in an experimental setting. Dr. Diniz Behn discussed several modeling approaches, spanning multiple scales, which she has undertaken to investigate the intrinsic dynamics of these neurons and their role in sleep/wake regulation. Dr. Diniz began by explaining that in rodents, there are polyphasic transitions between states of wake, non-REM sleep, and REM sleep. She then demonstrated her use of survival analysis techniques to understand the role of orexin in sleep architecture based on EEG data. Dr. Diniz Behn also simulated the effects of orexin in a neuronal population model, and investigated the electrophysiological bases for these effects in a Hodgkin-Huxley-type model orexin neuron. Finally, in addition to sleep/wake she mentioned that orexin neurons have also been shown to be important in addiction and traumatic brain injuries.

Reaction¬-Diffusion Modeling in the NEURON Simulator

Bill Lytton (SUNY Downstate)

Dr. Lytton's talk covered new features of the NEURON simulator and some preliminary results obtained using these features. In his introduction, Dr. Lytton endorsed the use of complex computer models as experimental objects. The NEURON simulator is a widely used tool for studying detailed single cell and network models. In recognition of the growing importance of multi-¬scale modeling, Dr. Lytton's group has expanded NEURON's support for intracellular chemical dynamics. Their initial work has explored deterministic reaction-¬diffusion models with one-¬dimensional simulations, in particular neuronal calcium simulations in a dendrite. Calcium waves interact bidirectionally with electrical activity. They tested different distributions and densities of IP3 receptors in the dendrite, assessing the effects on speed and strength of calcium wave boosting. Future directions include stochastic reaction-diffusion in 3D spatial simulations with neural morphologies, and the ability to import models written in the Systems Biology and Virtual Cell Markup Languages.

Diversity and Details of Hippocampal Interneurons: Contributing to Functional Output

Frances Skinner (University of Toronto)

Dr. Skinner described her work regarding the development and use of a class of interneuron models in hippocampus that express subthreshold theta oscillations. There is a wide diversity in the properties of interneurons, and it is unclear how these diverse cells contribute to functional output. Dr. Skinner developed a biophysically based cellular model to examine how they could contribute to population theta rhythms. She used a computational approach in which she determined what in vivo-like conditions might support the reliable firing of these cells at theta frequencies. She found that noisy inhibitory inputs promote this and that biophysical properties that contribute to reliable firing differ from those contributing to subthreshold activities. Her work thus shows how hippocampal cellular details could support functional output. Furthermore, it demonstrates that linking sub-threshold and supra-threshold activities should be done with consideration of both in vivo contexts and biophysical specifics. Dr. Skinner's advice is to "neither ignore the details, nor be consumed by them".

Decomposition and Control of Physiological Limit Cycles (a talk in two parts). I: Eupnea, Tachypnea, and Autoresuscitation in a Respiratory Control Model. II: Evidence for a Stable Heteroclinic Feeding Pattern Generator.

Peter Thomas (Case Western Reserve University)

In his talk, Dr. Thomas considered two examples of adaptive regulation of central pattern generator (CPG) activity in response to varying operational demands: respiratory control, and control of a feeding pattern generator in the sea slug Aplysia californica. In the first example, he considered the behavior of a conductance-based respiratory pacemaker cell model, the Butera-Rinzel-Smith (BRS) conditional bursting neuron, when embedded in a closed-loop respiratory control model. Dr. Thomas showed that the closed-loop model is bistable, with one stable state (bursting activity) corresponding to "eupnea" or normal breathing, and a second stable state (beating activity) that may correspond to "tachypnea", or pathological rapid shallow breathing. The BRS conductances also show a novel "autoresuscitation" effect, in which a transient drop of blood oxygen content causes a large burst of inspiratory activity. In the second example, Dr. Thomas considered a nominal model for protraction and retraction of the mouthparts of Aplysia while feeding on seaweed. By varying a parameter, the underlying limit cycle (LC) driving the feeding pattern generator can be moved between a Hopf bifurcation and a heteroclinic bifurcation. When the LC is close to the heteroclinic bifurcation, the musculature responds by prolonging the retraction phase of the motion. Experimental results from Hillel Chiel's laboratory suggest that sensory feedback guides the timing of the feeding pattern generator by steering trajectories closer to or farther from a succession of fixed points.

FRIDAY, April 12, 2013

Same cell, different excitability profiles… one dynamical system may not be enough

Marco Herrera-Valdez (Universidad Nacional Autonoma de Mexico)

In his talk, Dr. Herrera-Valdez covered three interrelated stories: 1) models are often more complicated than they need to be; 2) Hodgkin-Huxley models often need to be extended or revised to include electrodiffusion; and 3) the single cell – single dynamical system paradigm does not make much sense at first sight. For the first story, the focus was on a reduction of a cardiac cell model from 14-dimensional system to three dimensions by separating large currents from small currents. The small currents can be considered a source of noise when comparing model traces to experiments. Dr. Herrera-Valdez then discussed how to add electrodiffusion to models, following the ideas of Goldman (1943). Finally, Dr. Herrera-Valdez then showed

that neurons of the same identified type lead to different electrophysiological profiles—that are not topologically equivalent— upon transition into the spiking regime.

A mathematical model for the frequency dependence of cholinergic modulation in PV+ basket cells
Emily Stone (University of Montana)
Parvalbumin positive (PV+) basket cells (BCs) are a major interneuron subclass mediating feed-forward inhibition in hippocampal circuits that are thought to provide a basic non-plastic rhythm. Dr. Stone discussed her modeling work that verified and quantified the recent experimental finding that cholinergic modulation relieves synaptic depression of PV+ CA1 BCs at gamma, but not theta, frequencies. Dr. Stone developed a phenomenological model unifying presynaptic short-term facilitation and depression. This minimalistic model was able to explain the frequency dependence of cholinergic modulation based on the interplay of time scales involved in the presynaptic plasticity process. In particular, models without a "hidden timescale" could not fit the data. Finally, a Markov chain Monte Carlo method was used to determine parameter correlations and reduce the model further.

Analysis of the stochastic shielding approximation for Markovian ion channel models via random graphs
Deena Schmidt (Case Western Reserve University)
Dr. Schmidt's talk was motivated by the observation that mathematical models of cellular and sub-cellular physiological mechanisms often involve random walks on graphs representing transitions within networks of functional states. Schmandt and Galan recently introduced a novel stochastic shielding approximation as a fast, accurate method for generating sample paths from a finite state Markov process in which only a subset of states are observable. Dr. Schmidt considered the problem of finding the optimal complexity reducing mapping from a stochastic process on a graph to an approximate process on a smaller sample space, as determined by the choice of a particular linear measurement functional on the graph. The partitioning of ion channel states into conducting versus non-conducting states provides a case in point. In addition to establishing that Schmandt and Galan's approximation is in fact optimal in a specific sense, Dr. Schmidt provided heuristic error estimates for the accuracy of the stochastic shielding approximation for an ensemble of Erdos-Renyi random graphs, using recent results from random matrix theory.

Things that bug me about single neuron models: Experiences with hippocampal and vestibular neuron modeling
Bill Holmes (Ohio University)
Dr. Bill Holmes reviewed activation curves representing voltage dependence of ion conductance. He discussed the numerical issues in fitting Boltzmann equation to data obtained from voltage-clamp experiments. He suggested two issues with activation curves: First, it assumes a two-state model and second, it requires reporting of biophysical signature half-activation voltage V1/2. He elaborated that there are many problems with the channel kinetics data that shifts the subsequent V1/2. In particular, he mentioned that V1/2 is affected by liquid junction potential, Donnan equilibrium, patch versus whole cell configuration, calcium dependent modulation, etc. Moreover, V1/2 values used in models are far from experiments. Dr. Holmes argued that the channel time constant expressions in literature are complicated with no straightforward interpretation and presented alternate simplified expressions. He emphasized the point that parameters V1/2 and slope factor often vary across different lab experiments, and the model results are quite sensitive to these parameters.

Dynamic Hopf bifurcation in spatially extended excitable systems from neuroscience
Lydia Bilinsky (Duke, Arizona State University)
Dr. Bilinksy introduced the concept of membrane accommodation, a phenomenon where an excitable nerve fiber does not enter into sustained oscillations as soon as a slowly rising injected current attains the constant-current firing threshold, but instead remains stable for some time afterward. The actual jump value depends on the initial value of the current and its functional form, termed the "memory effect", and is a case of slow passage through a Hopf bifurcation. Dr. Bilinsky extended this work to systems which are spatially extended and showed that in a FitzHugh-Nagumo cable, "complete accommodation" is possible, where sustained oscillations are not simply delayed, but in fact never occur. She explained this concept and predicted the minimum length for complete accommodation to occur utilizing the Wentzel-Kramers-Brillouin approximation. She also illustrated the existence of a "spatial memory effect" in a passive dendritic shaft studded with active dendritic spines in response to a slow current ramp.

Workshop 6

Sensory Systems and Coding
May 6-10, 2013

Organizers: Brent Doiron, Adrienne Fairhall, David Kleinfeld, and John Rinzel

Report by: Arjun Beri, Casey Diekman, Josh Chang

Mathematical analysis and modeling have played influential roles in the current and classical descriptions of sensory processing, object identification and representation. The bases for these descriptions have involved the properties of feedforward interactions, receptive-fields, and firing rates or spike counts and stimuli have typically been static in time and stereotypical (oriented bars, pure tones, ...). Successes include Hubel and Weisel (1981 Nobel Prize shared with Roger Sperry) and Barlow (Swartz Prize for Computational Neuroscience, 2009). There is a growing awareness that processing is not passive but active (e.g., Kleinfeld, Bower) that involves dynamic feedback loops and recurrent processing and that feedback may extend down to the sensory receptor level. This workshop will address the evolving research area of active sensory processing, such as the top-down responsive control of whiskers in the rat somatosensory system, and the mathematical modeling of these feedback systems and the principles and optimizations that might pertain. The notion of static receptive fields as described in over-idealized and restricted stimulus sets in laboratory settings is also under challenge when one considers that in real-world settings the scenes are much more complex and they are dynamic, constantly changing. A statistical framework for natural scene analysis seems much more appropriate. The workshop will consider the approaches of statistical representation of scenes and their possible realization in the brain. Furthermore, sensory systems are capable of rapid adaptation to scene dynamics, including the statistics of changing scenes, and models for such are under development (Fairhall, Riecke).

So, what does the brain do with the processed sensory input? What scene aspects/cues are used in object identification and segregation; what commonalities group different individuals together; how do we categorize objects?

Modeling challenges are presented by these questions and some will be addressed during the workshop. An interesting paradigm arises in the context of ambiguous scenes, such as the Necker cube or the face-vase image, in which multiple interpretations are perceived alternately. The dynamics of such alternations are stochastic and the differential equation models typically involve competition through mutual inhibition amongst the model neural subpopulations that are hypothesized to represent the two or more percepts. In the auditory context there are dynamic ambiguous stimuli that introduce another temporal layer and raise issues of what cues are used to define and track an auditory object through time.

Issues that arise in the neural representations of scenes lead naturally to neural coding. What language/means do neuronal systems use internally to encode the features of an image? These questions are usually addressed from an information theory point of view. In which context is the temporal patterning of spike trains significant or is the mean firing adequate to carry the information? How do cell ensembles mutually represent features, i.e., what is the population code? Perceptions must be developed on the fly. Given some sensory tuning properties how might the parameters be chosen amongst cells to give the most efficient and rapid population code?

Throughout the workshop we will ask about plausible mechanistic models that can implement the notions of active processing, coding strategies, adaptation features, and so on.

MONDAY, May 6, 2013

Workshop Introduction

Brent Doiron (University of Pittsburgh) and Adrienne Fairhall (University of Washington)

To start the workshop off, Drs. Doiron and Fairhall gave two examples of combining neural mechanics and sensory processing. Dr. Doiron focused on how input correlations are mapped to output correlations in the spike train. In earlier work, he found a relationship between output correlation and output firing rate: neurons that fired at higher rates transferred correlations more effectively. He then discussed data recorded from the somatosensory cortex pre- and post-whisker deflection where this relationship does not hold. To understand this, Dr. Doiron focused on a spiking network model with feed-forward inhibition, and demonstrated that inhibition acts as a source of decorrelation in this system. The inhibition makes the system sensitive and trial-to-trial independent, which improves whisker velocity coding as measured by Fisher information.

Dr. Fairhall discussed information processing in neurons and networks, and the role of excitability in neural coding. She introduced the basic coding model as a linear filter in series with a nonlinear decision function. To understand biological computation, Dr. Fairhall advocated a three-fold approach: 1) identify the algorithm, or the computation being performed; 2) instantiate the computation in a high dimensional model that describes the mechanism which is implemented by the biology; and 3) reduce to a low-dimensional model where we can extract the fundamental dynamical mechanisms responsible for the behavior. These three parts talk to each other and tell us about parameter invariance and robustness. Dr. Fairhall illustrated this by exploring neuronal feature selection in the Hodgkin-Huxley model.

Detection and Discrimination in Sensory Pathways: The Role of Synchrony

Garrett Stanley (Biomedical Engineering, Georgia Tech)

Dr. Stanley presented work on the role that neuronal synchrony may play in information coding, using examples from both the visual and somatosensory pathways. Sensory systems exist to extract relevant information from our sensory environment. One such piece of relevant information concerns the arrival of novel, salient sensory features, for which one may want to simply detect the presence. Another such piece of relevant information concerns the discrimination of fine details of the sensory scene. It has long been posited that these two processes place competing demands on our sensory systems, but this has not been explored in detail. Dr. Stanley's talk touched on these issues, and described a bottom-up mechanism for how adaptation modulates detection and discrimination. He concluded that stimulus-driven synchronizations help move information from one brain region to the next.

Active spatial perception in the vibrissa scanning sensorimotor system

David Kleinfeld (Physics and Neurobiology, University of California San Diego)

Dr. Kleinfeld continued to emphasize the value of the rodent vibrissa sensorimotor system as a model system to investigate active sensation. He touched on the following questions: How do we know where objects are relative our body? How do we use touch information to plan the next motor act? Dr. Kleinfeld discussed experimental results establishing a newly recognized zone of neurons that code rhythmic motion of the vibrissa, and identified monosynaptic connections of a minimal breathing and whisking circuit. These results led Dr. Kleinfeld to conjecture the primacy of inhalation as a master clock for orofacial behaviors.

A critical lesson from this work is that sensory signals from the external world are heavily processed before they reach cortex and - based on preliminary data - feedback from cortex can strongly affect this filtering.

Optimality and neural codes: Bayesian inference meets Barlow's efficient coding hypothesis

Jonathan Pillow (Psychology and Neurobiology, University of Texas)

In Dr. Pillow's talk, he introduced a Bayesian theory of efficient coding which connects two "big ideas" in theoretical neuroscience: Barlow's efficient coding hypothesis, and the Bayesian brain hypothesis. The efficient coding hypothesis asserts that neurons should maximize the information they convey about stimuli. This idea has provided a guiding theoretical framework for the study of coding in neural systems, and has sparked a great many studies of decorrelation and efficiency in early sensory areas. The Bayesian brain hypothesis, asserts that neural responses encode posterior distributions in order to support Bayesian inference. Dr. Pillow argued that there is nothing privileged about information-maximizing codes: they are ideal when one wishes to minimize entropy, but they can be substantially suboptimal in other cases. Bayesian efficient coding substantially enlarges the family of normatively optimal codes and provides a general framework for understanding the principles of sensory encoding. Dr. Pillow derived Bayesian efficient codes for a few simple examples, including study strategies for multiple choice exams, and concluded with an application to neural data.

Principles of Biological Design

Stephen Baccus (Neurobiology, Stanford University)

Dr. Baccus began by pointing out that the encoding of information in the nervous system has no perfect solution; design is a choice and involves a trade-off between different benefits. He discussed trade-offs and solutions in the retinal neural code in the context of global motion produced by eye movements. It has long been known that distant peripheral motion has strong effects on retinal responses, but the functional benefits of these effects have not been fully studied. Dr. Baccus showed that distant peripheral motion generates a common synchronization signal that allows neurons to switch between different versions of the scene, including an energy conserving mode, and a high-throughput mode that approaches maximal information transmission. Furthermore, switching between complementary representations of the same scene enables single units to convey diverse information, and avoids the drawbacks inherent to each neural code.

FLASH TALK: *iModel.org Demonstration*

Wyeth Bair (Biological Structure, University of Washington)

Dr. Bair demonstrated a tool his group is developing called iModel (Interactive Models for visual and neural), which allows one to explore computer models of neural computation at levels ranging from simple linear filters to large-scale networks of spiking units (www.imodel.org). Dr. Bair has used the tool to test models of the visual system under a wide variety of stimuli. Model outputs can be displayed conveniently, with the goal of emulating the experience of studying the visual system in experimental labs. Dr. Bair concluded by stating that he believes iModel can be a useful means of exploring any sensory system where there is a standard set of stimuli and reasonably well-described circuits.

FLASH TALK: *Whisker shape changes induced by touch*

David Golomb (Ben-Gurion Univ., Beer-Sheva, Israel and Janelia Farm, VA)

Dr. Golomb presented his use of dynamical systems theory to study why whiskers of land mammals are approximately conical. He considered a tapered whisker under contact with an object, and converted the Euler-Bernoulli quasi-static equation into a boundary-value equation. The equation has two solutions (one stable and one unstable) that coalesce in a saddle-node bifurcation. Beyond the bifurcation, the whisker slips off. Slip-off does not occur for cylindrical hairs for realistic parameters. Dr. Golomb suggested that slip-off events code radial distances of objects far from the whisker base. Experimental results show that conical whiskers can sweep pass textures in a series of stick-slip events, but cylindrical hairs are stuck.

Neural Information Processing Underlying Collision Avoidance Behaviors

Fabrizio Gabbiani (Neuroscience, Baylor College of Medicine)

Dr. Gabbiani focused on the locust brain as a model system to summarize the current understanding of the generation of visually guided collision avoidance at the level of neural networks, single neurons, and their ion channels. Visually guided collision avoidance behaviors are nearly universal in animals endowed with spatial vision, and several neural computations of broad relevance (specific tuning, non-linear multiplicative interactions of input variables, invariance of neural responses) are involved. Dr. Gabbiani found that the hyperpolarization-activated current Ih significantly affects the segmentation of spatially coherent stimuli, leading to collision avoidance behaviors. He showed that the generation of escape jumps is a multistage behavior, and suggested that information about distinct aspects of this behavior are "multiplexed" in the time-varying firing rate of a single neuron. Such multiplexing is likely to occur in other complex behaviors and in other neural systems as well.

FLASH TALK: Neurogenesis allows olfactory bulb to learn to decorrelate stimuli

Hermann Riecke (Northwestern University)

Dr. Riecke described a neurogenetic network model that learns to decorrelate odor stimuli over time. The model was motivated by the substantial turnover of granule cells in the olfactory bulb, even in adult animals. It is observed that with neurogenesis suppressed, the animals' capacity for perceptual learning is impaired. Dr. Riecke has developed a simple network model in which the connectivity adapts to the odor environment through the experimentally observed dependence of the survival of the interneurons on their activity. New granule cells (the dominant interneuron population in the bulb) are randomly connected to principal mitral cells. Importantly, these connections are reciprocal. The reciprocity of the connections between the principal neurons and the interneurons allows network restructuring to reduce the correlation of the representations of similar stimuli.

FLASH TALK: Control strategies for underactuated neural ensembles

Jason Ritt (Boston University)

Dr. Ritt's lab is interested in neurocontrol, defined as stimulating the nervous system to make it do something. Such control is underactuated: there are many more neurons than independent electrical or optical stimulators. Controllability is achievable in "bulk" problems (e.g. deep brain stimulation), and in small homogeneous ensembles (columnar stimulation). However, to reproduce sensory codes (i.e. for prosthetics) one might need to generate spike train patterns with finer grain than the number of stimulators. In Dr. Ritt's talk, he analyzed a network of heterogeneous integrate-and-fire neurons to understand how this might be possible. He derived conditions for when two neurons are pairwise controllable, which can be extended to large ensembles. Higher dimensional models allow additional strategies including depolarization block or partial inactivation, however one encounters issues with observability. Dr. Ritt concluded by advocating that a full test of sensory de/encoding should impose the activity and assess the behavioral response. There are some examples of this, but to take the program further we likely need to develop better stimulation technologies.

TUESDAY, May 7, 2013

How variability is controlled in the brain?

Tatyana Sharpee (The Salk Institute for Biological Studies)

Dr. Sharpee addressed the presence of multiple-variability, which typically refers to noise correlations in sensory neurons. The mechanism of noise correlation is such that two sources of noise compensate for each other. Thus, the nervous system does not have to eliminate these noises individually, thereby improving performance. Dr. Sharpee pointed out that this problem can be seen as a closed packing problem related to error-correcting code. She pointed out through a classical packing problem that disordered packing of elliptic objects pack denser than spherical objects. Dr. Sharpee described variability control in the brain through two examples, namely, (a) vision, such that correlations between retinal irregularities improve information transmission; and (b) audition, related to learning restriction.

Encoding a visual scene in the retina shows that neural encoding is such that the receptive fields are slightly elliptical as opposed to being uniformly circular. She presented a few results from the analysis; in particular, she argued that the data suggests that elliptical receptive fields have a higher information index in the presence of a non-uniform (i.e., scattered) lattice. She said that her theoretical model fitted well with the experimental data obtained. Moreover, correlations between two types of circuit irregularities (noise in center positions, noise in receptive field shapes) restore information transmission.

Dr. Sharpee then discussed the correlations in the noise of individual auditory neurons. Auditory encoding of bird songs is also critical in human study from the point of view of development of languages. Her objective was to understand how well a bird can differentiate the source of stimuli, given a certain response of the neurons. She points out that learning inverts the relationship between the signal and noise correlations. Noise correlations improve encoding of relevant songs, and are detrimental to encoding of irrelevant and novel songs.

Local circuit function in the olfactory bulb

Ben Strowbridge (Case Western Reserve University)

Dr. Strowbridge presented the olfactory system. The olfactory receptor is linked to one or two input stations. Olfaction involves spatial coding of olfactory inputs. Dr. Strowbridge discussed intracellular recording of dendrodendritic inhibition in rat olfactory bulb slices. Activation of one mitral cell does not recruit much self-inhibition. He briefly discussed the existence of two distinct classes of excitatory inputs onto granules. Dr. Strowbridge pointed out that serotonin is a tool to depolarize all mitral cells in a brain slice. There are multiple pathways to generate inhibition of mitral cells under physiological conditions. Sniffing suppresses large excitatory postsynaptic potentials (EPSPs).

Coordinated neuronal activity and its role in corticocortical signaling

Adam Kohn (Albert Einstein College of Medicine)

Through his work Dr. Kohn is interested in understanding how information is processed in the cortex. Sensory events do not recruit individual neurons, but rather populations or regions of neuronal activity. These events are stimulus driven and form a part of the ongoing activity. Local field potential (LFP) frequency composition is stimulus dependent. Cortical activity is coordinated, as is evident in spiking responses and in the local field potential. Coordinated activity depends on stimulus drive and behavioral state.

Dr. Kohn then explored the functional relevance, in particular how coordinated activity influences population coding accuracy. He observed that how coordinated activity influences the relaying of signals between cortical areas and the computations they perform is far less explored. To tackle this issue, simultaneous recordings were taken from populations of neurons in the superficial layers of primary visual cortex V1 of macaque monkeys, and from their downstream targets in the middle layers of V2. It is found that spiking activity in V2 neurons is associated with a brief increase in V1 spiking correlations. Stimulus manipulations that enhance brief timescale V1 synchrony lead to stronger coupling between these networks. Dr. Kohn showed results suggesting that the coordination of spiking activity within a cortical area influences its coupling with downstream areas. V1-V2 CCGs have a broad peak, and when Rfs are aligned, there exists a narrow peak. Sharp peaks are offset by 2.4 ms, consistent with direct coupling. Fluctuations in excitability associated with V2 gamma have little effect on V1-V2 coupling, inconsistent with the communication through coherence proposal.

Emergent dynamics in a model of visual cortex

Lai-Sang Young (Courant, New York University)

Dr. Young presented a computational model of activity in the primary visual cortex V1. The objective of the study comprises of model design and calibration (10000 neuron, 10 parameters), seeking a parameter patch with output matching multiple experiments. This is followed by considering dynamics of activity in V1 and provides a mechanistic explanation for observed phenomena. The long-term objective is to have testable predictions for real V1 with an understandable model. The V1 properties that motivate model design are in particular: localized receptive field, orientation tuning/selectivity, and spontaneous background fluctuations. Two-dimensional arrays of excitatory and inhibitory neuron clusters, where rows represent orientation, and columns represent hyper-column receptive fields. Moreover, connections within each cluster are both excitatory and inhibitory (E/I); and between hyper-columns there are long-range excitatory connections. Individual neurons are assumed to be integrate-and-fire neurons.

Dr. Young then presented a method to locate a patch of parameters that give realistic dynamics. She talked about emergent phenomenon of multiple firing events (MFE), which refers to sudden barrages of E/I firing in local populations. Dr. Young then discussed the results obtained from this study. In particular, there is strong competition between E/I populations leading to the phenomena of bursts of MFE interspersed with regions of homogeneity. Also, in intermediate regimes characterized by structured firing (MFEs), variable event sizes and often power laws are observed. She also argued that dynamical mechanisms in plausible model regimes occur, describing gamma oscillations in LFP. Moreover, dynamics are neither homogeneous nor synchronous, but highly structured, and there is presence of MFEs with characteristic signatures.

Spatiotemporal encoding/decoding of nonlinear dynamics with compressive sensing: neuro-sensory encoding in moth olfaction and flight

Nathan Kutz (University of Washington)

Dr. Kutz presented a talk that broadly dealt with modeling of high dimensional complex system with low rate modes approximating the space spanned by the full system. Neuro-sensory systems encode their functionality into persistent spatio-temporal patterns of neuron activity, or so-called neural codes. Networks of neurons in the antennal lobe (AL) of moths form non-local neural codes that compete dynamically with each other through lateral inhibition. This produces a robust signal-processing unit that increases signal-to-noise and enhances the contrast between neural codes. More broadly, many high-dimensional complex systems often exhibit dynamics that evolve on a slow-manifold and/or a low-dimensional attractor. Dr. Kutz in his talk proposed a data-driven modeling strategy that encodes/decodes the dynamical evolution using compressive (sparse) sensing (CS) in conjunction with machine learning (ML) strategies for constructing the observed low-dimensional manifolds. The integration of ML and CS techniques also provide an ideal basis for applying control algorithms to the underlying dynamical systems, thus revealing a method of how robust flight control, for instance, can be accomplished.

FLASH TALKS: Who's got rhythm? Envelope Temporal Coding in Primary and Non-primary Cortices

Heather Read (University of Connecticut)

Social communication between rats is rhythmic and interactive. Rat alarm calls are induced with nasal air puffs, evoking stereotypical freezing in other rats. Rat alarm calls have a fundamental frequency of 22 KHz. The behavioral limits for discriminating these rhythms are currently being explored by Dr. Read's lab. Training rodents on go/no-go tasks via synthetic rhythms achieves this discrimination. Experimental data suggests that rats were able to discriminate modulation frequency with 5Hz rhythm difference. The second problem they are interested in is what the cortical neural limits for discriminating rhythm and other cues are. They use Fourier intrinsic optical imaging to map cortical responses to sound. The third problem that she described relates to the major differences in sound processing between primary and ventral non-primary cortices. Primary and ventral non-primary areas respond to broadband and narrowband frequency sensitivity, respectively. A similar profile for spatial cues sensitivity was observed. Further, tetrode isolation of single neuron spike response recording techniques is used. Based on these recordings it was deduced that primary auditory cortex (A1) has high trial-by- trial reliability, whereas in contrast to low reliability of non-primary ventral auditory cortex (VAF).

FLASH TALKS: Input processing by olfactory bulb microcircuit

Alla Borisyuk (University of Utah)

Dr. Borisyuk described the olfactory system as comprising of inputs from the olfactory bulb and output being recorded from individual cells. The goal of her study is to examine the role of different pathways in shaping outputs from given inputs in the context of olfactory system. The results presented suggest that multiple sub networks independently sharpen sensory inputs. She showed that one can predict functional role of inhibition; in particular, slow inhibition shapes response on the time scale of inhalation, and fast inhibition shapes fine-scale temporal dynamics. She then explained that a prediction from the full model is that reducing both feed-forward and recurrent inhibition increases number of spikes, and it does not alter the onset latency or duration.

