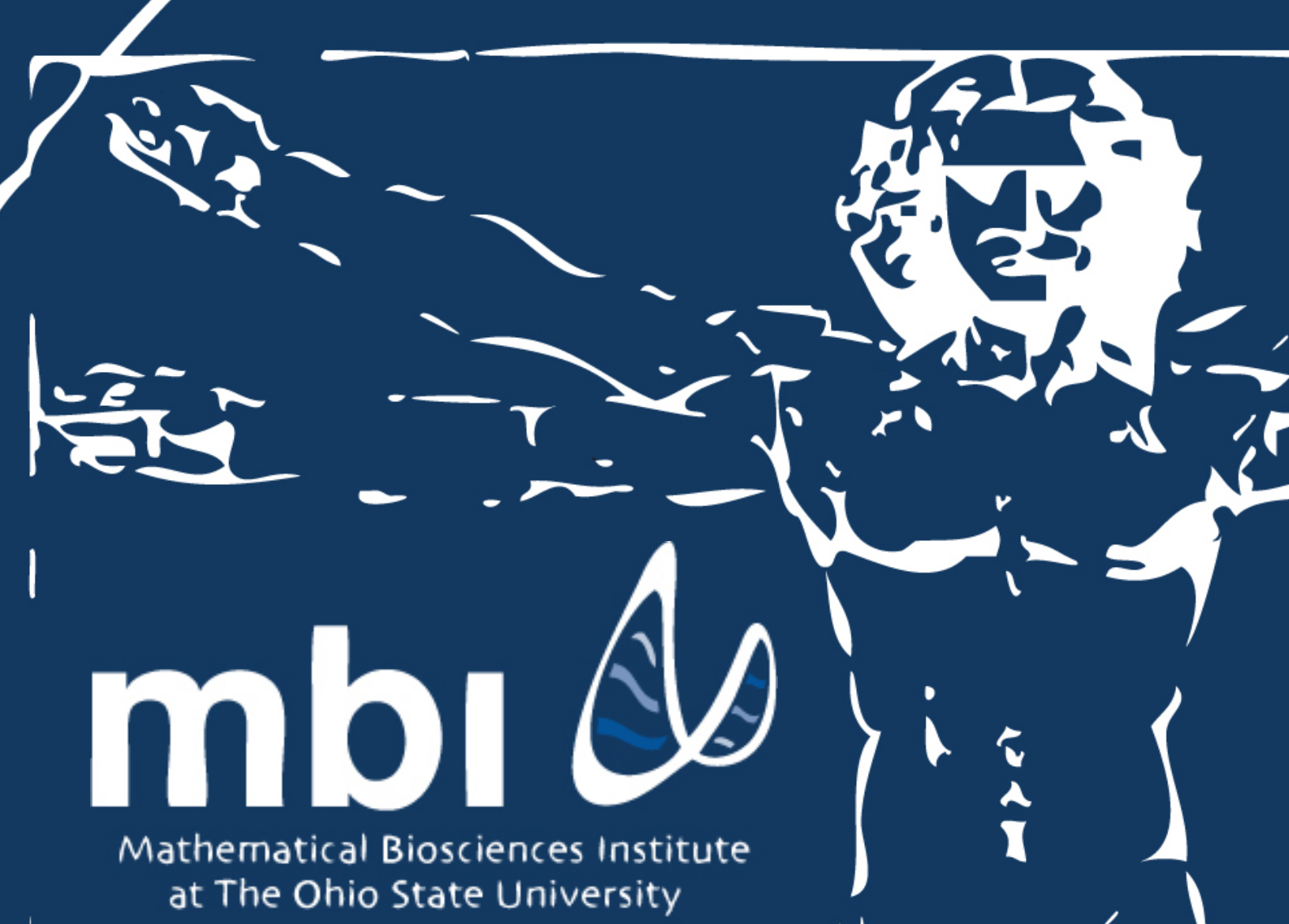


mbi

Mathematical Biosciences Institute
at The Ohio State University

SYSTEMS PHYSIOLOGY 2006-2007

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

Director's Letter

The Mathematical Biosciences Institute at the Ohio State University was created in 2002 in order to provide a national forum in research and education for the mathematical biosciences. Funded by the Division of Mathematical Sciences of the National Science Foundation, the Institute's goals are to catalyze interactions between the mathematical and biological sciences, and to nurture a nationwide community of scholars in this emerging field, through a variety of efforts aimed at the full range from undergraduates to senior researchers. The MBI aims to reinforce and build upon existing research efforts in mathematical biosciences, and quicken intellectual growth in this area.

The MBI runs "Emphasis Year" programs, concentrating on a broad range of topics in one area of bioscience, with six to eight one-week workshops preceded by tutorials. Additional "Current Topics" workshops introduce mathematical scientists to new opportunities for research. In the summer, the MBI runs educational programs based on tutorials and team projects led by MBI postdoctoral fellows. The topics of the first four emphasis years were Mathematical Neurosciences; Mathematical Modeling of Cell Processes; Genomics, Proteomics, and Bioinformatics; and Ecology and Evolution. This year was devoted to Systems Physiology.

The goal of Systems Physiology is to understand how various human organs and tissues are organized and regulated to produce their normal function and pathologies. The year at the MBI examined features of several human organ and tissue systems, including the cardiac system, the respiratory system, the microcirculatory system, the renal system, the visual processing system, the endocrine system, and the auditory system. Although these are at first glance quite different, the underlying theme was how cellular level behavior participates in the function of the whole and how feedback from the function of the whole contributes to the regulation of cellular level behavior. Understanding of these processes may lead to new insights into the causes of diseases and how they can be treated.

The autumn quarter was devoted to the heart and lung. It began with two weeks of workshops which dealt with cardiac electrophysiology and cardiac mechanics, followed by a workshop on the lung and the respiratory system. During winter quarter the MBI hosted a workshop on blood flow in the microcirculation, exploring questions of function, regulation, and adaptation, and another on the kidney, focusing on its cellular, tubular, and vascular physiology. Three spring quarter workshops dealt with the visual system, the auditory system, and insulin secretion and action, including type 2 diabetes. Most of the workshops were preceded by tutorials.

In addition to this rich program, the MBI held three shorter "Current Topic" workshops on Sleep/Wake dynamics (sponsored by the AFOSR); MicroRNA in Development and Cancer; and Chemogenomics. The last two workshops were sponsored by the College of Medicine at OSU.

This year, for the first time, the MBI held a workshop on "Opportunities in Mathematical Biology for Underrepresented Groups" and another one on "Over the fence: Mathematicians and biologists talk about bridging the curricular divide." Both workshops brought new and very enthusiastic communities into the MBI, and the enthusiastic conclusion was that such activities should continue in the future.

As in previous years, the MBI postdoctoral fellows organized a special workshop for young researchers in mathematical biosciences. Participants included 50 young researchers from all over the country. The workshop included poster presentations by young researchers as well as group discussions. There are currently 15 postdoctoral fellows at the MBI, each having two mentors, one from the mathematical sciences and another from the biosciences. Their research interests include neuroscience, systems biology, cell metabolism, mitochondrial models, immunology, tissue engineering, tumor angiogenesis, multiscale and hybrid modeling in computational biology, bioinformatics, ecology, wound healing, membrane proteins, biochemical networks, tuberculosis modeling, and statistical genetics.

This document provides a summary of events and talks that took place in the fifth year of the MBI. Further details can be found on the MBI website http://mbi.osu.edu.

Avner Friedman
Director

Table of Contents

MBI Mission

The explosion of research in the life sciences has created the need for new mathematical theories, statistical methods, and computational algorithms with which to draw knowledge from the rapidly accumulating data. The Mathematical Biosciences Institute catalyzes interactions between the biological, medical, and mathematical sciences through vigorous programs of research and education and nurtures a nationwide community of scholars in this emerging new field.

The mission of the MBI is:

- To develop mathematical theories, statistical methods, and computational algorithms for the solution of fundamental problems in the biosciences;
- To involve mathematical scientists and bioscientists in the solutions of these problems; and
- To nurture a community of scholars through education and support of students and researchers in mathematical biosciences.

Corporate Members

The MBI encourages involvement from those in private industry. The Institute offers incentives to pharmaceutical and bioengineering companies interested in becoming a Corporate Member.

Membership benefits include regular visits by MBI Directors to identify problems and topics of interest, where mathematical sciences could be helpful; follow-up to these problems by Institute Researchers; and invitation to present industrial challenges and problems to MBI audiences and to participate in MBI programs and workshops.

Current Corporate Members:

Pfizer
GlaxoSmithKline

Past Corporate Members:

Eli Lilly

Industrial Advisory Committee

The Industrial Advisory Committee, which includes members from industry, reviews the MBI programs and suggests new programs that would be of interest to biomedical companies.

Institute Partners

The MBI believes that biology is the new frontier of mathematics. Accordingly, it encourages other institutions to develop programs in mathematical biology. The MBI has introduced the Institutional Partnership program.

Under this program, faculty and students from the institute partners are encouraged to visit the MBI, and these visits are jointly funded by the institute partner and the MBI. The MBI also supports conferences and workshops in mathematical biosciences at campuses of IPs.

Annual meetings of institute partners feature research achievement of the MBI postdoctoral fellows, and discussions of education issues that arise in mathematical biology at the various institutions.

MBI's new location Jennings Hall, 3rd floor

Institute Partner List:

Arizona State University

Case Western Reserve University

COSNet

Drexel University

Florida State University

Howard University

Indiana University-Purdue University Indianapolis

Iowa State University

Michigan State University

New Jersey Institute of Technology

Ohio University

University of California at Irvine

University of Cincinnati

University of Georgia

University of Iowa

University of Maryland, Baltimore County

University of Michigan

University of Minnesota

Vanderbilt University

The MBI Has Moved !

The MBI is moving to historic Jennings Hall in August 2007. One of the university's oldest landmarks, Jennings Hall was known as the Botany & Zoology building when it first opened in 1914, and is now named after former OSU president Edward H. Jennings. Home to many biology classrooms and labs, nearly every student takes classes in this building during their careers.

The MBI's move into 9100 sq ft on the top floor will place it in the heart of spaces occupied by OSU's College of Biological Sciences (CBS), including being on the same floor with CBS research labs. Jennings Hall is also a very short walk to the OSU Medical complexes to the south and to the departments comprising the College of Mathematical and Physical Sciences to the north.

The MBI will nearly double its space for postdocs, visitors, and events, as well as house state of the art technology for event interaction and presentation, both local and remote. Come visit us!

Initiate Focused Math-Bio Research Groups

The MBI is calling for proposals for Focused-Discovery Groups (FDG). The FDG idea is for a group of researchers from different institutions to get together at the MBI for a period of (typically) one week in order to discuss, intensively investigate, and aim to resolve a significant problem in the biosciences. The MBI will pay the local expenses of the participants, and will provide facilities (office space, computer support).

Proposals should be sent to the Director or one of the Associate Directors. A proposal should describe the problem to be addressed (one or two pages) and list the people who have agreed to participate.

The proposed dates of MBI residence for the FDG should be between six months and one year from the time of submission.

Suggest New Ideas and Programs

The MBI programs are aimed at bringing mathematical scientists and bioscientists together to interact on significant problems from the biosciences. It is expected that such activities will also open new research areas for mathematicians and statisticians.

The MBI wishes to encourage the mathematical sciences community and the biosciences community to solicit program ideas.
Your suggestions may be submitted in the form of a preproposal for

- a workshop that falls within a thematic year;
- a stand-along workshop;
- an extended program, several months to a year; and
- a summer education program.

We welcome ideas from the broad spectrum of mathematical biosciences: you may focus more on the mathematics/statistics motivated by biology, or on biological problems which will require the development of new mathematical/statistical methods.

Please submit your ideas in the form of a few pages describing the background and motivation, and what the program is going to accomplish.

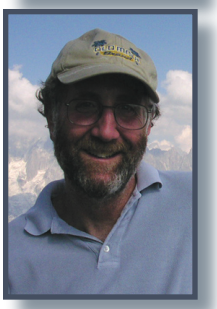
If you want to suggest a specific workshop, we would like to have a list of organizers, a description of the workshop, and a tentative list of speakers and participants.

Please contact the Director or one of the Associate Directors as you develop your ideas for preproposal:

Avner Friedman, Director: afriedman@mbi.osu.edu
David Terman, Sr. Asso. Director: terman@mbi.osu.edu
Libby Marschall, Associate Director: marschall.2@osu.edu
Dennis Pearl, Associate Director: dpearl@mbi.osu.edu
Andrej Rotter, Associate Director: arotter@mbi.osu.edu

People

Avner Friedman, 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 Governors.



David Terman, Senior Associate Director: The Senior Associate Director acts as the director during the director's absence, and designs and implements initiatives consistent with the MBI mission.

Three **Associate Directors** provide scientific advice and support to the director. Along with the director, they visit bioscience laboratories in the public and private sectors in order to initiate and nurture interactions with the institute. The Associate Directors together with the Senior Associate Director are responsible for arranging the mentoring program for postdoctoral fellows.

Dennis Pearl, Associate Director (Department of Statistics, OSU): Dennis is responsible for the education programs, as well as the evaluation process.

Andrej Rotter, Associate Director (Department of Pharmacology, OSU): Andrej provides leadership for the Current Topics Workshops.

Libby Marschall, Associate Director (Department of Evolution, Ecology, and Organismal Biology): Libby works with the Director on diversity issues.

Tony Nance Assistant Director: Tony is a full time staff member with duties that include oversight of the day-to-day operation of the MBI offices and supervision of the institute staff.

Nikki Betts, HR & Financial Manager: Nikki manages all human resources and financial activity in the MBI, including visa, travel, and reimbursement related activities. She also helps with program and reporting activities.

Stella Cornett, Program Assistant: Stella manages the web site; produces grant proposals and reports; produces print series for technical reports and works with publishers and authors on MBI publications; and receives participant abstracts and presentation materials and places them on the web.

Rebecca Martin, Office Associate: Rebecca provides direct office support for the Director; serves as primary point of contact to all outside the MBI; sends letters of invitation to all workshop and tutorial participants.

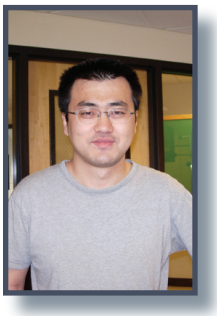
Matt Thompson, Program Assistant: Matt assists in fiscal processing, registration, human resources, promotion and advertising, including creation and distribution of MBI posters, brochures, and flyers; responsible for information given to all visitors.

Michael Siroskey, Systems Manager: Michael is responsible for all technology aspects of the 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.

Postdocs

Cohort 2004

Jianjun (Paul) Tian (Department of Mathematics, University of California, Riverside). Paul has been involved in many aspects of biology and medicine, namely: the quantitative study of brain tumor growth, virotherapy, radiotherapy, and chemotherapy by using partial differential equations; the quantitative study of disease ecology, particularly avian influenza virus, by using ODEs and Markov processes; genetic models and colored coalescent theory by using stochastic processes; the application of evolution algebras in genetics; immunotherapy of tumors by using delay ODEs; tumor data analysis by using statistical algorithms; and modeling of niche signals of neural stem cells and brain tumor genesis. His current research is in mathematical modeling of niche signals of neural stem cells and brain tumor genesis. His goal is to advance understanding of neural stem cell behavior; to provide insight into the origin of brain tumors; and to provide a rationale for neural stem cell treatment of degenerative diseases in the central nervous system.



Jin Zhou (Department of Statistics, University of Georgia). Jin Zhou's current research interests include microRNA target prediction, methods on rank aggregation, time series analysis in queueing system, and stochastic differential equation. His future projects include microRNA's role in human cancer. Specifically, he wants to know the answer for such questions: What's microRNA's expression signature on NCI60 cell lines of human cancer, and what is the relationship of microRNA's expression and mRNA's expression? Another project he is working on is the stochastic differential equation models for the spread of influenza virus in poultry and humans.

Cohort of 2005

Marko Djordjevic (Department of Physics, Columbia University). Marko's research interests are broadly in the area of computational biology and bioinformatics. More specifically, he is interested in computationally study regulation of gene expression by using ideas and methods from statistical physics. In addition to analyzing experimental data, his theoretical/computational research is also aimed at contributing to the experimental design. To accomplish a close interaction of theory with experiment, he is intensively collaborating with experimental biology labs. His current research is mainly directed to transcription regulation in higher eukaryotes, and aims to address the following questions: How to reliably infer protein-DNA interaction parameters and predict direct target genes of TFs? How RNA polymerase (an enzyme that transcribes genes) initiates transcription and how to accurately predict transcription start sites in genome? What are (some) principal limits in accuracy of the computational algorithms and high-throughput experimental techniques that are used to study transcription regulation?

German Enciso (Department of Mathematics, Rutgers University). While German is currently considering a more applied approach to mathematical biology, his dissertation research consisted of the study of certain abstract dynamical systems called monotone systems, which are associated with positive feedback and have strong stability properties. Using ideas from control theory, some non-monotone systems were studied using ideas from monotone systems theory. Applications were given to delay and reaction diffusion equations in molecular biology.

Paula Grajdeanu (Department of Applied Mathematics, University of Durham, England). Paula is interested in many aspects of mathematical biology including renal physiology; cell metabolism; immunology; and formulating mathematical models for various clinical problems. She believes that Math-Bio is a fascinating subject and she would like to be one who will lead other students in understanding the beauty, relevance, and importance of mathematics applied in real life problems.

Andrew Nevai (Department of Mathematics, University of California, Los Angeles). Andrew is interested in many aspects of mathematical ecology including the theory of competition for resources; species persistence and permanence within ecological communities; the dynamics of spatially (or otherwise) structured populations; individual and group foraging theory; behavior; and formulating ecological models that make use of mechanistic reasoning and principles. So far at the MBI, he has collaborated with Yuan Lou (OSU), Winfried Just (Ohio University), Tom Waite (OSU), Kevin Passino (OSU), Ben Bolker (University of Florida), Linda Allen (Texas Tech University), and Partha Srinivasan (MBI).

Richard Schugart (Department of Mathematics, North Carolina State University). Richard's research interests include mathematical modeling and scientific computing as applied to problems in wound healing and cartilage mechanics. His dissertation work included two problems in cartilage mechanics and is motivated by the need to quantify differences between normal and osteoarthritic mechanical and physico-chemical states in cartilage. The first problem involved the formulation and analysis of mathematical models for osmotically-induced volume change in articular cartilage cells and chondrons, which is the functional cell-matrix unit in cartilage. The second problem was the development of an accelerated numerical method for the continuous spectrum biphasic poroviscoelastic (BPVE) model of articular cartilage deformation. The research was directed under the supervision of his dissertation adviser, Dr. Mansoor Haider, and was in collaboration with the Orthopaedic Bioengineering Lab at the Duke University Medical Center. His current research is on wound healing, cartilage healing, and dialysis.

Partha Srinivasan (Department of Mathematics, Florida State University). Partha is working with Rolf Barth (Integrated Biomedical Science Graduate Program, OSU) in estimating the survival time of rats with melanoma metastatic to the brain after they have been treated with Boron Neutron Capture Therapy. In collaboration with the groups of Philip Grandinetti (Dept. of Chemistry, OSU) and Martin Caffrey (Dept. of Biophysics, Biochemistry and Chemistry, OSU), he is working on understanding the structure and dynamics of proteins in the cubic phase using solid state NMR. The measurement of the dipolar coupling between a half-integer quadrupolar nuclei and a spin-1/2 nuclei can lead to a better understanding of the structure and dynamics of proteins. He is currently working with Philip Grandinetti (Dept. of Chemistry, OSU) and Domique Massiot (CRMHT-Orléans, France) on designing experiments that will allow for the measurement of this dipolar coupling term.

Brandilyn Stigler (Department of Mathematics, Virginia Tech). Brandilyn's research involves the development of a mathematical framework for the reverse-engineering of biochemical systems. The models used in this work are time- and state-discrete finite dynamical systems, described by polynomial functions over a finite field. This novel approach, rooted in computational algebra, uses Groebner-basis techniques to build the set of all discrete models that fit time series data and to select minimal models from this set. The method has been specifically designed for experimental data from biochemical networks, where the data may take the form of time series of mRNA, protein, and/or metabolite concentrations. This work is currently being applied to an oxidative stress response network in yeast.

Postdocs

Cohort of 2006

Edward Green (Department of Applied Mathematics, University of Nottingham). Edward's interests lie in the broad areas of: mathematical modeling, tissue engineering, fluid mechanics, and free boundary problems. His research is concerned with developing idealized mathematical models of biological phenomena. These models allow us to gain more insight into the physical mechanisms underlying the behavior of the biological system, and make predictions which can be compared with experiments. For his PhD, he developed and studied models of cell aggregation in liver tissue engineering under the supervision of Prof. Helen Byrne and Dr. Sarah Waters. We looked particularly at the effect of cell-substrate adhesion on the aggregation process, and how the type and strength of interactions between cell populations affects the distribution of cells within the aggregates. Subsequently, he worked with Prof. Frank Smith at University College London on the problem of modeling fluid flow in bifurcating channels with flexible walls, which has applications to blood flow through arterio-venous malformations in the brain.

Yangjin Kim (Department of Mathematics, University of Minnesota). Yangjin received his Ph.D. in mathematics from the University of Minnesota in 2006 under the direction of Hans G. Othmer. His dissertation was on "Mathematical modeling of cell movement and tumor spheroid growth in vitro." A hybrid model that consists of a cell-based (discrete) model in an actively proliferating region and a continuum model in another area has been developed to explore tumor spheroid growth in an agarose gel. He is interested in the broad area of computational biology. Specifically, I am interested in cell mechanics, tumor growth, tumor angiogenesis, wound healing, and gene control. The application of the hybrid model includes many biological problems involving cell proliferation and division such as wound healing and invasive ductal breast carcinoma. Gene-controlled growth and irradiation therapies in colon cancer are under investigation.

Andrew Oster (Department of Mathematics, University of Utah). Andrew's biological research focuses are neuroscience and development, whereas dynamical systems along with bifurcation theory and perturbation methods make up his principal mathematical interests. In general, mathematical modeling interests him, particularly when it relates to physiology. His dissertation work at the University of Utah, under the direction of Dr. Paul Bressloff, was on the development of the primary visual cortex (V1), studying the emerging pattern formation associated with the plasticity in the afferents connecting the thalamus and V1. In its mature state, the primary visual cortex is dominated by regions that receive predominantly monocular drive, i.e., are mostly left or right eye driven. Such a region is referred to as an ocular dominance (OD) patch or stripe, depending upon its shape. For instance, in the cat the OD pattern is said to be blotchy, whereas in the macaque monkey, it has a stripe-like morphology.

Michael Rempe (Engineering Sciences & Applied Mathematics, Northwestern University). Michael uses computational and mathematical approaches to understand how neurons and networks of neurons function. For his PhD research he developed a numerical method for simulating neuron activity that is very efficient, even for simulations with detailed morphology. The approach is similar to those used in the neural simulation environments NEURON or GENESIS, but with some significant improvements that result in much increased computational efficiency. Here at the MBI, he is studying neurons in the rat hypothalamus that are both sensitive to temperature and are partly responsible for causing behavioral changes (like shivering) to maintain a constant body temperature. We are investigating, using computational approaches as well as experimental techniques, the mechanisms of temperature sensitivity, and why some cells in this region are sensitive to temperature while others are not.

Shuying Sun (Department of Statistics, University of Toronto). Shuying's research area is related to statistical genetics. She has interest in developing methods for analyzing complex genetic data. In particular, when she was at University of Toronto, she worked on haplotype inference for her doctoral thesis. She has also worked on projects related to mutation age estimation, and disease risk association studies using haplotype analysis. Currently at MBI, she is working on analyzing DNA methylation data and clustering compounds with many different features.

Barbara Szomolay (Department of Mathematics, Montana State University). Biofilms are matrix-enclosed bacterial populations adherent to surfaces or interfaces. They are responsible for a variety of bacterial infections as well as industrial problems. Barabara is interested in modeling resistance mechanism of biofilms including dosing strategies of biocide in order to optimize the biofilm thickness and the cost of the treatment. Biofilm models are reaction-diffusion equations, the qualitative properties of which are also of her interest. Her future plans include exploring other areas of mathematical biology - particularly, angeogenesis and quorum sensing.

Committees

Scientific Advisory Committee

The Committee consists of up to 15 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. The Committee reviews the budget issues and advises the Directors with respect to strategic priorities of the Institute.

Current members:

Reka Albert, Department of Physics, Pennsylvania State University
(1/1/06-12/31/08)

Adam Arkin, Howard Hughes Medical Institute, Department of Bioengineering, University of California, Berkeley
(1/1/07-12/31/10)

Herb Bresler, Department of Health and Life Sciences, Battelle Memorial Institute, Columbus, OH
(1/1/06-12/31/08)

Leah Edelstein-Keshet, Department of Mathematics, University of British Columbia
(1/1/05-12/31/07)

Lisa Fauci, Department of Mathematics, Tulane University
(1/1/05-12/31/07)

Sorin Istrail, Center for Computational Molecular Biology, Computer Science Department, Brown University
(1/1/06-12/31/08)

Nicholas P. Jewell, Biostatistics and Statistics, University of California, Berkeley
(1/1/07-12/31/10)

Kirk Jordan, IBM Computational Biology Center, Yorktown Heights, NY
(1/1/03-12/31/07)

Jim Keener, Department of Mathematics, University of Utah
(1/1/04-12/31/07)

Mark Lewis, Department of Mathematical and Statistical Sciences, University of Alberta
(1/1/07-12/31/10)

Philip Maini, Centre for Mathematical Biology, Mathematical Institute, University of Oxford
(1/1/06-12/31/08)

Linda Petzold, Department of Mechanical and Environmental Engineering, Department of Computer Science, University of California, Santa Barbara
(1/1/07-12/31/10)

Terry Therneau, Division of Biostatistics, Mayo Clinic College of Medicine, Rochester, MN
(1/1/04-12/31/07)

Frank Tobin, Scientific Computing & Mathematical Modeling, GlaxoSmithKline
(1/1/06-12/31/08)

Steven Vogel, Biology Department, Duke University
(1/1/07-12/31/10)

Past Committee Members:

Louis Gross, The Institute for Environmental Modeling, Department of Ecology & Evolutionary Biology, Mathematics Department, The University of Tennessee

Douglas Lauffenburger, Biological Engineering Division, Department of Chemical Engineering, Department of Biology, Massachusetts Institute of Technology

Gregory Mack, Department of Environmental Monitoring and Assessment, Battelle Memorial Institute, Columbus OH

Claudia Neuhauser, Department of Ecology, Evolution, and Behavior, University of Minnesota

Alan Perelson, Department of Theoretical Biology and Biophysics Group, Los Alamos National Laboratory

Mike Reed, Department of Mathematics, Duke University

John Rinzel, Center for Neural Science and the, Courant Institute of Mathematical Sciences, New York University

Stephen Ruberg, Department of Clinical Data Technology and Services, Eli Lilly and Company, Indianapolis

Terrence Speed, Department of Statistics, University of California, Berkeley

John Taulbee, Epidemiology and Biometrics Division, Procter & Gamble Company, Cincinnati

John Tyson, Department of Biology, Virginia Polytechnic Institute and State University

Michael S. Waterman, Department of Mathematics, University of Southern California

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

Financial Oversight Committee

The Financial Oversight Committee (FOC) consists of six to eight people with financial and management experience chosen primarily from the The Ohio State University and from the Columbus community. One member is from the Scientific Advisory Committee and who serves as liaison between the two committees.