Cortical adaptation predicts perception during an auditory task – with a twist

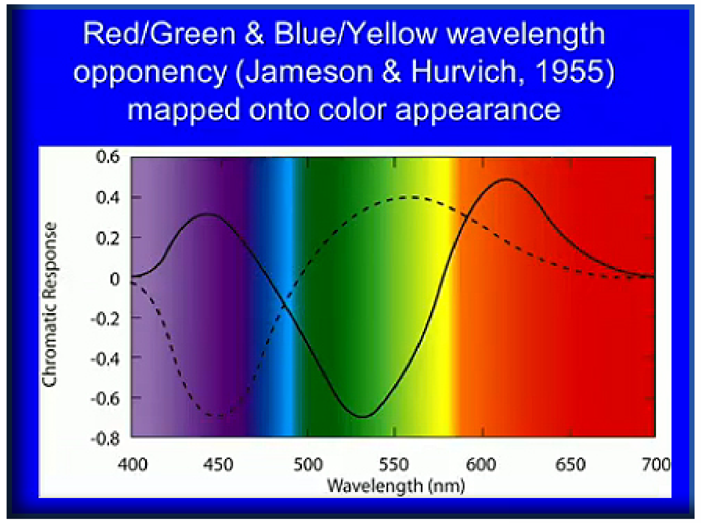
Bernhard Englitz (Ecole Normale Superieure, Paris, France)

Perception is not uniquely determined by a stimulus but depends on internal and external dynamics and context. Dr. Englitz presented a study of contextual effects in audition using the tritone paradox, where a pair of complex (Shepard) tones separated by half an octave can be perceived as ascending or descending. Presenting the biased Shepard pairs to ferrets, neuronal responses from primary auditory cortex were obtained. In the study each Shepard tone was decoded using the population vector. Experiments suggested that the bias sequences induce localized adaptation in neural recordings, and this adaptation is also present in human MEG recordings. In contrast with standard absolute distance decoder for Shepard tones, which fail in this case, the decoder developed by Dr. Englitz is trained to take into account the stimulus history. Direction-selective cells adapt differentially and provide a local predictor of the directional percept. Moreover, human MEG data suggests that local adaptation correlates with directional judgment. These results suggest that the stimulus context may be encoded by sustaining the adapted, negative afterimage of the preceding stimulus, and that this mechanism may generate global pitch-direction judgments from local pitch-direction selectivity.

FLASH TALKS: Forbidden colors and hidden aspects of perceptual opponencies

Vince Billock (Wright Patterson)

In his work, Dr. Billock, showed that forbidden colors and biased hallucinations are examples of ordinary neural mechanisms stimulated in extraordinary ways. The principle of opponent processing in sensory neuroscience is of critical importance. Color opponency is an established fact in perception. Dr. Billock presented a method to make it break down by retinally stabilizing equiluminous red/green or blue/yellow bipartite fields. The border perceptually melts away and the colors flow and mix into one another, creating forbidden colors in a variety of multistable percepts. Making the colors equiluminant is crucial; if the luminances of the retinally stabilized colors are not properly equated, subjects see multistable color switching or hallucinatory colored textures instead. The results can be understood if color opponency is softwired, like a winner-take-all network, with interactions that are disabled under the same conditions that disable perceptual binding. In addition to disabling a perceptual opponency, it is also possible to find hidden opponencies in spatial vision. Dr. Billock presented a methodology to bias and stabilize flicker-induced hallucinations that are typically chaotic. This suggests a geometric opponency: concentric circular geometries bias photopic hallucinations to illusory fan-shapes and vice versa; and similarly for clockwise and counter-clockwise spirals. Elementary hallucinations arise from familiar mechanisms stimulated in unusual ways.


Red/Green & Blue/Yellow wavelength opponency (Jameson & Hurvich, 1955) mapped onto color appearance

FLASH TALKS: Sensory prediction in the natural world

Stephanie Palmer (University of Chicago)

Dr. Palmer's lab is interested in understanding how neural populations in the brain make predictions in the extrinsic world. This is carried out by studying the optimal population code needed for the task of predicting the future of a given stimulus by the brain. Dr. Palmer described, in particular, a problem of population code in retinal ganglion cells which entailed looking for signatures of coding the future stimulus. Dr. Palmer described an experiment in which a horizontal jittering bar is presented as a visual stimulus, the recorded data is analyzed using information theory, and a correlation structure for optimality of coding is constructed. She then presented work involving more naturalistic stimuli, for instance, fish motion, insect motion, motion of water, etc., and discussed their use as stimuli to understand how the brain solves the prediction problems.

WEDNESDAY, May 8, 2013

Neuronal circuit dynamics in the mouse parietal cortex during virtual navigation

Christopher Harvey (Harvard Medical School)

Dr. Harvey's talk discussed the problem of how neural circuits underlie decision-making. As a model system, he focused on the task of navigation in mice. There are many processing steps involved in navigation. The subject has to take sensory cues and self-information cues, combine them with location information and memory, plan the movement, and execute the movement. The posterior parietal cortex (PPC) has an important role in navigation and in many cognitive behaviors; however, the neuronal circuit dynamics underlying PPC function are not well understood.

Dr. Harvey's group studied circuit activity dynamics in the PPC of mice during navigation-based choice tasks, using a combination of a virtual reality system and two-photon microscopy. The mice ran in a virtual world and had to recall visual cues in order to determine which direction to turn. While the mice were performing this behavioral task, neurons in the PPC were recorded. These methods allowed the visualization of the fact that during working memory tasks the PPC activity dynamics are best characterized as choice-specific sequences of neuronal activation, rather than long-lived stable states, implemented using anatomically intermingled microcircuits. Using PCA, they were able to classify groups of these cells by their responses.

Less than meets the eye: shape encoding under partial occlusion in the primate brain

Anitha Pasupathy (University of Washington)

Dr. Pasupathy presented her group's work on the representation of shapes in the brain, particularly the representation of objects when they are partially occluded. Almost all objects in visual scenes are occluded, even though humans are often not conscious of this fact. Humans and other animals effortlessly recognize objects despite partial occlusion. When objects are occluded, they form accidental contours in images. The accidental contours do not give information about the shape of the occluded object.

The question is whether neurons encode information about real and accidental contours differently, and how missing contours are encoded. Dr. Pasupathy's group studied neurons in visual cortex V4, which are sensitive to shape and contour. Neurons in V4 are selective for certain shape features like convexity and angular position. They found that contextual stimuli can modulate and sometimes suppress the response of V4 neurons so that they are able to ignore false contours. They also found that certain neurons (in particular curvature sensitive neurons) modulate their firing rate in the presence of occluders, without external suppression.

Perceptual saliency by integrating olfactory context and feature

Jing Wang (University of California San Diego)

The odor landscape, like the visual world, is highly cluttered and noisy. Since more is known about visual percepts, previous studies on the visual system provide some clues for how the olfactory system works. Like the visual system, feature integration theory - the theory that the early visual system encodes low level features - applies to the olfactory system. From there, both top-down and bottom-up processing may occur.

Dr. Wang presented recent unpublished data from the fruit fly Drosophila to support the idea that the mushroom body, a higher olfactory center that is able to integrate top-down and bottom-up information, is important for perceptual saliency. His work showed that the mushroom body is required for olfactory learning. Food odor and conspecific social cues, represented by separate glomeruli in the antennal lobe, are integrated in the mushroom to enhance behavioral attraction to food. A hunger-dependent neuropeptide signal modulates neural activity in the mushroom body to control the intensity of foraging behavior in Drosophila. His group identified several key factors in this process, among them insulin and expression of MPY receptors. Through olfactory processing by glomeruli DM1 and DM2, Drosophila react to odors in highly context-specific manners depending on factors such as hunger state and mating state.

Words, metrics, and a thesaurus for a neural population code

Elad Schneidman (Weizmann Institute of Science)

Dr. Schneidman discussed the design principles of neural code. Some of the goals when studying this subject are identification of the vocabulary for the code, the rules for use of the code to convey information, and identification of synonyms for neural words. A first step in this study is to identify firing patterns in networks of neurons. Typically, in neuronal networks, pairwise correlations are weak. Yet, as Dr. Schneidman points out, weak pairwise correlations do not imply that the network as a whole is weakly correlated.

Pairwise maximum entropy models have been used successfully to describe correlations in neural networks, but they are missing some features. Many common patterns of neuronal firing are missing, and pairwise models are not sufficient for modeling spatial-temporal patterns. To overcome the deficiencies in pairwise models, Dr. Schneidman introduced the reliable interaction model, which is a higher order model than pairwise maximum entropy models. Reliable interaction models are beneficial for decoding and can be learned online and hierarchically. In this way, they may more-realistically mimic learning in the brain. Using this model, the code for large populations of neurons can be learned.

Motor Sculpting of Sensory Codes

Surya Ganguli (Stanford)

Dr. Ganguli discussed sensorimotor coding with respect to the learning of birdsongs. It is thought that in the bird song system, as well as many other systems of motor learning, a sensorimotor feedback loop is involved. Anatomically, there is evidence for such a system in songbirds, where nested sensorimotor loops connect the cochlea to motor pathways which generate song. A bird is able to hear its own song, and learning requires feedback from its own vocalizations.

Many species of birds have a sensory period where they are listening but not singing. In this period they form memories of their own father songs. One hypothesis for learning is that a bird minimizes the distance between its own auditory feedback and the father song, through a comparison circuit in the brain. This hypothesis is however undermined by the presence of one-shot learning, where a bird is able to learn a song without comparing it to its own song or any other songs.

Dr. Ganguli introduced a new paradigm for the learning of birdsong, where the bird learns a forward model that it can use to predict sensory feedback, and an inverse model where it can map song back into motor patterns. This model for learning has an anatomical basis and is able to explain latencies found in learning.

FLASH TALK: *Recurrent connectivity & single neuron dynamics in the generation of rhythms*

Tatjana Tchumatchenko (Columbia University)

In this talk, Dr. Tchumatchenko gave a brief overview of global oscillators in the brain. There are many different types of neurons involved in generating oscillations. Both excitatory and inhibitory neurons play a role in the generation of rhythms, and neurons tend to have their own frequency preferences. The question is how frequency preferences of individual neurons combine to produce a global oscillation frequency across a network.

Particular attention was given to the generation of gamma rhythms in networks. Dr. Tchumatchenko found that gamma rhythms could be generated via the strong coupling of inhibitory neurons through gap junctions. Her work concentrated on the resonance properties of such networks, which she analyzed using mean field theory of a noise driven recurrent network, where spiking was modeled using threshold crossing. She found that spiking rate decreases with adaptation.

FLASH TALK: *Mechanisms for higher-order correlations in neural circuits*

Andrea Barreiro (Southern Methodist University)

Dr. Barreiro's talk pertained to the modeling of the measured activity of neural circuits composed of many neurons. These recordings are typically performed over a large number of neurons, where one is sampling from a very high-dimensional space. The question is whether one can capture the behavior of the network that is due to higher-order correlations.

Dr. Barreiro studied this problem in the context of understanding the retinal ganglion (RG) circuit. Many cells in RG have higher order correlations, for example midget cells. These cells tend to have bimodal distributions for their synaptic currents - which is a feature that is not captured by pairwise interaction models. Dr. Barreiro introduced the dichotomized gaussian common input model, which overcomes the limitations of lower-order models.

The structure and function of correlated neural activity

Kresimir Josic (Mathematics University of Houston)

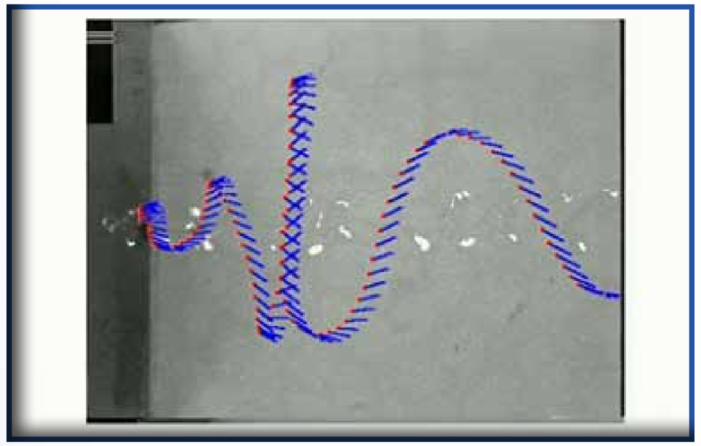
Due to the development of recording techniques that allow for the simultaneous recording from many cells, it is now possible to study and observe the joint activity of neuronal population during sensorimotor, and cognitive tasks. Dr. Josic discussed correlations in populations of neurons, where many people have used pairwise models that are found by measuring the pairwise firing correlations. Dr. Josic explained how the cross-correlation function could relate architecture to population activity.

Correlations play a role in information encoding. Dr. Josic discussed how correlations relate to encoding in the neurons of the Vertical System (VS) in the lobula plate of the fly, where 20 strongly-coupled non-spiking neurons encode for the azimuth of the axis of rotation of a fly in flight. Strong coupling decreases variances in cell responses, and Dr. Josic believes that this fact allows motor neurons to only sample output from a few cells, rather than from the entire population of cells.

Interactions of sensory structure and environment and locomotory context determine odor plume tracking behavior

Mark Willis (Case Western University)

Dr. Willis talked about how animals use odor for navigation. His talk focused on two different types of animals - the American cockroach, and the moth. The American cockroach needs to be able to find mates and food in the dark, and it is known to rely on odor cues. The question is whether the moth, which moves about in possibly turbulent air, relies on the same navigational algorithms. To test this question, Dr. Willis' group put a moth into a cockroach like environment. His group found that flight patterns for moths are modulated by where they are with respect to odor plumes. This result is intriguing, since it implies that moths are able to solve an inverse source problem even in the presence of wind and turbulence.



Neural population dynamics during sensory and memory processing

Remus Osan (Georgia State University)

New experimental techniques have allowed researchers to explore the dynamics of larger and larger ensembles of neurons. This development has led to an increase in the size and complexity of neural data that is available. In accordance with this shift, the data analysis techniques have been shifting their focus from single-units to neural populations. Dr. Osan's group uses projection methods like Principal Component Analysis (PCA) and Multiple Discriminant Analysis (MDA) to facilitate the understanding and monitoring of the dynamics of neural populations recorded in the hippocampus and olfactory bulb.

Using PCA, Dr. Osan's group examined the representation of startle episodes, in order to differentiate between somato-sensory and memory components of the hippocampal representations. He also talked about how the dynamics of odor responses in the olfactory receptor neurons of awake rats are shaped by the temporal features of the active odor sniffing. The analyses that he presented indicate that the dynamics of neural representations depend non-linearly on odor identity and concentration, as well as breathing rhythms of the rats.

THURSDAY, May 9, 2013

Perception of sniff phase in mouse olfaction

Dima Rinberg (Janelia Farm Research Campus)

Dr. Rinberg discussed olfactory systems that encode odors by which neurons respond, and the time of response. In mammals, every sniff evokes a precise, odor-specific sequence of activity across olfactory neurons. Likewise, in a variety of neural systems, ranging from sensory periphery to cognitive centers, neuronal activity is timed relative to sampling behavior and/or internally generated oscillations. As in these neural systems, relative timing of activity may represent information in the olfactory system. However, there is no evidence that mammalian olfactory systems read such cues. To test whether mice perceive the timing of olfactory activation relative to the sniff cycle ('sniff phase'), optogenetics were used in gene-targeted mice to generate spatially constant, temporally controllable olfactory input.

Dr. Rinberg showed that mice could behaviorally report the sniff phase of optogenetically driven activation of olfactory sensory neurons. Furthermore, mice can discriminate between light-evoked inputs that are shifted in the sniff cycle by as little as 10 milliseconds, which is similar to the temporal precision of olfactory bulb odor responses. Electrophysiological recordings in the olfactory bulb of awake mice show that individual cells encode the timing of photo activation in relation to the sniff in both the timing and the amplitude of their responses. The work provides evidence that the mammalian olfactory system can read temporal patterns, and suggests that timing of activity relative to sampling behavior is a potent cue that may enable accurate olfactory percepts to form quickly.

Neuronal substrates of Temporal Prediction in Active Sensing

Charles Schroeder (Columbia University)

There are external rhythms and temporal predictability in many physical processes, for instance, biological motion. Additionally there are internal rhythms, in particular, neuroelectric oscillations, that reflect rhythmic shifting of neuronal ensembles between high and low excitability states. Dr. Schroeder presented the use of internal rhythms in active sensing using examples such as hand stimulation, whisking, sniffing, and saccadic sampling (visual sniffing patterns). He provided an example of internal rhythm inherent in natural active vision. He points out that there are two mechanisms in active vision - one that drives activity and another one that controls it. Dr. Schroeder presented ECoG data from humans (a network implementation of the prediction) obtained from patients who are suffering from epilepsy and are being evaluated for surgery. Two main responses are observed in the data given visual and auditory stimuli, namely, perfect phase oppositions between stimuli and responses, and in phase sensory evoked responses.

Dr. Schroeder further discussed the phenomenon of rhythm and said that not everything is rhythmic. In fact, activity switches between a rhythmic predictable mode and a random unpredictable mode. Dr. Schroeder also briefly discussed attentional selection in the "cocktail party" problem. Dr. Schroeder finished his talk by sharing a few open questions related to this problem; in particular, understanding disorders of brain dynamics and sensory/neuropsychiatric disorders like autism and schizophrenia.

The neural encoding of vestibular information during natural self-motion

Kathleen Cullen (McGill University)

The vestibular system is vital for maintaining an accurate representation of our motion and orientation as we move through the world. During movement, signals from the vestibular sensors encode head direction and velocity, and are relayed through the vestibular system to premotor areas and higher-order centers. The vestibular system is involved in translating reflexes to perception and voluntary behavior. The goal of many researchers in neuroscience has been to understand how the sensory pathways transfer information under normal circumstances, particularly the role of noise. The vestibular system is a good model system for studying such problems.

Dr. Cullen's lab has challenged the traditional notion that the vestibular system uses a linear rate code to transmit information. Instead, nonlinear integration of afferent input extends the coding range of central vestibular neurons and enables them to better extract the high frequency features of self-motion when embedded with low frequency motion during natural movements. Central neurons display a static nonlinear relationship between their output firing rate and afferent input, due to having a high-pass response. Not only is vestibular (self-motion) processing inherently multimodal, but the manner in which multiple inputs are combined is adjusted to meet the needs of the current behavioral goal. As Dr. Cullen demonstrated, this fact is apparent in the response of neurons involved in controlling saccadic eye movement.

Tactile object representation and the mechanisms of selective attention

Steven Hsiao (Neuroscience, Johns Hopkins University)

Dr. Hsiao discussed the mechanisms of information coding for attention in tactile object recognition, which depends on the integration of cutaneous inputs from the skin with proprioceptive inputs from the skin and muscles, and which depends on the attentional state of the animal. Cutaneous inputs provide information about the spatial form, texture, and motion of stimulus patterns on the skin, while proprioceptive inputs provide information about where these inputs are located in three-dimensional space and whether the hand or object is moving. Object recognition is then based on matching the previously stored representations of objects with the inputs from each of the contact points where the skin touches the object.

Neurons in the tactile receptive field are sensitive to different types of hand orientations or touch configurations. Some neurons are tuned to curvature (both in Area 2 and S2), and the responses to curvature in these regions occur almost simultaneously. Some neurons are sensitive for finger distances, which is one of the mechanisms behind perception of three-dimensional objects through touch. Dr. Hsiao also discussed the mechanisms of feature selection by attention. When an animal attends to a specific feature of a stimulus, like the orientation of a bar, neurons with similar tuning functions show increased firing rates and there is an increase in the degree of spike synchrony between neurons.

FRIDAY, May 10, 2013

Coordination of visual processing in cortex by network activity during natural viewing

Daniel Butts (Biology, University of Maryland)

Dr. Butts presented the hypothesis that the purpose of the primary visual cortex (V1) is not just to be "feature selective", but also to integrate feature selectivity with network influences. In addition to visual information from the thalamus, neurons in V1 receive inputs from other V1 neurons, as well as from higher cortical areas. This "non-classical" input to V1 neurons, which can be inferred in part from the local field potential, can modulate the "classical" feed-forward responses of V1 neurons to visual stimuli. Dr. Butts characterized this modulation in a variety of stimulus contexts using multielectrode recordings in awake primates. Because this network activity is by definition shared, it can serve to coordinate single neuron responses across a given region of cortex. Such network modulation plays a clear role during natural viewing, where saccadic eye movements result in stereotyped network activity. Thus these network influences to V1 neuron activity, which likely represent both coordinated processing within V1 and top-down influences, play a fundamental role in natural visual processing.

State dependence of noise correlations in monkey V1

Andreas Tolias (Neuroscience, Baylor College of Medicine)

In neuronal recordings, responses to the same stimulus are variable trial-to-trial. Dr. Tolias discussed correlated variability (noise correlations) in monkey V1. In awake monkeys, noise correlations are on average extremely low and depend on difference in preferred orientations. However, they do not depend on the type of stimulus. Under anesthesia, neural activity is dominated by state fluctuations and there are higher noise correlations. A single latent variable model can account for these state fluctuations and explain up to 40% of the variance. Dr. Tolias concluded by presenting a dense 3D mapping of population activity structure that can be used to assess effective connectivity.

Mechanisms and functions of human neocortical rhythms in sensory perception

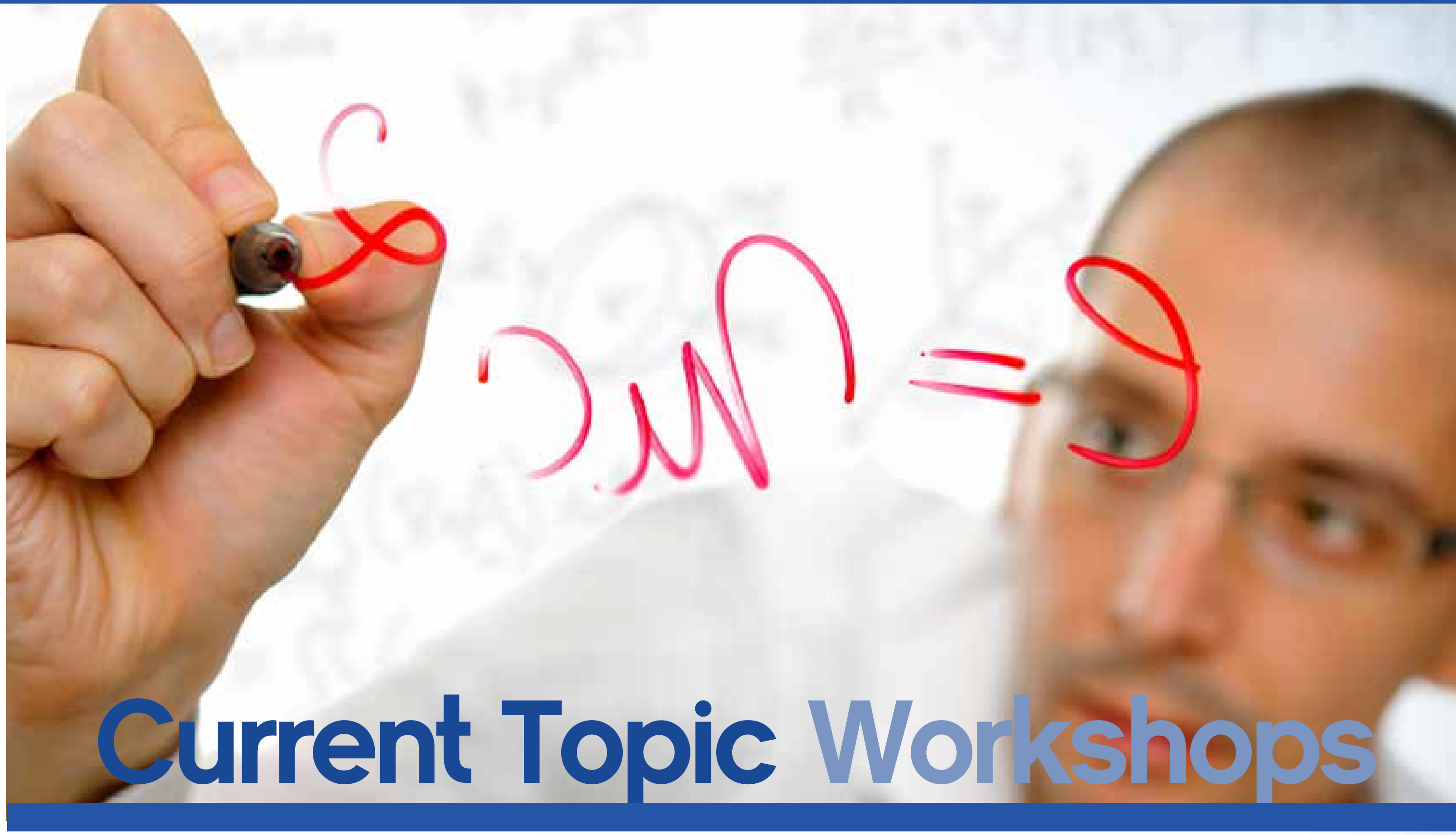
Stephanie Jones (Brown University)

Dr. Jones is interested in how non-invasively measured neocortical dynamics can mediate sensory perception in humans. Low-frequency neocortical rhythms are among the most prominent activity measured in human brain imaging signals such as electro- and magneto-encephalography (EEG/MEG). Elucidating the role that these dynamics play in perception, cognition, and action is a key challenge of modern neuroscience. Dr. Jones has recently combined human brain imaging, computational neural modeling, and electrophysiological recordings in rodents to explore the functional relevance and mechanistic underpinnings of rhythms in the primary somatosensory cortex (SI), containing Alpha (7-14Hz) and Beta (15-29Hz) components. In her talk, she reviewed findings showing that this rhythm impacts tactile detection, changes with healthy aging and practice, and is modulated with attention. Constrained by the human imaging data, her biophysically principled computational modeling work has led to a novel prediction on the origin of this rhythm: the rhythm emerges from the combination of two stochastic ~10 Hz thalamic drives to the granular/infragranular and supragranular cortical layers. Relative Alpha/Beta expression depends on the strength and delay between the thalamic drives. This model is able to accurately reproduce numerous key features of the human rhythm and proposes a specific mechanistic link between the Beta component of the rhythm and sensory perception. Further, initial electrophysiological recordings in rodents support these hypotheses and suggest a role for non-lemniscal pallidal thalamus in coordinating Beta rhythmicity, with relevance to understanding disrupt Beta in Parkinson's Disease.

Bijective maps between acoustic and cortical spaces

Alex Reyes (Center of Neural Science, New York University)

Dr. Reyes presented an axiomatic approach to the tonographic representation of sensory input, with the hope of being able to rule out models that are conceptually wrong. The tonotopic organization of neurons in auditory cortex is postulated to be the substrate for representing acoustic information. In this scheme, the characteristic frequency (CF) of each neuron changes systematically along one cortical axis so that the location of the active neuron indicates the frequency of the tone. However, there is accumulating evidence from experiments and simulations that are inconsistent with the main predictions of this simple place code. In vivo recordings demonstrate the gradient in CF is weak such that adjacent neurons may have very different preferred frequencies. Moreover, even a moderate intensity tone is likely to activate a large number of neurons, making it difficult to determine frequency using a place code. Dr. Reyes used mathematical analyses to derive bijective (and hence invertible) maps from the acoustic space to cortical space. He concluded that frequency is best represented in cortical space with groups of, rather than individual, neurons. Dr. Reyes further showed that classical columnar organization is generally not ideal for continuous maps from sensory space to cortex. This assumes that the nervous system tends to produce one-to-many mappings, that there are enough neurons to approximate continuous mappings, and that groups of neurons are close enough to each other to be approximated by intervals.