The FOC monitors all fiscal and management issues running the institute and send annual reports to the Scientific Advisory Committee.

Current members:

James E. Krygier (Chair), Special Assistant to the Dean, College of Mathematical & Physical Sciences The Ohio State University

Thomas Ewing, Associate Controller, Office of Business and Finance, The Ohio State University

Richard Hall, Associate Dean, College of Biological Sciences, The Ohio State University

William Henson (retired), Executive Project Manager, IBM

Terry Therneau, Division of Biostatistics, Mayo Clinic College of Medicine, Rochester, MN

Emphasis Year External Scientific Advisory Committee

Larry Abbott, Brandeis University, Department of Biology

Leah Edelstein-Keshet, Mathematics Department, University of British Columbia

A. James Hudspeth, Howard Hughes Medical Institute

Jay D. Humphrey, Texas A&M University, Biomedical Engineering

Peter J. Hunter, Bioengineering Institute, Faculty of Engineering, University of Auckland

Mike Reed, Mathematics Department, Duke University

S. Murray Sherman, Department of Neurobiology, Pharmacology, and Physiology, The University of Chicago

Local Scientific Advisory Committee

Sudha Agarwal, Department of Oral Biology

Irina Artsimovitch, Department of Microbiology, Departments of Pharmacology & Psychiatry

Ralf Bundschuh, Department of Physics

Helen Chamberlin, Department of Molecular Genetics

Meg Daly, Department of Evolution, Ecology, and Organismal Biology

Andrea Doseff, Heart and Lung Research Institute, Department of Molecular Genetics, and Department of internal Medicine

Martin Feinberg, Department of Chemical Engineering

Paul Fuerst, Department of Evolution, Ecology and Organismal Biology

Erich Grotewold, Department of Plant Biology

Richard Hart, Biomedical Engineering Department

Tim Huang, Center for Integrative Cancer Biology

Daniel Janies, Department of Biomedical Informatics

Doug Kniss, Department of Obstetrics and Gynecology

Stanley Lemeshow, Dean School of Public Health, Center for Biostatistics

Gustavo Leone, Department of Molecular Virology, Immunology, and Medical Genetics

Shili Lin, Department of Statistics

Stuart Mangel, Department of Neuroscience

Elizabeth Marschall, Department of Evolution, Ecology, and Organismal Biology

Deborah Parris, Department of Molecular Virology

Dennis Pearl, Department of Statistics

John Reeve, Department of Microbiology

Andrej Rotter, Department of Pharmacology

Wolfgang Sadee, Department of Pharmacology

Joel Saltz, Department of Biomedical Informatics

Larry S. Schlesinger, Division of Infectious Diseases & Center for Microbial Interface Biology

Petra Schmalbrock, Department of Radiology

Chandan Sen, Department of Surgery

Amanda Simcox, Department of Molecular Genetics

Parthasarathy Srinivasan, Department of Computer Science and Engineering and Department of Biomedical Informatics

Don Stredney, Biomedical Applications, Ohio Supercomputer Center

David Terman, Department of Mathematics

Visitors

Long Term Visitors 2006-2007

Baltazar Aguda, Bioinformatics Institute, Singapore

Elizabeth Allman, Mathematics and Statistics, University of Alaska, Fairbanks

Bassidy Dembele, Mathematics, Howard University

Gregg Hartvigsen, Biology, SUNY, Geneseo

Bei Hu, Mathematics, University of Notre Dame

Chiu-Yen Kao, Mathematics, The Ohio State University

Shannon LaDeau, Smithsonian, Migratory Bird Center, National Zoological Center

Yuan Lou, Mathematics, The Ohio State University

Bart Ng, Mathematical Sciences, Indiana University-Purdue University Indianapolis

John Rhodes, Mathematics and Statistics, University of Alaska, Fairbanks

Michael Schimek, Medical University of Graz, Austria

Ignacio Tello, Universidad del Departamento de Matematica Aplicada

Evelyn Thomas, Mathematics, Howard University

Linghai Zhang, Mathematics, Lehigh University

Anticipated Visitors 2007-2008

Baltazar Aguda, Bioinformatics Institute, Singapore

Greg Baker, Mathematics, The Ohio State University

Jon Bell, Mathematics and Statistics, University of Maryland, Baltimore County

Janet Best, Mathematics, The Ohio State University

Linda Chen, Mathematics, The Ohio State University

Adela Comanici, Mathematics, University of Houston

Hakan Ferhatosmanoglu, Computer Science and Engineering, The Ohio State University

Keith Gooch, Biomedical Engineering, The Ohio State University

Erich Grotewold, Plant Cellular and Molecular Biology, The Ohio State University

Jason Hsu, Statistics, The Ohio State University

Chiu-Yen Kao, Mathematics, The Ohio State University

Shili Lin, Statistics, The Ohio State University

Yuan Lou, Mathematics, The Ohio State University

Raghu Machiraju, Computer Science, Mississippi State University

Aleix Martinez, Electrical and Computer Engineering, The Ohio State University

Kevin Passino, Electrical Engineering, The Ohio State University

Tom Santner, Statistics, The Ohio State University

Chih-Wen Shih, National Chiao Tung University, Taiwan

Greg Smith, Applied Science, The College of William and Mary

Yvonne Stokes, School of Mathematical Sciences, University of Adelaide

Joe Verducci, Statistics, The Ohio State University

Ronald Xu, Biomedical Engineering, The Ohio State University

Yi Zhao, Mathematics and Statistics, Georgia State University

Graduate Students Visitation Program

This program is designed to engage advanced graduate students from around the country for an extended period (a quarter, semester, or year) in research and scholarship in mathematical biosciences. Each student works on a specific project, mentored by MBI faculty and postdocs. The goal of the program is to engage the students in research and scholarship, foster diversity, and at the same time connect them to the emerging math-bio community.

Program Participation 2006-2007

Tutorial on the Heart: September 18-20	24
Cardiac Electrophysiology and Arrhythmia: September 25-29	82
Cardiac Mechanics and Remodeling: October 2-6	76
Tutorial on the Lung: October 18	21
New Approaches to Modeling Sleep/Wake Dynamics and Cognitive Performance: October 26-27	60
The Lung and the Respiratory (Structure, Oxygen Transport): November 6-10	68
Tutorial on Microcirculation: January 19	25
Blood Flow in the Microcirculation: Function, Regulation, and Adaptation: January 22-26	63
The Kidney: Cellular, Tubular, and Vascular Physiology: February 19-23	76
Tutorial on RAxML: March 5-9	23
Workshop for Young Researchers in Math Biology: March 12-15	77
Opportunities in Mathematical Biology for Under-represented Groups: March 23-25	80
MicroRNA in Development and Cancer: April 12-13	243
Information Processing in the Visual System: April 23-27	74
Chemogenomics: May 8-10	53
Tutorial on Cellular and Organism Models for Glucose Homeostasis and Diabetes: May 18	23
Insulin Secretion, Insulin Action, and Type 2 Diabetes: May 21-24	65
Over the Fence: Mathematicians and Biologists Talk About Bridging the Curricular Divide: June 1-2	62
The Auditory System: June 25-28	60
Total	**1,255**

Long Term Visitors:

4 weeks - 3 months	5
3 months - 1 year	8
Total	**14**

Workshops

Overall Summary for Workshops 1 and 2

The goal of systems physiology is to understand how various human organs and tissues are organized and regulated to produce their normal function and pathologies. An integrated understanding of systems requires mathematics and the development of theory, supplemented by simulations. Moreover, theory cannot be relevant if it is not driven and inspired by experimental data. Thus, the goal of the Systems Physiology series of MBI workshops is to bring together theoreticians and experimentalists in order to catalyze a deeper understanding of these complex systems.

The first two workshops in this series held on consecutive weeks during fall of 2006 explored progress on mechanistic, functionally integrated, multi-scale mathematical models of the heart from molecular to cellular and whole organ scales. Workshop 1 concentrated on atrial and ventricular electrophysiology from models of the biophysics of single ion channels to predicting the electrocardiogram recorded at the body surface. Workshop 2 addressed the mechanical function of the heart from models of the biophysics and biochemistry of molecular motors to predicting the three-dimensional mechanical performance of the whole heart. The theme threading through this workshop was how mathematical models can improve the diagnosis and treatment of cardiac mechanical dysfunction during disease, and elucidate the mechanisms by which mechanical factors regulate cardiac remodeling in vivo.

The common scientific focus linking Workshops 1 and 2 was electromechanical interactions (excitation-contraction coupling and mechano-electric feedback), their neurohormonal and metabolic regulation, and the changes in these processes associated with cardiac arrhythmias and remodeling. The programs for the two workshops were designed to dovetail around these common themes, and a significant number of speakers and participants attended both workshops.

Workshop 1: Cardiac Electrophysiology and Arrhythmia, September 25-29, 2006

Organizers: James Keener, University of Utah, Salt lake City, UT; and Raimond Winslow, Center for Cardiovascular Bioinformatics & Modeling, Whitaker Biomedical Engineering Institute and Department of Biomedical Engineering, The Johns Hopkins University School of Medicine and Whiting School of Engineering

Day 1

Coleen Clancy (Cornell University) began the workshop by describing how Markov models of sodium channel kinetics are being used to understand the mechanisms of several cardiac arrhythmias. For one example, electrophysiological characterization of some Na+ channel mutants linked to Long-QT syndrome has revealed increased rates of channel recovery from inactivation. This mutation induced faster recovery from inactivation can allow channel reopening during repolarization and cause severe prolongation of the action potential.

Randall Rassmusson (SUNY Buffalo) then described his work on developing kinetic models of potassium ion channels beginning at the level of molecular structure. In the example of the Kv1.4 and Kv4.3 channels, which mediate various components of the cardiac transient outward current, activation occurs with a sigmoid delay. Inactivation has at least two components, often termed N-type and C-type inactivation. Both are functionally coupled to the process of activation. N-type inactivation occurs via a "ball and chain" mechanism. C-type inactivation is less well defined but involves residues at the outer mouth of the pore which are coupled to large scale movements of the intracellular pore mouth, S6, and other domains of the channel. These large scale changes mediate strong interactions between C-type and N-type inactivation which cause the rate limiting step for recovery to be

determined by the properties of C-type inactivation. These kinetic properties are essential for determining the restitution and recovery processes of the cardiac action potential.

John Lederer (University of Maryland) described experimental results showing depletion of calcium stores and calcium leak and hypothesized the existence of rogue ryanodine receptors (RyRs), that is, RyRs that are not located in the dyadic space and that are therefore not subject to local control. He hypothesized that these rogue RyRs may mediate increased leak of calcium from the SR that is believed to occur either during hyperphosphorylation of these receptors or in heart failure.

In the afternoon, Don Bers (Loyola University) presented two talks both dealing with calcium handling in cardiac cells. In the first, he described his group's experimental and theoretical work to characterize Cardiac L-type Ca Channels, RyR2s and SERCA2a. In addition, he presented data relating to the diffusion of calcium in the network SR. In the second talk, he focused on the Na-Ca Exchange process in cardiac myocytes. He described the challenge associated with characterizing the kinetics of NCX, because the calcium concentration in the vicinity of these channels is highly inhomogeneous, and may be subject to some kind of local control, similar but not the same as local control of RyRs.

Day 2

Yoram Rudy (Washington University, St Louis) presented two examples of how computational models can help elucidate arrhythmogenetic mechanisms. In the first example, the long QT cellular phenotype of HERG mutation was shown to result from the specific kinetic changes to IKr (the rapid delayed rectifier) and their effect during the action potential early after depolarizations are generated through an interaction between the mutant IKr channels and the L-type Ca2+ channels. In the second example, it was shown how the kinetic properties of IKs (the slow delayed rectifier), which are conferred by molecular subunit interactions, determine its participation in rate-dependent repolarization and facilitate its role as "repolarization reserve." This talk generated an interesting discussion among participants relating to the cause of EADs, with some discussants arguing that EADs are most likely related to spontaneous calcium release from RyRs with electrical activity generated by NCX, and thereby related to calcium overload. Others agreed with Rudy's hypothesis that EADs were related to the reopening of L-type calcium channels. It was evident from the ensuing discussion that the mechanisms underlying EADs are not fully understood.

Rai Winslow (Johns Hopkins University) described his group's effort to use computational models to understand heart failure. The cellular heart failure phenotype is characterized by action potential prolongation and reduction of both amplitude and rate of decline of the intracellular calcium transient. Their early studies revealed that while voltage-gated K channels were down-regulated in end-stage heart failure, this down-regulation could not explain AP prolongation of altered Ca transients. Instead, altered expression of the proteins involved in Ca cycling seemed to play the dominant role. He also described several new ways of modeling the calcium-induced calcium-release process in the cardiac myocyte.

Martin Falcke's (Hahn-Meitner Institute) talk focused on the challenge of modeling the dynamics of complex molecules, having several internal degrees of freedom, including inactive and active states. He presented a method to exactly calculate the distribution of hitting times to the active state. The method is suitable in particular for very small molecule numbers, i.e., in the range where other methods to calculate first passage probability densities (i.e., using a linear Fokker-Planck equation) fail.

Peter Hunter (University of Auckland) described the impressive work of the cardiac group in the Auckland Bioengineering Institute developing tissue and organ level simulations of myocardial activation. They have developed an instrument for imaging the 3D structure of myocardial tissue and as well as bidomain reaction-diffusion computational models that incorporate the measured structure at length scales of 0.2m -1.0mm. By comparing the propagation of activation wavefronts using these detailed structural models with coarser grained continuum models that approximate the fibrous-sheet structure on a larger length scale, they have been able to derive a conductivity tensor for the tissue that can be used in the intact organ level simulations. In this talk, he also described the use of the CellML model repository (www.cellml.org/models) for defining the cell equations and tissue constitutive laws, and the coupling of electrical activation based on reaction-diffusion equations to large deformation mechanics in the beating heart.

In the final talk of the day, Michael Miller (Johns Hopkins University) described computational anatomy as the use of infinite dimensional diffeomorphisms to study biological shapes. His informative review of this field included descriptions of the construction of the group of diffeomorphisms via flows, the model of anatomical orbit as a group action of diffeomorphisms on exemplars (deformable template) with associated metric structure, and the variational problems associated with inference of the hidden flows connecting configurations in the anatomical orbit. Applications included metric comparison of shapes in human anatomy and in growth and development sequences.

Day 3

Sasha Panfilov (University of Utrecht) led off the day by showing us the results of his whole heart modeling of reentrant patterns (i.e., scroll wave dynamics). First, he described his study of filament dynamics in anisotropic cardiac tissue, presenting a computational method that can be used to predict filament shapes in anisotropic tissue based on data on the arrival times of the excitation in a slab of cardiac tissue. The method is an extension of the 'minimal principle for rotor filaments' proposed by Wellner et al., (PNAS, v.99:8015-8018, 2002). Second, he reported on the development of an anatomically accurate computational model for the human heart. The model integrates knowledge about electrophysiology of the human heart from a single cell to the whole organ and allows study of mechanisms of cardiac arrhythmias in the human heart, where experimental interventions are limited. Studies of 3D organization of ventricular fibrillation in the human heart show that ventricular fibrillation in the human heart may be organized by a small number of vortex filaments (around 10) and should have much simpler structure than thought before.

Natalia Trayanova (Johns Hopkins University) followed this with a talk describing her work to develop a detailed bidomain model of whole rabbit heart and the use of this model to study the effect of field stimulus protocols at initiating and eliminating three dimensional reentrant arrhythmias. Additionally, she described recent efforts to develop computational models having highly detailed spatial structure.

Candido Cabo (SUNY) described experiments and theory relating to the maintenance of reentrant arrythymias in the thin epicardial layer overlaying an infarction. He described the extensive remodeling of ion channel function and gap junctional conductance that occurs in the border zone of the infarct. He also described the use of computer models of the infarcted canine heart to understand how the heterogeneities in ion channel function and gap junction conductance described experimentally lead to stable reentrant tachycardias.

Craig Henriquez (Duke University) discussed his efforts to develop detailed models of tissue which take the detailed cellular structure, including gap junctional distribution, into account, to study saltatory propagation in an extended tissue model. He also showed his recent work to developed three dimensional models that include both intracellular and extracellular membranes. He presented a brief overview of the evolution of cardiac tissue models and introduced a novel computational approach for studying propagation in three-dimensions at the microscale. In this model, individual myoctyes are represented as discrete units comprising an intracellular space, bounded by a membrane and embedded in an interstitium. The model builds off the work of Spach Heidlage (Circ. Res, 1995) and differs from the classical monodomain or bidomain models in that it can incorporate realistic cell morphologies, channel distributions, and cell-to-cell connectivities that are associated with an arrhythmogenic substrate. Simulations results are presented, which demonstrate how the framework can be used to study the effects of structural changes, such as those arising from disease and aging of the myocardium, on impulse propagation and signal waveshape that cannot be easily captured in traditional tissue models.

Michael Guevara (McGill University) showed experimental and theoretical results of studies of pacing of single rabbit myocytes, describing transitions in stimulus response patterns and hysteresis in these patterns. In particular, 1:1

synchronization can break down in several ways: there can be Wenckebach rhythms, alternans (2:2 rhythm), or a direct transition to 2:1 rhythm. In this talk, he provided evidence for these transitions in experimental work on single ventricular cells, as well as in ionic models and in the much simpler piecewise-linear FitzHugh-Nagumo equations. He also described how the dynamics can, on occasion, be reduced to the analysis of one-dimensional maps, wherein multistability (the simultaneous presence of two or more periodic rhythms, depending on initial conditions) arises.

Guy Salama (University of Pittsburgh) gave us an overview of current understanding of how fibrillation is maintained. There are currently two dominant hypotheses:

A) The Ômother rotorÕ hypothesis proposes the VF is maintained by a high frequency source (fixed or meandering) that drives activation waves at a dominant frequency through large regions of myocardium. At regions that cannot be driven at high frequencies, fribrillatory conduction appears at the boundaries resulting in more complex frequency distributions.

B) The multiple wavelet hypothesis posits that the continuous creation and annihilation of wavelets perpetuates VF. The splitting of wave fronts into daughter waves (i.e. wavebreaks) that perpetuates VF may occur when wave fronts meet anatomical and/or functional obstacles that cause unidirectional conduction blocks that form new reentry circuits.

He presented the results of several experiments intended to test and examine these hypotheses. In the first, it was shown that activation of volume-regulated chloride channels, ICl, vol transformed complex VF to a stable spiral. Thus, activation of ICl, vol by decreasing osmolarity (45 mOsM) has a major impact on VF dynamics by transforming random multiple wavelets to a highly organized VF with a single dominant frequency. In the second, he investigated the mechanisms underlying wave front instability in VF by localizing wave fractionation sites (the appearance of multiple waves) and their relationship to local, spatial dispersion of voltage (Vm) oscillations. The occurrence of wave fractionations were analyzed with respect to anatomical obstacles, fiber orientation and correlation of Vm oscillations at neighboring sites, prior to wave splits. Wavebreaks did not preferentially occur at anatomical obstacles (i.e., coronary vessels) but coincided with discordant alternans where Vm amplitudes and durations shifted from high-low to low-high on opposite sides of wavebreak sites. Therefore, nodes of discordant alternans cause wavebreaks most likely because they are sites of abrupt dispersion of refractoriness.

> “The model integrates knowledge about electrophysiology of the human heart from a single cell to the whole organ and allows study of mechanisms of cardiac arrhythmias in the human heart, where experimental interventions are limited.”

Day 4

Mario Delmar (SUNY) demonstrated that Cx43 remodeling may be one of the substrates responsible for life-threatening ventricular arrhythmias in patients with Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC). In his talk, he reviewed the clinical, anatomo-pathological and genetic characteristics of ARVC and described new data indicating that, at least in some cases, ARVC may be accompanied by loss of the structural and molecular integrity of the cardiac intercalated disc. The clinical features of ARVC may be related to significant remodeling of the intercalated disc structures, including gap junctions.

David Rosenbaum (Penn State University) described the significance of T wave alternans as a precursor of electrical dysfunction in heart via the onset of ventricular tachycardia and ventricular fibrillation. More specifically he described both experimental and theoretical studies of concordant and discordant altermnans.

Igor Efimov (Washington University, St Louis) gave us a detailed look at the complicated anatomy of the SA node and the AV node and the relationship between this anatomy and local reentry circuits. He also described recent experimental and

theoretical studies of the attempt to defibrillate tissue using small, rather than large stimuli. It was shown that if a reentrant pattern is anchored or pinned to an anatomical obstacle, it may be possible to dislodge it from its anchor using small properly timed stimuli. Once dislodged, the wave pattern may be more easily eliminated.

Ken Laurita (Case Western University) described how ventricular remodeling associated with myocardial infarction (MI) promotes a substrate that is the leading cause of ventricular arrhythmias. The usual cause of ventricular arrhythmias associated with late MI is, in part, reentrant excitation resulting from electrophysiological heterogeneity due to coexistence of infarcted, border zone, and viable myocardial tissue. To better understand the mechanisms of arrhythmogenesis associated with MI, studies have meticulously focused on altered ionic currents, action potentials, and cell-to-cell coupling associated with viable cells in the border zone. Likewise, abnormal conduction, such as wave break, impulse block, and slow conduction, has been well documented in late MI. However, the exact causal relationship between abnormal cellular electrophysiology, conduction abnormalities, and arrhythmogenesis associated with late MI is not completely understood. Novel experimental techniques can be used to illuminate the mechanistic relationship between abnormal cellular electrophysiology and arrhythmogenesis associated with late MI and, possibly, lead to new therapeutic approaches.

Sandor Gyorke (The Ohio State University) showed us his experimental evidence for lumenal calcium control of RyR, describing a detailed biophysical model for the mechanism of this lumenal control, via calsequestrin, junctin/triadin, and also showing how genetic and acquired defects in these mechanisms can lead to cardiac diseases such as arrhythmia and heart failure.

Clara Franzini-Armstrong (University of Pennsylvania) described the control of calcium release from the junctional cisternae of the sarcoplasmic reticulum (jSR) by giving us a detailed anatomical tour of the T-tubule-diadic subspace-SR release unit subspace.

Day 5

Saleet Jafri (George Masson University) discussed the use of computational models to how microstructural and physiological features affect the spatial spread of calcium sparks. The basic model consists of two dyads positioned on opposite sides of a T-tubule and the adjacent half sarcomeres. The model suggests that in order to simulate the spatial spread of calcium i.e. a full-width at half maximum (FWHM) of 2.0 microns seen in experiments, calcium release from both dyads must occur. The model also simulates the local depletion of the sarcoplasmic reticulum seen in experiments and suggests that this observed depletion is composed of large depletion of the junctional sarcoplasmic reticulum and small depletion of the network sarcoplasmic reticulum which appear as a small over all depletion due to the effects of the dyes used and confocal imaging techniques. The model then is expanded to include multiple release sites and is used to account for spontaneous calcium waves seen in calcium overload conditions.

Greg Smith (College of William and Mary) closed out the workshop by presenting a probability density approach to modeling heterogeneous calcium (Ca) release from stochastic functional units (SFUs) or "couplons" of cardiac myocytes. Coupled advection-reaction equations are derived relating the time-dependent probability density of subsarcolemmal subspace and junctional sarcoplasmic reticulum [Ca] conditioned on the state of each SFU. When these equations are coupled to ODEs for the bulk myoplasmic and SR [Ca], a realistic but minimal model of cardiac Ca-induced Ca release via local triggering of Ca sparks is produced. This modeling approach avoids the computationally demanding task of resolving spatial aspects of global Ca signaling, while accurately representing heterogeneous local Ca signals in a population of diadic subspaces and junctional SR depletion domains. The probability density approach produces Ca release that is graded with changes in membrane potential and depolarization duration and represents a new class of deterministic whole cell models that efficiently represent

important aspects of stochastic Ca channel gating and localized Ca dynamics.

Workshop 2: Cardiac Mechanics and Remodeling, October 2-6, 2006

Organizers: Andrew McCulloch, University of California San Diego, La Jolla, CA; and James Keener, University of Utah, Salt lake City, UT

Day 1

The program on Day 1 followed the discussions in Workshop 1 on myocyte calcium handling and excitation-contraction coupling mechanisms by focusing on the metabolic and neurohormonal networks and mechanisms that regulate excitation, calcium cycling and contraction in cardiac muscle cells. Physiologists have recognized for a century that the heart adapts its oxygen consumption and metabolic activity to meet the energy demands of the muscle when the workload of the ventricles changes.

Brian O'Rouke (Johns Hopkins University) described new experimental evidence for key roles of mitochondrial calcium dynamics and intracellular sodium on the tight coupling between excitation-contraction and bio-energetics in cardiac myocytes. A new mathematical model (Cortassa et al, 2006) suggests an important role for microdomains of calcium and creatine kinase. It suggests that mitochondria take up calcium rapidly, but slower decay kinetics facilitate diastolic accumulation of calcium in the mitochondria. A pathological increase in cytosolic sodium can decrease the mitochondrial calcium transient and diastolic calcium accumulation and impair the calcium-induced production of NADH thus resulting in a mismatch between work and energy production.