Current Topic Workshops

MBI Biosciences
Problem-Solving Workshop
July 16-20, 2012

Organizers: Jonathan Bell, Chris Breward, Helen Byrne, Huaxiong Huang, Donald Schwendeman and Siv Sivaloganathan

PSW@MBI was a week-long workshop where participating mathematical modelers tackled questions proposed by life science researchers. Similar workshops have provided fresh perspectives and new ideas to proposed questions and established new interdisciplinary collaborations between theoreticians and life scientists. The workshop gave the opportunity to practitioners and researchers in medicine and the biosciences who present problems to exploit the expertise of applied mathematical faculty, postdoctoral fellows, and graduate students in working toward solutions to their problems. Workshop Format Participants included between 50-60 applied mathematicians, statisticians and domain experts. Problems presented on the first day and participants divided into teams of 6-10 self-selected people each. The teams collaborated and brain-stormed on their problems, and presented their solution on the final day of the workshop. Problem presenters have domain knowledge, which was needed throughout the workshop and was available during the workshop to provide background information. Deliverables the teams prepared reports for the problem sponsors shortly after the end of the workshop.

2012 Workshop

for young researchers in mathematical biology

Organizers: MBI Postdocs

Report by: Franziska Hinkelmann and Rachel Leander

The workshop is intended to broaden the scientific perspective of young researchers (primarily junior faculty, postdocs, and senior graduate students) in mathematical biology and to encourage interactions with other scientists.

Workshop activities include plenary talks and poster sessions, as well as group discussions on issues relevant to mathematical biologists. Several abstracts will be chosen for short talks as well as to be presented as a poster.

MONDAY, August 27, 2012

Detectability in ecological systems: three nonstandard examples

Ben Bolker (McMaster University)

In the first talk of the workshop, Prof. Bolker introduced a variety of new methods in ecological statistics aim to estimate population densities, and other characteristics, when organisms sometimes go undetected. He presented three applications that address the same general question but come from an unusual perspective, emphasizing the fun and utility of applying basic probability theory to sampling in ecological systems. For example, in his research on mosquito population, he observes birds and can infer from bird blood samples, by how many different mosquitos they have been bitten.

A stage-structured model of honey bee colony population dynamics assessing impacts of pesticides and other stressors

Wanyi Zhu (Pennsylvania State University)

Dr. Zhu studies honey bee population dynamics. A healthy honey bee colony is a population of closely interacting individuals that form a highly complex society. As an aid to testing hypotheses for the causes of recent colony failure and to providing suggestions for management actions to promote recovery of honey bee population, she developed a worker-based, stage-structured model of honey bee population dynamics. Numerical simulation of a healthy colony exhibited seasonal patterns similar to published field data. Sensitivity analysis suggested critical thresholds of stage-based survival rates beneath which colony size decrease gradually. Also, if the social factor (brood care, transition rate and foraging), particularly precocious foraging, is interrupted beyond the critical threshold a rapid population decline is predicted and colony failure is inevitable. Her model suggested that a disrupted colony by varying social regulation factor in the colony might be able to produce sudden collapse symptoms similar to colony collapse disorder.

Enhanced surveillance on food-borne disease outbreaks: dynamics of cross-contamination via wash procedures

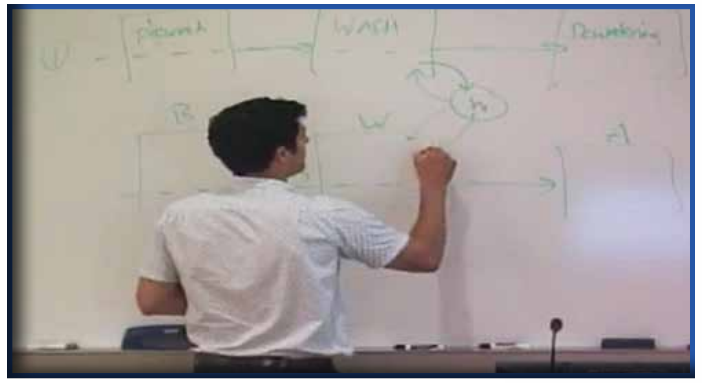
Daniel Munther (York Univeristy)

Dr. Munther developed and analyzed a three stage model of the processing/sanitization juncture in the fresh produce supply chain to better understand the geographic and temporal spread of food- borne diseases associated with fresh produce, which is crucial for informing adequate surveillance and control. The key feature of his model is its ability to describe basic dynamics of cross-contamination during wash procedures. He formulates general conditions under which the model predicts the potential for misdiagnosis of primary source contamination. He also discussed the importance of the model with regards to traceback studies, describing its ability to narrow parameter choices for detailed stochastic simulations as well as its "connect-ability" to models that include shipping and network dynamics. Finally, the model is useful for comparing various commercial biocidal wash procedures and is easily adaptable to include parameters such as temperature, turbidity, organic load, pH, etc.

Space competition therapy: using neutrophils to combat cancer

Antonio Bru (Universidad Complutense de Madrid)

Professor Bru proposed in his talk that ensuring the massive recruitment of neutrophils to tumor borders should successfully prevent tumor growth and lead to tumor involution. In his talk, he explained a series of theoretical, experimental and clinical works that support this hypothesis. The main mechanism of tumor growth is the surface diffusion of cells at tumor border. Only cells that can divide are those at the border, where there is still space available. Cells at the border continue to grow, and those within the tumor mass become quiescent and eventually necrotic. The importance of new cell movements lies in the fact that tumor growth must be conceived as a competition for space between the tumor and the host, and not for nutrients or other factors. An unexpected emergent behavior of neutrophils arising from tumor growth dynamics is its capability to compete for space with tumor cells. Then, the immune innate response of the organism plays the key role in the fight of tumors. If the organism is able to send enough neutrophils, the tumor will regress and necrose.



Comparing the Emergence of Chikungunya to Other Mosquito-borne Diseases

Carrie Manore (Tulane University)

In the next talk, Dr. Manore from Tulane University discussed her work on Chikungunya. Chikungunya is a re-emerging mosquito-borne infectious disease that is spreading rapidly across Africa and Asia with new epidemics occurring in Europe and some Indian Ocean Islands. Two common mosquito species, Aedes aegypti and Aedes albopictus, which occur all over the world, are competent vectors for chikungunya virus. She designed and analyzed an ordinary differential equation model with mosquito dynamics for the spread of chikungunya. The parameters of the model were found using current literature, existing data, and lab experiments. In her work, she also compared the spread of chikungunya to that of malaria. She was able to show that malaria and chikungunya are sensitive to different parameters in the model, indicating that standard mitigation strategies for mosquito-borne diseases such as malaria may not work as well with chikungunya. By applying sensitivity analysis she was able to hypothesize where future research and mitigation efforts can focus for greatest effect in controlling the spread of chikungunya.

Multiple time scales and mixed mode oscillations in intracellular calcium dynamics

Emily Harvey (Montana State University)

Dr. Harvey is interested in the oscillations seen in free intracellular calcium concentration, which are known to act as intracellular messages, relaying information within cells to regulate cell activity. Calcium plays a crucial role in a huge range of cellular processes including muscle contraction, secretion, neuronal firing and many other functions. A key feature of intracellular calcium dynamics is that some physiological processes occur much faster than others. This leads to models with variables evolving on very different time scales. She used geometric singular perturbation techniques (GSPT), which allowed her to exploit this separation in time scales to analyze the models. She used these techniques to explain the observed dynamics, including oscillatory patterns known as mixed-mode oscillations and complicated bifurcation structures.

TUESDAY, August 28, 2013

Illustrative examples of building collaborations between mathematics and biology/medicine

Greg Forest (University of North Carolina, Chapel Hill)

Dr. Forest began by explaining how he maintains healthy collaborations with biological and medical scientists. First, the science must be compelling and have the potential to generate new research directions. Second, the scientist must recognize that they need a mathematician's help in order to understand the system under study. Third, the mathematician must have a thorough understanding of the biology. And finally, biological solutions must come before mathematics. That is, the mathematician should focus on solving the biological problem and let the mathematics happen. Dr. Forest went on to describe several interdisciplinary projects that he is has contributed to, including the virtual lung project.

The virtual lung project is about mucus. Mucus is the primary defense mechanism of the lung. In order to maintain a sterile environment, foreign particles are trapped in mucus and then transported out of the lung before they have time to diffuse through the mucus layer. Dr. Forest's collaborators at the Cystic Fibrosis Center were able to observe how particles diffuse within the lung but they needed a mathematicians help to interpret their data. In this project, Dr. Forest's group uses mathematics to predict passage time distributions for various particles. In particular, they analyze experimental data on the diffusive paths of particles in order to identify a best fit model of the underlying diffusive process and then derive the distribution of first passage times through the mucus from the best fit model. Their analysis revealed that, unless the particles are extremely small, they do not experience simple diffusion within the lung's mucus. Dr. Forest's group also works to understand how mucus flows within the lung, with the goal of identifying physical and pharmaceutical therapies that optimize flow.

Evaluating the efficacy of drug treatment of influenza

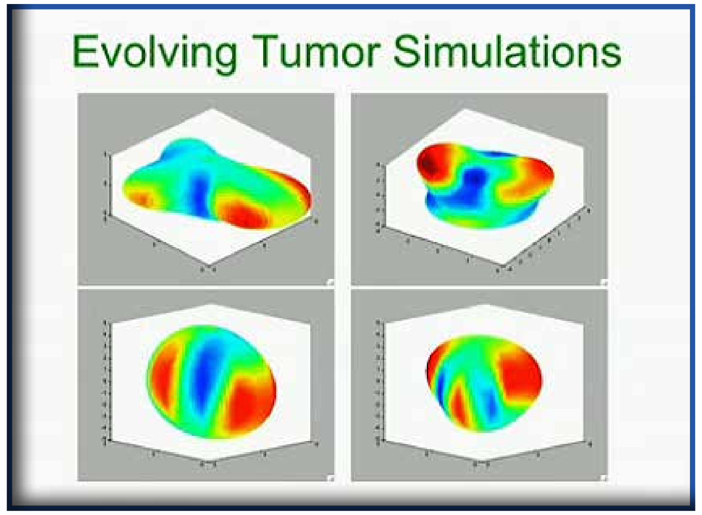
Hana Dobrovolny (Texas Christian University)

Dr. Dobrovolny began by reminding the audience that the influenza virus sickens millions of people every year. She went on to describe the structure of the flu virus, the basic mechanisms through which the virus infects cells, and actions of antiviral drugs. In particular, she explained that existing antiviral drugs include the adamantanes, which prevent viral RNA from escaping the viral capsid, and the neuraminidase inhibitors which prevent the virus from exiting infected cells. Patients are generally treated with a combination of these two drugs. Dr. Dobrovolny's research is aimed at evaluating and optimizing antiviral therapy. She works with a mathematical model that follows the concentration of target, eclipsed, infectious, and dead cells. The effectiveness of monotherapy is characterized by a drug's IC50 (the drug concentration that achieves half the maximal effect) and its Emax (the maximum possible effect that the drug can have). Drug resistance is generally defined by an increase in the IC50 of a drug. Dr. Dobrovolny explained that a reduction in a drug's IC50 is, in some cases, coupled with an increased Emax. Since patients are generally treated with a dose hundreds of times greater than a drug's IC50, some drug resistant strains may, in fact, be more susceptible to drug therapy. In light of these findings, Dr. Dobrovolny's group went on to evaluate the methodologies through which scientists assess the effectiveness of combination therapy. Currently, combination therapy is assessed for synergy or antogony. Dr. Dobrovolny's research group showed, however, that synergy does not determine the optimal drug combination. Furthermore, although experimentalists generally measure synergy at a single time point; it is, in fact, time dependent. Instead of measuring synergy, Dr. Dobrovolny suggests scientists measure the viral peak and the symptomatic duration. Further treatment refinement can be achieved by performing cost benefit analysis.

Modeling Cancer Immunotherapy

Lisette de Pillis (Harvey Mudd College)

Dr. de Pillis presented an overview of her research on tumor immune dynamics. She began by explaining that her research in this area is directed by oncologists and immunologists working at the center for mathematics of medicine (MoM) in Los Angeles. One of Dr. de Pillis's early modeling efforts was aimed at understanding asynchronous responses to chemotherapy. Her research showed that competition for resources is sufficient to explain asynchronous responses to chemotherapy. In particular, explicit delays in her model's differential equations are not necessary to explain delayed responses to chemotherapy. In addition, Dr. de Pillis's model predicted that chemotherapy could drive the system to the basin of attraction for the tumor free equilibrium. Dr. de Pillis has also used optimal control to identify more effective chemotherapy schedules. Her research suggests that scheduling can significantly alter treatment outcomes. Dr. de Pillis has also modeled the role that T cells and natural killer cells have in combatting cancer. Her models have been successful at reproducing experimental data on the response of cancer to immunotherapy and mixed therapy. As cancer is not a single disease but many diseases, Dr. de Pillis also builds models that are specific to specific cancers including melanoma, renal cell carcinoma and colorectal cancer. Most recently, Dr. de Pillis has begun to explore the spatial growth of tumors.



Applying Mathematical for Solid Tumor Growth in the Pharmaceutical Industry

Andrew Stein (Novartis)

Dr. Stein began by presenting a brief overview of the Modeling and Simulation Department at Novartis. The department consists of four groups: biological modelers, pharmacological modelers, statistical modelers, and programmers. The department's mission is to quantitatively integrate data across relevant studies to improve understanding and make predictions in order to inform decisions about drug design, selection, and dosage. As an industrial employee Dr. Stein enjoys working with a diverse group of scientists, access to high quality data, and opportunities to expand his skill set. He also recognizes certain drawbacks of industry employment: research must have practical value, publications must be approved by others, and there is no tenure.

Dr. Stein went on to describe some of the challenges of drug development. First, despite significant scientific advances, the cost of developing a drug doubles every eight years. Why: A new drug must be better than current drugs on the market. Easy to develop drugs have already been identified. Safety regulations are becoming increasingly stringent so that it is more difficult to meet approval criterion. And finally, early compound selection is, perhaps less effective and efficient than in the past. In particular, early compound selection is now based on optimizing binding affinity whereas it was previously based on animal models. Binding affinity may not be a good measure of a compound's therapeutic potential since absorption, distribution, metabolism, excretion, and toxicology are arguably of equal importance. Second, despite recent advances in cancer treatment the prognosis for most cancer patients remains grim. Dr. Stein explained that cancer is difficult to treat, in part, because it is heterogeneous. In fact, the genetic mutations that lead to a specific type of cancer vary not only between individuals, but within a single tumor. It is also difficult to measure cancer drug efficacy. Current measures include overall survival, quality of life, and, increasingly, progression free survival. Dr. Stein spent some time discussing progression free survival, which requires that the cancer be imaged and measured. This presents quantitative challenges that can be addressed through mathematical models. In particular, models can be used to relate drug dosage to tumor response. Dr. Stein described current efforts to quantify tumor growth, model individual tumor dynamics, determine the best drug dosage, model a population of patients, model heterogeneity in a population of tumors, and inform decisions to develop compounds for the market.

WEDNESDAY, August 29, 2013

Quantitative Experiment Design for Highly Uncertain Cellular Systems

Ann Rundell (Purdue University)

Professor Rundell's research goal is to create quantitative tools that support tissue engineering efforts to predictably direct the differentiation, integration, and organization of living cells. To support these efforts, her research addresses model-based optimal experiment design and model-based design of control strategies. Experiments to help understand, resolve, and direct cellular processes are expensive. It is therefore vital to design experiments that will be nearly optimal among available experiments in terms of the information they reveal and their likelihood of success. Her research group's approaches employ sparse grid methods to enable systematic and computationally efficient exploration over uncertain model parameter spaces with multiple potential model structures. She works in concert with collaborators to evaluate, refine, and extend her model-based experiment design and model-based control theory based approaches. In her talk, Professor Rundell introduced some of the challenges (and humorous incidents) in establishing a productive and rewarding collaboration between mathematicians, engineers, and life scientists.

Need for Computational Science & Mathematics to tackle Biological Problems in the Parallel Computing Era

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

Dr. Jordan from IBM Research gave an overview of High Performance Computing (HPC) directions and commented on the ever-increasing amounts of data driving some of the computing directions. Computation is playing an ever increasing and vital role in the biological and healthcare sciences. In many instances, scientists are developing mathematical models and using high performance computing to carry out analysis and simulations that provide insight into biological systems. The complexity of these models often demands increasing compute power and sophisticated mathematics for the solution. This is coupled with increasing amounts of data that must be analyzed. HPC is a tool frequently used to understand these complex problems involving large amounts of data in the life sciences. Through several very illustrative examples, he pointed out some of the computational trends that he believes hold opportunity for coupling high performance computing and mathematics to tackle life science problems.

Do humans optimally account for visual structure when making decisions?

Manisha Bhardwaj (University of Houston)

Dr. Manisha Bhardwaj is studying whether humans are capable of learning the underlying correlation structure in the given visual scenes. Consider the tasks of locating a friend in a crowd or finding a particular piece of paper in a pile. In these, and many other situations we need to find a target among distractors. The difficulty of such tasks depends on a number of factors. For instance, the task generally becomes more difficult as the number of distractors increases - typically it is harder to find a friend in large crowd. However, a friend wearing a red shirt will pop out in a crowd of people wearing blue. Hence the homogeneity among distractors is also important. In her research, she studies to what extent human observers take into account the homogeneity among distractors to detect a target. The subjects report whether a target stimulus (a vertically oriented ellipsoid) is present in a field of distractors (ellipsoids with non-vertical orientation). She demonstrated the study to the audience. The variability in the orientation of distractors is correlated. In the extreme cases, the orientations of all distractors are equal (perfectly correlated), or chosen independently.

THURSDAY, August 30, 2013

Statistical Mechanical Approaches to Biology and Medicine

Tom Chou (University of California, Los Angeles)

Dr. Chou presented two problems of theoretical biophysics: modeling histone coverage on DNA and modeling protein production-mRNA translation. Histones are proteins that regulate transcription by binding to DNA. Dr. Chou described a model of histone-DNA binding and explained how the model can be used to predict the mean coverage of DNA by histones at equilibrium. He went on to discuss protein production. Protein production is accomplished by molecular motors called ribosomes that bind to mRNA and assemble chains of amino acids. Dr. Chou explained that the process of protein production can be modeled as a totally asymmetric exclusion process, in which particles bind to and transverse a one dimensional lattice according to an exponentially distributed hopping process conditioned on the occupation of the next site. If the hopping rate is homogeneous along the lattice, it can be shown that such a process exhibits a steady state current. Furthermore, the steady state current can be solved for exactly. For protein assembly, however, the hopping rates are inhomogeneous because certain amino acids are rare. Dr. Chou explained how he characterized the steady state current for the inhomogeneous problem by using a finite segment mean field approximation. Using these methods Dr. Chou showed that just a small number of slow codons (3-6%) can significantly and maximally slow the rate of protein translation.

Effect of immunological defense against vector on disease transmission in Bird malaria

Suma Ghosh (University of Utah, Salt Lake City)

Dr. Ghosh presented her research which explores how immunological defenses against malaria vectors affect malaria transmission in bird communities. She began by explaining that flies are a vector of the malaria parasite. In particular, after feeding on the blood of an infected bird a fly may transmit malaria to healthy birds. Birds have developed two forms of defense against flies; behavioral defenses, such as preening, and immunological defenses, such as the inflammatory response. By restricting access to blood and damaging fly tissue, the inflammatory response reduces the size and quality of the blood meal. In addition, the inflammatory response may promote grooming behavior, and decrease the time a fly spends feeding on an individual bird. Dr. Ghosh presented a mathematical model that she uses to explore how immunological defenses affect the prevalence of malaria and the size of the fly population. Within the model immunological defenses affect the rate of fly departure, and fly fitness. Model simulations show that there is a nonlinear relation between disease prevalence and the fly departure rate, with disease prevalence first increasing and then decreasing as the departure rate grows. The fact that disease prevalence decreases as the departure rate grows may be explained by a concomitant decrease in the size of the fly population. Interestingly, this nonlinearity depends on the number of flies that feed on each bird.

A data-driven method for detecting coupling between dynamic biological rhythms

Benjamin Pittman-Poletta (Harvard)

Dr. Pittman-Polletta began by explaining that neurophysiological systems consist of multiple complex control systems that interact through nonlinear feedback loops. The data that we collect from these systems exhibit long range correlations, scale invariance, and rhythmic components at multiple frequencies. Rhythmic components represent underlying physiological processes. For example, QRS waves in heart rate data represent the contraction of ventricles. Rhythms in data may be coupled. In particular, neurophysiological data may exhibit phase-amplitude coupling in which the amplitude of a high frequency component changes with the phase of a low frequency component. In EEG data the high frequency rhythms are thought to represent local interactions between neurons while the low frequency rhythms are thought to represent integrative processing of large-scale neuronal assemblies. Dr. Pittman-Polletta examines neurophysiological data for phase-amplitude coupling with the goal of identifying feedback loops that control the underlying neurophysiological system. He discussed a method termed empirical mode decomposition, through which he extracts phase-amplitude couplings from noisy, irregular data.

MBI 10th Anniversary

Math Biology: Looking at the Future September 19-21, 2012

Report by: Hye-Won Kang, David Koslicki, and Jincheol Park

MBI's 10th Anniversary Meeting featured talks about areas in which exciting progress has been made in recent years and in which future advances can be expected.

WEDNESDAY, September 19, 2012

Life Redesigned: The Emergence of Synthetic Biology

Jim Collins (Howard Hughes Medical Institute; Dept. of Biomedical Engineering and Center for BioDynamics, Boston University; Wyss Institute for Biologically Inspired Engineering, Harvard University)

Dr. Collins talked about recent efforts to model and create synthetic gene networks and programmable cells after briefly defining what synthetic biology is and describing early history of it. A variety of re-engineered organisms were presented at the talk: schematic design of genetic toggle switch, whole-cell biosensors, RNA-switch, genetic switchboards for dynamic tuning cellular metabolism, programmable kill switch for microbes, and gene circuit blueprint. He finally discussed a variety of synthetic biology applications in biotechnology and biomedicine. Application includes drug-target identification, design of biofilm matrix, and microbial warfare.

The Missing Step: Statistical Inference from Big Data

(Nicholas P. Jewell) Biostatistics and Statistics, UC Berkeley

Dr. Jewell talked about challenges in the current age requiring of revolution in reliable inference. The features of data generated today can be characterized by very high number of observations with high number of dimensions without standard format. In addition, the questions today's science tries to answer to are not standard. In case study, he demonstrated how easily traditional inferential approach can break down under the presence of data of high volume. As examples of adjustment technology, super learner and targeted maximum likelihood were discussed. Ongoing debate between model-free and model approach was also covered in the talk and was demonstrated in case study that model free approach – K-means clustering - was not enough in detecting informative patterns.

Evolution of eusociality

Martin Nowak (Program for Evolutionary Dynamics, Harvard University)

Dr. Nowak defined that eusociality is an advanced form of social organization, where some individuals reduce their reproductive potential to raise the offspring of others. A simple model described by linear selection equations was presented for the origin of eusociality. He then compared eusociality strategy with solitary one in which all offspring leave to reproduce. From investigating the model, it was identified that expected life times of queen and reproductive rate of queen can contribute to selection of strategies. Finally, discussing limitations of inclusive fitness theory that it is complicated and practiced mistakenly, he argued that the simple model makes testable predictions without evoking inclusive fitness theory.

THURSDAY, September 20, 2012

The mathematics of the unconscious brain under general anesthesia

Emery Brown (Brain and Cognitive Science, MIT-Harvard)

Dr. Brown talked about the state of general anesthesia induced by drug (Propofol), whose mechanism is rarely known. Using three experimental paradigms, fMRI/EEG recording, high-density EEG recording, and intracranial recording, general anesthesia-induced loss of consciousness in humans is studied. Using statistical and mathematical analysis, he offered and tested several hypothesis for general anesthesia. He investigated why and how Propofol makes humans unconscious. It makes brain stem stop breathing and lose muscle tone. By measuring and analyzing oscillations of the brain rhythms, he studied why the anesthesia happens. He concluded that actively inducing emergence from general anesthesia may be clinically feasible (it is possible that the rat responds to the stimulation during the injection of Propofol).

Brain rhythms in health and disease

Nancy Kopell (Mathematics, Boston University)

Dr. Kopell talked about how brain rhythms and cognition are correlated. She introduced what are brain rhythms and how they are measured. She showed three case studies involving rhythms in disease: beta buzz with anesthesia, beta rhythms in Parkinson's disease, and beta rhythms and selective attention. In the first case, she investigated why Propofol enhances beta rhythms. Using geometric singular perturbation theory, she concluded that changes in decay constant of inhibition can lead beta buzz. In the second case, increased beta oscillations are observed in Parkinson's disease. Using a biophysical model of striatum, she concluded that changes in interaction of inhibition and cholinergic modulation in striatum can lead to pathological beta rhythm in Parkinson's disease. In the third case, she talked about how beta rhythms, selective attention, and disease are related. These three case studies can show how experimental neuroscience and mathematics can interact.

Modelling invasive processes in biology

Philip Maini (Mathematics, University of Oxford)

Dr. Maini talked about collective movement of cells in tissue which may be vital for normal development. He showed three different models: a vertex-based model to describe cell motion in the early mouse embryo, an individual-based model for neural crest cell invasion, and a model for acid-mediated tumor invasion. In the first model, multi-cellular rosettes form during AVE migration. Using a vertex model, he concluded that rosettes are essential for ordered migration and not for successful AVE migration. In the second model, he investigated migration of the neural crest cell. For robust invasion, cell invasion with one cell type is not enough and both leaders and followers are required. He concluded that cells at the front must be different from cells at the back. In the third model, , low PH inducing tumor cell proliferation is described using a reaction-diffusion model of cancer invasion. The model can suggest possible therapeutic strategies for tumor control. In the three models, he would like to answer important biological issues.

The mathematics of biological regulatory networks

Reka Albert (Physics, Pennsylvania State University)

Dr. Albert talked about interaction between genes, proteins, and molecules using network representation. The goal of the study is to identify abnormal behavior from topological changes in the network. She showed three cases: abscisic acid induced closure of plant stomata and disruption, respiratory infection of mice by two bacteria, and survival of cytotoxic T cells in T-LGL leukemia. Three case are based on two approaches: intracellular network discovery and integration of different types of regulation, and connecting intra-cellular network structure, network dynamics and cellular behavior. By studying stability, oscillation, Boolean dynamics, sensitivity, perturbation of the network, malfunctions or abnormal behavior of the biological network can be detected and diagnosed.

FRIDAY, September 21, 2012

Birds, brains, and B-Cells: Statistical mechanics for real biological networks

William Bialek (Lewis-Sigler Institute for Integrative Genomics, Princeton University)

Dr. Bialek presented three examples of biological networks (flocks of birds, neural networks, and zebrafish antibodies) in which emergent phenomena can be described via statistical mechanics. Along the way, he reviewed the argument that the maximum entropy construction gives a way of going directly from real data to the aforementioned abstract statistical mechanics model. Dr. Bialek also described that all these systems sit close to critical manifolds in the space of all possible models. This surprising fact is indicative of a deeper underlying concept that is still poorly understood.

The human genome: 10 years later

Lior Pachter (Mathematics, Molecular and Cellular Biology, and Computer Science, UC Berkeley)

Dr. Pachter began by giving a birds-eye view of the historical development of sequencing technology, from the sequencing of the first bacterial genome, to the first human genome, to the first human population to be sequenced. After this overview, Dr. Pachter expounded upon the paradigm that DNA sequencing is being increasingly used as a proxy for measuring a diverse range of biological properties: RNA-Seq measuring levels of expression, SHAPE-Seq analyzing RNA secondary structure, and dozens of other such *-Seq technologies.

Lastly, Dr. Pachter made the point that genomics involves extremely complicated and poorly understood systems where any rule almost always has an exception. For example, the concepts of a "gene" and a "metabolic network" are much more complicated than previously imagined and their analysis requires new, first-principles mathematical approaches.

Dissimilarity distances between surfaces

Ingrid Daubechies (Mathematics, Duke University)

Dr. Daubechies described new distances between pairs of two-dimensional surfaces that incorporate both local and global information. These distances were developed to assist biological morphologists in comparing different phenotypical structures (here, teeth and bones of primates and humans). These polynomial-time algorithms allow this computational geometry method to be applied to large datasets of digitized surfaces. This approach allows one to circumvent the time-consuming and tedious manual method of comparing pairs of teeth and/or bones.

Challenges in mathematical ecology: scaling and collective phenomena

Simon Levin (Ecology and Evolutionary Biology, Princeton University)

Dr. Levin discussed how the principle challenges in mathematical ecology remain the same: understand the dynamics of populations and connections to the structure of ecological communities. However, the scale of integration and the scope for interdisciplinary work has dramatically increased in recent years. Dr. Levin gave a wide range of examples to support this viewpoint ranging from the microscopic level, to the level of flocks of birds and schools of fish, to collective decision-making in human populations and the stock-market. The point was made that mathematics stands to contribute to many open problems in this area since, at all levels of scale, conflict of purpose or fitness leads to game-theoretic problems in understanding how cooperation emerges in Nature.

Current Topic Workshop 1

Mathematical and computational challenges in cilia- and flagella-induced fluid dynamics

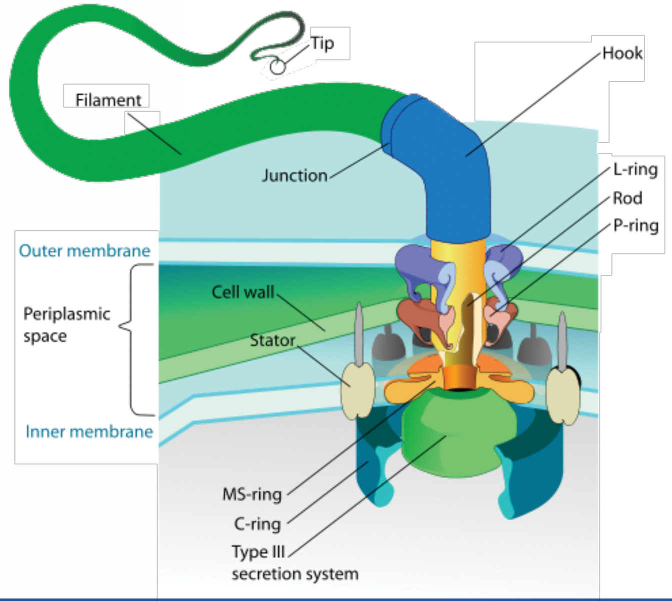
October 15-18, 2012

Organizers: Kenny Breuer, Greg Forest, Anita Layton, Matthias Salathe, and Peter Satir

Report by Organizing Committee

Cilia and flagella are ubiquitous in cell biology, acting either in a coordinated fashion to move surrounding fluid such as in lung airways, or as a propeller for cell locomotion such as on sperm or eukaryotic microorganisms, or as a sensory immotile but flexible antenna such as the primary cilia in essentially every cell in vertebrates and many vertebrate and invertebrate sense organs. The fluid dynamics induced by cilia and flagella, the mechanisms of coordination of motile cilia and flagella, and the fluid dynamic feedback to intra-ciliary and intra-flagellar transport and signaling, are essential to biology. The purpose of this workshop is to convene experts in biology, physics, mathematical modeling, and scientific computation to collectively assess progress and identify challenges to be undertaken in cilia- and flagella-induced fluid dynamics.

A list of outstanding challenges and computational strategies will be highlighted through lectures and subsequent discussions and open forums: (i) methods to compute and resolve the fluid-structure interaction of a cilium or flagellum, in either a viscous or viscoelastic fluid; (ii) stochastic (based on molecular motors) versus deterministic coarse-grained models of cilia and flagella beat cycles; (iii) the coordination mechanisms of cilia and flagella through the intervening fluid and/or the cells they emanate from; (iv) fluid mechanical sensing by the cilium or flagellum and the feedback response; (v) fundamental questions of optimization and efficiency (tuning of ciliary or flagellar motion or tuning of fluid properties to optimize motility or fluid transport; (vi) experimental and engineering approaches to support and challenge new modeling approaches. These challenges require assessment of current formulations and analysis of the governing equations for existing models, attention to accuracy, stiffness, time-stepping, adaptive mesh refinement, parallel implementation, and computing architectures.



> Cilia and flagella are ubiquitous in cell biology, acting in a coordinated fashion to move surrounding fluid such as in lung airways, as a propeller for cell locomotion such as sperm or eukaryotic microorganisms, and as an immotile but flexible antenna such as the primary sensory cilia in essentially every cell in vertebrates and many vertebrate and invertebrate sense organs. This workshop convened applied mathematicians, biologists, computational scientists, engineers and medical scientists to discuss current achievements and challenges in modeling ciliary and flagellar systems.

The opening morning session on "Ciliary patterning on the cell" was organized by Peter Satir, focusing on a number of different systems and conditions where cilia and fluid dynamics interact. One theme reiterated throughout the session and the rest of the meeting was structural specificity – this specificity determines the organization of the basal body with respect to the cell, and therefore the orientation of the effective stroke in motile cilia. Martina Brueckner pointed out that the intrinsic chirality of the axoneme combined with a directional stroke leads to directional fluid flow at the embryonic node, which is responsible for the correct left-right symmetry determination in the body. How the single motile cilia are coupled to give sufficiently strong fluid flow is an important issue that raises the possibility that ciliary mechanisms may have evolutionary fail-safe duplications. The question of ciliary coupling in the production of metachronism recurred throughout the meeting. Helle Paetorius pointed out that non-motile cilia can be bent by fluid flow, permitting measurement of stiffness parameters. Bending may be coupled to Ca^{2+} influx and subsequent ciliary signaling including ATP release that can influence response. Steve King introduced planaria as a model for mucociliary transport. The worm lays down a mucus layer on which its cilia beat to glide the organism forward. The ease of RNA knockout and molecular genetic tools with this organism open the possibility of using planaria as an assay to test how variable mucus composition affects transport. Lastly, Karl Lechtreck showed how minimal changes in ciliary structure via mutation influence efficiency of ciliary beating, and produce hydrocephalus. In addition, he showed that cargo transport into the cilium occurs by several different mechanisms some of which have unknown aspects suitable for further study. The variety of ciliary systems, as illustrated here, provides an excellent substratum with which to develop specific mathematical and computational models.

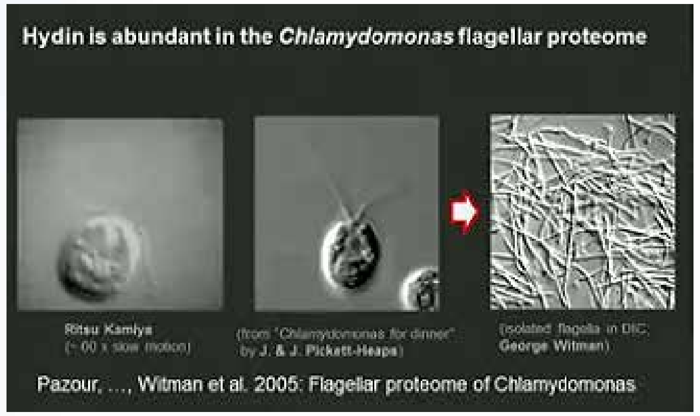
The afternoon session on day one, which was coordinated by Kenny Breuer, focused on "Physical and engineered systems." Engineered microsystems provide useful simple models to test hypotheses on transport induced by ciliary beating and on ciliary and flagellar induced cell motility. Presentations from Marc Fermigier and Ambarish Ghosh showed advances in artificial systems used to study a variety of the phenomena observed in biological systems. Rich Superfine presented a whirlwind tour through results from his group on design of engineered cilia responsive to magnetic forcing to mimic lung mechanics and as potential rheometers for complex fluid characterization. Kenny Breuer gave a brief overview of his use of idealized model systems that are abstractions of biological systems but can be effectively used to identify the underlying scaling and physics in the more complex real world. Arezoo Arkedan presented her work on bacterial motions and adhesion in complex fluid systems.

Many of the engineered systems use magnetic fields to actuate their motion. This is elegant and allows for complex control of single cilia or uniform control of fields of cilia, it doesn't allow for single cilia to evolve under independent forcing, and thus issues regarding synchronization, metachronal waves or hydrodynamic interactions are harder to explore under this paradigm. Independent actuation, illustrated in Zvonimir Dogic' talk on self-excited microtubules, poses an intriguing direction for future studies where molecular concentrations and gradients can provide local activation.

Two key appeals of the artificial cilia/swimmers that were expressed are (a) the ability to add novel functionality such as controlling the filament stiffness, the geometry, organization and packing, and thus explore novel physics, and (b) the possibility of using the artificial systems for purposes not related to their original function. An example of this was Rich Superfine's rheometer system for measuring mucus properties, or Ambarish Ghosh' nano-swimmers that might be used for some kind of controlled delivery.

The morning session of the second day centered on "Numerical methods and computations" and was coordinated by Anita Layton. There have been substantial advances in the development of numerical methods that seek to compute and resolve the fluid-structure interaction of a cilium or flagellum, in either a viscous or viscoelastic fluid. As noted in Lisa Fauci's keynote lecture, examples of numerical methods include resistive force theory, slender body theory, boundary integral methods, the method of regularized Stokeslets, immersed boundary methods, finite element/volume methods, etc. In a second lecture, Ricardo Cortez talked about modeling thin tubes in Stokes flow by combining the slender body theory with regularized Stokeslets. Multiscale methods that represent the detailed mechanical structures of a cilium or flagellum, and at the same time efficiently simulate the interactions among a larger number of cilia or flagella, would be helpful in the development of realistic, large-scale systems. The coupling of stochastic models of cilia and flagella beat cycles that are based on molecular motors and ATP concentrations, coupled with the axonemal details presented by Lechtreck, Sale and O-Callaghan pose as an outstanding modeling and computational challenge. Mitran's lecture on Wednesday afternoon suggested a possible platform for collaboration.

The afternoon session on day two focused on "Mechanisms of motility", coordinated by Matthias Salathe. Bill Davis presented novel data on an empirical model for determining the ciliary waveform using a double Gaussian, and on the organization of the periciliary layer with cell-attached and cilium-attached mucin chains. The mucins form an expansive glycocalyx that fills the periciliary space, excluding particles and in part explaining with novel insight the interface of the cilia space and the mucus layer. The mucus layer needs to be appropriately hydrated, otherwise the periciliary layer collapses. Furthermore, there are also clear interactions between cilia and the polymeric mucins in mucus. These data open up possibilities of new experimentation and modeling: do the mucin brushes on cilia change their hydrodynamic interactions, how do ciliary tips interact with mucins, how is mucus transported in three dimensional space, how is ion transport hydrating the airway surface with the new definition of the space? Guilherme Garcia's modeling of water and ion transport through the airway epithelium directly applies to the presentation of the novel periciliary space.



Hydin is abundant in the *Chlamydomonas* flagellar proteome

Pazour, ..., Witman et al. 2005: Flagellar proteome of Chlamydomonas

Zvonimir Dogic presented data on how a highly simplified model system consisting of filamentous microtubules and kinesin molecular motors organize into a wide variety of far-from equilibrium phases ranging from active gels, 2D nematic liquid crystals and spontaneously beating active bundles whose patterns resemble those of biological cilia. Taken together, these experimental observations exemplify how assemblages of animate microscopic objects exhibit collective biomimetic properties that are starkly different from those found in materials assembled from inanimate building blocks, challenging us to develop a theoretical framework that would allow for a systematic engineering of their far-from-equilibrium material properties.

W. Sale presented new evidence that the proximal axoneme, next to the ciliary transition zone, is unusually stable compared to the remainder of the axoneme. This observation may help reveal conserved proteins important for initiation of bending and propagation of bends from the proximal end of the axoneme. The observations will also impact models of ciliary bending. Model genetic organisms, such as Chlamydomonas, and human ciliated epithelial cells are revealing novel conserved genes required for normal movement, and that when such genes are defective result in PCD. Understanding the beating patterns in disease and specific knock outs of dynein motors and other regulatory elements is required for modeling effort possible to understand the function of these axonemal parts.

The morning session on the third day was organized by Greg Forest around the theme of "Mathematical modeling and simulations." Understanding large-scale mucosal transport in the pulmonary system will require the derivation of first-principles based, yet coarse-grained models of billions (carpets in tubular geometries) of synchronized vs. asynchronized cilia exert mechanical stress on the mucosal layer, itself a complex material as yet poorly understood. The session focused on coarse-grained or reduced models for many degree of freedom, active, biological systems. Examples were large-scale dynamics of motile (active) suspensions, pronuclear migration in early embryos, and collective synchronization of ciliary and engineered bacterial carpets. The basic approach is to sacrifice a great deal of the biological details of the individual agents (bacteria, flagella, motor-proteins) in the interest of finding reduced order models that can be analyzed and simulated to reveal how large-scale dynamic structures emerge from the collective interactions. ***Mike Shelley gave an overview of how an applied / computational mathematician approaches modeling macroscopic behavior of complex micro-swimmer suspensions.*** The modeling effort is motivated by experimental observations of "emergent properties" in bacterial suspensions on length scales much greater than individual particles. Both particle methods and mean-field methods were developed, for swimmers that mimic pushers (who push flow ahead of them) and pullers (who pull fluid toward them).

One can draw parallels between this model system and a fundamental challenge in modeling and understanding coordination of cilia or dysfunction associated with the inability of cilia to coordinate. That is, a model of a single small scale object (bacterium or cilium), the medium they are suspended in (viscous or viscoelastic fluid), how they communicate with one another (hydrodynamically through the intervening fluid, or with the substrate (cell) they are rooted in, or via engagement with the layer (mucus) above), and then the emergent behavior (cellular flow and concentration patterns in swimming bacteria or metachronal waves of coordinated cilia). The biological question for coordinated cilia and mucociliary clearance requires details of the cilium modeling, which is addressed in subsequent talks, and then how the cilium structure and force distribution couple with the fluid surrounding them and the mucus layer above to conspire to mucus clearance.

Shelley walked through a derivation of a kinetic coarse-grained model for a suspension of simple rod-like swimmers. Analysis and simulations showed the emergence of large-scale hydrodynamic instability that gave rise to nonlinear cellular flows qualitatively similar to experiments of concentrated bacteria. He then discussed the collective effects of motor proteins walking along microtubules may underlie the phenomena of "proper positioning" of the pronuclear complex preceding the formation of the mitotic spindle and cell division. This coarse-grained fluid/structure model revealed a simple torque-based instability that may explain the observation of rotation of the complex to line up the ensuing mitotic spindle with the cell axis.

Ramin Golestanian discussed models of hydrodynamic synchronization and surveyed his results toward finding the minimal mechanisms sufficient to synchronize or coordinate the motion of active objects that rotate and translate in a fluid. He discussed reduced mathematical models of how waving and rotating flagella may become synchronized. He then posed a model of bacterial carpets which are observed to self-organize their many flagella to create fluid pumps. This model was of an array of many pumping elements that are rotated individually by a given torque, and by the hydrodynamic interactions with all the other elements. He demonstrated that in certain regimes this set of elements could synchronize with each other and yield aligned pumps that could transport fluid. Both the Shelley and Golestanian presentations focused on special features (e.g., low Reynolds number) to finesse the computational challenge and extract understanding of the observed phenomena.

Forest gave a summary of diffusive and viscoelastic properties, using the tools of microrheology, for mucus harvested from human bronchial epithelial cell cultures. The robust dependence of these transport properties with mucus concentration was reported, whereas mucus concentration is known to rise during disease progression in cystic fibrosis, COPD, and other pathologies. The take-home message is that mucus in healthy and disease states has a spectrum of important timescales associated with flow and elastic responses, not surprising since there is a spectrum of physiological forcing frequencies (cilia, breathing, cough, and gravitational drainage). Any modeling of mucus clearance in lung airways will have to incorporate these rheological features of mucus.

The interactions during the workshop were numerous and rich. Connections were apparent between the biological systems and behavior, engineered systems and behavior, modeling and computational methods. The engineered systems folks and numerical modeling folks were clearly motivated to explore axonemal chirality, the role of calcium in motor-driven cilia forcing, and axonemal defects in regard to metachronism and fluid stress generation of primary cilia. Engineered systems work has thus far focused mainly on Newtonian fluids, although as with the numerical simulations, there is recent activity to explore viscoelastic systems. Superfine's recent PhD student, Briana Fiser, has created a new magnetic rod system and studied flow generation in viscoelastic fluids. It is an open problem (underscored by Bill Davis in the second day) to understand how the distribution of mucin proteins and their relative concentrations contribute to the overall performance and robustness of this and related biological functions. Forest showed results from unpublished microrheology experiments and data analysis on cell culture mucus that reveal clear rheological trends in mucus versus concentration of solids. A synthesis of the diverse methods and observations presented at the workshop to model efficacy of mucociliary clearance poses an important challenge and opportunity.

Current Topic
Workshop 2

Statistics of Time Warpings and Phase Variations
November 13-16, 2012

Organizers: J. S. Marron (UNC), J. O. Ramsay (McGill), L. Sangalli (Politecnico di Milano), A. Srivastava (Florida State)

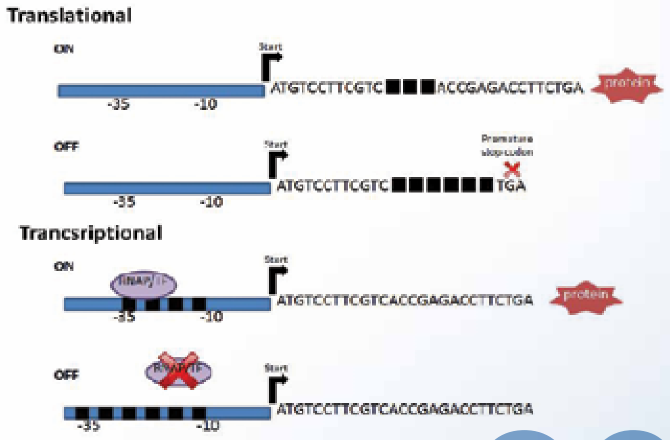
Report by: David Koslicki, Noelle Beckman, and Jay Newby

Background: A common feature of functional measurements of data over time, space and other continua, is that salient features in the resulting curves and surfaces vary in position from one recording to the next. For example, the growth patterns of children vary in the timing of puberty, human movements in activities like handwriting and golf swings speed up and slow down from one instance to another, seasonal events like hurricanes arrive early some years and late in others, and traffic jams vary in location over city streets from one day to another. At the same time, each of the events can also vary in intensity. We refer to positional variation as phase variation, and intensity variation as amplitude variation. It is now evident that many processes unfold over a system time that not only does not unroll at the same rate as physical clock time, but also tends to vary in a significant way from one realization of a functional event to another.

The registration or alignment of features in curves and images by smooth, one-to-one transformations of time or space, respectively, is an emerging hot topic that presents many challenges. From its beginnings with dynamic time warping in the late 50's, followed by the landmark registration methods of Fred Bookstein, the registration of brain images to a fixed atlas, and its widespread application in functional data analysis, statisticians have realized that nonlinear phase variation is pervasive in data distributed over continua. Happily, a considerable variety of methods for separating amplitude from phase variation now exist, and connections with shape analysis methods have been made. It seems time to do some comparative tests, review progress to date, and consider new research opportunities.

Workshop Ideas: Instead of the usual passive speaker - audience format, workshop activities will be centered around applying a wide variety of statistical methods to a common collection of data sets. The focus will be the various analytic approaches of several different Analysis Groups, to some common data sets, featuring careful discussion of the strengths and weaknesses of the various analyses.

Main presentations will be made by the Analysis Groups, who will agree to analyze (before the workshop) each of the agreed upon data sets, and will present their results at the workshop. For context, each data set will have an associated workshop participant, responsible for answering questions about the data while the analysis is under way, and who will (at the beginning of the workshop) give a brief description of the data, plus the main statistical questions. Following the analytic presentations, there will be group discussion with the goal of evaluation of the different methods used. It is anticipated that this will result in a list of the pros and cons of each approach, and in particular a clear view of the varying circumstances under which each method has advantages over the others.



TUESDAY, November 13, 2012

Time Warping of Neural Spike Train Data.

Wei Wu (Florida State University)

Dr. Wu introduced the spike train data-set on which participants of the workshop will compare spike-train alignment/registration techniques. After reviewing the basics of neural spikes (action potentials) and their recording via multi-electrode arrays, Dr. Wu posed the basic questions of “What is the mean trend of a spike train over many samples and many neuron sampling sites” and “What is the dispersion from this mean.” A few metrics between spike trains were suggested and the idea of smoothing spikes to obtain real-valued functions was introduced. The aim in analyzing this data is to translate between spike trains and a random target pursuit task (and conversely) when recording the primary motor cortex in primates.

Acute Myeloid Leukemia Data from Label-free Liquid Chromatography Mass Spectrometry.

Inge Koch (The University of Adelaide)

With the goal of finding clinically useful biomarkers to assist in the therapy and treatment of Acute Myeloid Leukemia (AML), Dr. Koch reviewed the process of obtaining the proteomics data that will be analyzed by the conference attendees. The details of liquid chromatography-mass spectrometry were reviewed. Under the assumption that proteins with different abundances are functionally related to disease processes, mass spectrometry was used to study the changes in protein expression in 5 patients over 3 technical replicates. Processing of this data included applying a log-transformation, smoothing (with a running median of 9), and interpolation to an equally spaced grid. These 15 pre-processed records will be analyzed by the conference attendees.

Functional Data Analysis of Juggling Trajectories.

Jim Ramsay (McGill University)

Dr. Ramsay described the collection of this data from an amateur juggler. The data was obtained from 10 trials of 11 to 13 juggling cycles (throwing, catching, and passing the ball in preparation for another throw). The measurements are positions in 3-space of the tip of the right forefinger of the juggler. The data was pre-processed with the Pspline smoothing package. The goal Dr. Ramsay stated was the registration (or alignment) of the 10 curves (in 3-space). He detailed a preliminary approach based on landmark registration.

Aneurisk data: Three-dimensional Vascular Geometry Dataset

Piercesare Secchi (Politecnico di Milano)

Dr. Secchi introduced the final dataset to be analyzed by workshop attendees in the form of blood vessel coordinates and radii obtained from 3D rotational angiographies of patients from two classes: those who have had a stroke and those who have not. The goal of analyzing this data is to test the medical hypothesis that pathogenesis of cerebral aneurisms is caused by geometry of blood vessels and its interaction with blood-flow dynamics. Preliminary analysis with principal component analysis and a quadratic discriminant analysis has resulted in predictive landmarks for rupture, but validation of these results (an improvement in predictive power) is the aim of analyzing these data with other functional data analysis techniques (such as landmark registration or other curve registry techniques).

Multivariate and Functional Principle Components without Eigenvalues

Jim Ramsay (McGill University)

Dr. Ramsay summarized the disadvantages of traditional principle component analysis (PCA), namely the restriction to utilizing least-squares approaches and the dependency of results on the particular basis utilized. A new approach was then introduced (called “parameter cascading”) that highlights the subspace spanned by the principle components. This method, in contrast to traditional PCA, also allows for the flexibility in treating nuisance parameters differently than structure parameters.

Conceptual Problems with Registration Techniques

Alois Kneip (University of Bonn)

Dr. Kneip raised a number of objections regarding a variety of registration and time-warping techniques (save landmark registration). Namely, that the current success criterion for curve registration is an ill-defined, qualitative notion of “main feature alignment.” Furthermore, most registration procedures are non-unique and posses no notion of consistency (i.e. registration of pre-registered records tends to change them). Dr. Kneip argued that these issues result in methods that are poorly adapted to statistical techniques. A number of criterion (namely, convexity and consistency) were then introduced to bypass these issues. Dr. Kneip argued that a method satisfying these criteria would be more adapted to statistical analysis.

A Formal Definition of Phase and Amplitude in Functional Data Analysis.

Anuj Srivastava (Florida State University)

Dr. Srivastava introduced a novel, flexible, rigorous, and general framework in which to perform time-warping and curve registration. After defining the function space and warping functions/group, Dr. Srivastava introduced a square-root-slope-function that naturally arises when considering orbits of a given function under the action of the warping group. It was demonstrated that such orbits are parallel under the Euclidean norm, a key and desirable property for the consistency of a registration technique. A broadly applicable registration technique using these tools was then mathematically derived.

Next, a wide range of real and synthetic data sets were then analyzed using this approach and compared to existing techniques. It was noted that this method can be applied in very general situations and yet still performs better than all existing techniques, at least on the data tested so far.

Time Warping and Marginal Screening.

Ian McKeague (Columbia University)

Dr. McKeague detailed the problem of detecting the presence of a significant predictor while taking into consideration time warping. As an approach to solving this problem, a procedure based on marginal regression was introduced. However, time-warping leads to non-regularity of the regression coefficient. To circumvent this, Dr. McKeague detailed a bootstrap procedure based on a local model (in order to better reflect small-sample behavior). The performance of this approach was evaluated using a simulation study. Dr. McKeague then noted that this difficult problem is still not completely solved and future work is needed to develop a computationally tractable way to compute p-values that’s robust under time-warping.

Registration Invariance.

Ian Dryden (University of Nottingham)

Dr. Dryden introduced his approach to functional data analysis as coming from the perspective of shape analysis via registration invariance. For example: Registration of closed curves that are invariant under some group of symmetries. Dr. Dryden detailed the advantages and disadvantages of working in either the ambient space or else the quotient space (with respect to a group of warping functions). This leads to two very different concepts of a mean shape: in the ambient space it is easier to analyze the mean of the shapes, while in the quotient space it is easier to analyze the shape of the means. Depending on which question on is trying to answer, this leads to an argument for the usage of one of two related means: the Karcher mean or the Fréchet mean.

WEDNESDAY, November 14, 2012

Automatic point correspondence for shape analysis

Ross Whitaker (University of Utah)

Dr. Whitaker and colleagues developed statistical point-based models of ensembles of similar shapes that do not rely on specific surface parameterization. They modeled surface point samples as sets of dynamic particles. Particle positions were optimized by gradient descent that minimizes the entropy cost function. The tools they have developed are available through Shapeworks software. Applications of this framework include analyzing hand bones of knockout mice, hip impingement, and osteochondroma. For example, Dr. Whitaker found differences in the shape and length of mouse bones similar to what was observed by scientists but was previously unquantifiable. With this approach, statistics of shapes can be quantified and visualized, such as the median shape or animal of a population.

Maximum Likelihood Registration of ICA Curvature Trajectories

Daniel Gervini (University of Wisconsin)

Dr. Gervini introduced a functional regression method that incorporates time warping as an intrinsic part of the model. The underlying model he used for the warping function was a semiparametric model. To ensure that the warping function was strictly increasing, he used a family of monotone hermite splines, which have an interpolating property. Hermite splines offer more flexibility, parsimony and interpretability than alternatives, such as integrated splines or monotonically-constrained B-splines. He used functional logistic discrimination to analyze the parameter estimates and will talk about this later in the conference.

Joint clustering and alignment of functional data: The k-mean alignment algorithm

Laura Sangalli & Simone Vantini (Politecnico de Milano)

Dr. Sangalli discussed the development of a k-means alignment algorithm, which jointly clusters and aligns curves. She described a procedure that efficiently clusters and aligns in k groups a set of curves. If the number of clusters k is equal to 1, the algorithm implements a Procustes aligning procedure, whereas if there is no alignment, it implements a k-means clustering of curves. Dr. Sangalli defined similarity index p and the class of warping function W to find an optimal function. The choice of p and W is problem-specific and defines what the phase and amplitude variability. (p,W) must satisfy properties that ensure that the aligning and clustering problem is well posed and the corresponding procedure is coherent.

Dr. Vantini gave a simulated toy example with two amplitude clusters (two template curves) with further clustering in the phase. Three different groups of curves were simulated with variability in both amplitude and phase. There was a big gain in similarity when introducing warping (k=1) and even further gain with other templates (k=2,3) compared to the original. Dr. Vantini also discussed the meta-equivalence theorem derived from the W-invariance property of d and gave some examples of W-invariant semi-metrics.

Joint modeling of phase and amplitude

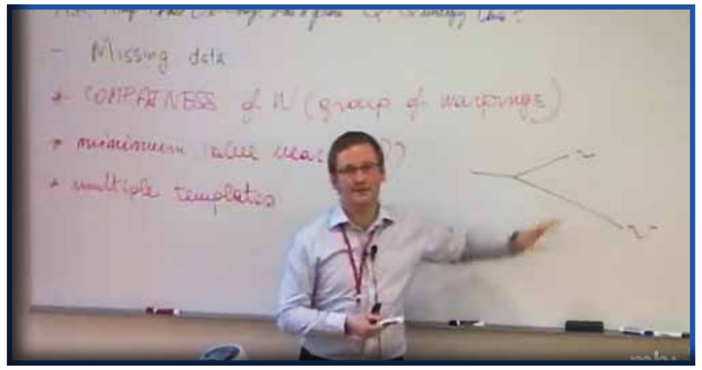
John Aston & John Moriarty
(University of Warwick/University of Manchester)

Part I: Joint modeling via PC and LME models

Dr. Aston introduced the problem of analyzing language models, which include not only amplitude and phase variation but also covariates of tone, vowel, sentence position, speakers, plus nine others. He discussed the development of a joint multivariate fixed effects model that included amplitude and phase using PCA. He discussed preliminary analysis using standard PCA for amplitude functions and walking functions and attained a mixed effects model solved iteratively using MS/REML. The model estimated curves in the original domain.