Miguel Aon (Johns Hopkins University) presented a systems biology approach to mitochondrial dynamics and arrhythmias. Two-photon microscopy was used to image mitochondrial membrane potential. A local burst of reactive oxygen species (ROS) gave rise to a synchronized collapse of membrane potential oscillations and NADH production. The experiments suggest a long-distance interaction between neighboring mitochondria. A percolation model was used to test the hypothesis that these findings were consistent with waves of ROS-induced ROS release. These findings could be very significant in the mechanisms by which reperfusion following ischemia can give rise to life-threatening ventricular arrhythmias.

Anushka Michailova (University of California, San Diego) presented recent models on how adenine nucleotides and magnesium regulate excitation-contraction coupling mechanisms in ventricular myocytes. In addition to powering ion pumps in the cell membrane and sarcoplasmic reticulum, ATP and ADP also buffer calcium and magnesium in the cell, and they sterically regulate certain key ion channels, especially the ATP-activated potassium channels that open during metabolic inhibition and help protect the ischemic heart.

Dan Beard (Medical College of Wisconsin) discussed the use of systems models to investigate the control of oxidative phosphorylation by feedback of primary substrates. A new mitochondrial model treats charged species as variables so that it is both elementally and charged balanced. Coupling this model with a whole myocyte model that includes ATP hydrolysis, adenylate kinase and creatine kinase reactions gave rise to results that show good agreement with in-vivo experimental measurements. Thus while calcium control may be significant, substrate feedback remains a primary control mechanism in bioenergetic control in the myocyte. Dr. Beard also advanced the appealing but disputed contention that sufficient data exist to develop a generation of more biochemically rigorous metabolic models that treat individual molecular species (Mg.ATP, ATP4-, H.ATP3-) rather than lumped reactants (ATP). This would provide a much firmer footing for predicting the effects of altered pH for example from the fundamental chemistry. It would also reconcile much of the apparent variability in the experimental literature that results from different chemical conditions.

John Solaro (University of Illinois at Chicago) shifted the emphasis from metabolic regulation to other cell signaling mechanisms and their specific contributions to regulating the contractile dynamics of the sarcomere. These mechanisms span

from short-term response to altered mechanical loading or neurohormonal stimulation to the long-term adaptations associated with development and the progression of disease. In the latter, the z-disk of the sarcomere contains a wealth of signaling molecules that together confer specific mechanosensing and mechanotransducing ability that may be disrupted in cardiomyopathy or other diseases. The myofilaments have key PKA phosphorylation sites on troponin I and myosin binding protein C that control both the release of activator calcium from the myofilaments and the kinetics of crossbridge interactions. There is also crosstalk between these control mechanisms and PKC signaling. PKC also docks at the z-disks allowing cross-talk between those pathways. The modeling challenge is to develop models in which calcium fluxes are coupled with myofilament activity and regulatory mechanisms because sometimes the effects on the myofilaments dominate the calcium-mediated effects.

Jeffrey Saucerman (University of Virginia) took a step in this direction by presenting a model that combined excitation contraction coupling mechanisms with PKA-mediated signal transduction. To validate and extend these models he used fluorescence resonance energy transfer (FRET) imaging of a recombinant molecular sensor of PKA activity expressed in isolated ventricular myocytes. By putting the network model in a spatially coupled model of the cell and using sensors targeted to different cell domains, he demonstrated the importance of spatially restricted p0ols of cAMP in the specificity of myocyte signaling.

Day 2

The second day focused on experiments and models regarding the basic mechanisms of cardiac muscle contraction at the level of the muscle, the sarcomere and the crossbridges.

Pieter de Tombe (University of Illinois, Chicago) reviewed the cellular and molecular mechanisms of the Frank-Starling "law of the heart" by which cardiac muscle develops increasing force of contracting with increasing stretch. An old hypothesis that a reduction in interfilament spacing as the cell stretches longitudinally and shrinks radially was re-energized by experiments in the 1990s in which cells were osmotically swollen or compressed. However these experiments are sensitive to experimental artifacts and the conditions of the muscle. Most importantly, filament spacing was not directly measured. De Tombe using the synchrotron at Argonne National Labs to perform x-ray diffraction on live cardiac muscles and they investigated the effects of exchanging components of troponin I in these preparations. The studies suggest that a single residue on troponin I was more important than interfilament spacing per se. The stretch sensing mechanism itself remains unidentified.

Jeremy Rice (IBM) described the development of a simplified systems model of myofilament activation mechanisms that accurately reproduces experimental observations and cooperative interactions between cross-bridge interactions and calcium activation without the need for a more explicit representation of the complex spatial interactions that these cooperative mechanisms depend on. The model compares well with experimental observations but the simplifications introduce inherent limitations.

Bryant Chase (Florida State University) presented the results of novel experiments in which the regulation of cardiac muscle contraction and its temperature dependence could be studied in vitro at the level of isolated filaments and molecular motors. He also presented a microscale model at the level of three thick filaments and 300 crossbridge heads, which his group used to

demonstrate the effects of filament compliance on apparent calcium sensitivity.

Paul Janssen (The Ohio State University) discussed the phenomenon of frequency dependence of cardiac muscle contraction and relaxation, which was first recognized by Bowditch in 1871. While physiological studies have focused on the frequency dependence of calcium cycling as the mechanism, Janssen showed new results from his lab suggesting that at higher and frequently more physiologically relevant frequencies (especially in small animals), the myofilaments themselves may be more important for frequency dependent regulation of relaxation kinetics.

Henk ter Keurs (University of Calgary), a cardiologist and physiologist, challenged mathematical modelers to consider how mechanical factors can lead to electric rhythm disturbances, especially in congestive heart failure. Clever experiments designed to introduce mechanical asynchrony and heterogeneity in isolated cardiac muscles showed that transient mechanical stretch induced intracellular calcium waves and triggered propagated contractions that may underlie the increased risk of arrhythmia in heart failure and other conditions associated with mechanically heterogeneous function.

Amir Landesberg (Technion in Haifa) summarized his theoretical model of cooperative myofilament activation and mechanics and used it to show that force rather than length is the most likely mediator of feedback in the heart. He also used the model to help explain how mechanoenergetics are impaired in the failing heart.

Day 3

Kevin Costa (Columbia University) summarized experimental and mathematical models of the cellular and tissue scale mechanics of the myocardium. Atomic force microscopy combined with finite element modeling is proving to be a useful way to probe subcellular mechanical properties. This approach can detect alterations in cell properties at a depth of up to 5% of the cell diameter from the membrane.

Michael Sacks (University of Pittsburgh) described the structure and mechanics of heart valves and illustrated the success of using microstructural measurement of collagen architecture to derive predictive constitutive models. An exciting new area of study is the mechanics of fibroblasts within the leaflets as the deform with the matrix.

Jeffrey Omens (University of California, San Diego) described mechanisms by which mechanical forces induce remodeling and functional changes in myocytes. For example, gene mutations of cytoskeletal proteins associated with inherited cardiomyopathy and heart failure attenuate stretch induction of hypertrophy. Fluid shear stress also affected intrinsic beating rates, and this effect was blocked by blocking adhesion receptors. There was discussion of the physiological significance of these fluid shears in myocytes, but Dr. Omens pointed out that the shearing of the wall induces fluid shear in the interstitium especially between laminar myocardial "sheets".

John Criscione (Texas A&M) introduced a theory for modeling tissue constitutive properties and advocated the use of non-traditional approaches to overcome the current limitations that constitutive laws to be identified reliably from biomechanical tests. These approaches rely on the derivation of response terms in the constitutive equation that are functions of strain attributes that are linearly independent or nearly so.

"The use of tissue engineering strategies creates an opportunity to develop in-vitro constructs that resemble living tissues but are more easily characterized and tested."

Jeff Holmes (Columbia University) described the process of post-myocardial infarction remodeling and the development of mathematical models of infarct scar properties based on their microstructure. The use of tissue engineering strategies creates an opportunity to develop in-vitro constructs that resemble living tissues but are more easily characterized and tested.

Day 4

Larry Taber (Washington University, St. Louis) described theoretical formulations for tissue growth and remodeling mechanics

and the significance of residual stress in growth mechanics theory. He illustrated this with examples of arterial hypertrophy and cardiac development. Experiments in the developing check embryo together with models helped to show how mechanical forces and specific structures are involved in the asymmetric morphogenesis that takes place during the critical looping stage of cardiac development.

Theo Arts (University of Maastricht) discussed how developing models of organ remodeling and adaptation can lead to the formulation of rules that can be used to minimize the parameters that must be measured. This is particularly valuable for developing patient-specific models, where available data are limited to those that are clinically accessible. Rules on how the heart remodels or its objective functions for optimal function can effectively limit the number of input parameters required for a comprehensive circulatory model from dozens to just 6 or 7.

Natalia Trayanova (Johns Hopkins University), who also attended Workshop 1, described models of mechanoelectric feedback in the whole heart. She described feedback mechanisms that have been incorporated into recent models from her group. The first was mechano-sensitive currents, which were included in the ionic model of the cardiac myocyte, and the second was the effects of strain on tissue electrical properties such as resistance and propagation distances. She illustrated the influence of these properties in two whole heart models. One showing how a low energy mechanical impulse properly timed can induce ventricular fibrillation and sudden death (Commotio Cordis) and another showing how the efficacy of a "thump" to the pre-cordium in terminating an arrhythmia is decreased in the ischemic heart. The next generation of models will include the active systolic motion of the heart walls.

Julius Guccione (University of California, San Francisco) described the use of finite element models of whole ventricular continuum mechanics to investigate the effects of surgical procedures and devices to improve the function of the failing heart. The models demonstrated that improved stroke volume rather than ejection fraction is a key outcome, and that reduced regional wall stress may be a better predictor of long-term outcomes than global hemodynamic indices.

Roy Kerckhoffs (University of California, San Diego) described a strategy for coupling whole heart models of ventricular electrical activation and mechanics with closed-loop systems models of circulatory hemodynamics. He illustrated the use of these models to investigate how cardiac resynchronization therapy using electrical pacing can improve the synchrony and efficiency of contracting in the dyssynchronous, failing heart. These models provide a potential strategy to optimize the efficacy and response rate of cardiac resynchronization therapy.

Day 5

Allistair Young (University of Auckland) introduced the latest magnetic resonance imaging methods for imaging cardiac mechanics and wall strains and the need for parametric models to reconstruct and interpret these data in patients and variety of experimental models including mice. He described results of studies showing alterations in regional heart wall mechanics associated with diabetes, aging, and dilated cardiomyopathy. Combining these functional measurements with continuum models of wall mechanics provides a strategy to identify myocardial material parameters in the intact heart by a semi-inverse analysis. Dr. Young also introduced the concept of a Cardiac Atlas project similar to those that have been very successful in studies of the brain.

Igor Efimov (Washington University, St. Louis) introduced optical electrical mapping and optical coherence tomography in the isolate heart. Panoramic imaging makes it possible to map action potential propagation over the entire outer surface of the heart with high temporal fidelity. Optical electrical mapping is sensitive to motion of the heart walls. Previous studies have used chemical electromechanical uncouplers that have the disadvantage that they affect cardiac electrical properties such as action potential duration and conduction speed. A new uncoupler eliminates shortening without affecting Ca transients or

other key features of cardiac excitation and recovery. By using structured light to reconstruct geometry and motion it should be possibly to reconstruct and eliminate motion algorithmically and in real-time. These methods will give new insights into cardiac mechanoelectric feedback.

Nic Smith (Oxford University) presented a comprehensive model of the heart that integrates electrical, mechanical, coronary vascular and metabolic properties. A key challenge for such models is properly accounting for the numerous cellular alterations associated with myocardial ischemia and hypoxia. In this respect, his newest models have detailed mechanisms for modeling the acidosis that accompanies loss of oxygen in the ischemic heart and mediates numerous alterations in electromechanical function.

Conclusion of Workshops 1 and 2

The workshops succeeded in generating vigorous discussion and many new opportunities for collaboration, especially between experimental and theoretical groups, but also between modelers who are increasingly focusing on coupled mechanisms such as electromechanics, mechano-energetics, fluid-solid interactions, and mechanoelectric feedback. Another important theme is multi-scale modeling, and the new opportunities that are becoming possible for extended spatial and temporal scales of cardiac models.

Mini-Conference on New Approaches to Modeling Sleep/Wake Dynamics and Cognitive Performance (Partially supported by the AFOSR)

Organizers: Janet Best, Department of Mathematics, The Ohio State University; David Terman, Mathematical Biosciences Institute; and Hans Van Dongen, Department of Psychiatry, University of Pennsylvania

The primary goal of this workshop was to address several important aspects of sleep/wake modeling, including interactions between the homeostatic and circadian processes, the link between sleep/wake dynamics, cognitive capabilities and performance and how individual differences should be incorporated into the models. The workshop lasted for two days and was divided into four, half-day sessions. During the first three sessions, the workshop addressed three primary themes that are described below. Each session consisted of a one-hour introductory talk and these were followed by several half-hour talks. The last half-day session consisted of a discussion of future challenges and modeling needs.

The theme of the first session was: Modeling the homeostatic system and how it interacts with the circadian system. Peter Achermann gave the introductory talk. He discussed successes and problems with the two-process model for sleep/wake regulation. Most current models for sleep/wake regulation are directly or indirectly based on this seminal model. The two-process model has been successful in accounting for the effects of acute sleep deprivation on sleep and performance; however, the model has been less successful in accounting for experiments involving chronic sleep restriction and subsequent recovery sleep periods. Clifford Saper presented his flip/flop switch model for sleep and wakefulness in the next talk. This model is based on detailed experimental studies of interactions between groups of neurons within the brainstem and hypothalamus. It clearly suggests many possibilities for mathematicians to make important contributions in developing and analyzing more detailed biological models for the sleep/wake cycle. Mark Blumberg then presented his work on how sleep/wake dynamics changes during development. This again raises unique opportunities for theoreticians to develop models that account for changes in sleep/wake dynamics across the lifespan. Domien Beersman and Sean Hill gave the final two lectures in this session. These presented detailed models for REM and nonREM sleep and for thalamocortical interactions during wakefulness and sleep.

The theme of the second session was: Modeling the link between sleep/wake dynamics and cognitive/psychomotor capabilities. David Dinges who discussed models for the link between sleep/wake dynamics and performance gave the introductory lecture. Most current models estimate the general trend of performance decline under conditions of sleep loss and/or

> "It clearly suggests many possibilities for mathematicians to make important contributions in developing and analyzing more detailed biological models for the sleep/wake cycle."

circadian misalignment. Dinges presented evidence that sleep/wake alterations have differential effects depending on the nature of the performance task—which is not accounted for in contemporary models. He further discussed the need to develop models in which parameters have specific physiological and/or neuropsychological correlates, so that the behavior of the model may be interpreted biologically and interventions may be incorporated appropriately. Giulio Tonoi presented a detailed biologically inspired model for synaptic homeostasis and cortical synchronization. His model suggests that the reduction of cortical synaptic strength may be key factors underlying the decrease in slow-wave activity between high and low sleep pressure conditions.

The theme of the third session was: Modeling individual differences. The introductory lecture was given by Derk-Jan Dijk who described research on how performance may depend on the circadian and homeostatic regulation of sleep. This was followed by lectures by Erik Olofsen and Christopher Mott. They described research related to trait-like individual differences in responses to sleep and circadian challenges. Such systematic individual differences tend to represent a considerable portion of the variance and therefore need to be accounted for. Olofsen and Mott presented new modeling strategies in order to address this important issue.

During the final session, the workshop participants broke up into three groups. Each group discussed one of the three themes in order to identified major challenges and opportunities for further research. Representatives of each group then presented a summary of these discussions to the entire workshop participants. Although issues related to sleep/wake, performance and individual differences have received previous studies; earlier models have been largely phenomenological and thus far have not accounted for many important aspects such as the cumulative effects of chronic sleep restriction. Recent progress in understanding the neuronal and neurochemical substrates underlying the sleep/wake cycle, as well as the development of theoretical tools for analyzing complex biologically inspired models, makes this an auspicious time to forge new modeling approaches. The workshop brought together a diverse and highly accomplished group of researchers across the spectrum from experimentation to mathematics. It provided a unique opportunity to exchange points of view, forge new collaborations and develop new approaches to modeling these important issues.

Workshop 3: Mathematical/Computational Modeling of Pulmonary Structure-Function Relationships in Health and Disease, November 6-10, 2006

Organizers: Kenneth R. Lutchen, Department of Engineering, Boston University; Jason H.T. Bates, Department of Medicine, University of Vermont; and Bela Suki, Department of Biomedical Engineering, Boston University

Introduction

The motivation for holding this workshop stems from the fact that current research on lung pathophysiology comes down, in large part, to the attempt to understand the link between structure and function. When such understanding becomes quantitative, it is embodied in mathematical and computational models capable of accurately predicting how lung function arises from anatomical structure. The past decade has seen major advances in both experimental techniques for determining both structure and function in the lung and in mathematical/computational models. These efforts have proceeded in parallel at many levels of scale encompassing a range from that of the molecule up through cells and tissues to the level of the entire organ in vivo.

Despite these advances, however, our quantitative understanding of the link between structure and function in the lung is far

from complete. In particular, there remain tremendous gaps in our understanding of how phenomena in the lung at one level of scale impact those at other levels. For example, although we can identify the major proteins, cells, interstitial matrix, and other individual constituents of the lung, we still have a very poor understanding of how they all act together to produce the complex nonlinear rheology of lung parenchyma that is measured at the tissue level which in turn determines how the tissue and the various cells stretch during breathing. Similarly, the airway smooth muscle cell has been recently demonstrated to manifest a rich set of dynamic behaviors, yet the extent to which these behaviors are important for bronchial responsiveness at the level of the whole organ remains obscure.

Understanding the lung as a complex multi-scale system presents formidable challenges, but we now have the tools to take these challenges seriously. Indeed, using computational tools to understand disease in terms of complex systems is recognized in the NIH Roadmap as central to the future of biomedical research. This workshop presents us with the opportunity to examine where we are currently, and where we need to go next, in applying the complex multi-scale systems paradigm to the lung.

Objectives

The structure of the workshop was designed to encourage free discussion and exchange of ideas. However, the following areas were identified as important foci for discussion.

1. Describe current lung modeling efforts at levels of scale from the molecule to the whole organ, and the role in this effort played by biophysical measurements and imaging.

2. Describe how anatomically-based stochastic modeling has been used to demonstrate emergent properties of the lung from the ensemble behavior of components at lower levels of scale.

3. Describe how perturbations applied to the lung at the whole organ level can influence constitutive properties at lower levels of scale.

4. Define new areas for research and new mathematical/computational approaches that can be applied to modeling the lung.

5. Discuss directions that might be of interest to funding agencies.

Strategy

Since a key goal of the workshop was to generate new research directions and collaborations in lung modeling, the program was structured so as to maximize the potential for discussion among participants. Thus, instead of a program characterized by people sitting passively listening to lectures, some of the attendees were asked to give relatively short state-of-the-art type talks intended to set the scene for extended discussions among all participants under the direction of moderators. This worked extremely well, for the most part, and resulted in some cases to more than 30 minutes of animated yet orderly exchanges between multiple participants.

Day 1

The first presentation was given by Ching-Long Lin (University of Iowa) on Multi-scale Simulation of Pulmonary Air Flow. Ching-Long demonstrated how, in collaboration with researchers at the University of Auckland, New Zealand, he has been using advanced computational methods to build anatomically accurate models of the branching pulmonary airway tree with which ventilation distributions can be accurately calculated using the methods of computational fluid dynamics. Jason Bates (University of Vermont) then followed with an overview of Modeling Emergent Behavior in the Lung, covering ensemble averaging of disparate mechanical behavior at the acinar level to predict whole organ function, percolation as a mechanism for understanding the progression of fibrotic disease, and the use of dynamic nonlinear networks as a vehicle for viewing the nature of disease processes. The discussion that followed touched on the key issue of "complexity" versus "complicatedness", and how interesting emergent behavior is not simply a function of the number of components involved, but rather depends

critically on these components interacting in nonlinear ways.

This session was designed to bring attention to the importance of keeping the ultimate clinical relevance of lung research in mind, and began with a presentation from Brett Simon (Johns Hopkins University) on Clinical Perspectives: Modeling in Acute Lung Injury. This presentation dealt with the gross features of acute lung injury in terms of its appearance on computed tomography of the chest and changes in lung mechanical function, and how these features can be understood in terms of recruitment and derecruitment of heterogeneously distributed regions of the lung. A particular point raised was the need to understand lung pathophysiology to the point where ventilation strategies can be tailored to the individual patient rather than being based, as they currently are, on population mean behavior. There is also a critical need to understand how ventilation is matched to perfusion in acute lung injury, and to identify the early effects in this disease. Steven George (University of California, Irvine) then followed with An Integrative Approach Towards Understanding Nitrogen Oxide Biology in the Lungs, in which he showed how NO is involved in a complex cascade of biochemical reactions affecting airway function, with particular pertinence to asthma. An extended discussion followed. He also asked the general question as to whether measuring NO in asthma is useful. NO is a molecule that has generated huge interest over the past decade, but it is produced in so many places in the respiratory system and in such variable amounts, that relating its levels in exhaled breath to pathological events in the lungs is a significant challenge.

Samir Ghadiali (Lehigh University) began the session with a presentation on Fluid-Structure Modeling of Cellular Deformation and Injury in Pulmonary Airways. This described an elegant use of finite element modeling to understanding how shear forces on epithelial cells cause cell damage, as measured in the laboratory. Subsequent discussion brought out the point that modeling stresses and strains within individual cells and between collections of cells represents a prime example of multi-scale phenomena. Next, Wayne Mitzner (Johns Hopkins University) talked about Modeling Airway Distensibility in the Lung, and showed how CT imaging has revealed the critical role of airway smooth muscle tone in determining the relative compliances of airways and parenchyma. This may explain, in large part, why the airways of asthmatic and normal individuals frequently respond very differently to deep lung inflation.

"In the face of the enormous complexity of biological systems such as the lung, and our burgeoning ability to apply computational methods to model them, the question of how far to go becomes key."

This session began with Akira Tsuda (Harvard University) talking about Folding and Mixing. Here we saw how slight asymmetries in the airway tree combined with the dynamics of convective flow can cause a chaotic folding of streamlines with each successive breath that results in efficient mixing of gases and aerosols in the distal regions of the lung. This raises the novel but crucial point that gas and aerosol transport in the alveolus is not simply governed by diffusion, as classically thought, but also involves irreversible convective mixing. This talk was followed by Simulating Aerosol Deposition in the Lung: How Realistic Are the Current Models? by Chantal Darquenne (University of California, San Diego). This talk focused on the use of computational fluid dynamics in anatomically-based models of the airway tree to predict exactly where aerosols of a given size are deposited, and pointed out that 3-dimensional models with moving airway walls are necessary to accurately predict the deposition of small particles. The discussion that followed these talks got into the question of how accurate models of this sort have to be to be useful. In the face of the enormous complexity of biological systems such as the lung, and our burgeoning ability to apply computational methods to model them, the question of how far to go becomes key. Suggestions were raised that a fruitful direction for future research could be to combine detailed airway deposition and mixing models with models of bronchial blood flow to predict clearance of deposited agents.

Day 2

Jeffrey Fredberg, Harvard University, talked on the Scale-free Behavior of Cells, and described the dynamics of the cell as that of a soft glassy material in which the constituents are tightly packed and so become trapped in local energy wells that thermal agitations are not generally sufficient to overcome. Extra energy from hydrolysis of ATP and from imposed mechanical stretch may then conceivably supply the extra energy required, leading the weak power-law rheology characteristic of cells. This is thus a multi-scale phenomenon where the complex dynamics of micro-constituents of the cell combine to produce the macroscopic rheology measured experimentally. Ben Fabry (Erlangen University) followed up on these ideas with a talk on Nonlinear Viscoelasticity of Living Cells in which he explained that cells exhibit a curious nonlinear type of rheology that exhibits a power-law mechanical impedance over many decades of frequency: discussion then centered on how these findings can be explained on the basis of the hopping of components out of energy wells.

Hiroko Kitaoka (Osaka University) began with a presentation of her Morphogenesis-based 4D Model of the Alveolar Structure in which she showed how a space-filling elastic structure with rigid walls can be made to expand and contract like an acinus, and to behave similarly to in vivo microscopy images from real lungs. This model explains closing volume in the lung as arising from liquid films covering the alveolar mouth at low lung volumes. Dimitrije Stamenovic (Boston University) then talked about Micromechanics of the Lung: from the Parenchyma to the Cytoskeleton – the Unifying Role of Distending Stress. This talk dealt with the general question of how a cell resists changes in shape, as it must do in many situations in the body. The stability of cell shape can be attributed to a combination of connectedness amongst its components and the existence of pre-stress which produces stability through the tensegrity mechanism. This is a general mechanism that also has relevance to the stability of alveolar structures.

Eric Hoffman (University of Iowa) began with Lung Structure from Imaging and gave a spectacular demonstration of some of the latest x-ray imaging methods applied to the lung, and showed that these methods can yield crucial functional information such as levels of inflammation throughout the lung. This was followed by Michael Sanderson (University of Massachusetts) who talked about Video Imaging of Parenchymal Mechanics in which he showed how the dynamics of airway constriction can be viewed in explanted slices of lung. These two talks served to show that no matter how sophisticated computational modeling of the lung becomes, it is nothing without high-quality data to keep it grounded in the real world. Participants entered into a lively discussion about the possible uses these experimental methods could be put in order to validate existing models of the lung and to generate new ones.

Joe Anderson (University of Washington) gave a talk on the Impact of Airway Gas Exchange on the Multiple Inert Gas Elimination Technique. He showed that the results of the classic multiple inert gas elimination technique (MIGET) for determining ventilation/perfusion relationships in the lung can be in error if one assumes that all gas exchange takes place within the alveolar regions of the lung and neglects the fact that some highly soluble gases are also exchanged through the walls of the conducting airways. This raises the possibility of developing a MIGET technique for the airways. Kim Prisk (University or California, San Diego) then followed with a talk on Gas Mixing in the Periphery of the Lung: Insights from Modeling and Microgravity in which he showed some unique gas washout data collected in the Space Shuttle and in planes flying in parabolic orbits. In particular, the phase III slopes of helium and sulfur hexafluoride change rank order in brief (a few seconds) versus sustained (hours to days) microgravity, and hypotheses relating to distribution of blood flow and edema fluid in the lung may explain this.