Part II: Non-Gaussianity and Gaussian Process Regression (Work in progress!) (John Moriarty)

Dr. Moriarty discussed how to achieve independence and orthogonality in the covariates and to deal with sources of non-Gaussianity (e.g. sampling distribution may not be Gaussian even though population distribution is Gaussian). The modeling framework discussed by Drs. Aston and Moriarty attempted to account for these different issues: PCA selects best orthogonal subspace and ICA maximizes independence and deals with non-Guassianity.



Emergency Math Group at Emory

Alessandro Veneziani (Emory University)

Dr. Veneziani gave an overview of methods, applications, and software developed by his group. They have developed image processing methods, PDE theorems, and numerical approximations to study cardiovascular-related problems. Dr. Veneziani's group is also developing software to make these methods available. Challenges of their work include dealing with uncertainty of parameters and models and noise of measurements. They have a repository of cardiovascular data on AneuriskWeb. Dr. Veneziani briefly introduced the tutorial, the type of data available on AneuriskWeb, and numerical simulations they can perform on the data.

On the separation of amplitude and phase variation in finite point processes

Victor Panaretos (Ecole Polytechnique)

Dr. Panaretos modeled spike trains as discrete random measures of a finite point process assuming a finite inhomogeneous Poisson process and a canonical model for phase variation. Phase variation was modeled as overdispersion using a Cox Process in which phase variation was the variation of a random mean measure and amplitude variation was Poisson variation conditional on this. On average, the warpings were the identity and they can be understood as the Frechet mean with respect to the Wasserstein distance. The Wasserstein distance integrates registration and geometry in a single unified setup. Dr. Panaretos developed explicit expressions for the Wasserstein mean and warping functions. He generated spike trains with random intensities using the Cox process and found the Wasserstein mean does better than the naïve mean. After aligning the warped processes, it resembled the Poisson process. The post-warping density was better than the naïve density at estimating the true density, though it was a little biased.

NMR Spectra for 40 wines

Jim Ramsay with Martha Mueller
(McGill University/University of Copenhagen)

Dr. Ramsay introduced a graphical technique to remove phase variation using NMR spectra from wine. NMR spectra of wine are characterized by sets of sharp peaks containing two or more spikes in a fixed pattern with spike heights having fixed ratios. He illustrated his technique from a selected small section containing a quadruplet peak pattern and used order 7 B splices in order to get a smooth third derivative. He plotted the second derivative versus the first derivative to reveal the structure in the data. With the wine spectra data, this resulted in a heart shaped structure. After log-transforming spectra data, the initial four peaks were joined by other peaks, and the heart shaped structure became much more complex, showing couples, triplets, and quadruplets. Dr. Ramsay suggested functional data analysis can be used with spike data and plotting derivatives is useful for depicting amplitude variation by removing phase variation.

Bayesian protein analysis

Ian Dryden (University of Nottingham)

Dr. Dryden's group preprocessed the proteomics data by performing baseline extraction with cubic spline and smoothing with wavelet smoothing and cubic spline. They used Dr. Srivastava's methods of the square-root velocity function (q-function) for warping functions in a Bayesian framework. The group developed likelihood models for the q-function using a Guassian process. Dr. Dryden's group simulated the posterior, registered curves with map registration, and produced exploratory t-statistics. Using a strong prior, there was a significant difference in non-responders and responders after controlling for the false discovery rate, but with a uniform prior, there were no significant differences. With dimension reduction using Guassian mixture humps, they found significant differences in curves at peak locations with strong and uniform priors (adjusting for multiple comparisons using FDR).

SRSF FDA Protemics

Derek Tucker (Florida State University)

Tucker and colleagues presented their results of the proteomics data analyzed with the square-root slope function approach and elastic shape analysis of curves and found very good alignment. The elastic method gave better alignment than MBM and MSE methods. Their elastic method also performed better based on cumulative cross sectional variance of the aligned functions compared to MBM and MSE methods. Tucker did an analysis of the warping functions using horizontal fPCA and an analysis of aligned functions using vertical fPCA. For the latter, most of the information was captured in the first few directions of the fPCA. Tucker verified results from jointly modeled phase and amplitude components with random samples and found similarity between simulated and original data. Their elastic method improved the classification rate when using pair-wise distances alignment and cumulative match characteristic curves.

Joint clustering and alignment of functional data: The k-mean alignment algorithm

Laura Sangalli (Politecnico de Milano)

Dr. Sangalli introduced functions for the similarity index and group of warping functions. Her group used K-medoid alignment and block K-medoid alignment (accounts for repeated measurement structure of data). They found that there was a gain by using alignment and the best method was affinity. They found similarity with the K-mediod alignment with affine warping similarity index increased with k-clusters up until k=2. They found the K-medoid alignment affine warping (k=1) was a really good depiction of drift in the measurements of the patients. For the block K-medoid alignment, they aligned within each patient first, and then aligned across patients. They found the best fit was affine transformation within patients, and the simple shift worked well across patients. Warping increased similarity up until k=2. The main conclusions of the study were that warping underlying phenomenon seemed truly affine, clustering in amplitude is worth further investigation, and respondents versus non-respondents can be discriminated by using area under the peaks.

Aligning unlabeled TIC Chromatographs Data

Xueli Liu (City of Hope)

Dr. Liu used several different methods to analyze the total ion count (TIC) chromatographs data. The data exhibited rigid shifts in time and had major peaks that follow similar patterns. Before further analysis of the data, peaks within the data needed to be aligned. Dr. Liu spoke of major challenges in aligning peaks, including the enormous number of peaks to be aligned, the importance of the peak locations rather than the entire curve, and the automated alignment procedure. She compared pairwise curve synchronization and curve alignment by moments to an alternative method, the automated pairwise piecewise landmark registration (APPLR). The alternative APPLR method gave the best fit to the data compared to the other two methods. It had the highest maximum average intensity, whereas the other two methods gave similar maximum average density to the data. The alignment average from APPLR recovered the pattern in the original data very well.

Fisher Rao Alignment of Proteomic Data

Inge Koch (University of Adelaide)

Dr. Koch presented work done jointly with Xiaosun Lu and J.S. Marron at UNC-Chapel Hill. The group used an approach of warping based on the Fisher Rao metric. She compared results using align functions with new and old warpings. For spike 7, new warping aligned the spikes better, and the sample orderings based on the height of the spikes were the same. For spike 9, old warpings aligned the spikes better, and the sample orderings based on the height of the spikes were different.

THURSDAY, November 15, 2012

Simulated warping of measured data

Yoav Zemel (Lausanne)

Instead of using the typical data sources, Yoav's observations come from a point process with a random intensity measure. The general strategy for aligning can be summarized in the following three steps:

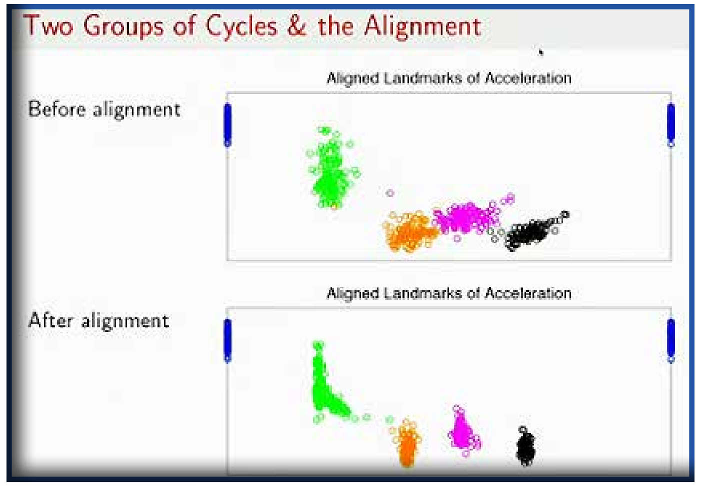
(1) Estimate a smoothed version of the observations
(2) Determine empirical Wasserstein mean
(3) Use a template to register the observations

The results show that the skewness of the warped register indicates the true data can be distinguished from the simulated observations.

How similar are the simulated data to real data?

Xiaosun Lu (UNC Chapel Hill)

Xiaosun compares real and simulated data by aligning functions through time warping. They then perform a principal component analysis and find that the simulated data is well separated, but not real data. A unique observation is that paths are different both vertically and horizontally. Then, class 1 data is compared against class 3 and 4, and it is found that real data has a large Z-score.



Registration of quasi-registered warping spaces: are they complete?

Wei Wu (Florida State)

Wei focuses on data generated by square-path movement: four different paths, with a record of 60 trials in each path. Furthermore, smoothed spike trains are used for simplicity. They ask, "what if we want to do more than just registration?" In other words, given two spike trains, can we determine how different they are? After aligning the warping functions, and performing a principal mode analysis, the speaker shows that this can be done in certain cases, but significant challenges must be met before a general method is developed.

Unifying amplitude and phase analysis

Pantelis Hadjipantelis (Warwick-Manchester Group)

Pantelis is concerned about how the warping can be used rather than how it's done. Projection methods provide a convenient framework for physically relevant warping results. Once the observations are registered, they use projections to adequately characterize amplitude. Given type I and II data, they are able get a 16% prediction rate, slightly less than 17% reported by others. While a slightly relaxed smoothing requirements yield better results. The speaker is optimistic about the general usefulness and robustness of prediction-based methods.

Method of multiple coaligned warping templates

Heiko Wagner

Heiko starts by representing data with a simple SPA decomposition. First he notes that the standard method is at heart ab iterative method for computing warping function. Instead, he uses a Taylor approximation (1st order) to represent warping function; then he uses a B-spline basis for the coefficients. Of course, there are some artifacts from the registration that show up because of 1st order truncation, but they can eliminate by taking n larger. Interestingly, he notes that the (0, 1) restriction might be relaxed (to the chagrin of those in the audience); otherwise edge effects might be unavoidable.

FRIDAY, November 16, 2012

Entropy-based Gradient Descent.

Ross Whitaker (School of Computing, University of Utah)

Dr. Whittaker introduced a method of curve registration that utilizes an entropy-based descent method. While typical curve registration techniques regularize the family of warping functions, the surprising aspect of this entropy-based technique is that such regularization is not needed. In simulated examples, the family of warping functions is somehow constrained to be regularized by virtue of the gradient descent. Dr. Whittaker postulated why this might be the case and indicated areas of future investigation.

Image Registration: Tracking the Motion of Vascular Geometry

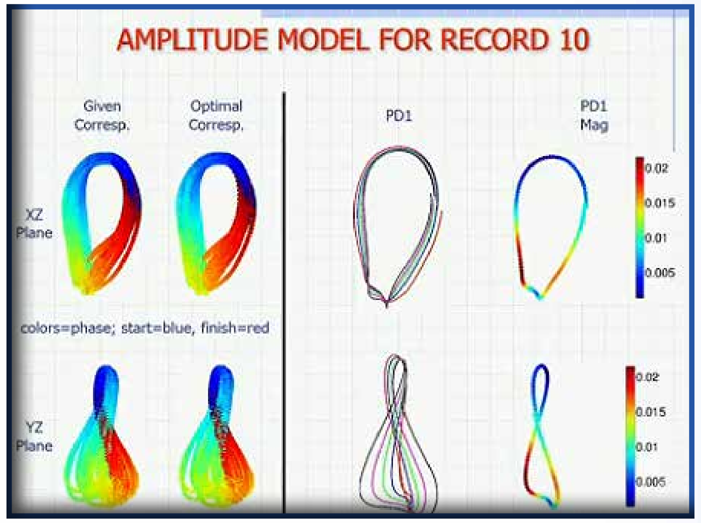
Alessandro Veneziani
(Mathematics and Computer Science, Emory University)

Dr. Veneziani addressed the issue of registering a discrete time-series of images resulting from 3D rotational angiographies. As a related issue, alignment of knee and patella positional data was also introduced. Both problems reduce to an inverse free-structure interaction problem. Dr. Veneziani detailed a principle component analysis of the data but noted that such an approach is not viable in practice due to the high computational cost. Possible methods to circumvent the necessity of solving a Navier-Stokes-like problem were discussed.

Registration of Surfaces using Square Root Functions and Square Root Normal Fields.

Sebastian Kurtek
(Department of Statistics, The Ohio State University)

Dr. Kurtek discussed the registration of surfaces via defining two surface transformation functions: a square root function and its normalized counterpart. Both transformations utilize the magnitude of the normal vector at a given point on the surface under consideration. The advantage of transforming the surfaces in this fashion is that under composition with a group of warping functions, orbits remain parallel under the Euclidean norm. So-called square root normal fields also have the added benefit of explicitly formulating the cost for stretching, bending, and rotating one surface into another. Other topics discussed herein included geodesics between surfaces, alignment summary statistics and parallel transport problems.



Quick Discussion on dissemination

CTW participants

Ramsay opened up discussion on how to disseminate results of the workshop. He urged participants to collaborate on a product instead of working in isolation. Products discussed include a special section, monographs, survey, or book and the advantages of publishing electronically versus in print.

Prediction of glyphosate level from chromatograms

Helle Sorensen (University of Copenhagen)

Dr. Sorensen presented an analysis of chromatogram data from rapeseed plants provided by Dr. Christensen. The complete dataset included 2400 observations with 26 curves corresponding to seven levels of glyphosate exposure. The goal of the analysis was to predict glyphosate exposure from the chromotgram data. Dr. Sorensen was able to align curves using registration within groups with the same exposure but not among groups with different glyphosate exposure. She found that there is a clear association between glyphosate exposure and chromatogram data but could not distinguish low exposure. Dr. Sorensen concluded that alignment was not useful in this analysis.

Using curve registration to improve evolutionary predictions in function-valued traits

Kristin Irwin (Washington State University)

Kristin Irwin studied function-valued traits in which phenotypic traits vary continuously over some axis. In particular, she was interested in growth curves of flour beetles, Tribolium castaneum. Growth during the larval stage influenced adult size, a correlate of fitness. Irwin argues that information on development time may be lost with phase warping. Irwin found a unique decrease in mass for flour beetles during the larval stage due to their behavior. This resulted in a negative covariance between size at earlier and later ages. She would like to know whether she should warp this covariance function before using it in the growth function.

Modelling varved lake sediment to detect past environment and climate changes

Per Arnqvist (Umea University)

The goal of this research was to reconstruct past climates over thousands of years using lake sediment cores from Kassjoen as a proxy. Dr. Arnqvist and colleagues have ca. 6400 varves, which represent years. Varves are sediment cores related to seasonal patterns based on their color, with bright colors being minerogenic material indicative of winter and darker colors being organic material indicative of spring, summer, and fall. From grey scale values of images, they constructed curves related to seasonal patterns. They characterized climate by the shape of these profiles by using k-means clustering on the landmarked registered functions and found seven different climate scenarios. Mean curves for the seven clusters showed one or two peaks and curves with large or low variation. Large variation was indicative of cold climate and low variation of warmer climate.

Current Topic Workshop 3

Mathematical Challenges in Biomolecular/ Biomedical imaging and Visualization

February 18-22, 2013

Organizers: Anne Gelb, Michael Knopp, Arthur Olson, and Guowei Wei

Report by: Duan Chen, Josh Chang, and Jon Lo

The emergence of complexity in self-organizing biological systems poses exciting challenges to their quantitative description and prediction. The imaging and visualization of complex biomolecules, such as proteins, DNAs, RNAs, molecular motors and viruses, are crucial in understanding and conceptualization of biomolecular systems, which in turn can have significant impact in biomedicine, rational drug design, drug discovery and gene therapy. On the other hand, biomedical imaging and visualization are indispensable tools for examining, revealing and diagnosing diseases, and for monitoring the effectiveness of medical treatments. Mathematics provides foundations for visualization and principles for the design of biomolecular/biomedical imaging modalities, such as single-molecule fluorophores, confocal imaging, X-ray crystallography and tomography, cryoelectron microscopy, and magnetic resonance force microscopy, nuclear magnetic resonance (NMR), magnetic resonance imaging (MRI), ultrasonography, positron emission tomography (PET), etc. Currently, mean curvature flow, Willmore flow, level set, generalized Laplace-Beltrami operator and partial differential equation transform are commonly used mathematical techniques for biomolecular surface generations and visualization. Additionally, wavelets, frames, harmonic analysis and compressive sensing are popular tools for biomolecular visualization and image processing. Moreover, topology, differential geometry, and geometric measure theory are powerful approaches for the multiscale modeling of biomolecular structure, dynamics and transport. Finally, persistently stable manifold, topological invariant, Euler characteristic, Frenet frame and machine learning are vital to the dimensionality reduction of extremely massive biomolecular data. These ideas have been successfully paired with current investigations and discovery of molecular biosciences. Mathematical challenges include the well-posedness of mathematical models under physical and biological constraints, lack of maximum-minimum principle, numerical analysis of multiply coupled partial differential equations, effectiveness of approximation theory and the modeling of complex biomolecular phenomena.

Bruker 700 Mhz. Nuclear Magnetic Resonance (NMR) spectrometer.

This weeklong MBI workshop, in conjugation with the Mathematics Planet Earth (MPE) 2013 initiative, will seek greater understanding of imaging and visualization. It provides a forum to bring together mathematicians, biological and biomedical scientists to exchange ideas and results related to research in biomolecular/biomedical imaging and visualization, and to foster interdisciplinary research collaborations. It will also stimulate information flow of "biology to mathematics" and facilitate advances in biological science as a result of "mathematics to biology".

MONDAY, February 18, 2013

Introduction to biomedical imaging and visualization Biomolecular/Biomedical Imaging Technologies

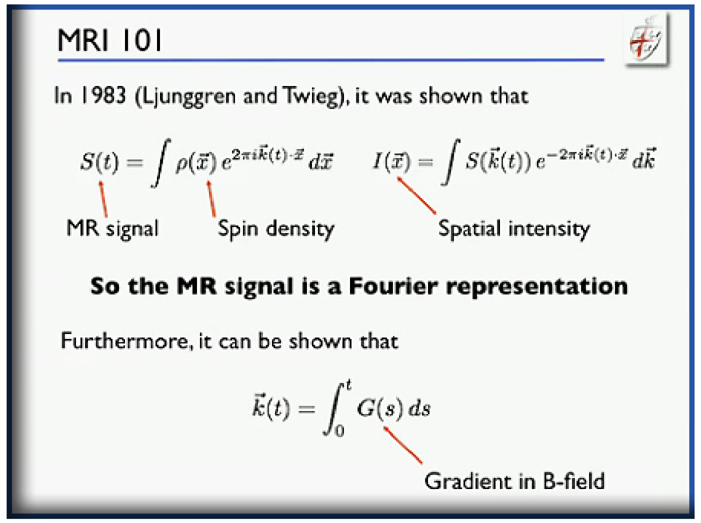
Michael Knopp (Ohio State University)

Dr. Knopp first introduced the team of medical imaging in Ohio State University. He briefly talked about some imaging technologies including whole-body non-invasive MR imaging, 7T MR imaging, etc. Hybrid imagings, such as PET/CT, SPECT/CT, MRI/Angio, MRI/PET, MRI/Optical, US/optical, were also used for biomedical imaging development. The key for developing targeted therapeutics is to understand biological characterizations observed by biomedical imaging. DCE-MRI (Dynamic Contrast Enhanced MRI) is one of imaging technologies discussed in the talk. Through DCE-MRI, we can understand the time from basic level to maximum level of vascular density. Finally, the speaker stated that biomedical imaging is at the cross-section of many scientific and engineering developments. In nearly every aspect of imaging there are math challenges, the most frequently unanswered ones are those that seek to derive quantity biomarker readouts assessing morphologic functional and molecular characteristics and their change during therapeutic interventions.

Incorporation of Prior Fourier Domain Edge Information in the L1 Minimization Problem for Compressed Sensing

Edward G. Walsh (Brown University)

After Dr. Walsh introduced the imaging facilities, he gave a short introduction for NMR (Nuclear Magnetic Resonance)/MRI. An MRI scanner is a device in which the patient lies within a large, powerful magnet where the magnetic field is used to align the magnetization of some atomic nuclei in the body, and radio frequency magnetic fields are applied to systematically alter the alignment of this magnetization. This causes the nuclei to produce a rotating magnetic field detectable by the scanner. As well as MRI helps us understand anatomical structures, functional Magnetic Resonance Imaging (fMRI) reveals functional information. In applications such as fMRI, full, uniformly-sampled Cartesian Fourier (frequency space) measurements are acquired. In order to reduce scan time and increase temporal resolution for fMRI studies, one would like to accurately reconstruct these images from a highly reduced set of Fourier measurements. Compressed Sensing (CS) has given rise to techniques that can provide exact and stable recovery of sparse images from a relatively small set of Fourier measurements. For example, if the images are sparse with respect to their gradient, total-variation minimization techniques can be used to recover those images from a highly incomplete set of Fourier measurements. In this talk, Dr. Walsh proposed a new algorithm to further reduce the number of Fourier measurements required for exact or stable recovery by utilizing prior edge information from a high resolution reference image. This reference image (routinely acquired during fMRI studies for anatomic landmarking of activations), or more precisely, the fully sampled Fourier measurements of this reference image, can also be used to provide approximate edge information.



MRI 101

In 1983 (Ljunggren and Twieg), it was shown that

$$S(t) = \int \rho(\vec{x})\, e^{2\pi i \vec{k}(t)\cdot\vec{x}}\, d\vec{x} \qquad I(\vec{x}) = \int S(\vec{k}(t))\, e^{-2\pi i \vec{k}(t)\cdot\vec{x}}\, d\vec{k}$$

MR signal

Spin density

Spatial intensity

So the MR signal is a Fourier representation

Furthermore, it can be shown that

$$\vec{k}(t) = \int_0^t G(s)\, ds$$

Gradient in B-field

Semiautomatic Extraction Algorithm for Images of the Ciliary Muscle

Chiu-Yen Kao (Claremont McKenna College)

Dr. Kao began this talk with an introduction to eye anatomy including ciliary muscle. The ciliary muscle is a ring of striated muscle that controls accommodation for viewing objects at varying distances. Optical coherence tomography (OCT) imaging is typically used to image the ciliary muscle. Due to the darkness of OCT imaging, it is hard to determine the region of ciliary muscle. In this talk, a semiautomatic extraction algorithm for images of ciliary muscle was presented. The algorithm is based on the region scalable model that draws upon intensity information in local regions at a controllable scale, so that it can segment images with intensity inhomogeneity. Gradient descent flow for minimizing scalable fitting engery leads to integro-differential equations and FFT is used to accelerate the speed of numerical calculation. The method is used to have morphological assessment of the dimensions of the ciliary muscle in Visante Anterior Segment Optical Coherence Tomography images.

Numerical Approximation Methods for Non-Uniform Fourier Data

Anne Gelb (Arizona State University)

In this talk, Dr. Gelb discussed the reconstruction of compactly supported piecewise smooth functions from non-uniform samples of their Fourier transform. This problem is relevant in applications such as magnetic resonance imaging (MRI) and synthetic aperture radar (SAR). At the beginning of this talk, two standard reconstruction techniques, convolutional gridding (the non-uniform FFT) and uniform resampling, were summarized, and some of the advantages and the difficulties were discussed. One of the challenges in Cartesian reconstruction is the Gibbs Phenomenon. Dr. Gelb then demonstrated how spectral reprojection could be used to mollify both the Gibbs phenomenon and the error due to the non-uniform sampling. She showed that incorporating prior information, such as the internal edges of the underlying function, could greatly improve the reconstruction quality. Finally, an alternative approach to the problem that uses Fourier frames is proposed.

Specific modelling of endothelial dysfunction map-Challenges

P. Nithiarasu (Swansea University)

Dr. Nithiarasu first discussed the importance of the endothelium in regulating vessel homeostasis, which is reflected by its effect on vascular tone and by its role in mediating vasodilatory responses to many physiological stimuli. Purine and pyrimidine nucleotides are important modulators of endothelial function. Purinergic signaling and conducted responses can depend on how flow regulates the interactions between ligand and receptor at the endothelium. Regulatory pathways are also influenced by wall shear stress, via mechanotransduction mechanisms. The speaker reviewed the most relevant computational models that incorporate a more realistic physical model and boundary conditions. The models have been proposed to date, and propose a general framework for modeling the responses of the endothelium to alteration in the flow, with a view to understanding the biomechanical processes involved in the pathways to endothelial dysfunction. Simulations were performed on a patient-specific image-based stenosed carotid artery to investigate the influence of wall shear stress and mass transport phenomena upon the agonist coupling response at the endothelium.

An Orthogonal Solution and Kernel Correction Algorithm for Inverse Source Problems with Applications in Fluorescence Tomography

Haomin Zhou (Georgia Institute of Technology)

At the beginning, Dr. Zhou mentioned that this is a joint work with Shui-Nee Chow and Ke Yin. In this talk, he presented a new approach to solve the inverse source problem arising in Fluorescence Tomography (FT). In general, the solution is non-unique and the problem is severely ill-posed. It poses tremendous challenges in image reconstructions. In practice, the most widely used methods are based on Tikhonov-type regularizations, which minimize a cost function consisting of a regularization term and a data fitting term. An alternative method, Orthogonal Solution and Kernel correction Algorithm (OSKCA), was proposed by Dr. Zhou for overcoming the major difficulties, namely the non-uniqueness of the solution and noisy data fitting, in two separated steps. First the speaker found a particular solution called orthogonal solution that satisfies the data fitting term. Then a correction function was added in the kernel space so that the final solution fulfills the regularization and other physical requirements, such as positivity. Moreover, there is no parameter needed to balance the data fitting and regularization terms. In addition, he used an efficient basis to represent the source function to form a hybrid strategy using spectral methods and finite element methods in the algorithm. The resulting algorithm can drastically improve the computation speed over the existing methods. It is also robust against noise and can greatly improve the image resolutions.

Effectiveness of Using Prior Information in Compressive Sensing and Image Denoising

Weihong Guo (Case Western Reserve University)

When there is not enough observed data or the data contains excessive noise, it is challenging to reconstruct the image of interest. Dr. Guo presented her recent work on how to effectively use prior information to significantly improve the compressive sensing reconstruction. Using compressive sensing reduces sampling/imaging time cost and saves storage spaces; however, it is hard to reconstruct high quality images with low sampling rates and excessive noise. In her new approaches, she incorporates prior information to supplement the deficiency of available data. She explored geometric, support and regularity prior etc. and illustrated the ideas in compressive sensing reconstruction and image denoising. All the priors are extracted from the observed data. Various numerical results and application show the effectiveness of incorporating prior by comparing with several existing algorithms, for example, TV regulation, Edge compressive sensing etc.

TUESDAY, February 19, 2013

Signal and image restoration: solving ill-posed inverse problems

Rosemary A. Renaut (Arizona State University)

Dr. Renaut provided a broad overview of approaches for solving the ill-posed inverse problems associated with signal and image restoration. She paid particular attention to solutions based on spectral decomposition (singular value decomposition to be specific). A generalized Picard-condition analysis shows that choice of basis is of critical importance as inadequate precision or inaccurate computation of basis results in error propagating into the solution. Yet, being able to compute basis vectors in arbitrarily high precision does not tell one how many vectors to include. Dr. Renaut introduced a statistical technique for testing vectors based in comparison to white noise.

These techniques are usually accompanied by regularization of which L-p variants such as Tikhonov regularization are popular. This type of regularization, however, usually impacts the solution of the inverse problem. This fact raises the complication of finding appropriate weighting parameters, where one desires a better technique than exhaustive search. The main idea is that regularization parameters should be updated dynamically in the reconstruction algorithm. Using “unbiased predictive risk” as a metric, one is able to pick regularization parameters based on the “goodness” of a solution. Under appropriate conditions, with appropriate weighting of data terms, it was shown that the best parameter value for Tikhonov regularization is one.