One of the high points of the workshop took place on the evening of Day 2. Peter Macklem, Professor Emeritus of Medicine, McGill University, gave a public lecture entitled Complexity, the Origins of Order and the Respiratory System: A Physician's View in which he outlined a grand and imaginative view of disease as a complex dynamic process. Weaving together the work of luminaries such as Prigogine and Kaufmann with his own thoughts, Dr. Macklem explained how living systems can be viewed as open systems maintained at just the right distance from thermodynamic equilibrium by the continual input of energy from the environment. Examples such as temporal variations of airway resistance in asthmatic subjects versus normal individuals indicate that variability of just the right kind and degree is a crucial part of health, and that changes in these rhythms can be indicative of respiratory

disease.

Day 3

Ken Lutchen (Boston University) presented a talk on Modeling Lung Mechanical Function in which he showed how it is possible to infer the distributed nature of airway narrowing throughout the lung by combining 3-dimensional imaging of the lung with measurements of lung mechanical impedance before and after bronchoconstriction. This talk demonstrated how important it is to be able to combine experimental modalities in order to generate sophisticated and biologically relevant computational models of the lung. Jose Venegas (Massachusetts General Hospital) followed with a talk on Paradoxical Airway response to Bronchoprovocation, a Manifestation of Complex System Behavior, in which he showed how key features of the pattern of distribution of ventilation defects throughout the lung can be understood to arise from self organization among individual lung units that interact with each other over limited scales of distance. These two talks illustrated perfectly two of the most important uses of distributed computational modeling for understanding lung function. On the one hand, one can make the model as anatomically accurate as possible in order to explain the details of observations made through lung imaging. On the other hand, one can construct a more idealized model that is not as precise in its details, but which captures some essential element or reality in an idealized fashion, and then use this model to gain insight into the general nature of a mechanism responsible for an important feature of reality.

Brent McParland (University of Sydney) talked on Determinants of Hyperresponsiveness. This talk focused attention back on the experimental data necessary to validate computational models of the lung, and raised a number of issues related to the question of what causes airways hyperresponsiveness in asthmatic individuals. This question remains unanswered, but generated a lively discussion in which airway smooth muscle mass, the role of the airway epithelium, and synergistic interactions between multiple mechanics were raised as important factors. Geoff Maksym (Dalhousie University) then followed with a talk on Variations of Lung Function in Asthma at Short and Long Time Scales. This brought attention back to the dynamical nature of lung disease, and prompted discussants to consider the possibility that the airways are in a continual state of contracting and relaxing, so that a snapshot of the configuration of the airway tree at a given point in time may not bear any relation to the configuration at a sufficiently later time point. It also raised the question of when the temporal variation in airway caliber good is and when it is problematic.

Bela Suki (Boston University) began with a fascinating talk on Hierarchical Force Transmission in the Lung: Some Modeling Results Relevant to the Normal and Emphysematous Parenchyma in which he described renormalization theory in scale-free systems and showed how this may apply to the lung parenchymal network of alveolar walls. He also demonstrated a spring network model of the parenchyma which can be made to exhibit morphological features highly reminiscent of emphysematous lung tissue when the springs in the network are progressively broken according to the stress they experience. Jim Butler (Harvard University) then gave the final presentation of the workshop on Scale-free Methods from Physics in which he gave further insights into renormalization theory and showed how systems near a phase transition can exhibit long-range correlations that lead to power laws in both structural and temporal characteristics. He also related these concepts to the Ising model from statistical physics and the energy-well models currently being used to model cell rheology. These talks constituted a fitting end to the semi-formal part of the workshop by raising very fundamental issues about how dynamics and structure arise spontaneously from complex systems, and how this might happen in a variety of ways in the lung.

Day 3 ended with a vivid and general discussion amongst the participants about where future funding opportunities for lung modeling studies could lie. The session then ventured into the general issue of how (or how not) to define key concepts such as systems physiology and emergent behavior.

Day 4

The workshop continued on the morning of Day 4 with two general discussions. The first, chaired by Jason Bates, covered further issues related to defining what systems biology means to those investigating the lung, and touched on how to sell the idea of complexity and systems biology as applied to the lung to the general scientific community. The second session, chaired by Bela Suki, dealt with specific disease research that might be advanced through the systems biology approach, and raised concepts such as heterogeneity of phenotype, synergy between different mechanisms, and the importance of understanding disease dynamics as a means for early intervention.

Conclusion

There was uniform agreement at the end of the workshop that it had been a great success. Many of the currently most active and visible scientists in lung research were present, and all participants were particularly enthusiastic about the extended discussion sessions following (and sometimes during) the scheduled presentations. There was also widespread enthusiasm for continuing to keep the group in contact by arranging gathers at national meetings such as the Annual Meeting of the American Thoracic Society. Emphasis was placed on the recruitment of new devotees to the lung complex systems community in the form of graduate students and postdocs. In summary, the workshop was a highly stimulating and worthwhile experience for all attendees, and is certain to result in new scientific collaborations.

Workshop 4: Blood Flow in the Microcirculation: Function, Regulation, and Adaptation January 22-26, 2007

Organizers: Timothy W. Secomb, Department of Physiology, University of Arizona; and Daniel A. Beard, Department of Physiology, Medical College of Wisconsin

Introduction

The purpose of this workshop was to bring together mathematical modelers and experimental physiologists working on various aspects of the microcirculation. The microcirculation plays a key role in systems physiology, linking organ and systems functions with cellular and molecular level processes. To distribute and remove material and heat as needed throughout the body via convection in the blood and diffusive exchange with surrounding tissue, the microcirculation brings blood close to every point in the tissue. This workshop focused on three aspects of the microcirculation: blood flow and mass transport; short-term regulation of blood flow; and long-term (structural) adaptation of blood vessels, including angiogenesis.

Day 1

Timothy Secomb (University of Arizona) opened the workshop with an historical overview of research on the microcirculation, looking back to the pioneering work of Harvey and Malpighi in the 17th century, Poiseuille in the 19th century, and Krogh in the early 20th century. Mathematical analysis of transport (via reaction-diffusion modeling) began with Krogh, while quantitative analysis of network flows began with Zweifach and Lipowsky in the 1970s. These pioneering works established the foundation for much of what was presented and discussed in the workshop.

Theoretical modeling of the microcirculation often requires data on the structure of microvascular networks. Erik Ritman (Mayo Clinic College of Medicine) reviewed non-destructive three-dimensional imaging methods, such as multi-slice computed tomography, confocal-type microscopy, and destructive methods such as progressive serial-section histology. Data obtained using three-dimensional micro-computed tomography can be used to describe underlying properties of network structure. For example, the ratio of perfused volume to vessel cross-section area in a vascular network shows systematic changes not only with vessel generation, but also during growth and development, and in response to exercise training.

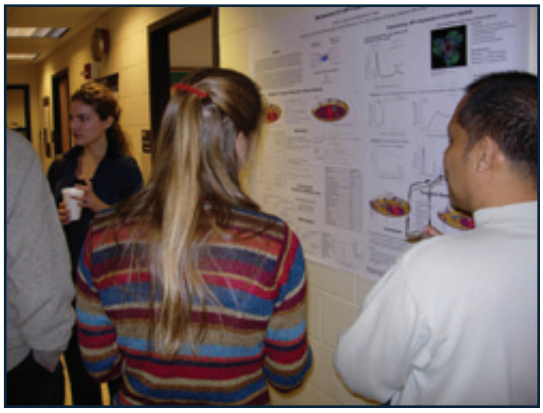
Ghassan Kassab (Purdue and Indiana University School of Medicine) presented his work on coronary circulatory structure and function. Over more than a decade, he has amassed an enormous data set of coronary vessels sizes, connectivities, and positioning in the heart. Based on the evolutionary-optimization approach introduced by Cecil Murray and using his data

set as a starting point, Dr. Kassab has explored the scaling properties of vascular trees and shown that the minimum-energy hypothesis can describe observed morphometry.

James Bassingthwaighte (University of Washington) has been a leader in the field of mass transport and exchange of solutions between the blood and tissue for several decades. He emphasized the use of models as hypotheses to be tested by experimental observations. Hypothesis testing in this setting typically requires matching model simulations to data based on optimization. As examples of this approach, he presented results from modeling tracer oxygen transport and adenosine transport in the heart. For the case of oxygen transport, data were obtained from PET imaging; for the case of adenosine transport and metabolism, data came from indicator dilution experiments on isolated perfused hearts. In both cases, comparing the model to the data yielded novel information about processes not directly observed experimentally.

In the final session of the day, Axel Pries (Charité - Universitätsmedizin Berlin) led an informal discussion on modeling practices and collaboration with biologists. The group used the opportunity to brainstorm on how to effectively promote and apply computational modeling in the biomedical community. This discussion was continued throughout the workshop.

Day 2



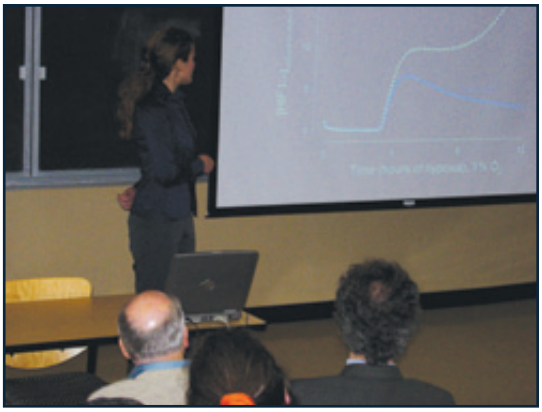
The second day of the workshop focused on mass transport in the microcirculation. Roland Pittman (Virginia Commonwealth University) is a leading experimentalist in the area of oxygen transport. Reviewing experimental approaches and historical and recent findings in this area, he gave a picture of what can and cannot be measured by different techniques, and pointed out that experimental limitations may provide opportunities for modeling. In discussing oxygen delivery, he made the point that experimentalists and modelers should interact as early as possible. Modelers should not start building models without talking to a biologist. Ideally, experimentalists should have the input of computational modelers when planning and designing experiments. Early models (going back to Krogh) assumed that the majority oxygen is delivered to tissue by capillaries. Later experiments found that up to 2/3 of oxygen lost from systemic blood diffuses from the arterioles, raising questions about where the oxygen goes. This question was successfully addressed using a combination of experimentation and computational modeling. A question about oxygen consumption in walls of arterioles was raised by controversial measurements suggesting enormous consumption rates. A well-planned combination of experiments and modeling has helped to resolve this question.

Daniel Goldman (University of Western Ontario) has developed computational methods for simulating oxygen transport in microcirculatory networks, accounting for the heterogeneity arising from the three-dimensional structure, nonuniform blood flow, and vasomotion. He argued that the heterogeneity of blood flow and oxygenation, particularly apparent during certain pathophysiological states, is best captured by 3D models, which are computationally expensive. Based on elegant 3D simulations of blood flow and oxygen transport, Dr. Goldman presented a number of applications, including model-based analysis of oxygen transport in muscle in sepsis. During sepsis, local control of microcirculatory flows is disrupted and capillary flows become more heterogeneous. Also, increased oxygen utilization is observed in sepsis, compounding the effects of impaired microcirculation. Dr. Goldman's simulations shed light on the impact of vasomotion on oxygen supply.

Nikolaos Tsoukias (Florida International University) presented a series of integrative models of nitric oxide biotransport and calcium dynamics in the microcirculation. Nitric oxide (NO) plays roles in numerous physiological processes, including

an important role as a vasodilating signaling molecule. As a molecule that is synthesized and reacts in different cell types, the transport of NO is critical to its function as a signaling molecule. Rapid binding of NO to hemoglobin in the blood leads to the potential for NO synthesized in endothelial cells to be washed away in the blood before it can diffuse to sites of action in smooth muscle cells. A set of competing transport models was presented to explain how NO escapes scavenging by hemoglobin and to predict the NO concentration profile in and around an arteriole. Dr. Tsoukias also introduced electrophysiology models for endothelial and smooth muscle cells. Models for both cell types were constructed, parameterized, and tested. Integration of these models provides predictions that agree with observations on vasomotion in isolated small vessels, suggesting that ionic currents in endothelium and smooth muscle are closely coupled.

Day 3



The focus on Day 3 was on regulation of blood flow. Jefferson Frisbee (West Virginia University) spoke about control of arteriolar wall diameters in the regulation of blood flow, focusing on the mechanisms of peripheral vascular disease in metabolic syndrome. Many mechanisms, including myogenic control, shear-induced release of vasoactive factors, upstream conducted response, and gap-junction communication between endothelial and smooth muscle cells, are involved in blood flow regulation. Yet we lack an understanding of how these players work together in an integrated fashion. Understanding how they fail to work properly in disease is an additional challenge. A theme of Dr. Frisbee's presentation was that while physiologists can measure several variables related to a particular system or condition, it is difficult to be sure that the right variables are being measured in the appropriate experiments. It is hoped that computational modeling can help to understand existing observations in the field and to uncover new knowledge.

Timothy Secomb took up Dr. Frisbee's challenge by speaking about computational modeling of microvascular blood flow regulation. Focusing on short-term regulation in response to hemodynamic stimuli (pressure and shear) and metabolic stimuli driven by local oxygenation, Dr. Secomb and colleagues have constructed an integrated mathematical model that describes physiological control in a simplified network. The model allows the control components to be computationally dissected to determine how each works individually and how they work together to maintain blood flow in response to changing pressure and to change blood flow in response to changes in oxygen demand.

Mette Olufsen (North Carolina State University) presented work on whole-body regulation of blood flow. Based on noninvasive data obtained on human subjects, Dr. Olufsen and colleagues are attempting to understand how blood flow is regulated in the closed loop circulatory system during orthotic stress (sudden posture change). Given the limited amount of data that can be measured clinically, and the complexity of the whole-body circulatory system, the inverse problem of model identification is difficult. Many (more than 100) parameters are necessary to simulate the system and simulations with pulsatile blood flow are computationally expensive. Dr. Olufsen's presentation initiated a discussion on issues related to developing large-scale models in the face of uncertainty in terms of data and parameter value estimates.

Day 4

The fourth day focused on structural changes in the microcirculation. James Hoying (University of Arizona) discussed the process of neovascularization, by which microcirculatory networks are enlarged within a tissue to deliver more blood. He emphasized that several processes must occur in a coordinated way for successful neovascularization of regions that have become ischemic because of interrupted blood supply. Vascular growth alone is not sufficient. Vessels must also become mature and stable, and must be able to develop tone in order to regulate blood flow. These properties arise through the coordinated action of several growth factors. A further requirement is the ability to expand the diameters of existing vessels that are not directly exposed to

"Modelers should not start building models without talking to a biologist, and ideally, experimentalists should have the input of computational modelers when planning and designing experiments."

ischemic conditions, so that downstream ischemic tissue is perfused. These multiple interacting processes suggest a need for mathematical models, to provide an integrated view of neovascularization.

Shayn Peirce (University of Virginia) described agent-based methods for simulating the formation of microvascular networks. In this approach, the tissue is represented as an array of cells (agents) which respond to local conditions according to a prescribed set of rules. One application of this approach is to investigate the role of the vasa vasorum (microcirculation within artery walls) in atherosclerosis. Dr. Pierce emphasized two important points about modeling. The complexity of the model should be appropriate to the problem being studied and the available data. If the model is too simple or too complex, the scientific payoff will be left. The second point is the need to compare model predictions with experimental data independent of that used in the initial definition of the model.

Axel Pries (Charite - Universitatsmedizin Berlin) spoke on the topic of structural adaptation in the microcirculation. The underlying hypothesis is that each vessel segment adapts according to the local stimuli that it experiences, including hemodynamic and metabolic signals. The early concept that structural diameter is controlled by responses that tend to maintain a constant level of shear stress leads to an instability in which networks of parallel vessels are reduced to a single pathway. Similarly, the previous concept that wall thickness is controlled by solely by circumferential stress is found not to agree with experimental data. This has led to development of theoretical models in which interacting effects of wall shear stress, circumferential stress, metabolic signals and upstream conducted responses are simulated. These models predict network structures that are consistent with experimental observations on flows in complex microvascular networks.

Day 5

Aleksander S. Popel (Johns Hopkins University) discussed angiogenesis from a systems biology perspective. The directed growth of a vascular sprout requires not only the ability of endothelial cells to proliferate and migrate in response to gradients of growth factors but also the upregulation of matrix metalloproteinases, extracellular matrix, proteolysis and release of matrix-binding growth factors. Dr. Popel has developed molecular-based computational models to serve as modules in multi-scale integrative models of these processes and a framework or incorporating these models into multi-scale rule-based models, spanning the levels from the molecular to microvascular.

In the final presentation of the workshop, Daniel Beard (Medical College of Wisconsin) spoke about the integrated physiology of cellular energy metabolism and oxygen transport to the microcirculation. A number of important problems related to cardiac function in disease require a mechanistic model of coronary blood-tissue exchange and cellular metabolism in the heart. Dr. Beard showed how ex vivo data from isolated mitochondria and in vivo data on blood flow, tissue oxygenation, pH, and metabolite concentrations, can be integrated into a systems level model of cardiac tissue metabolism and transport. An interesting challenge to emerge from Dr. Beard's talk is that when detailed cellular metabolic pathways are incorporated into the transport model, simulations become computationally expensive. Methods are needed to efficiently simulate transport in three dimensions, and/or to effectively homogenize the three-dimensional problem in a one-dimensional representation that represents the heterogeneity present in the system in vivo.

Conclusion

In terms of stimulating scientific discourse, the workshop was an unqualified success. The structure of the workshop, with a limited number of invited lectures, a series of brief poster talks preceding each of the three poster sessions, and ample time for informal discussions, allowed participants excellent opportunities to present their own work and to gain a sense of current theoretical and experimental work relating to the topics of the workshop. The administrative support provided by MBI was

first rate. Many participants stated that this was an exceptionally useful and enjoyable conference.

In addition, broad discussions were started on the first day of the workshop and continued through the week, regarding how to help computational modeling make a greater impact on experimental physiology. It was decided to organize a collection of tutorial/review papers to be published in a special issue of Microcirculation, the journal of the Microcirculatory Society. An outline of the issue was drafted and authors for potential chapters were identified. The plan was presented to William Jackson (the Editor-in-Chief of the journal), who approved and encouraged the initiative, and contributions are in preparation.

Workshop 5: The Kidney: Cellular, Tubular, and Vascular Physiology
February 19-23, 2007

Organizers: Harold Layton, Department of Mathematics, Duke University; Leon Moore, Department of Physiology and Biophysics, SUNY Health Sciences Center; S. Randall Thomas, Univ Evrey Val I-Agora; and Alan Weinstein, Department of Physiology and Biophysics, Weill Medical College of Cornell University

Introduction

The workshop focused on the application of mathematical models to elucidate renal function. Physiologists, biophysicists, modelers, and mathematicians presented recent work and discussed current controversies and emerging issues. Topics included: membrane transport; cell-to-cell signaling; initiatives in database construction and web-based modeling resources; the urine concentrating mechanism; and renal hemodynamic control.

Day 1

The first day and a half was divided between models of ion channels and sodium-dependent cotransporters, and models of polarized vascular and epithelial cells, where each cell is an ensemble of interacting membrane transporters.

Peter Jordan (Brandeis University) opened with a study of ion channel gating; he showed how the gating mechanism of potassium exhibits complex backbone realignments and side chain reorganizations.

Benoit Roux (University of Chicago) continued with biophysics of K channel permeation. A modeling hierarchy was displayed in which high-resolution atomic data informed molecular dynamic models, which in turn, informed simple models of channel function.

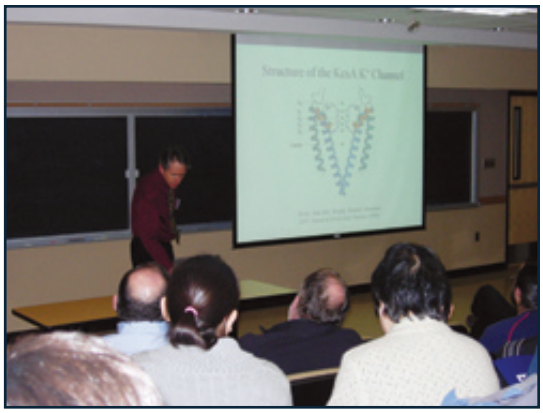
Mark Schumaker (Washington State University), described three steady-state framework models. The single particle model describes a channel whose pore can be occupied by only one ion at a time; it has been used to model sodium conduction through gramicidin. The Grotthuss conduction model describes proton conduction through gramicidin; it incorporates potentials of mean force for proton occupation and water reorientation calculated by Pomes and Roux. Berneche and Roux developed a model for conduction through the narrow pore of the KcsA potassium channel, using a mean force potential for pore occupation by two or three potassium ions.

Donald Loo, (University of California, LA) explained how glucose is actively transported across the apical membrane of proximal tubule cells by Na+/glucose cotransporters (SGLT's). SGLT1, the paradigm for this class, functions by an alternating access mechanism via a series of conformational changes induced by substrate-binding and membrane voltage. Simulations based on an 8-state kinetic model for SGLT1 indicate that external sugar increases the occupancy probability of inward-facing conformations at the expense of outward-facing conformations.

Ian Forster (University of Zurich) proposed a kinetic model for the reabsorption of inorganic phosphate (Pi) across the luminal membrane of renal proximal tubule. This reabsorption is secondary-active, driven by the electrochemical Na+ gradient. NaPi-IIa is responsible for up to 80% of Pi reabsorption in the mammalian kidney; it operates with a stoichiometry of 3Na+: H2PO42-, and +1 charge is translocated per cycle. Expression of cloned NaPi-II transporters in Xenopus oocytes has allowed experimental characterization. Forster's model represents the ordered substrate binding in an alternating access carrier scheme.

Workshops

Electrogenicity arises from the voltage-dependent reorientation of mobile charges of the empty carrier and one Na+ binding partial reaction. Binding order appears to be 2Na+ first, then H2PO42-, and finally Na+.



Alan Weinstein (Weill Medical College of Cornell) ended the day with a mathematical model of flow-dependent water transport in rat proximal tubule (PT); the model has been extended to include microvillous torque, and to incorporate torque-dependent solute transport. Coordinated regulation of luminal and peritubular transporters was required to represent the overall impact of luminal flow on Na+ reabsorption. When torque-dependent Na+ reabsorption in the model agrees with that observed in mouse (PT), the model tubule shows nearly perfect perfusion-absorption balance. This model is an important step toward simulation of glomerulotubular balance.

Day 2

Thomas Pallone (University of Maryland at Baltimore) continued Day 1's theme with a talk on vasoactivity and ion channel architecture of the descending vasa recta (DVR) wall. The renal medulla is supplied with blood by DVR) and ascending vasa recta (AVR). Medullary blood flow modulation has been tied to urinary concentration and salt excretion regulation. DVR contractility is imparted by pericytes (smooth muscle remnants). To identify membrane transporters responsible for local vascular resistance, DVR have were isolated and patch clamp experiments were performed on pericytes and endothelium. Vasoactive agonists depolarize the pericyte cell membrane through a combination of calcium-dependent chloride channel activation and potassium channel deactivation, and, fast voltage gated sodium channels yield prominent currents. Both pericytes and endothelial cells are electrically coupled via gap junctions.

Aurelie Edwards (Tufts University) has modeled endothelial ion transport. The model includes major ion channel classes, Na+/Ca2+ exchange (NCX) and Na+/K+-ATPase a1 and a2 isoform distributions in the plasma membrane. Ca2+ release from SR stores is assumed to occur via ryanodine (RyR) and inositol tri-phosphate receptors. A significant Na+ concentration difference between cytosol ([Na]cyt) and microdomains ([Na]md) necessitates restriction of inter-compartmental diffusion. The model predicts resting ion concentrations compatible with experiments and [Ca]cyt temporal changes similar to those observed upon NCX inhibition.

Sheldon Weinbaum, (City College of New York) ended the morning with a revised Starling hypothesis. The classical Starling equation for transcapillary fluid flow predicts an unrealistically large volume of lymph formation. A revised hypothesis takes cognizance of the fact that the capillary filtration barrier consists of a gycocalyx layer in series with endothelial clefts. The cleft is a non-discriminatory pathway in which a relatively high fluid flow rate precludes protein accumulation. Thus, colloid osmotic forces act across the glycocalyx, and the oncotic pressure of interstitial fluid does not directly determine fluid balance across the capillary endothelium.

In the Renal Physiome session, S. Randall Thomas (CNRS Univ. Evry Val d'Essonne, Evry, Essonne, France) described a quantitative kidney parameter database (QKDB) to provide centralized access to measured parameter values, anatomical features, and functional characteristics at all scales from membrane transporters to the whole organ, both in humans and in animals. He then described a new project underway to build an integrated multi-organ modeling environment focused on regulation of blood pressure and fluids homeostasis--- an extension of the classic Guyton model.

Next, Peter Harris (University of Melbourne, Victoria, Australia) presented a 3D "virtual kidney" interface that has been developed for access to experimental data and parameter values abstracted from the Quantitative Kidney Database (QKDB).

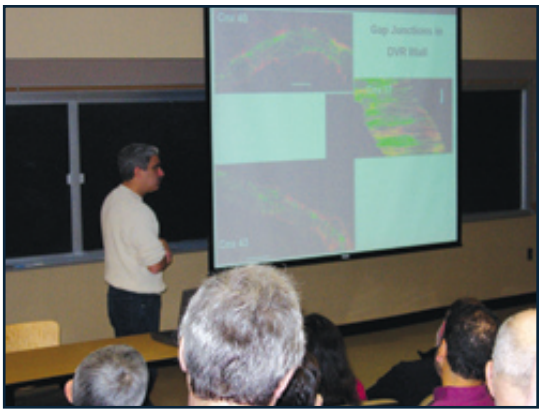
Selection of a structure provides a link to the QKDB search facility and then to relevant parameter values and literature extracts. A menu lists the repository of mathematical models, which may be run on a local machine or on remote machines.