Convolutional Gridding and Fourier Frame Approximation

Guohui Song (Clarkson University)

The technique of convolutional gridding (CG) has been widely used in applications with the reconstruction of a signal using non-uniformly sampled compactly supported spectral data, such as in Magnetic Resonance Imaging (MRI). In particular, one desires the reproduction of edges or other special patterns in the original signal. The conventional method for solving such problems is the use of interpolation in k-space in order to approximate gridded Fourier data, so that one is able to easily compute the Fourier partial sum. Such interpolation can be computationally expensive since one needs to solve large linear systems.

Convolutional gridding offers some advantages over the interpolation-based methods. In CG, one convolves the k-space signal with a windowing function, which can have compact support. One then inverts this convolved function using the Fourier partial sum and recovers the original function in x-space by dividing by the windowing function. The error analysis of this method, however, is not fully understood. Convolutional gridding can be considered an approximation of the Fourier frame method, a more-accurate yet time-demanding method. Using this interpretation, Dr. Song provided an appropriate error analysis. Moreover, he proposed a generalized convolutional gridding (GCG) method based on the use of banded rather than diagonal matrices, as an improved frame approximation that retains some of the speed advantages of convolutional gridding.

Differential geometry based multiscale modeling of solvation

Zhan Chen (University of Minnesota)

Solvation, the electrostatic interaction between solute and solvent, is an elementary process in nature and is of paramount importance in many sophisticated chemical, biological and biomolecular processes. The understanding of solvation is an essential prerequisite for the quantitative description and analysis of biomolecular systems.

There are two general classes of solvent models. Explicit solvent models describe both solute and solvent at the atomic scale. These models are complicated and quickly become computationally intractable. Implicit solvent models are simpler because they operate under the assumption of a mean-field continuum solvent, where ion-ion and solvent-ion interactions are neglected. Implicit solvent models, particularly those based on the Poisson-Boltzmann (PB) equation for electrostatic analysis, are established approaches for solvation analysis. However, ad hoc solvent-solute interfaces such as those found by the Van der-Waals method are commonly used in the implicit solvent theory and have some severe limitations like the formation of geometric cusps.

In work jointly with Professors Guowei Wei and Nathan Baker, Dr. Chen introduced differential geometry based multiscale solvation models that allow the solvent-solute interface, electrostatic potential, and even electron densities to be determined by the variation of a total free energy functional. In this manner, the model can incorporate environmental effects and ionic interactions. The models are used to estimate solvation free energies, protein-protein binding affinities, ion channel charge transport rate.

Geometric modeling of subcellular structures, organelles, and multiprotein complexes

Kelin Xia (Michigan State University)

In biology, the structure of multiprotein complexes determines their functionality. Many previous attempts at understanding structure have been geometric. Geometric modeling not only provides visualizations of shapes for large biomolecular complexes, but also fills the gap between structural information and theoretical modeling, enabling the understanding of function, stability, and dynamics. Purely geometric methods have limitations, however, because they can be physically incorrect. Furthermore, such methods can be computationally undesirable because of the introduction of geometric singularities.

Using the principle that geometric models should be coupled to physical models, Dr. Xia introduced a suite of computational methods for the representation of biomolecular complexes. Particular emphasis was given to the modeling of cryo-electron microscopy data. Their method incorporated electrostatic interactions in the Poisson-Boltzmann framework. In this method, Lagrangian-triangle meshes are employed for the surface presentation. On the basis of this representation, they developed algorithms for surface area and surface-enclosed volume calculation, and curvature estimation. A set of six cryo-electron microscopy images representing typical subcellular complexes was used to demonstrate the efficacy of the proposed algorithms in handling biomolecular surfaces and in finding possible drug binding sites.

Dictionary Learning & Compressive Imaging

Larry Carrin (Duke University)

Compressed sensing is concerned with the recovery of a sparse signal from very few measurements. In recent years, different variants of compressed sensing have been developed. Dr. Carrin presented two statistical variants of compressed sensing, which allowed parameter-free reconstruction of randomly observed images and videos. In this way, pure images and video sequences were reconstructed in much higher spatial and/or temporal resolution than they were acquired.

Dr. Carrin's statistical approach to compressed sensing relied on the Indian buffet process that acts as a sparsity-promoting prior distribution on the number of dictionary elements incorporated in a reconstruction. The idea is that each signal can be represented as a sparse linear combination of dictionary elements where no prior assumptions are made about the number of dictionary elements. The dictionary elements and the dictionary size are both learned directly from the data. A beta prior is placed on the probability of incorporating each dictionary element. In this way, the number of dictionary elements is distributed according to a Poisson distribution.

In the spirit of compressed sensing, a 4500 frame per second camera was developed using random observation and a normal 30 frame per second camera. Random observation was achieved using a sampling scheme where light is blocked by a vibrating aperture. Applying the statistical method above to the sampled data yield a video sequence that had exceeded the Nyquist limit for reconstruction.

General Convergent EM-Type algorithms

Ming Yan (Rice University)

Poisson Noise, also known as shot noise, is common in many imaging applications like in CT or MRI. In such cases, one desires to invert the image signal which is convolved by a compact operator and polluted by noise and background emission. Framed in such a manner, the problem becomes a statistical estimation problem that yields an energy optimisation problem. Usually, regularity in the solution is desired, so a convex regularization term is used in this energy. Such is the case with Total-variation denoising, where an L-1 term is incorporated into the energy functional. In this talk, Dr. Yan introduced Expectation Maximization (EM)-Type algorithms for the relaxation of such energies. In his method, EM is complemented by Bregman iteration, which ameliorates the problem of regularized reconstructions suffering from contrast reduction. Dr. Yan presented results of his method applied to the denoising of several noisy images.

Incorporating Edge Information in Fourier Reconstruction Schemes with Application to Magnetic Resonance Imaging

Adityavikram Viswanathan (California Institute of Technology, Computing and Mathematical Sciences)

When considering the reconstruction of a compactly supported piecewise-smooth function from Fourier data, one encounters the Gibbs phenomenon, where oscillatory behavior is found near non-differentiable portions of the function. In Fourier imaging modalities such as magnetic resonance imaging (MRI), this phenomenon manifests as a loss of detail in the neighborhood of tissue boundaries (due to the Gibbs ringing artifact) as well as long scan times necessitated by the collection of a large number of spectral coefficients (due to the poor convergence properties of the reconstruction method).

In this talk, Dr. Viswanathan presented a framework for incorporating edge information - for example, the locations and values of jump discontinuities of a function - in the reconstruction. He showed that a simple relationship exists between global Fourier data and local edge information. The approximate singular support of the desired function can be incorporated into a generalized conjugate partial Fourier sum using a concentration factor. Knowledge of such edges, either a-priori or estimated, enables the synthesis of high-mode spectral coefficients beyond those collected by the MR scanner, using existing data. Incorporating these synthesized coefficients in an augmented Fourier partial sum reconstruction allows for the generation of scans with significantly improved effective resolution. Further use of spectral re-projection schemes can result in the elimination of all Gibbs artifacts. Numerical results showing accelerated convergence and improved reconstruction quality will be presented.

WEDNESDAY, February 20, 2013

Challenges in Validating and Annotating Cryo-Electron Microscopy Data

Wah Chiu (Baylor College of Medicine)

Cryo-electron microscopy (cryo-EM) is an imaging modality that allows the visualization of structures in cells across multiple spatial scales. It has been successfully applied to determine structures of large macromolecular assemblies (>1 MDa) out to near atomic resolutions (3-5 Å). This type of microscopy has made it possible for researchers to address questions such as how P22 phages assemble themselves and the location of phage assembly complexes within cells. However, most studies that report structure based on cyro-EM reconstruction have lacked rigorous and quantitative assessment on the quality of the map and model.

In this talk, Dr. Chiu presented case studies of how the maps and models are validated objectively using statistics. In his method, the data are split in order to estimate the spatial precision of the reconstruction. In this way, this method is able to offer an unbiased estimate of the spatial resolution of a reconstruction. His method was applied to the reconstruction of P22 package protein, where a traveling salesman algorithm was used to find the backbone of the protein structure.

Extracting structural information from electron tomograms

Niels Volkmann (Sanford Burnham Medical Research Institute)

Electron tomography is capable of providing a complete, molecular resolution three-dimensional mapping of entire proteomes including their detailed interactions, provided that one is able to extract information efficiently and accurately. As a result, methods for high-throughput processing are desirable. Standard template-matching approaches have the interpretation of being Bayesian classifiers as long as the template and the target are nearly identical and the noise is independent and identically distributed, Gaussian, and additive -- conditions that are not well met in real images. As a consequence, many false hits are generated by this method in areas of high density such as membranes or dense vesicles.

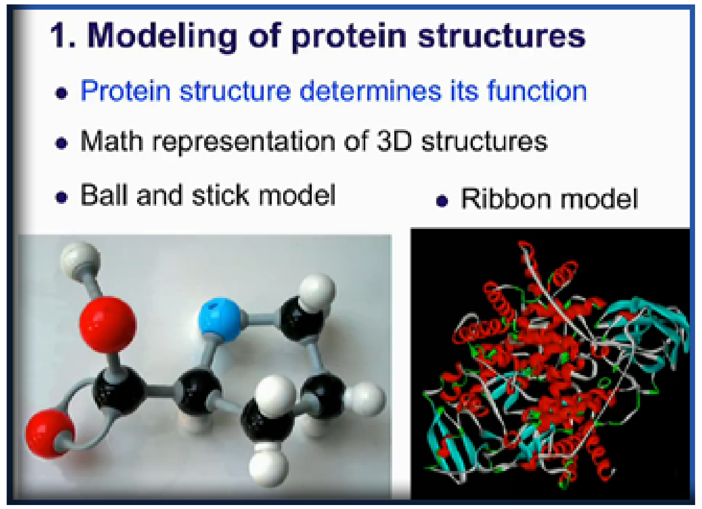
As an alternative, Dr. Volkmann introduces a new method based on template matching using reduced representations. Reduced representations approximate the target by a small number of non-varying anchor points. These anchor points are then used to calculate the scoring function within the search volume. This strategy makes the approach robust against noise and against local variation. As Dr. Volkmann demonstrated, this method is a marked improvement over standard template-matching methods.

Operator splitting ADI schemes for nonlinear biomolecular solvation models

Shan Zhao (University of Alabama)

Biomolecular solvation analysis has many applications including drug design. There are classes of variational models for biomolecular solvation that require the solution of a pseudo-time coupled nonlinear partial differential equation (PDE). Based on a free energy minimization, a boundary value system can be derived to couple a nonlinear Poisson-Boltzmann (NPB) equation for electrostatic potential with a generalized Laplace-Beltrami (GLB) equation, where a potential-driven geometric flow PDE defines a smooth biomolecular surface that characterizes the dielectric boundary between biomolecules and the surrounding aqueous environment. The resulting boundary typically introduces some numerical instability issues in the solution of the time-dependent NPB equation.

In this talk, Dr. Zhao presented a method for avoiding nonlinear instability through the use of an operator splitting alternating direction implicit (ADI) scheme. In his method, the instability is completely avoided through analytical integration. He also presented a new fully implicit ADI scheme for solving the geometric flow equation that can help speed up computation. This scheme relied on the introduction of a factor in the PDEs that does not affect steady state, yet improves stability and accuracy. In his application of solving a coupled system for real biomolecules and chemical compounds, the proposed numerical schemes were found to be conditionally stable. Moreover, the scheme is stable to the usage of large time increments, thereby speeding up computation.



1. Modeling of protein structures

- Protein structure determines its function
- Math representation of 3D structures
- Ball and stick model
- Ribbon model

Finding three-dimensional ab-initio structure for single particle reconstruction using cryo-electron microscopy

Amit Singer (Princeton University)

One of the main challenges in reconstruction of three-dimensional structures from cryo-electron microscopy images is the poor signal-to-noise ratio. To ameliorate this problem, multiple images can be aggregated for use in reconstruction. This approach however leads to the difficulty of alignment of structures in images. Projection images contain thousands of individual, identical frozen-hydrated macromolecules at random unknown orientations and positions.

In his talk, Dr. Singer discussed methods for estimating the structure based on common-lines and class averages that do not require any prior model assumption. His method involves a quadratic optimization problem under orthogonality constraints of vectors in SO(3), which is a non-convex optimization problem. The solution of this problem is approximated through the use of semidefinite programming relaxation, providing a convex approximation to the original problem, or spectral relaxation, which translates the problem into an eigenvalue problem. Dr. Singer discussed an alternative to these methods called Least Unsquared Deviation (LUD) that uses semidefinite relaxation of a cost function involving a Gram matrix. Dr. Singer showed that for a probabilistic measurement model, the Gram matrix can be recovered with high probability.

The Phase Retrieval Problem

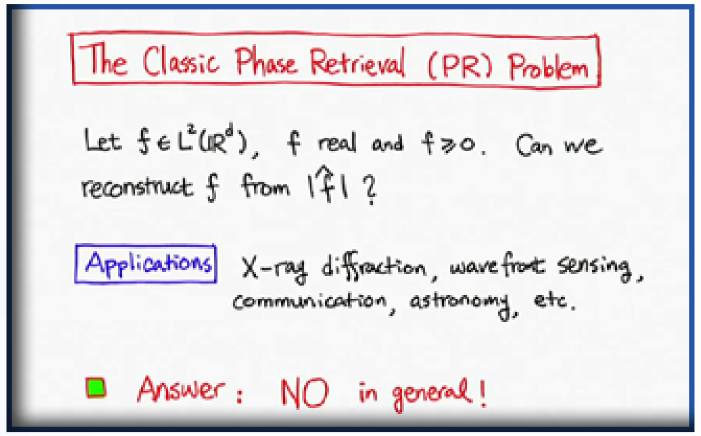
Yang Wang (Michigan State University)

The classical phase retrieval problem concerns the reconstruction of a function from the magnitude of its Fourier transform. A generalized variant of this problem involves the recovery of a function from inner products between its Fourier transform with a known vector. Phase retrieval is an important problem in many applications such as molecular imaging and signal processing. In this talk, Dr. Wang discussed conceptual difficulties in the phase retrieval problem, including ambiguity. In the phase retrieval problem, there is shift and reflection ambiguity. In the generalized phase retrieval problem, there is rotational ambiguity, where a vector can only be recovered up to a unit constant. Dr. Wang introduces the "phase retrieval property (PR)," where one says that a set of vectors has PR if and only if for any partition of the set into two subsets, either one or the other subset span R^d. The question of the rank of the set needed for a given dimension to yield the PR property is still an open question.

Multilevel Methods for Image Deblurring

Malena I. Espanol (University of Akron)

The blind convolution problem is commonly encountered in imaging applications, where an original true image has been convolved with an unknown kernel. This problem can be formulated as an ill-posed inverse problem where discretization of Fredholm integral equations of the first kind is required. Such problems are often solved using singular value decomposition with regularization.



The Classic Phase Retrieval (PR) Problem

Let $f \in L^2(\mathbb{R}^d)$, f real and $f \geq 0$. Can we reconstruct f from $|\hat{f}|$?

Applications X-ray diffraction, wavefront sensing, communication, astronomy, etc.

🟩 Answer: NO in general!

In this talk, Dr. Espanol presented wavelet-based multilevel methods for signal and image restoration problems as well as for blind deconvolution problems. In the resulting iterative method, orthogonal wavelet transforms are used to define restriction and prolongation operators. Different wavelets have different examples, for example the Haar wavelet operator preserves matrix structures, like Toeplitz, which can be exploited to obtain faster solvers on each level where an edge-preserving Tikhonov regularization is applied.

Direct Measurements of Transcription Under Torsion

Jie Ma (Howard Hughes Medical Institute, Cornell University)

The supercoiling of DNA is a physical feature that can affect DNA transcription. During transcription, both RNA polymerase (RNAP) and the nascent RNA chain need to rotate relative to DNA at an angular speed on the order of 100 rotations per minute. Since the resulting torsional stress is not able to immediately dissipate, it is able to impact the motion of the RNAP.

In this talk, Dr. Ma describes a series of experiments he performed in order to quantify the impact of torsion on transcription. Using an angular optical trap, where displacement of the DNA strand is modeled like a spring, Dr. Ma was able to directly measure the torque generated by RNAP. By also measuring the rate of transcription, he was able to find that indeed coiling plays an important role in transcription and that release of torsional strain does increase the rate of transcription.

THURSDAY, February 21, 2013

Modeling, Analysis and validation of molecular interactions from X-ray and electron microscopy

Chandrajit Bajaj (Computational Visualization Center, Institute of Computational Eng. & Sciences, Department of Computer Sciences, University of Texas at Austin)

In his talk, Dr. Bajaj explained that molecular shape and conformation elucidation is the problem of recovering the three-dimensional structure of an individual molecule, a protein or a macromolecular assembly at the highest possible resolution in its natural environment, which could be in situ (the cellular environment) or in vitro (aqueous environment). Despite the advances in X-ray imaging and Electron Microscopy (EM), it has been difficult to simultaneously achieve the three goals of recovering shape and conformation (i) at a high resolution, (ii) at the larger scale of protein assemblies, and (iii) with the particles in their natural environment. In particular, molecular structural feature resolution needs to be fine enough to be useful to visualize conformational changes of proteins upon binding of ligands; study sub-unit composition; understand the interaction between an antibody and its antigen; and study protein assembly in cells. In his talk, he highlighted current progress on several co-mingled computational mathematics algorithms for interpretation, modeling, analyzing and verifying molecular - molecular interactions using multiple imaging modalities, namely X-ray, single particle EM and electron tomography.

Geometric blind source separation methods and their applications in NMR spectroscopy

Eric Yuanchang Sun (Department of Mathematics and Statistics, Florida International University)

Nuclear magnetic resonance spectroscopy (NMR) is heavily employed by chemists and biochemists to study the structures and properties of chemical compounds. The measured data however often contain mixtures of chemicals, subject to changing background and environmental noise. A mathematical problem is to unmix or decompose the measured data into a set of pure or source spectra without knowing the mixing process, a so-called blind source separation problem.

In the talk, the speaker presented algorithms for blind separation of spectral mixtures in noisy conditions. The approach combines geometrical and statistical analysis of the data; the geometric approach is based on the vertexes and facets identification of cone structures of the data, while the statistical approach is on decomposing fitting errors when partial knowledge of the source spectra is available. Computational results on data from NMR, Raman spectroscopy and differential optical absorption spectroscopy show the applicability of the methods. This is joint work with Jack Xin from UC Irvine.

Finite Element Program Package for Solving a Nonlocal Dielectric Model for Protein in Salt Soluiton

Dexuan Xie (Department of Mathematical Sciences, University of Wisconsin-Milwaukee)

Calculation of electrostatic potential energy for proteins in ionic solvent is a fundamental task in the simulation study of the structure and biological function of proteins, catalytic activity, and ligand association. To reflect the polarization correlations among water molecules, several nonlocal dielectric models have been developed for a wide range of dielectric materials and dipolar liquids in the last thirty years. However, the study of a nonlocal model has been limited to the case of pure water solvent so far due to modeling and algorithmic complications. Most significantly, none of the current ionic models incorporate nonlocal dielectric effects. As the first step toward the direction of changing this situation, Dr. Xie recently proposed a nonlocal dielectric model for protein in ionic solvent, along side a new efficient numerical algorithm and program package for solving the model. In this talk, he gave their recent progresses a short review. He then described their finite element program package to show how they combine biomolecular tetrahedral mesh generation and visualization tools with their fast finite element solvers. With this package, they now can calculate and visualize the numerical solution of the nonlocal model by simply inputting a protein data bank (PDB) file of a protein immersed in salt solution.

Biomolecular surface/volume meshing and visualization for mathematical modeling

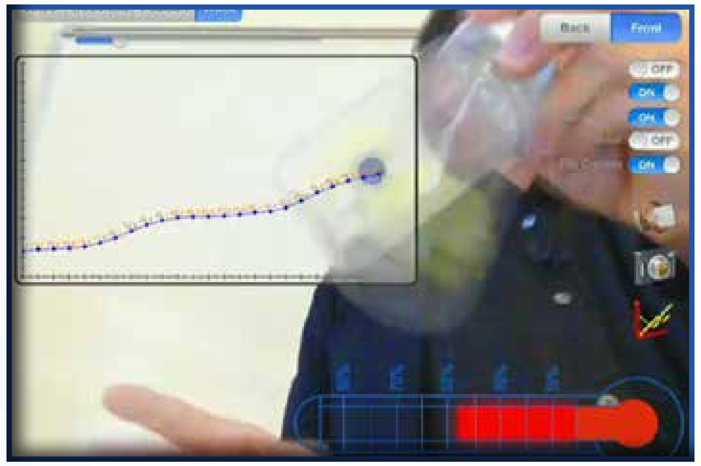
Benzhuo Lu (Institute of Computational Mathematics, Chinese Academy of Sciences)

It is a challenging task to generate a quality mesh that can be used for emerging mathematical modeling of biomolecular systems. In the first part, Dr. Lu presented a robust method and software (TMSmesh) developed recently to generate a manifold surface mesh for complex biomolecular surfaces. A Gaussian surface is used to represent the molecular surface. The method computes the surface points by solving a nonlinear equation directly, polygonizes by connecting surface points through a trace technique, and finally outputs a triangulated mesh. To guarantee the generated mesh is a manifold mesh, it is necessary to divide the surface into single-valued pieces along each x,y,z directions by tracing the extreme points along the fold curves on the surface. TMSmesh is shown be able to generate a quality surface mesh for arbitrarily large molecule in PDB. Volume mesh can be generated based on the TMSmesh surface mesh by applying a third-part software such as Tetgen. In the second part, he presented a visualization system MMV developed in his lab. MMV is also specifically designed for continuum-modeling community, featured by its multifunction of visualization, modeling and analysis of biomolecule, mesh, and simulation data.

Challenges in Interacting with Protein Interactions

Arthur Olson (Department of Molecular Biology, The Scripps Research Institute)

Biology has become accessible to an understanding of processes that span from atom to organism. As such, Dr. Olson indicated that we now have the opportunity to build a spatio-temporal picture of living systems at the molecular level. In their recent work they attempt to create, interact with, and communicate physical representations of complex molecular environments. He discussed the challenges and demonstrated three levels of interaction with protein interactions: 1) human perceptual and cognitive interaction with complex structural information; 2) interaction and integration of multiple data sources to construct cellular environments at the molecular level; and 3) interaction of software tools that can bridge the disparate disciplines needed to explore, analyze and communicate a holistic molecular view of living systems.



In order to increase the understanding and interaction with complex molecular structural information, they have combined two evolving computer technologies, solid printing and augmented reality. They create custom tangible molecular models and track their manipulation with real-time video, superimposing text and graphics onto the models to enhance their information content and to drive interactive computation. Dr. Olson and his group have recently developed automated technologies to construct the crowded molecular environment of living cells from structural information at multiple scales as well as bioinformatics information on levels of protein expression and other data. They can populate cytoplasm, membranes, and organelles within the same structural volume to generate cellular environments that synthesize their current knowledge of such systems.

The communication of complex structural information requires extensive scientific knowledge as well as expertise in creating clear visualizations. Dr. Olson and his group have developed a method of combining scientific modeling environments with professional grade 3D modeling and animation programs such as Maya, Cinema4D and Blender. This gives both scientists and professional illustrators access to the best tools to communicate the science and the art of the molecular cell.

Tunnels, Handles and Bottlenecks

Yiying Tong (Computer Science and Engineering Department, Michigan State University)

Dr. Tong presented a method for computing "choking" loops - a set of surface loops that describe the narrowing of the volumes inside/outside of the surface and extend the notion of surface homology and homotopy loops. The intuition behind their definition is that a choking loop represents the region where an offset of the original surface would get pinched. Their generalized loops naturally include the usual $2g$ handles/tunnels computed based on the topology of the genus-g surface, but also include loops that identify chokepoints or bottlenecks, i.e., boundaries of small membranes separating the inside or outside volume of the surface into disconnected regions. Based on persistent homology theory, their definition builds on a measure to topological structures, thus providing resilience to noise and a well-defined way to determine topological feature size.

Three-Dimensional Geometric Modeling and Visualization for Bio-Molecules and Imaging Data

Zeyun Yu (Department of Computer Science, University of Wisconsin at Milwaukee)

Biological structures provide rich information on their functions. Depending on the size and imaging resolution, a biological structure is often given as one of two common forms: (1) bio-molecules at atomic-resolutions typically obtained by X-ray crystallography or NMR, and (2) raster-scan images taken with various imaging devices such as optical or electron microscopes. Over the last decade, we have seen a rapidly increasing number of biological structures that are freely available through public databases such as the Protein Data Bank (PDB) and Electron Microscopy Data Bank (EMDB). Three-dimensional (3D) geometric modeling of these structures becomes critical not only for shape visualization, quantification, and analysis of the structures themselves, but also for mathematical simulations of their functions.

In this talk, Dr. Yu presented computational approaches to constructing high-quality surface mesh models from both bio-molecules and imaging data. In addition, he briefly discussed how volumetric (tetrahedral) meshes could be generated and optimized for finite element based numerical simulations. A software toolkit they recently developed will be demonstrated to support the pipeline of geometric modeling and visualization from bio-molecules and imaging data.

FRIDAY, February 22, 2013

Mathematical methods for biomolecular imaging, surface and visualization

Molecular geometry: a unified theory for understanding geometry in molecular worlds

Deok-Soo Kim (Hanyang University)

In this talk, Dr. Kim presented a unified theory of molecular geometry and demonstrated how the theory can be used for accurately, efficiently, and conveniently solving molecular problems. The molecular geometry theory is based on the beta-complex that is a derived structure from the Voronoi diagram of atoms and its dual structure called the quasi-triangulation. Voronoi diagrams are everywhere in nature and are useful for understanding the spatial structure among generators. Unlike the well-known ordinary Voronoi diagram of points, the Voronoi diagram of spherical atoms has been known to be difficult to compute. Once computed, however, it nicely defines the proximity among the atoms in molecules.

Dr. Kim introduced the Voronoi diagram of atoms and its dual structure, the quasi-triangulation, in three-dimensional space. Based on the quasi-triangulation, he defined the beta-complex which concisely yet efficiently represents the correct proximity among all atoms. It turns out that the beta-complex, together with the Voronoi diagram and quasi-triangulation, can be used to accurately, efficiently, and conveniently solve seemingly unrelated geometry and topology problems for molecules within a single theoretical and computational framework. The correctness and efficiency of solutions can be mathematically guaranteed straightforwardly. Among many application areas, structural molecular biology and noble material design are the most immediate application area. Several application examples were discussed in this talk: the most efficient/precise computation of van der Waals volume (and area); an efficient docking simulation; the recognition of internal voids and their volume computation, etc.

Mathematical Techniques in Structural Biology

Jack Quine (Florida State University)

Finding the structure of proteins from NMR or x-ray crystallography relies on mathematical methods. In this talk, Dr. Quine summarized the mathematical methods in studying the structure of proteins. The geometry of the curve is defined by quantities curvature and torsion along the curve. These are defined in terms of a Frenet frame. Discrete Frenet frames (DFF) are useful in calculations involving NMR structure of proteins. DFF computations show that under simplifying assumptions NMR can find that the structure of a kinked alpha helix.