Robert Moss's (University of Melbourne) aim was to simulate the clusters of nephrons and to understand how their behavior arises from individual tubule segments. Further, he aims to create models capable of predicting kidney function and effects of renal disease. He assumes that the kidney is a complex network and applies techniques from Dynamical Networks (a form of Graph Automata) and methods from Statistical Mechanics and Machine Learning. He presented a model of the nephron as a Graph Automata, where each node models a tubule segment, and difference equations model solute transport. This network will form the basis of multi-nephron models.

Day 3

The Wednesday sessions were mostly devoted to the urine concentrating mechanism and urea transport. Despite decades of experimental and theoretical work, many fundamental aspects of this mechanism remain mysterious and controversial.

The opening talk, by William Dantzler (University of Arizona) set the stage by summarizing the physiology of the urine concentrating mechanism. In the renal outer medulla, this mechanism depends on active transepithelial NaCl transport from thick ascending limbs and on a counter-current configuration of flows in tubules and vessels. In the inner medulla, the mechanism is not understood, and the anatomy of neither the outer nor the inner medulla is fully known. He and Thomas Pannabecker are engaged in a digital three-dimensional reconstruction of vascular and nephron segments in rat inner medulla, based on serial sections of resin-embedded tissue.



The second talk, by Thomas Pannabecker (University of Arizona), provided technical details of methods that are being used for the digital reconstructions described by Dantzler, and then he presented the most recent findings from their studies. These findings included population counts of collecting ducts, loops of Henle, and vasa recta; contact areas of vasa recta with collecting ducts, and loop-of-Henle segments that run laterally about collecting ducts near the papillary tip of the inner medulla.

Next, Erik Ilso Christensen (University of Aarhus, Denmark) presented his work with Xiao-Yue Zhai about reconstruction of entire mouse nephrons. Their studies, also based on digital reconstructions of serial sections, provide detailed information on mouse renal architecture. Their findings include: A tortuous course of descending thin limbs of long-looped nephrons and a winding course of thick ascending limbs of short-looped nephrons; thick ascending limbs of long-looped nephrons in central vascular bundles of inner stripe; three types of short-looped nephron bends; and evidence for absence of the water transporter AQP-1 in descending limbs of short-looped nephrons.

In the final session of the morning, Lise Bankir presented archival images from early research efforts in renal anatomy, and she made various comments on these images that are relevant to renal function. Also, she presented a movie by Reiner Beeuwkes that showed elements of renal anatomy in the human kidney.

The first afternoon talk, by Jeff Sands (Emory University), was on urea transport, which, in the collecting duct system, is mediated by UT-A1 and/or UT-A3 urea transporters. He reported work on regulation of UT-A1 by the antidiuretic hormone vasopressin. Vasopressin regulates UT-A1 acutely by increasing UT-A1 phosphorylation and plasma membrane accumulation, and UT-A1 is regulated through both PKA-dependent and PKA-independent cAMP pathways (PKA, protein kinase A). There are long-term changes in UT-A1 abundance in response to inner medullary osmolality changes.

Alan Verkman (University of California, San Francisco) described chemical "knock-out" by small molecules to probe components of the urine concentrating system. Phenotype analysis of transgenic mice lacking various components of the urine concentrating system, such as aquaporins, urea transporters, and the V2 receptor, have provided useful information on their roles in generating a concentrating urine. Selective small-molecule inhibitors of these proteins have utility for chemical knock-out studies that are not confounded by compensatory changes, as well as for development of clinical therapies. Dr. Verkman has established a small molecule discovery program with high-throughput screening: a collection of 300,000 drug-

like chemicals, the effects of which can be tested in part by automated pharmacological testing, and in part by small animal testing resources.

Mark Knepper (National Heart, Lung and Blood Institute) spoke on the analysis of cell signaling networks using proteomics methods and ODE-based modeling. Based on ODEs for cellular mass balance and for signaling mechanisms seen in cells, he and his colleagues have identified four processes common to all signaling pathways: changes in protein abundance; (b) changes in post-translational modifications; (c) changes in cellular location including cytosol-to-membrane translocation and cytosol-to-nucleus translocation; and (d) changes in binding of proteins to other proteins and lipids. His laboratory is developing quantitative approaches to measure these changes globally across the proteome of an individual cell type.

In Wednesday's final talk, Mariano Marcano (University of Puerto Rico, Río Piedras Campus) described two optimization problems for mathematical models of renal systems. The first was an algorithm to solve the nonlinear constrained optimization problem that arises in finding parameter sets that produce optimal performance (by various measures) of urine concentrating mechanism models. He showed how urine osmolality could be increased by changes in some uncertain parameters . In the second application, a nonlinear least-squares method was used to estimate parameters for a thermodynamically consistent kinetic model of ammonium transport by the NKCC2 cotransporter, which plays a role in the urine concentrating mechanism by its action in the thick ascending limb of Henle.

Day 4

The focus of the morning session was tubuloglomerular feedback (TGF), an intra-nephron reflex that regulates nephron blood flow and filtration rate in response to changes in the composition of the tubular fluid passing by the macula densa, a plaque of cells located near the beginning of the distal tubule. TGF contributes to renal autoregulation and is thought to balance glomerular filtration and tubular reabsorption.

Roland Blantz (University of California, San Diego) opened the morning session with a talk about interactions between the regulation of filtered load of sodium, metabolism of the proximal tubule, and TGF. He discussed how TGF balances the filtered load of sodium with the proximal nephron reabsorptive capacity. Kidney oxygen consumption is reciprocally influenced by NO suppression and angiotensin II increase, substances known to be regulators of TGF and renal vascular reactivity. Further, adenosine and ATP also mediate TGF. Dr. Blantz discussed consequences of alterations in interactions between TGF and renal metabolism in hypertension, early diabetes, and chronic renal failure.

Jurgen Schnermann (NIDDK/NIH) discussed experimental studies of TGF signal transmission. He reviewed the concept that NaCl uptake by NKCC2 in the apical membrane of macula densa (MD) cells is a crucial step in TGF signal transmission. He described how the basolateral membrane of rat MD cells expresses all subunits of Na,K-ATPase, and TGF responses were attenuated by ouabain in mice in which the alpha-1 subunit of Na,K-ATPase had been rendered ouabain-sensitive. Together with previous evidence that TGF responses are blunted by ATP depletion with antimycin A and uncouplers of phosphorylation, he concluded that these findings point to a role for an energy-dependent transcellular transport step in TGF signal transmission.

Darwin Bell (Medical University of South Carolina) discussed recent studies in isolated perfused glomeruli with attached MD segments. A double perfusion method permits direct observation of TGF response. He reviewed the MD signaling mechanism

and presented new results that show oscillations in cytosolic calcium in the thick ascending limb and early distal tubular cells that neighbor the MD.

Arterial blood pressure is an important determinant of renal blood flow (RBF) and glomerular filtration rate (GFR), and both are regulated over a wide range of blood pressure in a phenomenon is called renal autoregulation. The afternoon session focused on experimental data that has forced a reexamination of renal autoregulation mechanisms.

Anil Bidani (Hines VA Medical Center in Chicago) opened the afternoon session with an overview of current controversies concerning renal autoregulation. He then reviewed his research into the pathophysiology of chronic renal disease. His work has established that autoregulatory dysfunction plays a central role in the process of glomerulosclerosis and the progression of chronic renal failure.

Rodger Loutzenhiser (University of Calgary) began by noting that clinical studies demonstrate that systolic hypertension is linked to renal injury, and that the renal myogenic system can respond to changes in systolic pressure because of differences in kinetics of arteriolar constriction (200-300 ms) versus relaxation (~1 s). He reviewed experimental and model data that show that these features allow the afferent arteriole to adjust steady-state myogenic tone in response to the rapidly oscillating systolic blood pressure . The results suggest a role for calcium release rom the sarcoplasmic reticulum (SR) and involvement of SR calcium channels in mediating the response to oscillating systolic pressure.

Armin Just (University of North Carolina, Chapel Hill) discussed participation of mechanisms other than TGF and myogenic response (MR) in renal autoregulation. Renal blood flow (RBF) autoregulation is mediated by two major mechanisms: a fast MR (<10 s) and a slower TGF response (10-40 s). Dr. Just presented evidence that rats and mice have a third mechanism that contributes to RBF autoregulation; that mechanism is slower than TGF, independent of the A1 adenenosine receptor, but sensitive to furosemide.

Geoffrey Williamson (Illinois Institute of Technology) began by reviewing renal autoregulation (AR) dynamics, and the results obtained by spectral analysis of RBF and BP. He then described his model of the myogenic mechanism, which can reproduce a variety of experimental maneuvers and which can simulate myogenic-based AR triggered either by mean or by systolic pressure changes. He concluded that afferent arteriole diameter responses in the hydronephrotic kidney, when presented with various pressure waveforms, are better matched by model behavior with AR triggered by systolic pressure.

"The talk illustrated how new analytic methods can provide unprecedented insight into the processes that mediate renal autoregulation."

Ki Chon (SUNY, Stony Brook) presented results of high-resolution, time-varying spectral and transfer function analyses that reveal differences between hypertensive and normotensive rats in the two principal autoregulatory mechanisms, tubuloglomerular feedback (TGF) and the myogenic mechanism (MYO). The results support the hypothesis of TGF system multi-stability put forward by Layton and coworkers, as well as the concept, proposed by Holstein-Rathlou and coworkers, that there are interactions between the TGF and MYO responses. Both phenomena add complexity to RBF spectra. The talk illustrated how new analytic methods can provide unprecedented insight into the processes that mediate renal autoregulation.

Day 5

The focus of the final workshop session was nonlinear dynamics of renal autoregulation. The TGF and myogenic mechanisms share a common effector, the afferent arteriole, and both exhibit intrinsic limit-cycle oscillations that are known to interact. Further, the TGF system can exhibit irregular fluctuations that have characteristics of deterministic chaos.

William Cupples (University of British Columbia) opened the final session with a summary of hypotheses that attempt to explain the emergence of irregular TGF fluctuations in hypertensive rats. He pointed out the need for new experiments to resolve controversies.

Niels-Henrik Holstein-Rathlou (University of Copenhagen) discussed synchronization of TGF oscillations in normotensive rats and irregular fluctuations in spontaneously hypertensive rats (SHR). He reviewed data illustrating synchronization of TGF

oscillations in nephrons perfused by a common cortical radial artery, how coupling strength is enhanced in SHR, and how the TGF and myogenic systems synchronize oscillations. Synchronization is reduced in SHR, despite increased coupling strength. He hypothesized that synchronization loss reduces coordinated effectiveness of TGF and myogenic responses.

Donald Marsh (Brown University) described simulation studies designed to investigate two hypotheses. The first was that coupling strength between TGF and myogenic mechanism at the level of the vascular smooth muscle cell can serve as a bifurcation parameter. A model of TGF and the myogenic mechanism predicts that it does so within a range of parameter values that include measured values. The second hypothesis, tested with a simplified TGF model, was that coupling between cortical and juxtamedullary nephrons, which likely have much different oscillatory frequencies, may contribute to the complex TGF fluctuations in SHR. Simulations predict that juxtamedullary nephrons always operate in a chaotic mode and the chaotic domain increases to include cortical nephrons as the arterial blood pressure and the vascular coupling strength increase.

Anita Layton (Duke University) presented a bifurcation analysis of a model of two nephrons coupled through their TGF systems. The characteristic equation for two coupled nephrons reveals a number of parameter regions with differing stable dynamic states, a prediction verified by simulation studies, and which predicts fluctuations with a degree of spectral complexity consistent with experiments in SHR. This work supports the hypothesis TGF system multistability plays a central role in emergence of complex dynamics in SHR.

Harold Layton (Duke University) focused on nonlinear thick ascending limb (TAL) features that may add complexity to TGF. He showed how TGF signal transduction in a TAL model can produce infinite series of both harmonic and heterodyne frequencies. He then presented simulation studies which predict that the nonlinear properties of the sigmoidal TGF response also introduce harmonic and heterodyne frequencies. He concluded by illustrating how these frequencies can account for the many spectral peaks seen in SHR.

Leon Moore (SUNY, Stony Brook) demonstrated how TGF multistability can provide an explanation for experimental observations related to irregular TGF fluctuations in SHR, viz., multiple strong spectral peaks, abrupt switching in TGF oscillatory frequency, and asymmetrical TGF limit-cycle oscillations--- which are all predicted by a model that includes a detailed representation of TAL signal transduction. Dr. Moore then presented an analysis of nephron flow waveforms from a model of three coupled nephrons. The time series produced Poincare return maps and Lyapunov exponents consistent with deterministic chaos. Analysis of model records with time-varying spectral methods showed the presence of multiple interaction peaks and amplitude modulation; these were enhanced by an imposed low-frequency oscillation, a phenomenon observed in SHR.

The session concluded with a spirited Round Table Discussion that focused on the relative strengths and shortcomings of the mathematical models, and on the significance of irregular fluctuations in SHR.

Conclusion

By measure of the comments received by the organizers from the participants, the workshop was very successful. Among the organizers' goals, relative to a previous renal workshop in 1999 at the IMA, was to attract to the 2007 meeting more graduate students and junior researchers, more well-known physiologists, and more senior (and highly influential) renal physiologists. These goals were all achieved. Although many of us modelers have long believed that our modeling efforts are highly relevant to experimental work, it was gratifying to hear some of the physiologists say that it is now clear that renal modeling has matured to a level that allows it to inform the physiology.

2007 Workshop for Young Researchers in Mathematical Biology
March 12-15, 2007

Organizers: MBI Postdoctoral Fellows

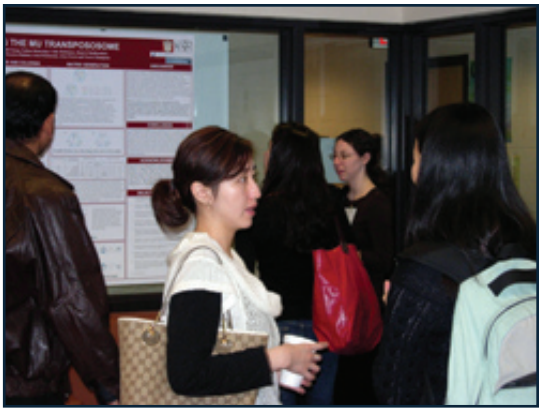
Introduction

This workshop was intended to broaden the scientific perspective of young researchers in mathematical biology and to encourage interactions with other scientists. Formerly the Young Researchers Workshop, the Workshop for Young Researchers in Mathematical Biology has become an annual event due to the success of the first two workshops.

The workshop participants (tenure-track faculty, postdoctoral researchers, and advanced graduate students) represented colleges, universities, and institutions from around the world. Each of these young researchers presented their work through a brief talk (1 – 3 minutes) and a poster presentation. The posters illustrated the breadth of research that composes the field of mathematical biology.

The workshop also featured the participation of eight leading researchers in the mathematical biosciences. Six of the researchers gave hour-long plenary talks, while the other two, who were top researchers in industry, led a panel discussion on mathematical biology in industry. With most of the leading researchers attending multiple days of the workshop, ample time was allotted for interactions with the young researchers.

Day 1



Lisa Fauci (Tulane University) opened the workshop with a presentation on the biofluid mechanics of reproduction. She began by raising a number of biomechanical issues with reproduction, which included the underlying mechanisms behind sperm-tail undulations, the means by which an oviduct picks up an oocyte cumulus complex, and the transplantation and implementation of an embryo in the uterus. She emphasized that this is a coupled system between the forces generated by the cilia and flagella and the viscous, incompressible fluid. The immersed boundary method provides a quick and accurate way for solving these problems with solid-fluid interactions. She concluded her talk with future directions, which included dealing with a full 3-D system and a non-Newtonian fluid, as well as the complex coupling among the ciliary beating, mechanical contractions, and the sperm motility.

Following the morning coffee break, some of the participants (for a list of speakers, see [1] below) made short presentations. The purpose of this session is for the young researchers to introduce themselves to the workshop participants and advertise their posters for the afternoon poster session. The talks covered such diverse topics as quantifying the impact of land ownership on forestry to using age-structured models of malaria on the dynamics of red blood cell infection.

The morning session concluded with hour-long discussion groups. The topics, chosen by MBI post-doctoral researchers and long-term visitors, were involving students with research in mathematical biology, interdisciplinary collaborations in mathematical biology, training mathematical biologists, and challenges in mathematical biology. All participants chose one of four topics and separated into their corresponding groups.

In the afternoon, Kirk Jordan (IBM Computational Biology Center) and Laura Potter (GlaxoSmithKline) led a panel discussion on mathematical biology in industry. Each panelist first made a 15-minute presentation, followed by a question-and-answer panel discussion. The panelists talked about their backgrounds, a number of projects at IBM and GlaxoSmithKline, and the skills needed for a young researcher in math biology to be successful in industry. Some of the critical skills they identified included a solid foundation in math and science with strong computational skills, an ability to work in teams on multiple, interdisciplinary projects, and strong communication skills, both verbal and written, while being able to get a point across quickly. Furthermore, a successful researcher needs to be able to complete a project in a timely fashion while being able to demonstrate the impact the work has for the company.

Workshops

"Some of the critical skills they identified included a solid foundation in math and science with strong computational skills, an ability to work in teams on multiple, interdisciplinary projects, and strong communication skills, both verbal and written, while being able to get a point across quickly."

A second round of short talks by the workshop participants (for a list of speakers, see [2] below) followed the afternoon coffee break. Cellular automata models to study carcinogenesis and the development of a new interval database representation for genome sequences were among the topics represented. The session concluded with the corresponding poster session for the morning and afternoon short-talk presenters.

Day 2

The second morning began with Kenneth Lange (University of California, Los Angeles) talking about finding correlations between relatives using Fisher's theory, which composes variances and covariances between two relatives based on combinatorial coefficients that summarize their relationship. After a brief overview of biometrical genetic history, he talked about recent extensions to Fisher's algorithm. One method was for X inactivation, where one of the two X chromosomes is shut off. Another extension was for the construction of inbred strains, such as inbreeding brother-sister mice for 10-20 generations. While these methods help control the genetic variations, new combinatorial techniques are required to calculate these complicated variances and covariances. Finally, he concluded with open statistical problems, which included establishing simple conditions for parameter identification, determining optimal mating designs, and designing fast algorithms to compute the necessary combinatorial coefficients.

Another round of short talks by the young researchers (for a list of speakers, see [3] below) followed the morning coffee break. Research areas ranged from using knot theory to find the topological conformation of DNA bound within a protein complex to applying the immersed boundary method to the motility of a dendritic spine. Other topics focused on using mathematical modeling to determine how heterogeneities in tissue properties affect the propagation of electrical signals through a sheet of the heart and to assess the role of male circumcision in the control of HIV.

For a second consecutive day, the morning session wrapped up with discussion groups. The topics were identical to the previous day, and the workshop participants were asked to choose a group other than the one they had already attended. There were a variety of topics discussed among the four groups over each of the two days. One issue discussed was the challenges of establishing and maintaining collaborations. Some of the suggestions out of the discussions included attending and giving seminar talks in other departments, learn the biology (even if it means asking stupid questions) and the language of biology, and look for sources of funding that encourage interdisciplinary research. Multiple groups also talked about the methods to best train students in mathematical biology. Some of the discussion items included developing courses with a mix of mathematicians and biologists, doctoral requirements for math biologists, and ways of involving undergraduates in research. It was mentioned that the National Research Council is emphasizing a more quantitative approach for the training of a biologist through the publication of Bio2010: Transforming Undergraduate Education for Future Research Biologists.

John Tyson (Virginia Polytechnic Institute and State University) spoke in the afternoon about the connection between complex network dynamics of interacting proteins and physiological properties of the cell. He emphasized that mathematics is essential to understanding the bridge between genetics and cell physiology. This approach was illustrated with a mathematical

model of cell cycle transitions in eukaryotes for a molecular network of the control of cyclin-dependent kinase (Cdk). Using basic principles of biochemical kinetics, he presented a conversion of the network diagram into a set of ordinary differential equations. In this example, he showed how changes in parameter values corresponded to alterations in the number and value of the stable steady states using bifurcation diagrams, which correlated Cdk activity with cell growth. He concluded that this "dynamical perspective of molecular cell biology" can be applied to any complex gene-protein network that regulates some behavior of a living cell.

Areas of research briefly covered in the afternoon short talks (for a list of speakers, see [4] below) included using polynomial systems over finite fields to reverse engineer biological networks from data to using control theory to find an optimal strategy for harvesting a fishery. Topics for mathematical models ranging from analyzing the brain microstructure to measuring the hazards of radiotherapy for the treatment of breast cancer were also presented. The afternoon session ended with the poster session for the morning and afternoon speakers.

Day 3

Alan Perelson (Los Alamos National Laboratory) opened the third day with a presentation on modeling the dynamics of hepatitis C viral infection. After an overview on viral hepatitis, he presented multiple mathematical models that measure the effectiveness of drug treatment, such as interferon, in blocking the production of the virus. By fitting a model to experimental data during the first few days of therapy, he showed that drug effectiveness could be determined in a short period of time. Thus, mathematics, in combination with clinical data, may predict the responsiveness of a patient to a treatment protocol within the first few days of therapy.

The morning session concluded with another round of short talks by workshop participants (for a list of speakers, see [5]). The range of topics included using delay differential equations to analyze insulin therapies for diabetic patients to identifying the molecular mechanisms behind why the protein level of p53 rises and falls in response to DNA damage.

"... mathematical insights, combined with experimental studies, have shown that not only optimal tissue architecture and number of stem cells minimize the risk of cancer, but also how that risk changes as the organism ages."

In the afternoon session, Natalia Komarova (University of California, Irvine) spoke about mathematical modeling of cancer. She began by talking about somatic evolution, the reproduction and death of cells inside the organ of an organism over tens of years, and the progression to cancer. This progression can be modeled as a stochastic process using evolutionary selection dynamics to determine the probability that a mutant cell, which leads to cancer, will take over. She continued by describing how mathematical insights, combined with experimental studies, have shown that not only optimal tissue architecture and number of stem cells minimize the risk of cancer, but also how that risk changes as the organism ages. She ended her talk by briefly characterizing the need to find optimal dosing strategies to maximize the success of drug therapy due to the problem of drug resistance by the cancer cells.

The final session of short talks (for a list of speakers, see [6] below) followed the afternoon coffee break. The diversity of topics included analyzing the role of T cell recirculation in HIV infection to better understanding the mechanical interactions between cells and type-I collagen gels. The last poster session immediately followed these short talks.

Day 4

The final session began with Robert Miura (New Jersey's Science and Technology University) talking about cortical spreading depression, which is associated with a migraine with aura. Cortical spreading depression is characterized by the propagation of slow chemical waves in the cortex resulting in massive changes in ion concentrations that are not normally found in the brain. Despite the slower temporal and larger spatial scales, the properties of the waves are similar to action potentials suggesting that mathematical neuroscience provides a framework to better understand the disease. After presenting a mathematical model on spreading depression, he described some of the mechanism believed to be important to the disease, including ion diffusion, spatial buffering, and cell swelling. He concluded that by understanding extreme phenomena like cortical spreading depression,

we can better understand a complex organ like the brain.

The workshop concluded with a panel discussion, led by Robert Miura, Joseph Mugisha (Makerere University, Uganda), and David Terman (The Ohio State University). The panelists first talked about how they got into the field of mathematical biology. Then they answered a variety of questions from the workshop participants. The questions ranged from finding positions outside of mathematics and biology departments to dealing with conflicting data for data-fitted models.

Conclusion

This workshop followed the success of the first two Young Researchers Workshops. Throughout the week, the young researchers were very pleased with the workshop structure, as there was time to meet the plenary speakers and interact with other participants. These interactions provided new insights into different areas and directions of research and opportunities to explore future research collaborations, as noted by many participants in the exit surveys. The overwhelmingly positive feedback from the participants has encouraged the organizers to have future Workshops for Young Researchers in Mathematical Biology.

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[4] Elena Dimitrova, Wandi Ding, Ramana Dodla, Heiko Enderling, Philip Gerlee, Jana Gevertz, Jeffrey Groff.

[5] Nicoleta Tarfulea, William Turkett, Jr., Alejandra Ventura, Haiyan Wang, Jin Wang, Liming Wang, Tongli Zhang.

[6] Sylvain Reboux, Timothy Reluga, Deena Schmidt, Oluwaseun Sharomi, Andrew Stein, Bo Su, Edward Swim.

Special Workshop: Opportunities in Mathematical Biology for Under-represented Groups March 23-25, 2007

Organizers: Carlos Castillo Chavez, Department of Mathematics, Arizona State University; Trachette Jackson, Department of Mathematics, University of Michigan; Simon Levin, Department of Ecology and Evolutionary Biology, Princeton University; and Abdul-Aziz Yakubu, Department of Mathematics, Howard University

Introduction

The purpose of this workshop was to bring together researchers from under-represented groups to broaden their scientific perspective and to develop connections with leading researchers in mathematical biosciences that will be important for their future careers. Plenary talks were given by leading researchers, and most participants either presented a poster on their current research or gave a 3-minute advertisement of their research. The workshop also featured a panel discussion on careers in mathematical biology. The workshop focused on three aspects of mathematical biology: ecology and epidemiology (including conservation biology and resource management); physiology and cancer; and genetics and genomics.

Day 1

Wayne Getz (University of California at Berkeley) opened the workshop with an inspiring talk entitled, Mathematical Ecologist: Nerd or Social-Ace? In the first part of his talk, Getz made a compelling case for the need for conservation and restoration programs. He pointed out that the world's population changed from 1.7 to 6 billion during the 20th Century, forests are now cut down at an ever increasing rate, global warming is a fact, new diseases -such as West Nile virus, Rift Valley fever, hanta virus, and XDR (extensively drug resistant) tuberculosis- are emerging or re-emerging, species are being lost at an incalculable rate, and heavy metals are polluting our food chain. In the second part of his talk, Getz had some good news: these problems have created an urgent demand for mathematical ecologists and epidemiologists. He pointed out that most people think of mathematicians as nerds. However, applying mathematics to ecological, resource management, conservation biology, and epidemiological problems provides great opportunity for travel, being outdoors, and feeling useful to boot. In his presentation, Getz illustrated various opportunities from his own work and that of his students. Among other things, he discussed: the role wolves play in Yellowstone in mitigating the effects of global warming, the structure of elephant societies and their conservation in the Samburu region of northern Kenya, the problem of culling elephants in Kruger National Park, the overexploitation of fisheries, circumcision as an intervention for managing HIV, and the impact of HIV on the reemergence of TB. Getz's opening talk established the foundation for much of what was presented and discussed in the workshop.