The geometry of the manifold of space polygons, with applications to statistical physics of polymers and 3d shape registration for proteins and biomolecules

Jason Cantarella (University of Georgia)

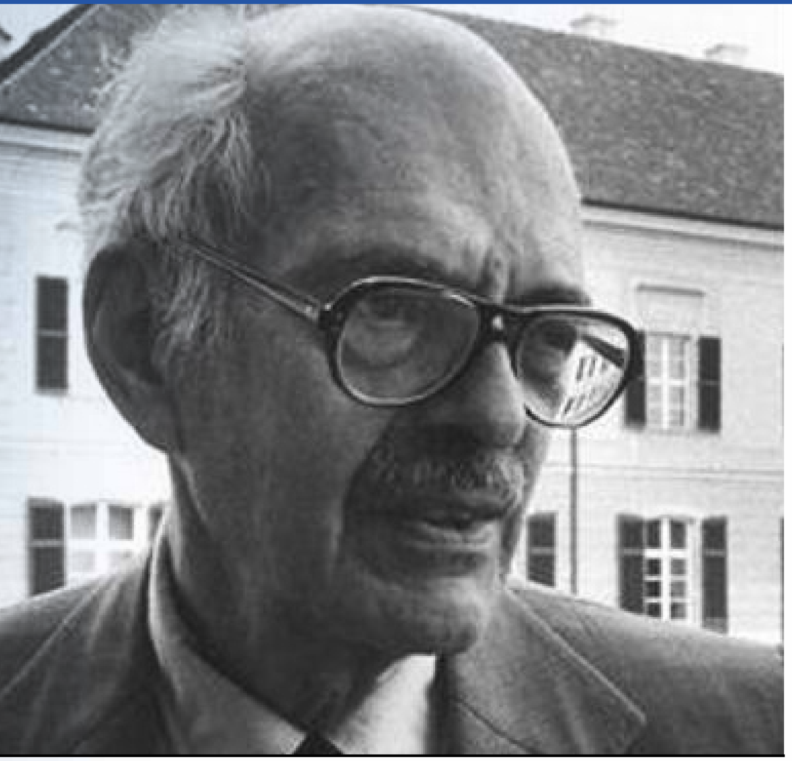
Jean-Claude Haussmann and Allen Knutson introduced a marvelous description of a certain space of framed space polygons (up to rotation and translation in R^3) as a space that is almost everywhere covered by the Grassmann manifold G_2(C^n) of orthonormal 2-frames in complex n-space. The standard Riemannian metric on the Grassmann manifold then induces a natural metric on this moduli space of framed polygons, within which we can make explicit and useful computations. This description yields a natural setting for many problems of interest in mathematical biology involving curves. In this talk, the speaker covered two applications. The first is predicting the statistical properties of a ring polymer in solution, which is considerably simplified by this framework. The second is curve registration and comparison in 3D, with applications to protein structures (here we are following Younes, Michor, Mumford, Shah, who used the corresponding structure for plane curves).

The Keyfitz Centennial Symposium on Mathematical Demography

June 24-28, 2013

**Organizers: John Bongaarts,
Hal Caswell,
Noreen Goldman,
Josh Goldstein, Ron Lee,
and Shripad Tuljapurkar**

Report by: Noelle Beckman, Paul Hurtado, Adrian Lam



Nathan Keyfitz (1913--2010)

Cosponsored by MBI and the OSU Institute for Population Research (IPR).

Nathan Keyfitz (1913--2010) made fundamental and highly influential contributions to demography over a long and productive career. His work was characterized by an elegance of approach and a depth of insight that came from a deep recognition of the interplay among models, data, and interpretation. This symposium, marking the 100th anniversary of his birth, will bring together a diverse set of scientists studying, to use Keyfitz's term, the mathematics of population.

The main goal of the Symposium is to serve as a forum for presentation of ongoing research on the mathematics of population. The program will encompass research on human and non-human populations, and both theoretical and applied research. In bringing together both mathematical demographers and population biologists, the symposium will adhere to Keyfitz's view, from his first book to his last, that population itself as an object worthy of study, not limited to particular species:

"[This book] tries to gather together, and as far as possible to systematize, the most relevant parts of that large body of mathematical theory concerned with the growth processes of human and animal populations."
Introduction to the Mathematics of Population (1968)

"... the general drift of their replies was that ... there was nothing that could be usefully added. We were monumentally wrong. We hadn't noticed the world of whales and birds and land animals, i.e., the world of biology."
Applied Mathematical Demography, 3rd Edition (2005)

The symposium program will be a mix of theoretical and applied work -- mathematical exercises as well as empirical work that make use of models and techniques that draw on mathematical demography.

The symposium program will be structured so as to encourage maximum exchange among scholars in attendance. Sharing of work in progress will be encouraged (and therefore there will be no requirement to prepare manuscripts of presentations). The goal is to stimulate discussion, cooperation, and collaboration.

MONDAY, June 24, 2013

Nathan Keyfitz and his work.

Hal Caswell (Woods Hole Oceanographic Institution)

Hal Caswell gave an introduction to the symposium and highlights of the work of Nathan Keyfitz. The symposium was a mix of human demographers and ecologists. In 1964, Keyfitz rediscovered matrix population models developed by Leslie. At the same time, stage-based models were developed by Lefkovitch and Rogers. In 1968, Keyfitz published the first book on the mathematics of populations. He published an important text on applied mathematical demography in 1977; subsequent editions were published in 1985 and 2005 (the latter with Caswell). Keyfitz recognized the importance of compiling data into readily analyzable form; the Human Mortality Database, the Human Fertility Database, and several databases under development by plant and animal demographers are part of his legacy.

Intrinsic Linkages in Dynamic Multistate Populations

Robert Schoen (Penn State)

The goal of intrinsic linkage is to analytically project population size and structure into the future from knowledge of the linkage parameter(s) and the dominant component of the population projection matrices. This idea was developed by Schoen in 2013, and in this talk he extends this approach for multistate models. Schoen gives examples of cohort analysis for the status of married and unmarried people of different age groups.

Sensitivity Analysis in Mathematical Demography

Hal Caswell (Woods Hole Oceanographic Institute)

Keyfitz performed sensitivity analyses in many ways and contexts. In 1971, Keyfitz published a paper on linkages of intrinsic age-specific rates in which he derived the sensitivity of many variables. Caswell discusses his work on sensitivity analyses of demographic calculations. He begins with an overview of sensitivity analyses in the context of population projection matrix models using matrix calculus. One application of sensitivity analyses is to selection gradients and the evolution of senescence. The sensitivity of the growth rate to the change of a parameter is a measure of the selection gradient. Hamilton showed that the selection gradient declines with age. Caswell discusses examples of plant demographic models that include both age and stage in multistate models which show that sensitivity to age-specific mortality were non-increasing and age-by-stage specific mortality were not.

An overview of Vertebrate Demography

Jean-Dominique Lebreton (CNRS)

The diversity of vertebrates includes fish, birds, mammals, reptiles, and amphibians and encompass around 64,000 species. In his talk, he discusses three major topics: vertebrates tend to be long-lived, how does longevity evolve, and what are the consequences in a changing world. Most vertebrates have a discrete life cycle, with a seasonal or nearly seasonal sexual reproduction, and primarily age-dependent variation in demographic traits. Dispersal is the rule and natal dispersal tends to be larger than breeding dispersal. Senescence is well-marked in mammals, but often masked by heterogeneity in birds. The demographic differences among vertebrates can be ordered on a "slow-fast gradient" best measured by generation time. This variation is strongly linked in an allometric fashion to body weight within groups of species sharing a common general body "bauplan." In relation with the allocation of energetic resources, maximum population growth rate is inversely related to generation time. He suggests that all long-lived species are better adapted to density-dependence and short-lived species evolved without density-dependence. Lebreton discusses consequences of longevity and demographic sensitivity of vertebrates in a changing world. Conservation status is poor when generation time is longer because of their greater sensitivity to exploitation. One can use generation time for a proxy of the critical parameter r_max. All hominoids (except for man) are classified as "endangered" by the International Union for Conservation of Nature (IUCN).

Estimating age structure in insect populations using the captive cohort method

James Carey (University of California, Davis)

Carey discusses an analytical framework and empirical requirements for the use of the death distribution of live-captured insects of unknown age to estimate age structure of their population in the wild. Existing methods, such as mechanical/physiological, biochemical, and genetic (transcriptional profiling) approaches, are costly in terms of money and time. Using captive cohort methods, Carey shows that the death distribution of live-captured individuals of unknown age can be used to: (1) determine the exact age structure of hypothetical stationary populations (i.e. life table identity); ii) estimate the age structure of wild populations using a simple model and reference life tables; and iii) estimate quantitative changes in population mean age and qualitative changes in the age extremes (young and old). He illustrates this approach with field studies of the Mediterranean fruit flies populations in Greece.

TUESDAY, June 25, 2013

Demographic patterns in populations of long-lived and iteroparous mammals

Jean-Michel Gaillard (CNRS)

The speaker presents a comparative study of the elasticities of long-term stochastic growth rate and transient dynamics with respect to change of a given vital rate on short-lived versus long-lived mammalian populations. The studies shown that while the change in vital rate has an immediate positive effect on population growth, the indirect effect on growth via the change in age structure depends on the generation time of the underlying species. In fact, the indirect effect of change in age structure can be negatively correlated to population growth and its impact on the long-term stochastic growth rate cannot be compensated by the direct increase in population growth. Also, slow species have more attenuated transience than the fast species. It is concluded that longer generation time acts as a buffer on the influence of change of a vital rate.

New theory needed to explain the evolution of senescence

Annette Baudisch (Max Planck Institute for Demographic Research)

Hamilton in 1966 proposed an adaptive framework, by a perturbation analysis in changing mortality rate over different ages, and it was concluded that senescence is inevitable. In this talk, the speaker reports a generalization of this framework to allow for perturbation of fertility rate and mortality rate simultaneously. And it is shown that contrary to Hamilton's result, depending on the age where the effect of senescence breaks even, evolution may or may not select for senescence, thus reconciling the existence of species without senescence.

Evolvability of the Human Life History

James Holland Jones (Stanford University)

The speaker reports an analysis of the Utah Population Database from 1820 to 1900, focusing on the evolvability of human life histories. The variability of indicators including age at first and last reproduction (AFR/ALR), interbirth intervals (IBI) are compared between mothers and their offsprings. By using novel method, the relatively large dataset is matched using the animal model framework. It is shown that while AFR and ALR alone does not have strong correlation across generations, the joint correlation of AFR ALR, and IBI alone shows significant correlation between an individual and its offspring. It is argued that human life history might be heritable and thus might be evolvable.

On the evolution of intergenerational division of labor, menopause and transfers among adults and offspring

Ronald D. Lee (National Institute of Demographic Studies)

In this talk, the evolvability of menopause is argued using a cooperative game theory framework in which the younger adults are playing against older adults. In contrast to the non-cooperative situation, the average fitness of the whole group increases when older adults sacrifices their reproductive opportunity to afford more childcare, freeing up younger adults for more reproductive activities. Menopause evolves as a result of this exploitation of comparative advantage between young and old adults in fertility. It is further argued that further specialization occurs when the older adults foraging time further decreases below her subsistence needs, which is possible only with food transfers to the grandmother in the cooperative setting.

WEDNESDAY, June 26, 2013

Modelling the accumulation of small-effect deleterious alleles in the evolution of senescence

David Steinsaltz (University of Oxford)

The speaker presents a general nonlinear model for the evolution of senescence. It was argued that Hamilton's earlier model, which treats mutations that act only at a single age are not an approximation of the realistic mutation-driven changes in full age-specific demographic schedules. A number of computations are presented at the end of the talk where the deviation of the equilibrium of the general model from Hamilton's linear model is illustrated.

Mathematical Demography of Aging

Anatoli Yashin (Duke University)

Starting an observation of the Gompertz mortality curve, which is related to the decline in resistance to stresses with increasing age, the speaker proposed that measured and non-measured biomarkers together characterize biological mechanism involved in regulation of aging. A stochastic differential equation model incorporating physiological state, health and longevity is proposed to explain how changing environmental conditions affects genetic variability, which indirectly affects lifespan through physiological variables. Two examples are presented where the model is being tested with demographic data.

Multiregional Demography: Migration and Population Redistribution

Andrei Rogers (University of Colorado at Boulder)

The speaker gave an introductory talk surveying different aspects of multiregional demography. By drawing on demographical data in the US during 1900-2000, the development of modeling the age and spatial dynamics of multi-regional populations, as well as modeling and estimating the age and spatial structures of migration flows are presented. Different practical ways of dealing with irregular and missing data are presented in connection to projection and forecasting.

Taylor's law of fluctuation scaling: from bacteria to humans and beyond

Joel Cohen (Rockefeller University)

Taylor's law refers to L. R. Taylor's observation in 1961 that the variance of population density is proportional to a power of mean population density. A recent empirical work on the number of oak trees on plots of land in the Black Rock Forest during 1928-2009 is presented, where it is demonstrated a new consequence of Taylor's law, namely, that the logarithm of variance of number of Oak trees across the plots has a linear dependence on the logarithm of mean of biomass. Similar observations are made concerning the populations in different municipalities and regions of Norway during 1978-2010. The speaker went on and gave a historical perspective on the significance of Taylor's law, which seems to capture some fundamental properties across populations of human, bacteria and plants.

Are low-fertility populations sustainable?

Nan Li (United Nations Population Division)

Dr. Li began with an overview of how demography affects pension systems. In many developing countries fecundity rates have dropped below 2.1, posing challenges for traditional means of family-supported care of individuals who have left the workforce. Japan, for example, has experienced reduced mortality and fecundity in recent decades, stressing their pay-as-you-go system and prompting a large tax increase to sustain the program for the near future. In this talk, he focused on the potential benefits of self-funded programs like the 401K in the U.S. Comparing the difference between the pension burdens of the two systems (pay-as-you-go vs. self-funded) in certain periods could provide relevant information to the decision on whether or not to establish funded pension systems to cope with low fertility. To make these comparisons, he introduced a time-referred old-dependence ratio (ODR) and compared this measure where old individuals were either supported by members of their cohort (CODR) or of the same period (PODR). These quantities can be computed for all the countries and areas of the world. Examples were given for China Japan, and Republic of Korea, which indicated that low-fertility populations are sustainable, but require more sophisticated means to sustain.

Formal demography of kinship

Emilio Zhageni (Queens College – CUNY)

Dr. Zhageni introduced the Keyfitz equations, which model the frequencies of different kinship relationships, i.e., whether a focal female individual has surviving children, her mother, grandmother, etc. The goal of his talk was to illustrate how these equations are still relevant to understanding population and demographic dynamics, to discuss their limitations, and show how microsimulation (individual-based) modeling is generating renewed interest in these equations. The first part of his talk focused on HIV/AIDS related maternal orphans in Africa, and projecting these trends forward into the future. This was done from the perspective of children and of mothers. He then discussed changes in the experience of kin death over a demographic transition using data from Sweden. In this context, certain shortcomings of the Keyfitz equations could be addressed via microsimulation, for example, the age of when an individual first experiences the death of kin (e.g. a grandmother). For the remainder of his talk he discussed the "sandwich generation" – women with children and multiple older generations in need of care – and the impact of different kinship scenarios on factors like resource availability and health. The results presented by Dr. Zhageni's illustrate how rigorous modeling of the demography of kinship is important for understanding a suite of issues including family dynamics, the extended impact of demographic shocks, consequences of changing the life course, kin inequalities in access to resources, intergenerational transfers, and to corroborating and building individual-based computational models.

THURSDAY, June 27, 2013

Measuring Trends in Nuptiality

Juha Alho (University of Eastern Finland)

Dr. Alho began by introducing a modeling framework for the stochastic formation of marriages considered in continuous time. The models are parametrized in terms of a fundamental measure of nuptiality, the relative propensity to marry, and the mutual attraction of potential spouses. The models were then extended to include age structure, and yield a well defined arrival process model of marriages. Dr. Alho demonstrated that if the overall intensity of nuptiality is taken to be a weighted average of the intensities of the two sexes, under a particular rescaling, then different choices of scale lead to alternative concepts of population of risk, and as such to different two-sex models. Dr. Alho also discussed statistical estimation of the model parameters, and examples of using this framework in stochastic microsimulation.

Applied Demographic Modeling for Rubella

Jessica Metcalf (Oxford University)

Dr. Metcalf began with a history and overview of Rubella (aka German measles). Infection of women during their first months of pregnancy can cause those children to be born with Congenital Rubella Syndrome (CRS) characterized by blindness, deafness and other developmental defects. She then described the current vaccination program for the disease, and gave a brief overview of the kinds of SIR models that have been built to assess the affect of vaccines on the disease dynamics. In particular, vaccination decreases the number of infections in the population and increases the age of infection, as expected from such models. Dr. Metcalf then presented similar data focusing on young women (who would be harmed most by infection) who instead experience an increase in CRS burden from some vaccination programs. Based on models that incorporated age structure and focused on CRS incidence, Dr. Metcalf went on to explain this outcome – a hump-shaped relationship between percent vaccination coverage and CRS incidence among newborns –in terms of the increased age of infection that results from widespread (but imperfect) vaccination programs. These finding were then considered in a stochastic metapopulation framework, and compared with data from multiple countries. Together, the deterministic and stochastic model results suggest that this counterintuitive relationship between CRS incidence and vaccine coverage was robust to multiple model assumptions, and that CRS incidence would be decreased if rubella vaccine coverage matched or exceeded the current measles vaccine coverage in countries like South Africa, however heterogeneity in vaccine coverage, local rubella extinction, and human population movement could still leave some districts at risk.

Modeling Temporal Changes in Inequality

Hui Zheng (The Ohio State University)

Dr. Zheng introduced the use of Variance Function Regression (VFR) to problems in demography, specifically, the study of inequality. This approach permits estimation of how the mean and variance of response variables each depend on covariates of interest. This was done using General Linear Mixed Model (GLMM) framework with the embedded VFR model to implement a Hierarchical Age-Period-Cohort (HAPC) regression model that captures the effects of age within the contexts of time periods and cohorts. This framework was then applied to understanding the connections between across-cohort, across-period, and across-age factors affecting U.S. health disparity using National Health Interview Survey data from 1984-2007. The results showed very strong age-related health effects (as expected) as well as strong cohort and period effects, with cohort effects contributing more than period to changes in variance over the timeframe of the survey data. Dr. Zheng also presented results using these methods to look at variation in mortality using the Human Mortality Database.

Demography of Social Mobility

Rob Mare (University of California, Los Angeles)

In this talk, Dr. Mare presented a mix of original research and an overview of existing literature on the formal demography (i.e., mathematical demography) of social mobility. The talk began with two papers by Nathan Keyfitz that presented a simplified framework for modeling the influence of demographic processes on social mobility. In reviewing the literature, Dr. Mare found thousands of papers on the general topic of movement between different kinds of social classes, most of these authored by sociologists and economists, however most are demographically uninteresting or completely lacked a demographic component. Dr. Mare then provided an overview of influential papers that also illustrate the historical prominence (or lack thereof) of demography and formal demography (mathematical demography) in social mobility research. Next, approaches to modeling multigenerational effects were discussed in the context of remote ancestral effects that have been found in data sets like the Qing Dynasty Imperial lineage, where differential fertility and marriage processes were essential to capturing multigenerational trends in the data. The short and longer run implications of such effects depend on whether mobility processes depend on the characteristics of one sex or both sexes. Next, Dr. Mare compared one- and two-sex models using a more recent example of multigenerational reproductive trends related to college education in the U.S., using PSID (Panel Study of Income Dynamics) data. Dr. Mare concluded by summarizing the knowledge gaps that exist at the interface between demographic and social mobility research regarding applications of one- and two-sex models, family dynamics, and by illustrating the many (as yet unexplored) multigenerational models that exist in this context.

When does the Human Dependency Ratio Become Binding?

Shripad Tuljapurkar (Stanford University)

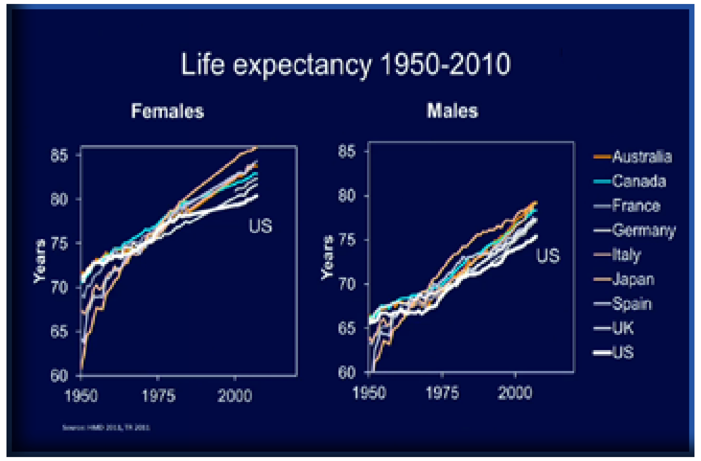
Dr. Tuljapurkar began by introducing the dependency ratio: the number of young and non-working old supported by an average worker. He also illustrated how it relates to reproduction rates and age distributions in a population. This ratio is a principal determinant of realized per-capita consumption, which in turn depends on productivity, and desired per-capita consumption, and in large part drives human wellbeing. Dr. Tuljapurkar summarized how realized per-capita consumption depends on worker productivity, population size, labor force and desired consumption rates in a static mathematical form to define the Dependency Burden, a measure of dependency. Before the rise of the modern industrial state, population growth rate determined the dependency ratio and hence affected wellbeing. In the reverse direction, fertility and mortality varied with wellbeing, and hence so did growth rate. Moving from a static framework to a dynamic one results in a feedback system that yields a population equilibrium at which dependency is binding. The speaker used Hawaii (ca. 10,000 years ago) as an example, and contrasted that case with post-industrial countries, where worker output is higher and the link between fertility and wellbeing has weakened. Dr. Tuljapurkar ended by describing how following industrialization, the growth of wellbeing depends on growth in productivity, consumption, and dependency. That is, the growth rate of dependency can and does become binding.

FRIDAY, June 28, 2013

Stochastic demography of tropical and subtropical plants
Carol Horvitz (University of Miami)
Horvitz uses matrix and integral projection models to address ecological, evolutionary, and applied demographic questions of perennial tropical and subtropical plants. She discusses the results of various projects including the effect of hurricanes on the impact of native seed predators; integrating selection on quantitative traits across the life cycle when selection gradients vary over time; trade-offs due to the cost of reproduction; how harvest regime of non-timber forest products affects longevity of trees; life expectancy of pioneer vs shade-tolerant tropical trees; the impact of rarely occurring long distance dispersal vectors to invasion speed; and effectiveness of bio-control agents on invasive trees and shrubs; and others. Horvitz concludes that elasticity of stochastic growth rates in different environments depends on the future; cost of reproduction can be offset if environments beneficial for juveniles come after high reproduction; selection on traits depends upon environments; and mortality trajectories over the lifetime depend on stage structure.

Nathan Keyfitz, the beginning and the end: investigations into human development at the beginning and end of human life
Steven Orzack (Fresh Pond Research Institute)
Keyfitz interests encompassed mathematics, statistics, music, and politics. The last paper Keyfitz published was with Orzack on all the famous scientists Keyfitz knew. Orzack presented analyses of the demographic and genetic trajectory of the human sex ratio from conception to birth and analyses of the dynamics and statics of morbidity and mortality across the course of human life and across cohorts.

Projecting mortality at the end of the epidemiological transition
John Bongaarts (Population Council)
Bongaarts discusses key trends in the causes of death and gives an overview of different mortality projection methods. The death rate has decreased with time, and the rate of decrease is lower for females than males. The key cause of this difference is smoking. Future declines in mortality rates may slow down due to difficult to treat diseases. The U.S. mortality projections may be too conservative as Eurostat projects predict longer life spans for Europe. Bongaarts discusses mortality projections based on the Social Security Administration Actuaries, the Lee-Carter projection method, best practices (Oeppen & Vaupel), and suggestions made by the 2011 technical panel of the Social Security Advisory Board to adjust predictions by smoking and obesity. He suggests mortality projection can be improved by taking into account trends in causes of death, which requires further research.



Insights into human survival: from the South Pacific to East Asia
Noreen Goldman (Princeton University)
Goldman's early work was inspired by Nathan Keyfitz and examined the implications of mortality for a broad range of phenomena: dating the time of settlement of the Nukuoro society; examining the impact of mortality change on life expectancy; and identifying the cause of high mortality among never-married individuals in contemporary Japan. She then discusses her ongoing work in biosocial surveys: the extent to which clinical and other biological markers enhance mortality prediction in older populations. She also discusses how perceived age by interviewers rather than physicians or one's self are better predictors of health, and is currently determining why.

2013
Undergraduate
Research Program
May 20 - August 16, 2013

The goal of this program is to introduce students to exciting new areas of mathematical biology, to involve them in collaborative research with their peers and faculty mentors, and to increase their interest in mathematical biology. The program consisted of three parts - each including a mix of educational and social experiences: a two-week introduction to mathematical biology (May 20 - 31, 2013); an eight-week individualized research experience as part of a research team at one of the eight participating host institutions; and a week-long Capstone Conference.

The two-week program featured tutorial lectures, computer labs, lab tours, and short-term team efforts designed to introduce students to a variety of topics and methods of research in mathematical biology. The lectures were given by several distinguished researchers. Jim Keener kicked off the two-week program with an overview of Mathematical Biology showing how movement and reaction underlying biological processes are modeled with dynamical systems and other mathematical tools. Giovana Guidoboni provided an introduction to fluid dynamics and the partial differential equations used in tissue and blood modeling. Dennis Pearl led a discussion of estimating evolutionary histories using the tools of statistical phylogenetics. Neuroscience was represented by Bard Ermentrout and Janet Best, each providing tutorials on computational and mathematical neuroscience respectively. Winfried Just presented an overview of disease dynamics, and Sebastian Kurtek discussed statistical image analysis. Each of these tutorials were accompanied by a computer lab to introduce them to computational aspects of the problems under study - leaving them with strong practice in MatLab, R, XPPAUT, and various web applications. The students also participated in short-term team investigations in these various areas. The labs and investigations were led by Dennis Pearl and MBI postdocs Michael Schwemmer, Rachel Leander, and Franziska Hinkelmann.

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

For the 16 MBI supported students, the end of the two-week program marked the start of their summer-long projects at one of the host institutions. These included projects at Arizona State University supervised by Jay Taylor; at the University of California-Irvine supervised by Frederic Wan, John Lowengrub, and German Enciso; at the University of Georgia supervised by Caner Kazanci; at the University of Houston, supervised by Kresimir Josic, Zachary Kilpatrick, and Will Ott; at Indiana University-Purdue University Indianapolis supervised by Julia Arciero and Yaroslav Molkov; at University of Pittsburgh supervised by Bard Ermentrout; at the Ohio State University supervised by Sebastian Kurtek and Laura Kubatko; and at the Virginia Biomathematics Institute at Virginia Tech supervised by Reinhard Laubenbacher.

The Summer Program ended with a weeklong Capstone Conference celebrating all of the nationwide efforts of undergraduate researchers in the mathematical biosciences – not just those of the MBI sponsored REU students. This student-centered conference featured a graduate studies recruitment fair for Institute Partner Schools (16 programs participated); panel discussions on job and graduate opportunities in mathematical biology; keynote talks from prominent mathematical bioscientists geared toward student interests; an opening reception and a mid-week social event at the Columbus Zoo & Aquarium followed by a dim sum banquet dinner. Most importantly, the capstone conference offered undergraduate students doing research projects in the mathematical biosciences an opportunity to present their work on the national stage. This included 24 half-hour oral presentations and 40 poster presentations on individual and team projects. This next generation of mathematical biologists were all actively engaged in the lively discussions around each topic and made the conference a terrific success.

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

2013

Summer Graduate

Program at NIMBioS

June 17-28, 2013

The 2013 Summer Graduate Workshop, co-sponsored by NIMBioS, the Mathematical Biosciences Institute and the Centre for Applied Mathematics in Bioscience and Medicine, began with a full slate of modeling lectures and computer activities scheduled for the two-week program. The program, which ran from June 17-29, was hosted at NIMBioS in Knoxville, TN this year. It featured instructors from across North America whose research expertise is mathematical modeling in biological systems using real data. Some of the techniques covered included Maximum likelihood and Bayesian approaches to inference, parameter estimation, model identifiability, uncertainty and sensitivity analysis, and data assimilation. Applications of connecting data to models will come from epidemiology, ecology (including global change biology), evolution, microbiology, physiology, pharmacokinetics, and systems biology. Activities included lectures, computer exercises and research projects. In addition to attending lectures and completing computer activities, each of the 40 participants will work in teams on a specific research project and present findings at the end of the program. Instructors included Tom Banks, North Carolina State University; Ben Bolker, McMaster University; Ariel Cintron-Arias, East Tennessee State University; Marisa Eisenberg, University of Michigan; Kevin Flores, North Carolina State University; Paul Hurtado, Math Biosciences Institute; Denise Kirschner, University of Michigan; Simeone Marino, University of Michigan; Vasileios Maroulas, University of Tennessee-Knoxville; Kiona Ogle, Arizona State University. Also assisting were NIMBioS Postdoctoral Fellows Jeremy Beaulieu, Jiang Jiang, Keenan Mack, Gesham Magombedze, Calistus Ngonghala, Chris Remien and Dan Ryan.