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Next, Abdul-Aziz Yakubu (Howard University) presented his work on the implications of linkages among subpopulations for the stability and resilience of exploited species. Yakubu used his work with Michael Fogarty and his students on the resilience of inshore American lobster (Homarus americanus) to high levels of exploitation in coastal areas to start a discussion on the role of mathematics in developing and providing scientific advice for conservation and restoration programs. In an article that appeared in the Washington Post on Friday November 3, 2006, an international group of ecologists and economists warned that the world will run out of seafood by 2048 if steep declines in marine species continued at current rates. Yakubu used the article to highlight the need for mathematical rigor in studying the impact of overfishing, pollution, and other environmental factors on marine species.

In the afternoon, Rachel Kuske (University of British Columbia) presented her work on the question of whether transients+ instabilities + noise = structure. Kuske pointed out that transient or unstable behaviors are often ignored in considering long time dynamics in the deterministic world. However, stochastic effects can change the picture dramatically, so that the transients can dominate the long range behavior. Coherence resonance is one relatively simple example of this transformation, and we consider others such as noise-driven synchronization in networks, disease dynamics in vaccinated populations, and amplitude-driven phase dynamics. The challenge is to identify common features in these phenomena, leading to new

approaches for systems of this type. Some recurring themes in her talk included the influence of multiple time scales, cooperation of both discrete and continuous aspects in the dynamics, and the remnants of underlying bifurcation structure visible through the noise.

Carlos Castillo-Chavez (Arizona State University) has been a leader in the field of mathematical epidemiology, ecology and demography. Castillo-Chavez reminded us that Tuberculosis lives in about 2 billion individuals but primarily in an inactive state. The emergence of HIV and malnutrition and famine in various parts of the world increases the likelihood that a large number of individuals will develop an active form of the disease. What would be the consequences of TB re-emergence? He discussed some potential outcomes that would add to the global health issues that we face today. In addition, Castillo-Chavez talked about the role of dynamic social landscapes on disease evolution. In this context, he used his work in collaboration with various researchers (graduate students, postdocs, and others), to discuss the role of cross-immunity on the evolution and dynamics of influenza; the impact of behavioral changes, long periods of infectiousness, variable infectivity, co-infections, prostitution, social networks, and vaccine efficacy on HIV dynamics; the role of exogenous re-infection, variable progression rates, vaccination, public transportation, close and casual contacts (generalized households) on tuberculosis dynamics and control; the impact of life-history vector dynamics on dengue epidemics; and on the identification of time response scales for epidemics like foot and mouth disease (Uruguay). Castillo-Chavez also discussed the role of dispersal and disease as enhancing mechanisms of ecological diversity. He pointed out research opportunities on problems at the interface of homeland security and disease invasions (natural or deliberate) and on models for the spread of social "diseases" like alcoholism and ecstasy. Castillo-Chavez also demonstrated models for the spread of extreme ideologies and their impact on cultural norms. In addition, Carlos Castillo-Chavez mentioned his successful Mathematical and Theoretical Biology Institute or MTBI which focuses on providing research opportunities at the interface of the biological, computational and mathematical sciences from the undergraduate to the graduate and postdoctoral levels and SUMS (Strengthening the Understanding of Mathematics and Science) which is designed to provide a successful university experience for students from underrepresented groups and to enhance their prospects for future academic success.

On Friday's final session, Janet Best (Ohio State University) spoke on Parkinson's: a multi-scale, environmental view of a neurological disease. Parkinson's Disease (PD) is the most common movement disorder in the U.S. It is a neurodegenerative disease, involving progressive loss of dopaminergic neurons in the basal ganglia. In the first part of her talk, Best reviewed the etiology of PD, emphasizing the role of environmental neurotoxins and the factors that may underlie the specificity of the affected cell population. The second part of the talk focused on experimentally-observed changes in neuronal firing patterns that accompany PD and that may be result in the motor symptoms. She and her collaborators have constructed a neuronal network model for the increases in correlated activity within the subthalamic nucleus and globus pallidus of the basal ganglia following the onset of PD. They applied dynamical systems methods to understand transitions between irregular and rhythmic, correlated firing in the model. Best used geometric singular perturbation theory and one-dimensional maps to illustrate how an excitatory-inhibitory neuronal network with fixed architecture can generate both activity patterns for possibly different values of the intrinsic and synaptic parameters. In conclusion, Best discussed hypotheses arising from the model as well as ongoing experiments to test these predictions.

Day 2

The second day of the workshop focused on physiology and cancer. Michael Reed (Duke University) started the session and spoke on Control Mechanisms in One-Carbon Metabolism. Reed informed us that one-carbon metabolism, consisting of the folate cycle, the methionine cycle, and glutathione synthesis is a small part of cell metabolism, but it is crucial for cell division, DNA methylation, and the manufacture of glutathionine; the body's defense against oxidative stress. Deficiencies in one-carbon metabolism have been associated with important human health concerns including heart disease, some cancers, depression, and birth defects. He then described a number of biochemical control mechanisms that insure that important reactions in one-carbon metabolism are protected against large variations in dietary input. In his talk, Reed demonstrated how these mechanisms are analyzed by discussing how stochastic fluctuations propagate through biochemical networks.

Trachette Jackson (Michigan University) presented her work on Modeling the Cellular, Molecular, and Tissue Interactions Associated with Tumor Induced Angiogenesis. Vascular endothelial growth factor (VEGF) is one of the most potent, specific and intensively studied tumor angiogenic factors. Recent experiments show that VEGF is the crucial mediator of downstream events that ultimately lead to enhanced endothelial cell survival and increased vascular density within many tumors. The newly discovered pathway involves up-regulation of the anti-apoptotic protein Bcl-2, which in turn leads to increased production of interleukin-8 (CXCL8). The VEGF-BCL2-CXCL8 pathway suggests new targets for the development of anti-angiogenic strategies including short interfering RNA (siRNA) that silence the CXCL8 gene and small molecule inhibitors of Bcl-2. Jackson discussed her efforts on developing and validating mathematical models of sustained angiogenesis and vascular tumor growth that are able to predict the effect of the therapeutic blockage of VEGF, CXCL8, and Bcl-2 at early, middle, and late stages of tumor progression.

Richard Rand (Cornell University) followed with his talk on Differential Delay Equations in Gene Copying. Rand analyzed a model of gene transcription and protein synthesis which has been previously presented in the biological literature. The biology of the problem may be described as follows: A gene, i.e. a section of a DNA molecule, is copied (transcribed) into messenger RNA (mRNA), which is transported out of the nucleus of the cell into the cytoplasm, where it enters a subcellular structure called a ribosome. In the ribosome the genetic information encoded in the mRNA produces a protein (a process called translation). The protein then enters the nucleus where it represses the transcription of its own gene. The model takes the form of an ODE (ordinary differential equation) coupled to a DDE (delay differential equation), the state variables being concentrations of messenger RNA and protein. Sources of the delay include the time required for transcription and translation to occur. The delay is assumed to depend on the concentration of mRNA and is therefore state dependent. Linear analysis gives a critical time delay beyond which a periodic motion is born in a Hopf bifurcation. Lindstedt's method is applied to the nonlinear system, resulting in closed form approximate expressions for the amplitude and frequency of oscillation. Rand discussed how results of the perturbation method are shown to be in good agreement with those obtained by numerical integration.

The first afternoon talk given by John Guckenheimer (Cornell University) who presented his work on Multiple Time Scales in Neural Systems. Guckenheimer pointed out that the Hodgkin-Huxley model of the action potential is a landmark of twentieth century biology. Mathematical analysis of even simplified versions of this model encounters surprisingly subtle phenomena involving the bifurcations of dynamical systems with multiple time scales. In his lecture, he surveyed recent mathematical research in this area and speculated on its biological implications.

Next, Janet Best, Carlos Castillo-Chavez, Lou Gross and Abba Gumel lead an informal discussion on careers in mathematical biology. The group used the opportunity to brainstorm on where to look for jobs, how to secure the best jobs, and tenure expectations. This discussion was continued throughout the workshop.

The day ended with quick presentations by students, postdocs and young faculty. This was followed by a poster session.

Day 3

The last day's focus was on physiology and cancer; and genetics and genomics. Avner Friedman (Mathematical Bioscience Institute, The Ohio State University) ended the physiology and cancer session with his talk on multiscale models of tumors.

At the restriction point of its first growth phase G1, the cell must decide whether to go into the S phase, apoptosis, or the quiescent phase G0. A similar decision is made just before the cell is ready to go into mitosis. The above decisions are affected by the cell's environmental conditions, e.g., hypoxic neighborhood, overpopulation, etc. When some genes are mutated, the decision to go into S may be made in spite of unfavorable conditions, such as hypoxic conditions, and this leads to tumor proliferation. Friedman spoke about a multiscale model that deals with the effects of gene mutation during the time a cell spends in each phase, as well as during the absolute time. After formulating the general model, he used a simpler model with situations whereby the cells are divided into only three different populations: proliferating, quiescent, and dead cells to describe mathematical results such as global existence and bifurcation for PDE free boundary problems. In addition, he highlighted open problems on extension of these results to models which include several classes of cells.

Warren Ewens (University of Pennsylvania) lectured on training for, and career opportunities in, genomics and bioinformatics. Ewens pointed out that the volume of data available from the human genome and the genomes of other species leads to the need for research in the assimilation and analysis of very large data sets. This analysis is largely statistical, but cannot be carried out by statisticians alone - a meaningless analysis will likely result if not carried out in conjunction with a biologist. Ideally, what is now needed, and will be needed even more in the future, is a new type of scientist who is trained in computational, statistical and biological fields. Clearly the training of such people presents challenges. Ewens described these challenges and the research opportunities that are available for researchers trained in this way.

In the final presentation, Ryan Hernandez (Department of Biological Statistics and Computational Biology, Cornell University) spoke about the work of Carlos Bustamante's group on developing statistical methods for inference in population and comparative genomics. Hernandez highlighted several approaches for testing evolutionary hypothesis regarding the importance of natural selection and demographic history in patterning genetic variation. In addition, he discussed research and educational opportunities in the development of population genetic theory as well as the application of various tools to make inference from genome-wide data sets, and methods for association mapping in natural and domesticated populations.

Conclusion

In terms of exposing a large number of individuals from under-represented groups to opportunities in mathematical biology, the workshop was an unqualified success. The structure of the workshop, with a limited number of invited lectures, a series of brief poster talks preceding the poster session, and ample time for informal discussions, allowed participants excellent opportunities to present their own work and to gain a sense of current theoretical and experimental work relating to the topics of the workshop. The panel discussion on careers in mathematical biology was a big hit. The administrative support provided by MBI was first rate. Many participants stated that this was an exceptionally useful and enjoyable conference.

Current Topics Workshop on MicroRNA in Development and Cancer, April 12-13, 2007

Organizers: Carlo Croce, Department of Molecular Virology, Immunology and Medical Genetics Human Cancer Genetics Program, The Ohio State University; Avner Friedman, Mathematical Biosciences Institute; George Calin, Human Cancer Genetics Program, The Ohio State University; and Shili Lin, Department of Statistics, The Ohio State University

Introduction

The microRNA meeting at the Ohio State University was a great opportunity to learn about new discoveries in the exciting field of microRNAs directly from the persons involved in these groundbreaking advances. MicroRNAs (miRNAs) are small non-coding RNAs that regulate the expression of protein-coding genes. Alterations of miRNA genes have been detected in many human tumors. MicroRNAs expression profiling has been exploited to identify miRNAs that are potentially involved

in the pathogenesis of human cancers. Profiling has allowed the definitions of signatures associated with diagnosis, staging, and progression and response to treatment of human tumors. In addition, profiling has been exploited to identify microRNAs genes that are downstream targets of activated oncogenic pathways or that are targeting protein coding genes involved in cancer.

The workshop drew 250 participants. The two-day workshop was organized around three themes: general microRNA, bioinformatics, and cancer. In what follows, we summarize the talks in each of the themes.

General MicroRNA

The first speaker was Victor Ambros (Dartmouth Medical School) who is the leader of the team that discovered the first ever microRNA in the early 1990s. He first described general aspects of microRNA biology and then presented a model of the interaction between a miRNA and a target as a two-step hybridization reaction: nucleation at an accessible target site followed by hybrid elongation to disrupt local target secondary structure and form the complete miRNA-target duplex. The next speaker was Philip Sharp (Massachusetts Institute of Technology in Boston), a Nobel Prize winner in Physiology or Medicine in 1993 for the identification of the RNA splicing. He described how miRNAs represent a large set of master regulators of gene expression: They constitute 1-4% of human genes and are predicted to regulate 30% of mammalian protein-encoding genes by interactions with their 3' untranslated regions (UTRs). He presented data regarding the characterization of the short RNAs in mouse embryonic stem cells, as well as about the new technology of sequencing to identify new types of small RNAs and unravel unknown miRNAs important for the function of hematopoietic cells.

"...alteration in miRNA genes and other non-coding RNAs play a critical role in the pathophysiology of many, perhaps all, human cancer."

Carlo Croce (The Ohio State University), the discoverer of the involvement of microRNAs in human cancers, presented a general view of this new field. He pointed out that alteration in miRNA genes and other non-coding RNAs play a critical role in the pathophysiology of many, perhaps all, human cancer: both in cancer initiation and progression. Currently, the main mechanism of microRNoma (defined as the full complement of microRNAs present in a genome) alteration in cancer cells seems to be represented by aberrant gene expression, characterized by abnormal levels of expression for mature and/or precursor miRNA sequences in comparison with the corresponding normal tissues. Amy Pasquinelli (University of California, San Diego, CA) discussed the evolving roles of microRNAs in animal gene expression. Targets are co-expressed at relatively low or undetectable levels in the same tissues as the miRNAs predicted to regulate them. Additionally, genes that are highly co-expressed with miRNAs usually lack target sites. Therefore, many animal genes are under evolutionary pressure to maintain or avoid complementary sites to miRNAs. Thus, the miRNA pathway broadly contributes to the complex gene regulatory networks that shape animal tissue development and identity.

Frank Slack (Yale University) presented new data about the roles of conserved miRNAs from the let-7 family. One examples is the Caenorhabditis elegans pumilio homolog, puf-9, that is required for the 3'UTR-mediated repression of the let-7 microRNA target gene, hbl-1. Joshua Mendell (Johns Hopkins University) talked first about the augmentation of tumor angiogenesis by a Myc-activated microRNA cluster, the miR-17-92 genes. These findings establish a role for microRNAs in non-cell-autonomous Myc-induced tumor phenotypes. In the second part of the talk he focused on a hexanucleotide element that directs microRNA nuclear import.

Bioinformatics in MicroRNA

The presentations in this session, ranged from analyzing microRNA promoters, target predictions and combination of predicted targets, to quality and reliability of microRNA microarray platforms. Darlene Goldstein (Institut de Mathematiques, Switzerland) devoted her talk to discuss the difficulties of working with three different commercial microarray platforms for generating microRNA expression data. These platforms are Invitrogen, Exigon, and Ambion. From the results presented, it appeared that none of them produced any reliable quantitative information, although the same technician was able to generate

high quality mRNA microarray data. This raised the question of whether the microRNA microarray technologies have reached a satisfactory level of quality to ensure reliable data scientific investigation.

The topic of transcription binding in microRNA promoters was discussed by Shane Jensen (University of Pennsylvania). He described an improved statistical method for scanning promoter sequences for transcription factor (TF) binding sites with known TF binding motifs. The basic idea of the proposed method is to turn the "scanning score" into a (posterior) probability, which is uniformly interpretable among all TFs and promoter sequences. Different scoring thresholds for matches can be made with reference to the same probability scale. Application to scan the microRNA promoters of Arabidopsis identified five TF motifs that are substantially over represented in the promoter of microRNAs compared to those of protein coding genes. A number of open questions were also discussed, including how to account for evolutionary conservation to look for conserved binding sites across species.

In addition to RNA22 and DIANA-microT, there are a number of other computational algorithms/tools for predicting microRNA targets. One of the problems encountered is that the various prediction tools may produce lists of targets that have limited overlap. Therefore, it is of interest to consolidate such results to provide an improved information basis before engaging in costly experiments, this was the topic discussed by Michael Schimek (Medical University of Graz, Austria). Currently proposed methods for combining target lists include similarity score and rank aggregation. As an alternative, Schimek proposed a stochastic procedure to test for random degeneration of paired rank lists. The idea is to create a sequence of binary numbers that represent rank similarity of the two lists. Based on this binary sequence, one determines the point from which on the difference between the two rankings degenerate into noise. This would lead to the identification of a sequence of objects that have a high degree of assignment consistency.

Artemis Hatzigeorgiou (University of Pennsylvania) talked about combined computational/experimental approaches for the identification of novel microRNAs and the analysis of their functions. She described several tools developed in her group for analyzing the genomic organization and function of microRNAs, in particular, DIANA-microT, TarBase, and miRGen. Furthermore, she described the development of a microRNA gene finder based on support vector machine (a machine learning technique). The specificity of the algorithm was estimated both computationally and experimentally using a microarray. The role of single nucleotide polymorphisms (SNPs) within microRNA targets was also discussed.

MicroRNA target detection and microRNA precursor discovery through computational algorithm/software RNA22 were among the topics of Isidore Rigoutsos' (IBM T.J. Watson Research Center) presentation. RNA22 differs from most of the other computational algorithms for target predictions in that the method is pattern-based rather than relying on conservation of multiple species. It has been a long-held notion that microRNAs bind to the 3' un-translated regions (3'UTRs) of the targeted genes. However, his computational approaches indicate that microRNA must be also targeting transcripts through their 5'UTRs and coding sequences. Furthermore, his experimental results suggest that a typical microRNA could target up to thousands of genes. According to his estimate, more than 90% of the genes in mammals are likely to be controlled by microRNAs.

The Role of MicroRNA in Cancer

In the second day of the meeting, the focus was on the miRNA roles in cancer. Michael McManus (UCSF Diabetes Center) presented the efforts to aggregate an international consortium for transgenic and knock-out miRNA mice. This will be an invaluable resource for the scientific community and for miRNA-related investigations. Zizimos Mourelatos (University of Pennsylvania School of Medicine) identified a motif within the Ago proteins, which bears significant similarity to the m(7)G cap-binding domain of eIF4E, an essential translation initiation factor. The conserved aromatic residues within the motif of human Ago2 is required for binding to the m(7)G cap and for translational repression but do not affect the assembly of Ago2 with miRNA or its catalytic activity. He proposed that Ago2 represses the initiation of mRNA translation by binding to the m(7)G cap of mRNA targets, thus likely precluding the recruitment of eIF4E.

Kenneth Kosik (University of California, Santa Barbara) presented a somatodendritic microRNAs identified by laser

capture and multiplex RT-PCR. Thomas Schmitgen (The Ohio State University) talk was about the microRNA profiling by quantitative RT-PCR, a techniques that he developed several years ago. He exemplified the power of this technique by the expression profiling that identifies microRNA signature in pancreatic cancer. Mark Rehsmeier (Universität Bielefeld, Germany) presented RNAhybrid: a microRNA target prediction that is easy, fast and flexible. RNAhybrid's flexibility was proved with the prediction of a non-canonical target site for Caenorhabditis elegans miR-241 in the 3'-untranslated region of lin-39. Michael Thomson (University of North Carolina, Chapel Hill) discussed the extensive post-transcriptional regulation of microRNAs and its implications for cancer. Mark Boldin from David Baltimore group (California Institute of Technology) discussed the role of miRNAs in the innate immune response to microbial infection. Paul Blower (The Ohio State University) presented the microRNA expression profiles for the NCI-60 cancer cell panel and its significance for understanding the effects of cancer therapy. The last speaker, George Calin (The Ohio State University, now at University of Texas) presented a new concept of cancer predisposition by microRNAs and its significance for early diagnosis in cancer patients.

Conclusion

The workshop brought leading researchers in microRNA together with statisticians and bioinformaticians. New groundbreaking advances in the field will require close interaction between these research communities. The workshop was a significant step in bringing these communities together.

Workshop 6: Information processing in the visual system, April 23-27, 2007

Organizers: Paul C. Bressloff, Department of Mathematics, University of Utah; and Alessandra Angelucci, Department of Ophthalmology, University of Utah

Introduction

The purpose of this workshop was to bring together mathematical modelers and experimental physiologists working on various levels of the visual system. A major emphasis of the meeting was the role of feedback and top-down influences in sensory processing. The traditional feedforward model of the visual system invokes a sequence of processing stages, beginning with the relay of retinal input to neurons in the primary visual cortex (V1), via the lateral geniculate nucleus (LGN) of the thalamus, and subsequent higher-order processing through a hierarchy of cortical areas. According to this model, neurons at each successive stage process inputs from increasingly larger regions of space, and code for increasingly more complex aspects of visual stimuli. The selectivity of a neuron to a given stimulus parameter (e.g., orientation, color, and depth) is assumed to result from the ordered convergence of afferents from the lower stages. A much more complicated picture is now emerging, in which the flow of information involves a dynamic interplay between bottom-up sensory processing and top-down influences of attention expectation and perceptual task.

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Day 1

Murray Sherman (The University of Chicago) started the workshop with his talk entitled The role of thalamus: relay functions and more. The LGN and pulvinar (a massive but generally mysterious and ignored thalamic relay) are examples of two different types of relay: the LGN is a first order relay, transmitting information from a subcortical source (retina), while the pulvinar is mostly a higher order relay, transmitting information from layer five of one cortical area to another area. First and higher order thalamic relays also stimulate other sensory systems, and it is now becoming clear that most of thalamus is comprised of higher order relays. Anatomical and physiological arguments were presented that challenged the conventional view that corticocortical communication is based on direct corticocortical connections, suggesting instead that higher

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order relays in the pulvinar play a major role. Thus the thalamus is not just a simple relay responsible for getting peripheral information to cortex: instead it both provides a behaviorally relevant, dynamic control over the nature of information relayed, and it also plays a key role in basic corticocortical communication.

Next, Martin Usrey (University of California, Davis) presented feedforward and feedback contributions to visual processing in the lateral geniculate nucleus. Thalamic LGN neurons receive feedforward input from retinal ganglion cells and feedback input from the primary visual cortex. Because LGN neurons are strongly driven by the retina and have receptive fields much like those of their retinal afferents, the LGN is generally regarded as a structure that simply relays retinal activity without doing much in terms of visual processing. Closer examination, however, reveals a more complex picture of LGN function, as LGN neurons can dynamically filter their retinal input. Results were presented from experiments in anesthetized and alert animals that examined the role of feedforward and feedback pathways in the spike transfer, surround suppression and attentional modulation of LGN neurons.

Greg Smith (The College of William and Mary) finished the morning with a talk on feedback inhibition and throughput properties of network models of retinogeniculate transmission. Computational modeling has played an important role in the dissection of the biophysical basis of rhythmic oscillations in thalamus that are associated with sleep and certain forms of epilepsy. In contrast, the dynamic filter properties of thalamic relay nuclei during states of arousal are not well understood. Two modeling studies were presented concerning the throughput properties of the visually driven dorsal lateral geniculate nucleus (dLGN) in the presence of feedback inhibition from the perigeniculate nucleus (PGN). First, a minimal integrate-and-fire-or-burst (IFB) two-layered network was used to model the visually-driven dLGN/PGN system, and to determine its response characteristics as a function of stimulus parameters such as contrast, temporal frequency, and spatial frequency of stimuli. In the second study, a stochastic version of the IFB model was formulated in terms of a multivariate probability density function that satisfies a conservation equation with appropriately defined probability fluxes and boundary conditions. The stochastic model exhibited a wide range of responses to constant drive including asynchronous burst and tonic spikes, sleep spindle-like rhythmic bursting, and oscillations in population firing rate that are distinguishable from sleep spindles due to their amplitude, frequency, or the presence of tonic spikes.

In the afternoon, Vivien Casagrande (Vanderbilt Medical School) presented her talk entitled The evolution of parallel visual pathways in primates. This talk addressed several key questions concerning the evolution of the primate visual system. How did parallel pathways evolve in primates? Are magnocellular (M), parvocellular (P) and koniocellular (K) pathways homologous across primates? Are cortical visual areas and compartments within areas homologous across primates? Do homologous pathways, areas and cortical streams exist in non-primate mammals? Where the evidence for homology is strong what does this suggest about function? Were the earliest primates really nocturnal?

David Fitzpatrick (Duke University Medical Center) talked about recent experiments that explore the development of direction selectivity in primary visual cortex of the ferret using intrinsic signal and in vivo 2-photon calcium signal imaging. Evidence was presented that direction columns, unlike other columnar systems, emerge a few days after eye opening and this emergence depends on visual experience. The impact of visual experience on the emergence of direction columns was visualized in individual visually naive animals that were exposed to a motion training stimulus. After 10-12 hours of stimulation, direction columns become evident and gradually strengthened. These effects of visual experience were strikingly limited to the cortical neurons that were activated by the training stimulus, and reflected a rapid increase in the

direction selectivity of individual layer 2/3 neurons. Hence, visual experience appears to play a critical role in the emergence of direction selective cortical responses.

Day 2

The second day continued with the theme of early visual processing. Robert Shapley (New York University) reviewed a local circuit computational model of a patch of the input layer 4Ca of the primary visual cortex (V1) of the macaque monkey. The model consisted of integrate-and-fire neurons with biologically plausible synaptic conductances. The model could account for the distributions of orientation and spatial frequency selectivity across the population of V1, and also the relative prevalence of linear and nonlinear spatial summation in V1 neurons. It was suggested that a crucial controlling variable is the relative strength of corticocortical inhibition relative to excitation in the local circuit. Experiments on responses to spatially extended stimuli indicated there is also a strong influence of long-distance, possibly feedback, interactions on V1 neurons.