NIMBioS
National Institute for Mathematical and Biological Synthesis

CAMBAM
Centre for Applied Mathematics in Bioscience and Medicine

Colloquium

Leslie Loew
Boehringer Ingelheim Chair in Cell Sciences Professor of Cell Biology, Professor of Computer Science and Engineering Director, R. D. Berlin, Center for Cell Analysis and Modeling University of Connecticut Health Center
The Virtual Cell Project - September 10, 2012

Michael C. Mackey
Director of the Centre for Applied Mathematics in Bioscience and Medicine
Using mathematics to understand, treat, and avoid hematological disease - October 22, 2012

Lisa Fauci
Mathematics, Tulane University
Spiny Disks, Flexible Fibers and Waving Rings: Explorations in Phytoplankton Fluid Dynamics - November 5, 2012

Peter Mohler
Director, Davis Heart and Lung Research Institute, OSU Medical Center
New Paradigms for Human Excitable Cell Disease November 19, 2012

Prahlad T. Ram
Department of Systems Biology, UT MD Anderson Cancer Center
Mathematical and experimental analysis of biological networks to identify targets for therapy December 3, 2012

John Reinitz
Statistics, Ecology & Evolution, and Molecular Genetics & Cell Biology, The University of Chicago
Transcriptional control in the Drosophila blastoderm January 7, 2013

David Van Essen
Anatomy & Neurobiology, Washington University St. Louis
The Human Connectome Project: Computational Challenges and Opportunities - January 28, 2013

Robert Miura
Mathematical Sciences, NJIT
Cortical Spreading Depression and Neurovascular Coupling - February 11, 2013

Dirk Gillespie
Molecular Biophysics and Physiology, Rush Medical College
Calcium movement in cardiac muscle - February 25, 2013

Lou Gross
Ecology and Evolutionary Biology and Mathematics, University of Tennessee
Savannas, Invasions and Lessons from Some Mathematical Models - March 4, 2013

Samuel Kou
Department of Statistics, Harvard University
Statistical sampling in protein folding - March 25, 2013

Robert Nosofsky
Indiana University
Categorization-Based and Recognition-Based Memory Search: Combining Formal Modeling and Brain-Imaging Approaches - April 15, 2013

Katherine Pollard,
University of California, San Francisco
Human accelerated regions drive unique expression patterns during embryonic development - April 22, 2013

Veronica Vieland
Vice President for Computational Research Battelle Chair in Quantitative and Computational Biology Director, Battelle Center for Mathematical Medicine Professor of Pediatrics and Statistics The Research Institute at Nationwide Children's Hospital & The Ohio State University
Is the universe made of information? - April 29, 2013

Visitor Seminars

Tim Lewis
University of California, Davis
Limb coordination in crayfish swimming: the neural mechanisms and mechanical implications January 30, 2013

Heiko Enderling
Center of Cancer Systems Biology, Tufts University School of Medicine
An integrated view of cancer stem cells in solid tumors February 12, 2013

Stephan Van Gils
University of Twente
Local bifurcation analysis in neural field equations with transmission delays - February 13, 2013

Drew Purves
Head, Computational Ecology and Environmental Science Group, Microsoft Research , Cambridge UK
and
Mark Vanderwel
University of Florida
Joined-up modelling in ecology (and biosciences in general!): likelihood, Bayesian, and all that February 26, 2013

LieJune Shiau
University of Houston, Clear Lake
Periodically stimulated adaptive integral-and-fire neuron February 27, 2013

Zhe (Sage) Chen
MIT/HMS/MGH
Uncovering rat hippocampal population codes: topological vs. topographic maps - March 6, 2013

Mingming Wu
Cornell University
Directed Cell Migration: Experiments and Modeling March 12, 2013

Martin Wechselberger
University of Sydney
Neuronal Excitability and Canards - March 13, 2013

Peter Ashwin
University of Exeter
Designing computational systems using heteroclinic networks - March 27, 2013

Andrea Barreiro
Southern Methodist University
Low-dimensional descriptions of neural networks April 2, 2013

Mike Reed
Duke University
Liver Metabolism and Public Health - April 16, 2013
Cell Metabolism and Neuroscience - April 23, 2013

Vince Billock
Wright Patterson
Synchronized neurons and sensor-fused rattlesnakes: Using neural synchronization to understand sensory integration and sensory enhancement in rattlesnakes, cats and humans - April 17, 2013

Yi Sun
University of South Carolina
Modeling, Simulation, and Analysis for Hodgkin-Huxley Neuronal Network Dynamics - April 23 ,2013

John Rinzel
Center for Neural Science and Courant Institute of Mathematical Sciences, New York University
Dynamics of Perceptual Bistability - April 24, 2013

Gemma Huguet,
Universitat Politécnica de Catalunya
Dynamics of perceptual switching in tri-stable visual stimuli - May 1, 2013

Edward Lungu
University of Botswana
Interaction between malaria parasite and the host immune system - May 15, 2013

Postdoc Seminars

Duan Chen
Free boundary-based multiscale/multiphyics modeling, simulation, and analysis of complicated biological systems - September 13, 2012

David Koslicki
Topological Pressure - September 27, 2012

Michael Schwemmer
Rational Analysis in Task Switching - October 11, 2012

Hye-Won Kang
A mathematical model for miR-9, let-7, and EMT in lung cancer - October 25, 2012

Leopold Matamba Messi
The Rayleigh-Ritz Method for Total Variation Denoising November 1, 2012

Seminars

Franziska Hinkelmann
Algebraic Theory for Discrete Models in Systems Biology
November 8, 2012

Adrian Lam
Evolution of Conditional Dispersal: ESS in Spatial Models
November 29, 2012

Paul Hurtado
Population and infectious disease ecology: How biotic and abiotic factors can shape host population and parasite dynamics - December 6, 2012

Rachel Leander
Granulomas and Model-based derivation of intermitotic time distributions - January 17, 2013

Jay Newby
Spontaneous activity from stochastic ion channels in the Morris-Lecar model of a neuron - January 24, 2013

Josh Chang
Kenel-based shape regularization with application to image segmentation and tracking - January 31, 2013

Kang Ling Liao
Analysis on Mathematical Models of Somitogenesis in Zebrafish - February 14, 2013

Casey Diekman
Generalized Rivalry Networks: Reduction, Dynamics, and Derived Patterns - February 28, 2013

Lucy Spardy
A dynamical systems analysis of afferent control in a neuromechanical model of locomotion - March 7, 2013

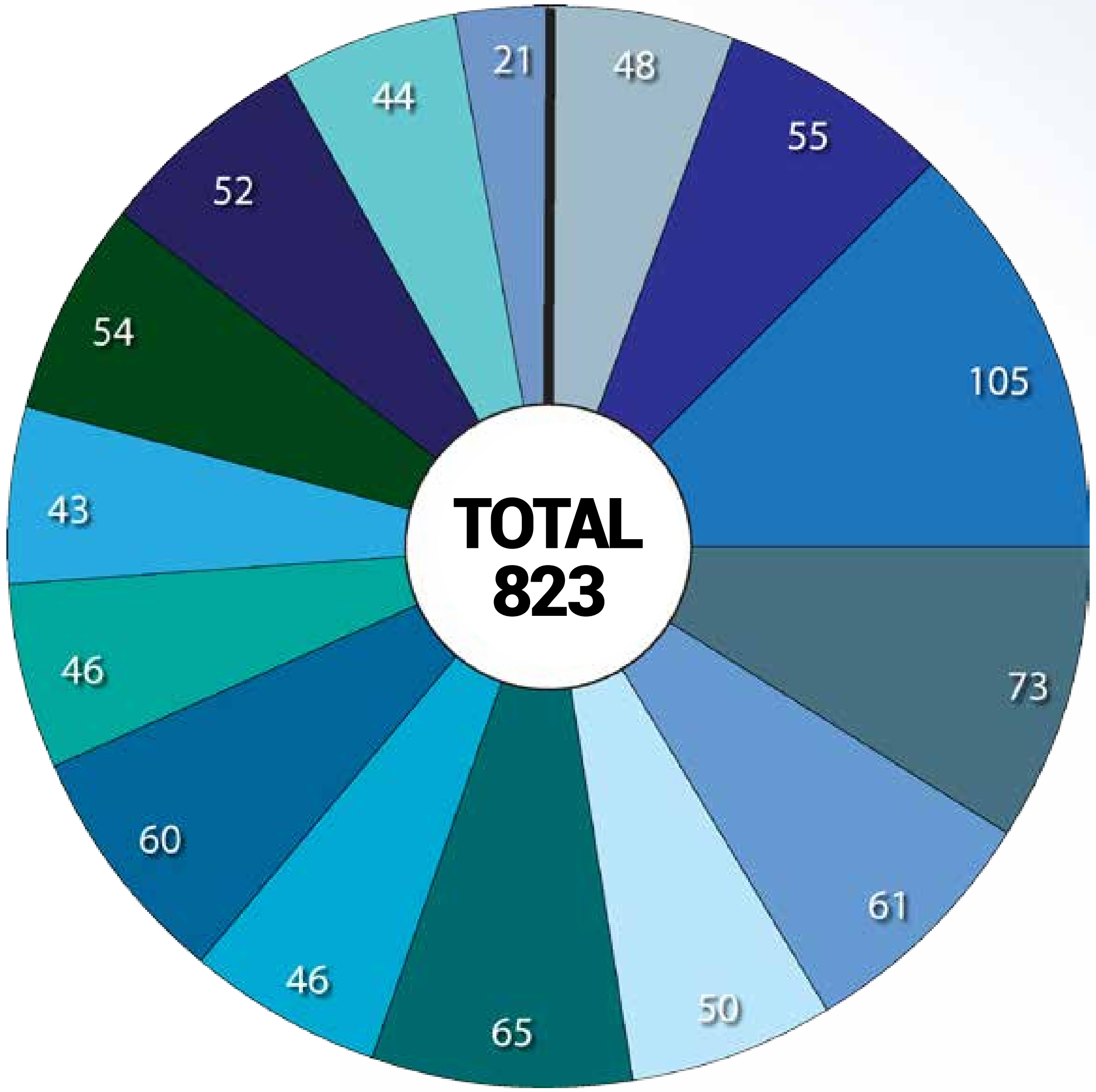
Noelle Beckman
The influence of vertebrates, insects, and pathogens on patterns of early plant recruitment in a Neotropical forest March 14, 2013

Arjun Beri
An individual-based model of emergent properties in ant colony dynamics - March 28, 2013

Jon Lo
Analysis and modeling of cell polarization in budding yeast - April 18, 2013

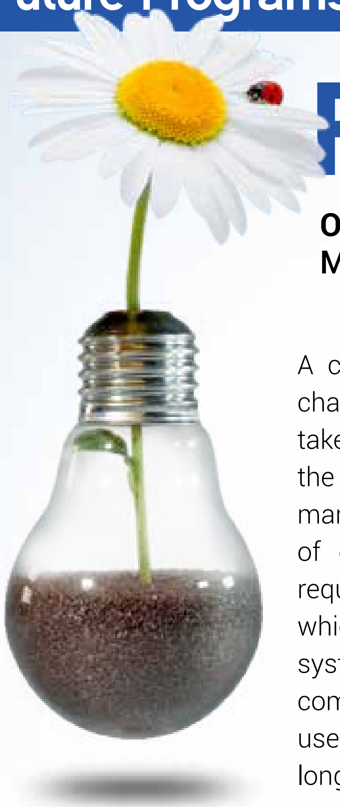
Jincheol Park
Recapitulating 3D Architecture of Chromatin using Hi-C data - April 25,2013

Program Participation



This graph represents the total number of supported participants for each event during the 2012-2013 emphasis year

- ■ MBI BioSciences Problem-Solving Workshop (July 16-20, 2012)
- ■ 2012 Workshop for Young Researchers in Mathematical Biology (WYRMB) (August 27 - 30, 2012)
- ■ Math Biology: Looking at the Future (September 19-21, 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 15-18, 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)
- ■ CTW: Mathematical Challenges in Biomolecular/Biomedical Imaging and Visualization (February 18-22, 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)
- ■ Undergraduate Research Program: Two-week Program (May 20-31, 2013)
- ■ The Keyfitz Centennial Symposium on Mathematical Demography (June 24-28, 2013)
- ■ Undergraduate Research Program: Capstone Conference (August 12-16, 2013)



Fall 2013 Ecosystem dynamics and management

Organizers: Jordi Bascompte, Chris Cosner, Alan Hastings, Marc Mangel, Jim Sanchirico, and Mary Lou Zeeman

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

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

Events 2013

July 29 - August 2, 2013
CTW: Teaching Discrete and Algebraic Mathematical Biology to Undergraduates

August 26-29, 2013
Workshop for Young Researchers in Mathematical Biology

September 16-20, 2013
Workshop 1: Sustainability and Complex Systems

October 7-11, 2013
Workshop 2: Rapid Evolution and Sustainability

October 28-Nov 1, 2013
CTW: Mathematics Guiding Bioartificial Heart Valve Design

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

Spring 2014

Frontiers in imaging, mathematics and the life sciences

Organizers: Monica Hurdal, Paul Kulesa, Mauro Maggioni, Allen Tannenbaum and Ross Whitaker

This one semester program will bring together researchers from mathematics, imaging technology, biology, and the life sciences to explore new ways to bridge these diverse disciplines, and to facilitate the use of mathematics for key problems in imaging, medicine, and the life sciences in general.

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

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

The broadening scope of imaging as a way to organize our observations of the biophysical world has led to a dramatic increase in our ability to apply novel processing techniques and to combine multiple channels of data into sophisticated and complex mathematical models including biological systems, physiological function and dysfunction. These challenging aspects demand concepts from compressive sensing, learning and information theory, and novel algebra-geometric/topological techniques that accordingly will constitute some of the key topics of this MBI program.

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

Events 2014

January 13-17, 2014
Workshop 1: Visualizing and Modeling Cellular and Sub-Cellular Phenomena

February 10-14, 2014
Workshop 2: Morphogenesis, Regeneration, and the Analysis of Shape

March 17-21, 2014
Workshop 3: Integrating Modalities and Scales in Life Science Imaging

April 21-25, 2014
Workshop 4: Analysis and Visualization of Large Collections of Imaging Data

J. Cushing, R. Costantino and S. Robertson
Life stages: interactions and spatial patterns
Bulletin of Mathematical Biology, Vol. 74 (2012) pp. 491-508 (Published)

K. Zhao
Global dynamics of classical solutions to a model of mixing flow
Journal of Dynamics and Differential Equations, Vol. 12-F Issue 2 (2012)

T. Li, K. Zhao, R. Pan and R. Pan
Global dynamics of a chemotaxis model on bounded
SIAM Journal on Applied Mathematics (2012)

K. Zhao
Long-time dynamics of a coupled Cahn-Hilliard-Boussinesq system
Communications in Mathematical Sciences, Vol. 10 (2012)

K. Zhao
Large time behavior of density-dependent incompressible Navier-Stokes equations on bounded domains
Journal of Mathematical Fluid Mechanics (2012)

M. Lai, R. Pan, K. Zhao and .
Initial boundary value problem for 2D viscous Boussi- nesq equations
Rational Mechanics and Analysis, Vol. 199 (2012) pp. 739-760

T. Li and K. Zhao
On a quasilinear hyperbolic system in blood flow modeling
Discrete and Continuous Dynamical Systems, Vol. 16 No. Series B (2012) pp. 333-344

K. Zhao
Global regularity for a coupled Cahn-Hilliard-Boussinesq system on bounded domains
Quarterly of Applied Mathematics, Vol. 69 (2012) pp. 331-356

E. Green, A. Bassom and A. Friedman
A mathematical model for cell-induced gel compaction in vitro
Mathematical Models and Methods in Applied Sciences (2012) (Accepted)

R. Cressman and V. Krivan
Two-patch population models with adaptive dispersal: the effects of varying dispersal speeds
Journal of Mathematical Biology (2012) (Published)

D. Chen and G. Wei
Quantum dynamics in continuum models for proton transport-Generalized correlation
Journal of Chemical Physics, Vol. 136 No. 134109 (2012)

J. Chifman
The core control system of intracellular iron homeostasis: A mathematical model
J Theor Biol, Vol. 300 (2012) pp. 91-99

M. Golubitsky and C. Postlethwaite
Feed-forward networks, center manifolds, and forcing
Discrete and Continuous Dynamical Systems - Series A, Vol. 32 (2012) pp. 2913-2935

M. Golubitsky, D. Romano and Y. Wang
Network periodic solutions: patterns of phase-shift synchrony
Nonlinearity, Vol. 25 (2012) pp. 1045-1074

J. Feder, R. Gejji, S. Yeaman and P. Nosil
Establishment of new mutations under divergence and genome hitchhiking
Philosophical Transactions of the Royal Society B: Biological Sciences, Vol. 367 No. 1587 (2012) pp. 461-474

D. Janies, J. Aaronson, S. Handelman, J. Hardman, L. Kawalec, T. Bitterman and W. Wheeler
Analysis and visualization of H7 influenza using genomic, evolutionary and geographic information in a modular web service
Cladistics (2012) (In Press)

Y. Kim and H. Othmer
A hybrid model of tumor-stromal interactions in breast cancer
Bull. Math. Biol. (2012) (Submitted)

Y. Kim, S. Lee, Y. Kim, Y. Kim, Y. Gho and H. Hwang
Regulation of Th1/Th2 cells in asthma development A mathematical model
J. Math. Biol. (2012) (Submitted)

W. Lo, L. Chen, M. Wang and Q. Nie
A Efficient and Robust Method for Steady State Patterns in Reaction-Diffusion Systems
Journal of Computational Physics (2012) (In Press)

W. Lo, S. Zhou, A. Lander and Q. Nie
Robust and Precise Morphogen-mediated Patterning: Tradeoffs, Constraints and Mechanisms.
(2012) (Submitted)

B. Shtylla and J. Keener
A mathematical model of ParA filament-mediated chromosome movement in Caulobacter crescentus.
Journal of Theoretical Biology, Vol. 307 (2012) pp. 82-95 (Published)

R. Tien and S. Ellner
Variable cost of prey defense and coevolution in predator-prey systems
Ecological Monographs (2012) (In Press)

A. Friedman, B. Hu and C. Xue
A three dimensional model of chronic wound healing: analysis and computation
DCDS-B (2012) (In Preparation)

F. Hinkelmann and A. Jarrah
Inferring Biologically Relevant Models: Nested Canalyzing Functions
ISRN Biomathematics (2012) (Accepted)

S. Zhou, W. Lo, J. Suhalim, M. Digman, E. Gratton, Q. Nie and A. Lander
Free Extracellular Diffusion Creates the Dpp Morphogen Gradient of the Drosophila Wing Disc
Current Biology (2012) (In Press)

V. Gay, P. Hemond, D. Schmidt, M. O. Boyle, Z. Hemond, J. Best, L. O. Farrell and K. Suter
Hormone secretion in transgenic rats and their electrophysiological activity in gonadotrophin releasing-hormone (GnRH) neurons
(2012) (Submitted)

R. Grima, D. Schmidt and T. Newman
Exact solution of the master equation of a gene regulatory network with a transcriptional feedback loop
(2012) (Submitted)

A. Matzavinos, A. Roitershtein, B. Shtylla, Z. Voller, S. Liu and M. Chaplain
Stochastic modelling of chromosomal segregation: Errors can introduce correction
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C. Xue, C. Chou, C. Kao, C. Sen and A. Friedman
Propagation of Cutaneous Thermal Injury: A Mathematical Model
Wound Repair and Regen, Vol. 20 No. 1 (2012) pp. 114-122

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The mathematical analysis of biological aggregation and dispersal: progress, problems and perspectives
Dispersal, individual movement and spatial ecology: A mathematical perspective (2012) (In Preparation)

H. Jain, N. Moldovan and H. Byrne
Modeling stem/progenitor cell-induced neovascularization and oxygenation around solid implants
Tissue Eng. Part C Methods (2012) (In Press)

Y. Kim and S. Roh
A hybrid model of cell proliferation and migration in glioblastoma
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B. Szomolay, T. Eubank, R. Roberts, C. Marsh and A. Friedman
Modeling inhibition of breast cancer growth by GM-CSF
J. of Theor. Biol. (2012) (Accepted)

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Evolutionary Convergence to Ideal Free Dispersal Strategies and Coexistence
Bulletin of Mathematical Biology, Vol. 74 No. 2 (2012) pp. 257-299

A. Sharma and D. Chowdhury
Error correction during DNA replication
Physical Review E, Vol. 86 No. 011913 (2012) (Published)

Y. Wang, P. Paszek, C. Horton, H. Yue, M. White, D. Kell, M. Muldoon, M. Muldoon and D. Broomhead
A systematic study of the response of a NF-kB signalling pathway to TNFalpha stimulation.
Journal of Theoretical Biololgy, Vol. 297 (2012) pp. 137-147

J. Tian, Z. Jin and T. Xie
Mathematical model for two germline stem cells competing for niche occupancy
Bulletin of Mathematical Biology, Vol. 74 No. 5 (2012) pp. 1207-1225

D. Yang, J. Tian and J. Wang
A solvable hyperbolic free boundary problem modeling tumor regrowth Applicable Analysis (2012)

J. Tian and J. Wang
Global stability for cholera epidemic models
Mathematical Sciences, Vol. 232 No.1 (2012) pp. 31-41

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The replicability of oncolytic virus: defining conditions on tumor virotherapy
Mathematical Sciences and Engineering, Vol. 8 No. 3 (2012) pp. 841-860

T. Li, R. Pan and K. Zhao
Global dynamics of a chemotaxis model on bounded domains with large data
SIAM Journal on Applied Mathematics, Vol. 72 No. 1 (2012)

J. Tian, A. Friedman, J. Wang and E. Chiocca
Modeling the Effects of Resection, Radiation and Chemotherapy in Glioblastoma
Journal of Neuro-Oncology, Vol. 91 No. 3 (2012) pp. 287-293

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Finite-time perturbations of dynamical systems and applications to tumor therapy
Discrete and Continuous Dynamical Systems - B, Vol. 12 No. 2 (2012) pp. 469-479

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The Mutation Process in Colored Coalescent Theory
Bulletin of Mathematical Biology, Vol. 71 No. 8 (2012) pp. 1873-1889

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Lecture Notes in Mathematics, Vol. 1921 (2012)

F. Rassoul-Agha, M. Balazs and T. Seppalainen
Existence of the zero range process and a deposition model with superlinear growth rates
Ann. Probab., Vol. 35 (2012) pp. 1209-1249 (Published)

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Random average process and random walk in a space-time random environment in one dimension.
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Analogues of the Hirsch and Smale theorems for cooperative Boolean and discrete systems
Journal of Difference Equations and Applications, Vol. 18 No. 2 (2012) pp. 233-238

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Algorithmic & complexity results for decompositions of biological networks into monotone subsystems
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Boolean Models Can Explain Bistability in the lac Operon
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Identifying differentially methylated genes using mixed effect and generalized least square models
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How old is this mutation? - A study of three Ashkenazi Jewish founder mutations BMC Genet., Vol. 11 No. Series 39 (2012)

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Genome-wide DNA methylation profiling in 40 breast cancer cell lines Advanced Intelligent Computing Theories and Applications, Vol. 6215 (2012) pp. 277-284

S. Sun, Z. Chen, P. Yan, Y. HUANG, T. Huang and S. Lin
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A Mathematical Model of the sleep/wake cycle
J Math Biol.,Vol. 60 (2012) pp. 615-644

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Large-scale phylogenetic analysis for the study of zoonosis and assessment of influenza surveillance
Scalable Computing: Practice and Experience, Vol. 8 (2012) pp. 143-146

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Multiscale modeling of electrical and intracellular activity in the pancreas: The islet Tridomain equations
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Effect of Periodic Disinfection on Persisters in a One-Dimensional Biofilm Model (2012) (In Preparation)

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Linking network structure and stochastic dynamics to neural activity patterns involved in sleep-wake regulation
(2012) (In Preparation)

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Downregulation of LRP6 inhibits growth of melanoma cells
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A role-playing exercise that demonstrates the process of evolution by natural selection: Caching squirrels in a world of pilferers Am. Biol. Teach, Vol. 73 (2012) pp. 208-216 (Published)

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Y. Guo
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SIAM Journal on Applied Dynamical Systems (2012) (Accepted)

S. Dai, D. Li and K. Zhao
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D. Yang and Y. Guo
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L. Zheng, H. Othmer and H. Kang
The effect of the signaling scheme on the robustness of pattern formation in development Interface Focus, Vol. 2 No. 4 (2012) pp. 465-486 (To Appear)

P. Hurtado
Within-Host Dynamics of Mycoplasma Infections: Conjunctivitis in Wild Passerine Birds
Journal of Theoretical Biology, Vol. 306 (2012) pp. 73-92

A. Beri, R. Azencott and I. Timofeyev
Calibration of Stochastic Volatility Model under Indirect Observability of the Volatility Process (2012) (In Preparation)

R. Azencott , A. Beri, Y. Gadhyan, N. Joseph, C. Lehalle and M. Rowley
Realtime Market Microstructure Analysis: Online Transaction Cost Analysis (2012) (In Preparation)

A. Beri, D. Chowdhury and H. Jain
Agent-based and Macroscopic PDE models for foraging dynamics of competing ant colonies, and associated boundary interactions (2012) (In Preparation)

J. Wenstrup, M. Deacon, I. Comeras, V. Schumemann, D. Fix, S. Liyanarachchi, S. Sun, M. Baze, M. Clendenning, S. Thibodeau, H. Lynch, H. Hampel and A. De La Chapelle
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D. Chen, J. Roda, C. Marsh, T. Eubank and A. Friedman
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Bulletin of Mathematical Biology (2012) (Published)

M. Schwemmer and T. Lewis
The robustness of phase-locking in neurons with dendro-dendritic electrical coupling
Journal of Mathematical Biology
(2012) (Published)

D. Chen and A. Friedman
A two-phase free boundary problem with discontinuous velocity: Application to tumor model
Journal of Mathematical Analysis and Applications (2012) (Published)

L. Hu, D. Chen and G. Wei
High-order fractional partial differential equation for molecular surface construction
Molecular based Mathematical Biology (2012) (Published)

P. Thomas, C. Wilson and C. Diekman
Spontaneous autoresuscitation in a model of respiratory control
Conf Proc IEEE Eng Med Biol Soc (2012) pp. 6669-6672 (Published)

Y. Wang, T. McMillen, M. Golubitsky and C. Diekman
Reduction and dynamics of a generalized rivalry network with two learned patterns SIAM Journal of Applied Dynamical Systems, Vol. 11 (2012) pp. 1270-1309 (Published)

H. Kang
A multiscale approximation in a heat shock response model in E.coli BMC Systems Biology, Vol. 6 No. 1 (2012) pp. 143 (Published)

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A new method for choosing the computational cell in stochastic reaction-diffusion systems Journal of Mathematical Biology, Vol. 65 No. Series 6-7 (2012) pp. 1017-1099 (Published)

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A mathematical model for microRNA in lung cancer
PLoS One, Vol. 8 No. 1 (2013) (Published)

E. Martin, A. Friedman and W. Lo
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Journal of Theoretical Biology, Vol. 317 (2013) pp. 2. 20-29 (Published)

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PLoS ONE, Vol. 8 No. 2 (2013) (Published)

C. Diekman, C. Fall, J. Lechleiter and D. Terman
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Biophysical Journal (2013) (In Press)

A. Lam and Y. Lou
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Journal of Mathematical Biology (2013)

R. Azencott , A. Beri, A. Jain and I. Timofeyev
Sub-sampling and Parametric Estimation for Multiscale Dynamics Communications in Mathematical Sciences (2013) (To Appear)

H. Kang and T. Kurtz
Separation of time-scales and model reduction for stochastic reaction networks Annals of Applied Probability Vol. 23 No. 1 (2013) pp. 529-583 (Published)

R. Azencott , A. Beri, Y. Gadhyan, N. Joseph, C. Lehalle and M. Rowley
Realtime market microstructure analysis: online Transaction Cost Analysis Quantitative Finance (2013) (Submitted)

K. Liao, X. Bai and A. Friedman
The role of CD200-CD200R in tumor immune evasion
J. Theor. Biol. (2013) (Accepted)

D. Koslicki
Quikr: a Method for Rapid Reconstruction of Bacterial Communities via Compressive Sensing
Oxford Journal of Bioinformatics (2013) (Under Review)

R. Cressman and V. Krivan
Two-patch population models with adaptive dispersal: the effects of varying dispersal speeds
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Two-patch population models with adaptive dispersal: the effects of varying dispersal speeds
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2013

Mathematical Neuroscience