Ralph Freeman (University of California, Berkeley) presented a talk entitled Dynamic spatial processing originates in early visual pathways. He stated that several investigations in the visual system have established that coarse spatial features are processed before those of fine detail. Although it is generally assumed that this is a cortical function, there are features of early visual pathways that provide the basis for a coarse-to-fine sequence. Neurophysiological studies in the lateral geniculate nucleus were presented that provided evidence for this possibility. A computational model was used to support the idea that the known temporal dynamic features in the visual cortex may be accounted for by a feedforward process.

Steven Zucker (Yale University) focused on principles of computational abstraction in the visual cortex. The long-range horizontal connections in superficial layers of primary visual cortex (V1) are thought to facilitate contour integration. A model of long-range horizontal projection fields was presented that formalizes good continuation based on the natural geometry of curves and surfaces. In addition to explaining contour integration, it could also be applied to the computation of texture and shading. It was also shown how the model quantitatively predicts the neuroanatomical spread in projection distribution, its non-monotonic variance, and differences found between individual neurons. The model was further extended to handle stereo (V1 and higher-area interactions) and color (long-range horizontal connections between cells in cytochrome oxidase blobs). Numerous predictions about function and physiology were made.

Next, a joint talk was given by Amiram Grinvald and David B. Omer (Weizmann Institute for Science, Rehovot, Israel) on the dynamics of evoked and ongoing activity in the behaving monkey. Previous findings from Voltage Sensitive Dye Imaging (VSDI) experiments done on anesthetized cats indicated that the amplitude of ongoing spontaneous activity (primarily synaptic potentials) is large, suggesting that it may play an important role in cortical processing by affecting evoked activity and therefore the final behavior itself. This talk presented experimental VSDI data on cortical activity in the primary visual cortex of a behaving monkey during both evoked and ongoing conditions. This indicated that ongoing activity is richer in awake animals compared to anesthetized preparations. However, the exact functional role of spontaneous activity remains to be evaluated.

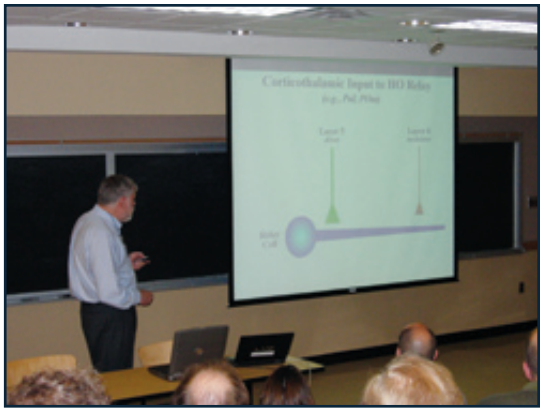
A key emergent property of the primary visual cortex (V1) is the orientation selectivity of its neurons. Mriganka Sur's (MIT) talk reviewed recent experiments demonstrating remarkable bottom-up and top-down plasticity in orientation networks of the adult cortex. It was shown how neurons in V1 of alert, behaving monkeys exhibit short-term orientation plasticity after very brief adaptation with an oriented stimulus, on the time scale of visual fixation. Adaptation with stimuli that are orthogonal to a neuron's preferred orientation did not alter the preferred orientation but sharpened orientation tuning. Thus, successive fixation on dissimilar image patches, as happens during natural vision, combined with mechanisms of rapid cortical plasticity, actually improves orientation discrimination. Experiments on behaving monkeys, in which information about future stimulus locations can be acquired in one set of trials but not in another, were used to demonstrate that V1 neurons signal the

acquisition of internal representations. Together, these studies demonstrate that vision is inference, and its basis is continually recalibrated even at the earliest stages of cortical processing.

Day 3

Another joint talk was presented by an experimentalist and a theoretician. David Ferster (Northwestern University) and Kenneth Miller (Center for Neurobiology and Behavior, New York) presented data showing how salient tuning properties of V1 cells can be achieved, including contrast-invariant orientation tuning, cross-orientation suppression and surround suppression (suppression evoked by stimuli outside the classical receptive field). A model was then presented showing that the surround suppression data can be understood if V1 is an inhibition-stabilized network: one in which recurrent excitation alone is strong enough to produce instability, but in which feedback inhibition stabilizes the network. Finally, a similar network architecture was used to explain the findings of Grinvald and colleagues on the structure of V1 spontaneous activity (see talk of Grinvald and Omer on Day 2).

The most common paradigm for studying visual cortical processing has been to examine the activity of single neurons in response to artificial stimuli such as bars and gratings. While this approach has been highly successful, very little has been learned about how groups of neurons jointly respond to natural scenes. Charles Gray's (Montana State University) talk reviewed recent experimental data on spike activity from small groups of 3-10 well isolated, single units in the primary visual (striate) cortex of anesthetized cats and alert monkeys and analyzed their responses to the repeated presentation of short episodes of time-varying natural scenes (movies). It was shown how the responses of striate neurons to movies are brief, decorrelated, and exhibit high population sparseness. Adjacent neurons differ significantly in their peak firing rates, even when they respond to the same frames of a movie. Hence complex natural scenes evoke highly heterogeneous, but sparse, responses within local populations that can be transiently synchronized, and thereby reveal features of visual cortical dynamics not readily apparent in response to simple stimuli.



Ning Qian (Columbia University) focused on modeling binocular depth perception based on physiological properties of binocular cells in the visual cortex. It was shown that binocular disparity maps can be effectively computed from stereograms with a population of complex cells, without explicit feature matching. A unified theory for understanding depth effects of both horizontal and vertical disparities was described, and then used to account for a family of depth illusions. Finally, the problem of da Vinci stereopsis was reviewed and a simple model for determining the location and ocularity of monocularly occluded regions was presented based upon disparity-boundary-selective cells.

Day 4

The fourth day turned to the role of feedback in information processing. Risto Miikkulainen (The University of Texas at Austin) reviewed a computational approach to modeling the primary visual cortex as a self-organizing map in a dynamic equilibrium with afferent, lateral, and feedback input (LISSOM). Such a map organizes into orientation, direction, ocular dominance, and color selective patches, and develops selective patchy lateral connections between them. The model demonstrated how the map could recover from retinal and cortical injury, as well as how psychophysical phenomena such as tilt aftereffects and contour integration might arise in it. For instance, the model suggested how Kanizsa-type illusory contours could arise based on feedback from a higher area, a prediction that has subsequently been verified through VSD optical imaging on macaque V1.

A number of phenomena in visual perception can be related to the assignment of 'border ownership', a hypothetical process of detecting contours of objects and assigning them to the corresponding image regions. Border ownership assignment relates

to the interpretation of the image in terms of a 3D layout of objects and the perception of shadows and transparent overlay; it affects recognition of form and deployment of attention; figures draw attention, while shapes of the ground tend to be ignored. Rudiger von der Heydt (Krieger Mind/Brain Institute, Johns Hopkins University) reviewed evidence for border ownership coding in the visual cortex of macaques and discussed recent neurophysiological experiments on the relationship between figure-ground organization and attention. These new results showed that border ownership coding and voluntary (top-down) attention influences are combined in single neurons of area V2 and share critical neural circuitry. Thus, the phenomena of figure-ground organization may reflect the general process of recoding a visual image representation into a more efficient data structure that enables further, object-based processing.

A border between two image regions normally belongs to only one of the regions; determining which one it belongs to is essential for surface perception and figure-ground segmentation. Von der Heydt and colleagues have observed that border ownership is signaled by a class of V2 neurons, even though the ownership value depends on information coming from well outside the classical receptive fields of the cells. In this presentation, Zhaoping Li (Department of Psychology, University College London) presented a network model of V2 in which V2 is able to generate the ownership signal by itself, without requiring any top-down mechanism or external explicit labels for figures, T junctions, or corners. In the model, neurons have spatially local classical receptive fields, are tuned to orientation, and receive information (from V1) about the location and orientation of borders. Border ownership signals that model physiological observations arise through finite range, intra-areal interactions.

Andreas Burkhalter (Washington University School of Medicine) continued the day's theme with his talk on Inhibitory control of excitation in feedforward and feedback circuits between lower and higher areas of mouse visual cortex. Primate visual cortex contains multiple functionally specialized areas which are linked by feedforward (FF) and feedback (FB) connections within a hierarchical network. This talk presented anatomical and physiological data highlighting analogous functional circuits in mouse cortex. One of the major findings of studies in mouse is that FB connections generate smaller fast GABA-A receptor-mediated postsynaptic inhibitory currents than FF inputs. One reason for this is that FB synapses are more strongly depressing than FF synapses and that they deplete more quickly during repetitive stimulation. Another reason is that fast spiking neurons in the FB pathway have a more positive spike threshold (-36 mV) than in the FF pathway (-44 mV), which may decrease the number of simultaneously active interneurons and lower the inhibitory output of the FB circuit. In addition to the pathway-differences in fast synaptic inhibition, it was also shown how slow GABA-B receptor-mediated inhibition is much more powerful in the FF than in the FB circuit. The possible implications of this for contextual processing were also discussed.

Alessandra Angelucci (University of Utah), Lars Schwabe (Swiss Federal Institute of Technology) and Paul Bressloff (University of Utah) gave a joint experimental/theory talk concerned with the neural circuits underlying surround modulation in macaque V1. First, experimental data was presented providing evidence that feedback connections are the most likely substrate for far surround modulation, whereas feedforward and horizontal connections are likely to underlie "near" surround modulation. An anatomically and physiologically constrained recurrent network model of macaque V1 was then described, in which both horizontal and feedback connections contribute to contrast-dependent increases in RF size and to near surround modulation, whereas feedback connections underlie far surround modulation. To account for the anatomical observation that excitatory feedback axons have a weaker inhibitory effect than horizontal and feedforward connections (see previous talk by Burkhalter), feedback neurons in the far surround were assumed to exert their suppressive influence via contacts with excitatory neurons in the near surround. A central prediction of the feedback model was that the "suppressive" far surround of V1 neurons can be facilitatory under conditions that weakly activate neurons in the RF center. Finally, experimental data was presented that confirmed this prediction.

Recurrent feedback in the visual cortex can potentially be conceptualized as a mechanism for mediating the influence of prior beliefs in a hierarchical Bayesian inference framework. Tai Sing Lee's (Carnegie Mellon University) presentation considered the computational problem of 3D shape inference based on monocular and binocular cues. Evidence was presented suggesting that neuronal tuning and neuronal interaction in the primary visual cortex encode ecological statistical priors between 3D scene structures and 2D images relevant for 3D inference. These sensitivities, together with evidence on the response dynamics of neurons in the early visual cortex, are consistent with the hierarchical Bayesian perspective on visual processing.

Day 5

Many receptive fields in lateral geniculate nucleus (LGN) are biphasic in time, i.e. a bright (dark) excitatory phase is followed by a dark (bright) excitatory phase. Dana Ballard (University of Texas at Austin) described a hierarchical model of predictive coding and simulations that capture these changing neuronal response properties. The model was composed of two areas, resembling the LGN and primary visual cortex (V1). Model V1 attempted to predict its LGN inputs, while neurons in LGN signal evaluated the difference between actual input and the V1 predictions. After training on natural images, model V1 receptive fields resembled simple cell receptive fields. In addition, the spatio-temporal response profile of LGN model neurons was biphasic in structure, resembling the biphasic response structure of neurons in cat LGN. The model predicted a specific pattern of influence of feedback, where LGN receptive fields that are aligned over a simple cell receptive field zone of the same polarity decrease their responses and neurons of opposite polarity increase their responses due to feedback. This phase-reversed pattern of influence was recently confirmed in neurophysiology. These results corroborate the idea that predictive feedback is a general coding strategy in the brain.

Jack Gallant (University of California, Berkeley) ended the workshop with his talk entitled Feature-based attention dynamically changes shape representation in area V4. Top-down processes such as attention and memory enable selective filtering of sensory information in order to meet behavioral demands, but the mechanisms underlying this process remain unknown. Most evidence supports the idea that attention highlights attended locations or features by enhancing neuronal responses but does not change stimulus selectivity. However, some theoretical work suggests that attention might alter the way neurons encode visual information. Two experiments were described demonstrating that feature-based attention alters the multidimensional tuning curves of many V4 neurons, thereby dynamically changing the way that shape is represented in this area. Such results suggest that memory and decision-making processes required for natural vision are integrated into the basic processes of visual representation and distributed widely across the neocortex.

Conclusion

In terms of stimulating scientific discourse, the workshop was an unqualified success. The structure of the workshop, with a limited number of invited lectures, two panel discussions, and ample time for informal discussions, allowed participants excellent opportunities to present their own work and to gain a sense of current theoretical and experimental work relating to the topics of the workshop. The administrative support provided by the MBI was first rate. Many participants stated that this was an exceptionally useful and enjoyable conference.

One of the significant aspects of the meeting was the growing interplay between theory and experiments, as demonstrated by several talks given jointly by an experimentalist and a theoretician. The possible role of mathematics in vision science was also the theme of a particularly lively panel discussion. A major distinction was made between two classes of model: a) abstract mathematical models without direct connections to real data ("bubble universe models"), and b) more detailed computational models with strong connections to data. There was considerable disagreement about the value of one approach versus the other. Some viewed detailed models as "overfitting data" without providing real insights, particularly given the problem of data selection. Others felt uncomfortable with abstract models and wanted detailed circuit models that made very specific predictions. A number of important outstanding theoretical questions were also identified. How does the brain signal information using sparse codes and few spikes? How can nonlinear dynamics be used to understand the behavior of large number of cells studied using the rapidly growing technology of multielectrode devices?

Current Topics Workshop on Chemogenomics, May 8-10, 2007

Organizers: Paul Blower, Department of Pharmacogenomics, The Ohio State University; Joe Verducci, Department of Statistics, The Ohio State University; John Weinstein, NCI; and Stan Young, NISS

Introduction

Chemogenomics is defined as the use of genomics to measure the system-wide effect of a compound on an intact biological system, either single cells or whole organisms. It combines high-throughput genomics or proteomic profiling with chemoinformatic and statistical analysis to study the response of a biological system to chemical compounds. Cellular response is measured by phenotypic readouts in a high-throughput assay. Chemogenomics also investigates the consequences of differential gene/protein expression on cellular response to compound treatment. For example, expression levels of membrane transporters can have a dramatic effect on compound potency.

The purpose of the conference was to bring together experts from chemistry, genomics, statistics, and computer science to discuss their research into essentially interdisciplinary topics, such as the response of cancers to drug treatment and other biological processes that cannot be understood by studying individual genes or proteins in isolation. Relational databases, such as the NCI-60 datasets provide significant opportunities for large-scale datamining and applications of statistical modeling of drug potencies based on mRNA/protein/miRNA expression, alone or in combination with aspects of molecular structure of the drug candidates. By bringing together key individuals from the different disciplines, we hope to make future planning and analyses more comprehensive.

Day 1

John Weinstein (National Cancer Institute, Bethesda, MD) opened the workshop with an historical overview of research on molecular profiling and integrated analysis of the 60 human cancer cell lines (the NCI-60) used by the National Cancer Institute (NCI). These pioneering works established the foundation for much of what was presented and discussed in the workshop. Since 1990, the NCI-60 has been used to screen >100,000 compounds. To take advantage of the pharmacological profiling, the NCI-60 have also been the subject of numerous genomic, proteomic and other '-omic' profiling studies. The NCI-60 panel constitutes the most comprehensively profiled set of cells in existence, and they have proved rich in information about drug mechanisms of action and chemoresistance/sensitivity. Weinstein pointed out that value of this data is best realized when biomedical scientists use integrated information from multiple sources for hypothesis generation follow by experimental validation. An example that illustrates this procedure is based on the relationship between L-asparaginase activity and the enzyme asparagine synthetase. Based on data from four different transcript expression platforms and a comparative genomic hybridization, his group developed a rationale for the possible use of L-asparaginase against ovarian cancers which has now progressed from studies in the NCI-60 cell lines to clinical trials.

"Numerous CALGB LCSC studies have had a major effect on the way doctors currently diagnose, predict outcome, select appropriate treatment, document complete remission, and monitor residual disease in adults with acute leukemia."

Clara Bloomfield (The Ohio State University) briefly reviewed the many contributions that the Cancer and Leukemia Group B (CALGB) Leukemia Correlative Science Committee (LCSC) has made to correlative science for adult leukemia for almost 25 years. Its work initially focused on the use of immunophenotyping for diagnosis and prognosis of acute lymphoblastic leukemia and acute myeloid leukemia, but has, for the last 15 years, refocused on the clinical use of cytogenetic and molecular genetic markers in acute myeloid leukemia and acute lymphoblastic leukemia as well as in chronic lymphocytic leukemia. Numerous CALGB LCSC studies have had a major effect on the way doctors currently diagnose, predict outcome, select appropriate treatment, document complete remission, and monitor residual disease in adults with acute leukemia. Now research is moving toward molecularly targeted therapy in acute and chronic leukemias and use of molecular

abnormalities in acute leukemia for selecting treatment.

Georges Natsoulis (Iconix Biosciences, Inc., Mountain View, CA) informed us of a large-scale chemogenomics database developed from in vivo treated rats. Approximately 600 different compounds, including more than 400 FDA approved drugs, 60 drugs approved in Europe and Japan, 25 withdrawn drugs, and 100 toxicants, have been profiled in up to 7 different tissues of rats (representing over 3,200 different drug-dose-time-tissue combinations). Rats were treated in multiple doses, multiple times, and in biological triplicate. Gene expression profiles were collected from up to seven different tissues. More than 200 hematology, clinical chemistry, histopathology, and pharmacology assays were performed in the same animals. The Iconix group systematically mined the gene expression domain of this dataset using an SVM based two-class supervised classification method. More than 300 thoroughly cross-validated linear classifiers (signatures), each composed of an average of 45 genes, were identified. We verified that these signatures resolve distinct and uncorrelated end-points. Some genes recur in a large number of signatures. The occurrence of genes across signatures follows a power law distribution. These genes are therefore forming a scale free network. The hubs of that network (as few as 400 genes in a given tissue) are sufficient to recreate all signatures with no appreciable loss in classification performance. This finding opens the possibility of creating a multi-endpoint diagnostic device. The utility of pairing clinical pathology assessments with gene expression data was illustrated using three anti-neoplastic drugs: carmustine, methotrexate, and thioguanine, which had similar effects on the blood compartment, but diverse effects on hepatotoxicity. Dr. Natsoulis' group at Iconix demonstrated that gene expression events monitored in the liver can be used to predict pathological events occurring in that tissue as well as in hematopoietic tissues. Their data base and methods provide the context and supporting tools to accelerate accurate interpretation of mechanisms of toxicity and pharmacology of chemicals and drugs.

John Overington (Inpharmatica Ltd., London, UK) described the construction of a large-scale chemogenomics database, extracted from published data, linking chemical structures to biological activities. Although the published literature contains many data-points, they are typically inconsistently reported and inaccessible to large-scale analysis and data-mining. Thus, such a database will provide an invaluable resource for chemogenomic data mining allowing for the consistent and rapid identification of patterns in both target and compound space. In his talk, Overington outlined the construction of the database and some of the challenges in deploying such systems. The talk also focused on critical issues of data preparation and clean-up, normalization of chemical structure data and biological protocols, and quality assessment.

Peter Willett (University of Sheffield) discussed aspects of chemical similarity searching, which is widely useful for mining chemogenomic data. Although chemical similarity searching has been available for many years, there is ongoing interest in techniques that could enhance their effectiveness, in particular, data fusion techniques. Because of the great diversity of chemical structures and a range of types of biological activity, it is unlikely that any single measure will be optimal in all domains. Combining results from multiple sources is expected to enhance effectiveness over that of a single source. Willett discussed two types of data fusion, combining results from different similarity measures or different descriptor sets (structural features), and combining results from multiple starting points (reference structures). In the former case, the best performance across a wide range of activity types when combining similarity measures with different characteristics, but results were variable. In the latter case, the evidence suggested that enhancement was greatest with the most diverse reference structures.

Wolfgang Sadee (The Ohio State University) described a series of studies that use informatics approaches to associate compounds or compound classes with relevant gene families in the NCI-60 cell lines, followed by experimental validation. These studies exemplify the utility of chemogenomics in combination with rapid in vitro testing of drug candidates in selected cell lines expressing the target gene. In one study, the scientists used a custom 70-mer oligonucleotide arrays to analyze gene expression of membrane transporters and channels. By analyzing correlations between gene expression and the potencies of anticancer drugs, the study identified numerous potential drug-transporter relationships. For example, two follow-up studies focused on the multiple drug resistance gene ABCB1 and the cystine-glutamate exchanger SLC7A11. Significant negative

correlations suggested potential mechanisms of drug resistance. Experimental studies validated several such relationships by using small molecule inhibitors of selected transporters or siRNA knockdown which increased substrate potency. Sadee concluded that expression patterns of other selected transporter genes may also prove useful in predicting anticancer drug response.

Day 2

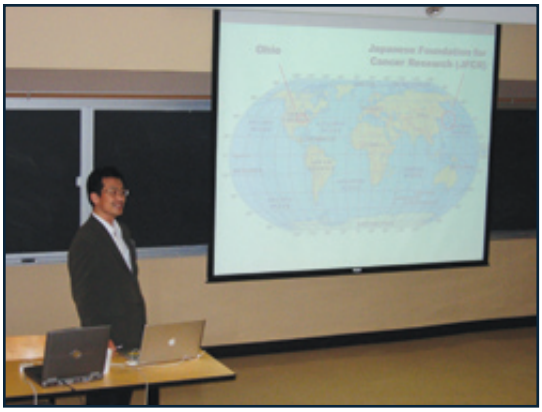
Stan Young (NISS, RTP, NC) presented joint work with Paul Fogel and Doug Hawkins on non-negative matrix factorization. This technique is particularly useful when there are many more predictor variables than observations, such as what occurs with datasets derived from microarrays, proteomics, metabolomics, etc. There are typically correlations among variables; indeed, the many variables/predictors cannot all be independent of one another. The correlations can be utilized to improve the statistical analysis. Dr. Young presented new inferential methods that combine statistical testing with non-negative matrix factorization. The methods were demonstrated using microarray and metabolomic datasets. Papers and code for these methods can be found at http://www.niss.org/irMF.

David Covell (NCI) described strategies for analyzing compounds tested in the NCI-60 by data integration using self-organizing maps of structural and biological response patterns which segregates compounds into groups that share a similar mechanism of action. They built statistical models to predict compound cytotoxicity (growth inhibition) and hollow fiber (HF) activity based on physicochemical properties including ALogP, Lipinski score, molecular weight, hydrogen bond acceptors, hydrogen bond donors, parent atom count, rotatable bonds, polar surface area, and unique feature count. They found that molecule size and structural complexity contribute significantly to compound potency in cytotoxicity and HF assays. The models were statistically valid and can be used as a filter to eliminate most of inactive compounds in a large set and select a small set for experimental follow-up.

Justin Lamb (Broad Institute/MIT) demonstrated how the Connectivity Map uses gene-expression profiling to identify new therapeutics and potential adverse drug effects. Genome-wide transcriptional analysis provides a comprehensive molecular representation of cellular activity, suggesting that mRNA expression profiling could serve as a practical universal functional bioassay. High-throughput high-density gene expression profiling solutions raise the possibility of capturing the consequences of small molecule and genetic perturbations at library and genome scale, respectively, and associating these disparate perturbations with each other and external organic phenotypes to discover decisive functional connections between drugs, genes and diseases. His talk described the technology platform set up at the Broad, including methods of analysis and interpretive tools. He also provided examples illustrating how the expression profiles of a large collection of bioactive small molecules can be used to reveal signaling cascades, annotate complex phenotypes, predict adverse drug effects, and identify potential human therapeutics.

Dimitris Agrafiotis (Johnson & Johnson) presented new algorithms for mining large data sets. His talk highlighted key algorithmic advances that expand, by several orders of magnitude, the number of compounds that can be assessed as potential drugs, and offer a preview of a new informatics platform that is being developed at J&J PRD for the effective delivery and visualization of structure-activity. Receiving special emphasis was a novel self-organizing algorithm for extracting the intrinsic structure and dimensionality of large experimental observation spaces, and its application on some challenging problems in computational chemistry and biology. A complete review has just been published in J Chem Inf Model. 2007.

Eric Kaldjian (Gene Logic) described a practical approach to multi-platform microarray analysis for clinical applications. Gene Logic has created a prototypic oncology database using multiple microarray platforms to investigate cross-platform correlations and develop methods for integration of different types of genomic information. A set of infiltrating ductal carcinomas of the breast and patient-matched morphologically normal breast samples has been evaluated by CGH arrays, three types of mRNA gene expression arrays, microRNA expression arrays, and SNP arrays. The initial step in this investigation was to assess aCGH results on this sample set in the context of known copy number gains and losses in breast cancer. Gene copy number gain at the 17q11-12 region (associated with erb-B2 amplification) was correlated with gene expression patterns as analyzed by three gene expression micro-array platforms. Differences in miRNA expression between normal and cancer confirmed recent reports. High-level grouping of samples based on chromosomal aberration analysis combined with gene expression correlation may be a way to generate a candidate "biologically validated" biomarker gene set. Although multi-platform analysis of the same



clinical sample is feasible, before the value for clinical application can be exploited, a new analytic approach must be defined. This approach will likely require novel database structures for linking extremely large amounts of data, as well as innovative algorithms that join data of different types.

Panel Discussion

At the end of the day, we held a "reversed table" discussion where participants sat up on the front stage and speakers sat as an audience. Each participant briefly described his or her own interests and asked the speakers about how their research might relate. It afforded a frank discussion about limitations, and became a good brainstorming session about promising directions for research.

Day 3

Gerhard Mueller (GPC Biotech AG) described the privileged structure concept and its application to design of kinase inhibitors. Target proteins of pharmaceutical relevance (the drugable genome) cluster into multi-member gene families, offering a systematic approach that can be addressed by chemogenomics. The privileged structure concept takes advantage of densely populated protein families that exhibit family-wide molecular recognition characteristics by encoding conserved structural/functional commonalities into gene family-specific small-molecule inhibitors. These gene family-specific inhibitors contain a (possibly) generic scaffold that can be functionalized (using medicinal chemistry principles) to produce highly active and selective compounds for specific targets (family members). Mueller gave several examples of the application of the privileged structure concept to protein kinases that led to the design of recently launched kinase inhibitors.

Takao Yamori (Japanese Foundation for Cancer Research) described how his research group established a panel of 39 human cancer cell lines (termed JFCR39), on which they used a data-mining tool COMPARE to build a database of chemosensitivity measurements, according to the methodology in NCI60. They examined JFCR39 for the feasibility in predicting molecular targets of test compounds. Then, the molecular targets of novel compound MS-247, FJ5002 and ZSTK474 (2) were successfully identified as topoisomerases I and II, telomerase and PI3-kinase, respectively, by the COMPARE-guided approach. Among them a novel PI3-kinse inhibitor ZSTK474 showed remarkable therapeutic efficacy against human cancer xenografts. They further investigated the gene expression profiles in JFCR3 and in JFCR45, another panel of 45 human cancer cell lines (3), and identified those genes whose expression levels were correlated with the chemosensitivities of cancer cells. Transfection or knockdown of some of such genes indeed altered the cellular sensitivity to certain drugs. These results indicate that those genes may play key roles in determining the chemo-sensitivity in cancer and also might serve as new targets for sensitizing cancer cells to chemotherapy. To find disease-specific biomarkers, they comparatively analyzed the protein expression profiles across JFCR39 using SELDI-TOF MS System. They found a 12kDa protein expression specifically associated with colon cancer. It was identified as prothymosin, which could be a potential biomarker for colon cancer. Furthermore, they selected four proteins whose expressions show significant correlations to chemo-sensitivities. One of them was identified as the ribosomal P2 protein, which could be a potential biomarker for predicting sensitivity to PI3-kinase inhibitors (4). Therefore, mining data sets from JFCR39 provide valuable information in identifying candidates for a new drug, target, and biomarker.

Paul Blower (The Ohio State University) described informatics and experimental studies of chemoresistamce in the NCI-60. The talk was divided in two parts. The first set of studies was done in collaboration with Wolfgang Sadee's group and overlapped with his presentation on Day 1. The second part of the talk focused on microRNAs which are small noncoding RNAs that downregulate target mRNAs either by degradation or by translational inhibition, which have been implicated in cancer genesis and progression. To complement the existing NCI-60 datasets described by Weinstein on Day 1, they measured expression levels of microRNAs in the NCI-60. Comparison of microRNA expression patterns and compound potency patterns showed significant correlations, suggesting that microRNAs may play a role in chemoresistance. To pursue this they tested the effect of altered microRNA levels on cytotoxic potencies for a set of structurally diverse compounds in three human

cancer cell lines of the NCI-60 panel. In one case, mir-21 expression significantly affected cytotoxic potency for 36% of compound-cells pairs tested, confirming a role for microRNAs in anticancer drug response.

Conclusion

In terms of stimulating scientific discourse, the workshop was an absolute success. The structure of the workshop, with a limited number of invited lectures from diverse disciplines focused on a common goal, proved surprisingly enlightening to all participants. Most feedback remarked on how much more beneficial this format is compared with the more typical large conference, highly specialized paper presentations that have become standard in established disciplines. The format afforded ample time for informal discussions, allowed participants excellent opportunities to discuss their own work with others, and to gain a sense of current theoretical and experimental work relating to the topics of the workshop. The administrative support provided by MBI was first rate. Many participants stated that this was an exceptionally useful and enjoyable conference.

Workshop 7: Insulin Secretion, Insulin Action, and Diabetes, May 21-24, 2007

Organizers: Arthur Sherman, Laboratory of Biological Modeling, National Institutes of Health; Richard Bertram, Department of Mathematics, Florida State University, Les Satin, Department of Pharmacology and Toxicology, Virginia Commonwealth University

Introduction

The purpose of this workshop was to bring together mathematical modelers and experimental physiologists working on several topics related to diabetes, including insulin secretion from pancreatic beta-cells and insulin action on receptors in muscle, fat, and the brain. Defects in each of these areas, and probably all acting in concert in most cases, have been implicated in the pathogenesis of type 2 diabetes. Regulation of beta-cell mass is also a key concern in type 1 diabetes and was addressed in the meeting.

Day 1

Manami Hara (Department of Medicine, University of Chicago) led off the meeting with a presentation of her groundbreaking work on imaging pancreatic islets in vivo. These studies have shown that islets do not attain their normal, rounded (elliptical) form until about 10 weeks after birth, and initially take on a streak-like morphology that follow the vasculature. Much work will be needed to unravel the implications of this over the next few years.

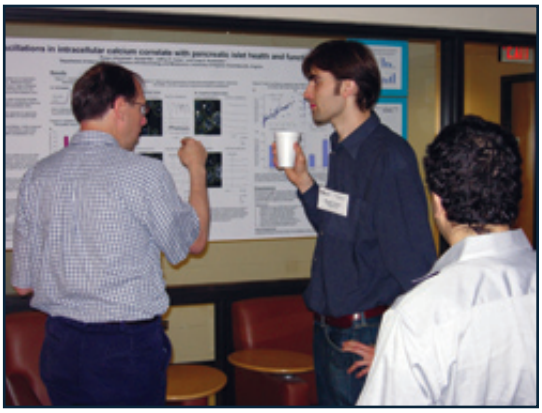
Richard Benninger (Department of Molecular Physiology and Biophysics, Vanderbilt University) followed with his data on calcium wave occurrence in islets, imaged in a novel microfluidics device in which unequal concentrations of the stimulus glucose can be applied to both halves of the islet. He reported the intriguing finding that waves die out with distance when triggered at the edge of the islet, and fail to penetrate the sub-threshold region. He was also the first of several experimentalists to present his own modeling efforts, an encouraging development in this field. Theorists at the meeting expressed strong interest in applying traveling wave and homogenization ideas to this system in order to explain the wave propagation failure in more detail.

Arthur Sherman (Laboratory of Biological Modeling, NIDDK, NIH) gave an overview of exocytosis, including work from his lab on a new model for insulin granule dynamics, which suggests based on kinetic arguments that the long-sought "metabolic signal" that amplifies calcium-dependent secretion must act at a slow step of vesicle resupply from a reserve pool to the plasma membrane.

Debbie Thurmond (Biochemistry and Molecular Biology, Indiana University School of Medicine) showed data that this second, amplifying phase of insulin secretion may be due to the effect of glucose to remodel the cortical actin network, allowing vesicles to dock onto sites on the plasma membrane.

The endoplasmic reticulum (ER) is important for insulin secretion both because it is the site where insulin molecules are folded

and packaged into secretory vesicles and because it is the major internal store for calcium, and as such, regulates the cytoplasmic free calcium that governs vesicle exocytosis. James Johnson (Cellular and Physical Sciences, University of British Columbia, Canada) spoke about his data indicating the existence of sub-stores of calcium, each with its own function and its own receptors to control calcium efflux.



Anders Tengholm (Medical Cell Biology, University of Uppsala, Sweden) has done pioneering measurements on ER calcium but spoke on his more recent work using cutting-edge FRET-based imaging techniques to measure cAMP in living cells in real time. cAMP undergoes oscillations in phase with cytosolic calcium, which likely represents a coincidence detection system to enhance insulin secretion when both glucose and the potentiating hormone glucagon like peptide 1 (GLP-1) , derived from glucose-sensitive intestinal cells, are present. This work is of great current clinical relevance as new drugs have recently come on-line that can mimic or enhance the effects of GLP-1 (see Mari, Day 3 below). It also inspired much discussion on how to account for the complex data with the current mathematical models for calcium and metabolic oscillations (see Day 2 below).

> "A previously unreported phenomenon in which calcium amplitude and oscillation period increase dramatically was explained as a switch from electrical to glycolytic oscillations and another new phenomenon of subthreshold calcium oscillations was predicted by the model and then observed in the Satin lab."

Posters were presented by Bradford Peercy (Laboratory of Biological Modeling, NIDDK, NIH) on a mathematical model of Tengholm's cAMP data; Mike Roper (Chemistry and Biochemistry, Florida State University) on a new method for simultaneous measurement of insulin and glucagon release from islet beta and alpha cells, respectively; Morten Gram Pedersen (Information Engineering, University of Padova, Italy) on a mathematical model of exocytosis; and K. V. Venkatesh (Chemical Engineering, Indian Institute of Technology Bombay, India) on a mathematical model of insulin signaling in skeletal muscle.

Day 2

Jean-Claude Henquin (Unit of Endocrinology and Metabolism, Catholic University of Louvain, Belgium) continued and deepened the theme from Day 1 on the effects of calcium to trigger insulin vesicle exocytosis, and the unknown metabolic signal that potentiates the effect of calcium. He presented data on SUR1 (-/-) knockout mice lacking the ATP-dependent potassium channel (KATP), which is thought to play the leading role in transducing glucose metabolism into a rise in cytosolic calcium. Such mice still show evidence of the amplifying pathway and sometimes exhibit calcium oscillations as well, depending on age of the mouse and cell culture conditions. He suggested that another potassium channel takes over for the KATP channel in the knockout and may be present as well in the wild-type mouse.

Henquin was followed by Colin Nichols (Cell Biology and Physiology, Washington University School of Medicine, St. Louis), a leading expert on the relationship between KATP channels, beta cell excitability and disease. He discussed how both diabetes, and the opposite syndrome, hyperinsulinism can result from abnormal KATP activity, the former when KATP is too active, inhibiting insulin secretion, and the latter when KATP is not active enough, permitting inappropriate insulin secretion despite low glucose. Paradoxically, if the organism can compensate for the resulting hypoglycemia, the organism can over time progress to hyperglycemia (i.e. diabetes). This progression may be the result of unchecked beta-cell electrical activity and calcium entry leading to calcium-dependent apoptosis.

Richard Bertram (Department of Mathematics and Institute for Molecular Biophysics, Florida State University) presented an emerging mathematical model that unifies the fast (tens of seconds) and slow (several minutes) oscillations observed in calcium, insulin secretion and various metabolic parameters, such as oxygen consumption, NAD(P)H, and mitochondrial membrane potential. The model proposes that the fast oscillations are essentially ionic in origin whereas the slow are due to glycolytic oscillations that pace mitochondrial respiration. Les Satin (Pharmacology, Virginia Commonwealth University School of Medicine) followed up with a discussion of experimental tests of the model, including an account of the patterns of response to elevation of glucose. A previously unreported phenomenon in which calcium amplitude and oscillation period increase dramatically was explained as a switch from electrical to glycolytic oscillations and another new phenomenon of subthreshold calcium oscillations was predicted by the model and then observed in the Satin lab. MBI postdoc Paula Grajdeanu met Bertram and the workshop and has begun to work with him on an extension to the model to include the citric acid cycle.

Gary Cline (Internal Medicine, Yale University School of Medicine) described experiments with stable isotopes of carbon (13C) to unravel the complex pathways taken by metabolites as they pass through the mitochondria. A main focus was on flux through pyruvate carboxylase (PC), an alternative to the more standard pyruvate dehydrogenase that is particularly highly expressed in beta-cells. Cline suggested that flux through PC leads to the generation of NADPH in the cytosol, which may act as a novel second messenger from the mitochondria to the cytosol, possibly related to the aforementioned amplifying pathway. He laid down a challenge for mathematical modelers to help sort out these complex phenomena.

Keith Tornheim (Biochemistry, Boston University School of Medicine) presented his data supporting a role for glycolytic oscillations, which in fact formed the experimental grounding for the model presented earlier in the day by Bertram. Tornheim's view, however is somewhat different, in that he proposed that each oscillation is terminated by a drop in AMP, whereas the in the mathematical model of Bertram and colleagues termination is due to depletion of the substrate fructose-6-phophate.

Posters keyed to the Day 2 oral sessions were presented by Pranay Goel (Laboratory of Biological Modeling, NIDDK, NIH) on finite element modeling of a special calcium sub-compartment located between the ER and the beta cell membrane; Les Satin (Pharmacology, Virginia Commonwealth University School of Medicine) on a test of a novel blocker of the Na+-Ca2+ exchanger; Arthur Sherman (Laboratory of Biological Modeling, NIDDK, NIH) on a model of ER calcium dynamics; Christine Hallgreen (Physics, Danish Technical University) on modeling of fatty acid metabolism; and Craig Nunemaker (Internal Medicine, University of Virginia Health System) on the use of calcium oscillations to assay the viability of islets for transplantation therapy in type 1 diabetes.

Day 3

The first talk on Day 3 by Orian Shirihai (Pharmacology and Experimental Therapeutics, Tufts University School of Medicine) completed the theme of metabolism. He showed stunning images of mitochondrial fission and fusion events in beta-cells and presented a cellular automaton model of the phenomena. Shirihai's hypothesis is that this is a form of bacterial sex that enables the cell to maintain mitochondrial quality in the face of free radical production, to which the beta-cells are particularly sensitive.

Morten Gram Pedersen (Department of Information Engineering, University of Padova, Italy) launched the theme of whole-body physiology with a talk on entrainment of insulin secretion by exogenous glucose pulses and synchronization of the islets in the pancreas through mutual entrainment. The latter is effected by pulsatile release of insulin, which in turn results in plasma glucose oscillations through regulation of glucose release by the liver.

Andrea Mari (Institute of Biomedical Engineering, Padova, Italy) presented his model for assessing beta-cell function. The model is inspired by the landmark models of Grodsky and Cerasi but simplified to make it suitable for parameter estimation

in clinical trials. The model has been used to demonstrate the ability of a new class of diabetes drugs based on mimicking or enhancing the potentiating effect of GLP-1 on insulin secretion (see Tengholm, Day 1).

Chiara Dalla Man (Department of Information Engineering, University of Padova, Italy) described the glucose clamp technique and the minimal model of Bergman, both used for assessing insulin resistance, which is a key contributor to type 2 diabetes in combination with deficient insulin secretion. She reported her own work to extend the Bergman model to the oral glucose tolerance test, which is much less invasive than the intravenous glucose tolerance test used by Bergman.

Jake Kushner (Division of Endocrinology, Children's Hospital of Philadelphia) presented his elegant cell lineage tracing studies, which show that beta-cell proliferation is mainly due to replication of ordinary existing beta-cells, not of specialized progenitor cells. He graphically illustrated alternative branching processes corresponding to those two hypotheses, which have the potential to be turned into fully mathematical models. This issue is central to both type 1 and type 2 diabetes, as both diseases are characterized by reduced beta-cell mass, and the results address the potential for therapies to regenerate beta-cells.

Gianna Toffolo (Department of Information Engineering, University of Padova, Italy) continued the theme begun by Dalla Man of extensions to the Bergman minimal model with applications to assessment of beta-cell function and hepatic glucose extraction, two key clinical parameters for diagnosing and predicting the development of type 2 diabetes. In particular she showed the extension to the oral glucose tolerance test of Bergman's disposition index, which is essentially the product of insulin secretion and insulin action indices, and measures the ability of the beta-cell to compensate for insulin resistance. It has been shown to predict the development of type 2 diabetes.

Posters keyed to the Day 3 oral sessions were presented by Masayoshi Seike (Sysmex Corporation, Japan) on a glucose management system to assist diabetic patients and doctors in developing a personalized treatment plan based on whole-body glucose and insulin measurements; Rachel Altura (Pediatrics, Columbus Children's Research Institute) on a new protein, survivin, that regulates beta-cell mass after birth; Junghyo Jo (Physics and Astronomy, Seoul National University, Korea) on a mathematical model for islet size distribution; and Jiaxu Li (Mathematics and Statistics, Arizona State University) on an analysis of Hopf bifurcations in a delay-equation model for ultradian (two-hour) oscillations in plasma insulin, glucose and glucagon.

Day 4

Rohit Kulkarni (Joslin Diabetes Center, Boston) has studied the effects of insulin on its own secretion by showing defects in islet integrity and function in the beta-cells isolated from mice whose beta-cells lack insulin receptors. In his talk he went several steps further to discuss double knockouts of the insulin-like growth factor and the insulin receptor on beta-cells and of insulin receptors on beta-cells and the liver.

Ranganath Muniyappa (Diabetes Unit, NCCAM, NIH) spoke about the connections between endothelial dysfunction and the metabolic syndrome (insulin resistance). He and his colleagues Michael Quon and Monica Montagnani have studied how insulin stimulates production of the vasodilator NO and how this effect of insulin is selectively impaired in insulin resistance. Muniyappa reported on work in progress to extend the Quon model of insulin signaling to include the effects on NO. MBI postdoc Partha Srinivasan met Muniyappa at the workshop and has begun to work with him on a mathematical model of NO production and its effects.

Insulin affects plasma fatty acid levels as well as glucose by its actions to suppress lipolysis in fat cells. Vipul Periwal (Laboratory of Biological Modeling NIDDK, NIH) discussed an extension of the Bergman minimal model (see Dalla Man,

Toffolo, Day 3) to include these effects and to derive an index of insulin effectiveness in suppressing lipolysis. Bayesian analysis was used to choose among a family of models, with preference indicated for one in which insulin acts on lipolysis in a separate compartment from its effect on glucose.

In addition to its effects in the periphery, largely fat and muscle, insulin has important roles in the hypothalamus, where it is involved in feeding behavior and in the counter-regulatory response to hypoglycemia. Glucose-sensing neurons have important similarities with beta-cells, such as KATP channels and their use of glucokinase rather than hexokinase as the initial and rate-limiting step in glycolysis. Vanessa Routh (New Jersey Medical School) spoke about the integration of glucose and insulin signals in hypothalamic neurons.

Merrimack Pharmaceuticals stands out among biotech companies in that it integrates data collection, data analysis, and modeling in house as well as in collaboration with a major academic lab, run by company co-founder Peter Sorger at MIT. Jonathan Fitzgerald (Network Biology, Merrimack Pharmaceuticals) gave a presentation about some of their modeling efforts on insulin growth factor (IGF) signaling, which shares many downstream components with insulin signaling, and supports the company's initiatives in cancer biology. He illustrated lessons from simple modules within the pathway of interest, emphasizing that such modeling is a "journey, not an endpoint" – with patience and time, the lessons learned from the model building process will hopefully pay off in commercial products.

Michael Blinov (Center for Cell Analysis and Modeling, University of Connecticut Health Center) described the BioNetGen software that he helped develop while at the Los Alamos National Laboratory and continues to develop in his current position. The software automatically generates a set of reactions from a set of canonical rules, with carefully chosen assumptions to limit the combinatoric explosion of variables.

Conclusion

"...this is an ubiquitous theme in all of biology because life must always struggle to maintain a balance between stability in the face of environmental fluctuations and adaptability to secular environmental changes."

The goal of the conference was to "prime the pump" to stimulate more mathematical modeling applied to the study of diabetes, opening up the minds of experimentalists and clinicians to the possibilities of modeling, and bringing new mathematical talent into the field. We consider the meeting a success as a start in this direction. Many of the leading experimentalists came to the meeting and indicated that they both enjoyed the interactions and were eager to collaborate with modelers. A number of specific plans were made for collaboration between experimentalists and mathematicians, both the MBI fellows and the invited guests. It was also apparent from the discussions that much progress was made in overcoming the language barriers that exist between the experimentalists and the mathematicians. There was also noticeable interest among the biologists in learning to do some modeling themselves, as evidenced by their attention to the software demonstrations at the end of the meeting. Such efforts will not, in our view, replace the broader analytical power brought by specialists in theory, but can lead to genuine results and enhance appreciation for what mathematics can do.

Many young scientists were involved, which was gratifying, and these individuals had the opportunity to be mentored, leading to at least one job offer, to Junghyo Jo, a new physics Ph. D. from Korea. Most of the participants were able to present at least a poster to the group. In addition, two MBI postdocs (Partha Srinivasan and Paula Grajdeanu) have begun research projects with workshop speakers.

What can Math do for Diabetes? What can Diabetes do for Math?

Historically, research into the types of dynamical systems featured at this meeting has been critical for the development of the mathematics of oscillations, especially bursting oscillations, for which there is now a well-developed general theory that transcends the particular systems that launched the field. Future development in this area is likely to call upon better ways to parameterize particular systems, combining dynamics with statistics. Participant Andrea Mari made a plea for more robust software to obtain clinically useful fits of models to whole-body data; current state of the art programs are still not up to the job.

Workshops

Diabetes is a good focus for mathematical biology both because it is a growing threat to the health of the nation and the world, and because it is by nature a disorder of systemic integration, involving many sub-systems (organs, tissues, cell types). This was evident at the meeting in the juxtaposition of models at many space scales (cell to organism) and time scales (milliseconds to decades). There was considerable discussion of how to integrate the models developed for one scale or the other.

One possible unifying thread that was identified was the observation that often the same molecules are involved in both acute and chronic responses. For example cAMP (Tengholm, Peercy) is involved both in the rapid potentiation of insulin secretion on time scales of seconds to minutes and the maintenance of beta-cell health and mass over months to years. The newest generation of diabetes drugs attempts to address both of these aspects, though human clinical experience is too recent and thus too scant to draw a conclusion as to long-term effects. Similar points could be made about the endoplasmic reticulum (Johnson) and the mitochondria (Shirihai) as actors in both fast timescale calcium handling and slow timescale integration of pro- and anti-apoptotic stress responses.

Even more broadly, this is an ubiquitous theme in all of biology, because life must always struggle to maintain a balance between stability in the face of environmental fluctuations and adaptability to secular environmental changes. Attacking such questions in many particular contexts has great potential to be the source of a theoretical biology that can emulate older disciplines such as theoretical physics in arriving at large universal truths.

Special/Curriculum Workshop: Over the Fence: Mathematicians and Biologists Talk About Bridging the Curricular Divide, June 1-2, 2007

Organizers: Linda Allen, Department of Mathematics and Statistics, Texas Tech University; Steve Deckelman, Department of Mathematics, Statistics and Computer Science, University of Wisconsin-Stout; Libby Marschall, Department of Evolution, Ecology, and Organismal Biology, Ohio State University; and Jennifer Galovich, Department of Mathematics, St. John's University (Committee Chair)

Introduction

The purpose of the conference was to bring together mathematics and biology educators who have developed successful biology-in-mathematics curricula with those who wish to develop such programs. The major goals of the conference were:

- Understand how to incorporate applications of and connections with biology into the undergraduate mathematics curriculum, and conversely.
- Understand how to accomplish this in different types of institutions, from small liberal arts colleges to large research universities. We tried to address opportunities for and benefits of, as well as barriers and impediments to, cross-disciplinary curriculum development in each of these types of institutions.
- Stimulate creation and revision of curricula that integrate mathematics and biology, the results of which will be published in MBI conference proceedings.
- Initiate and foster a continuing learning community.

The list of participants included 62 names, of which 19 were MBI fellows or visitors. Generally, there were about 40 - 50 in attendance at most of the presentations. Of the 43 non-MBI participants, 20 self-identified as members of departments of biology; of those 43, 14 were women. Since most of the MBI fellows did not attend, that means that close to half the audience were biologists –one of our goals! We had one participant from a community college, four from government or industry (including two from the Mayo Clinic), and a dozen or so from liberal arts colleges. The balance represented comprehensive universities of various sizes, or large universities. Although this group was not as

diverse in this way as we had hoped, it was still a pretty good balance. Also we intentionally invited 6 – 8 colleagues from historically black colleges and universities, however only two where able to attend. In the future, we should try to have more participants from community colleges and from HCBUs.

Our intent was that the plenary speakers and panelists would, as a whole, address the following concerns:

- Who should teach these courses? Mathematical biologists or biological mathematicians?
- Developing mathematics projects for biology students and biology projects for mathematics students.
- Presentation of models of successfully instituted biology-in-mathematics and mathematics-in-biology programs.
- Issues related to professional collaboration: What opportunities are available? What kind of "cross-training" is needed and how can one do it? How can we overcome communication, modes of inquiry and pedagogical differences?
- The politics of curriculum change.
- What are some strategies for incorporating biology applications into mathematics courses that have multiple audiences, e.g., calculus or introductory statistics?
- How do we respond to the issues raised in both the biology and mathematics communities by the appearance of the Bio 2010 report?
- From the biologists' perspective, what is the role and future impact of mathematics in the biology curriculum? And where in the curriculum?
- What software packages are available to support collaborative work?

We believe that most of these topics were addressed, if not formally, then in the very active and vocal plenary discussion sessions and coffee breaks.

Day 1

Claudia Neuhauser (mathematician/biologist) began by describing the program at the University of Minnesota, emphasizing the data-driven nature of biology (unlike mathematics) and the particular challenges that presents. She also discussed the various ways in which mathematics, statistics, and computation may be integrated directly into biology courses. Following Dr. Neuhauser's talk we had presentations and discussion from a panel representing three very different programs for undergraduate mathematics and biology collaboration.

Azmy Ackleh (mathematician), Jacoby Carter (ecologist) and Susan Mopper (biologist) told us about their UBM program at University of Louisiana at Lafayette, where students first do a project directed by Dr. Carter, using mark and recapture techniques to obtain population estimates of frogs in four ponds located at the USGS National Wetlands Research Center. Under the direction of Dr. Ackleh, students develop a structured population model which describes the dynamics of the frog populations in these ponds. During the second year of the two-year program, students are engaged with Dr. Mopper in a project whose goal is to understand the dynamics of native and invasive Louisiana Iris populations by conducting field studies and applying mathematical modeling techniques. In addition to these research opportunities, two new courses and two new seminars were developed to support the program.

Raina Robeva (mathematician) and Robin Davies (biologist) discussed their collaboration with colleagues at the University of Virginia and Sweet Briar College to develop undergraduate research opportunities, curriculum and a textbook in biomathematics, with a special focus on questions related to human health. Finally, Chris Leary (mathematician) and Gregg Hartvigsen (biologist), presented the Biomathematics Career Initiative at SUNY Geneseo where students from both mathematics and biology work together to model biological questions using mathematical tools, especially DNA hybridization technologies and ecological and epidemiological systems. A feature of this program is the plan to include students as early in their undergraduate careers as possible. This project has also entailed development of new courses and seminars.

After lunch, John Jungck (biologist) discussed issues of cross-disciplinary collaboration from the biologist's point of view, He reported on recent successes, many engineered by the BioQUEST Curriculum Consortium of which he is the PI, and the

challenges that face us ahead. Ethel Stanley (biologist), Director of BoQUEST, followed with a presentation of various resources, such as the BEDROCK problem-space collection and some intriguing reflections of her own on desiderata in biology education (field investigation, open-ended questions, appreciation for complex contexts).

The day ended with a vigorous discussion of a variety of issues, particularly the (disputed) need for calculus (vs. statistics) in the biology curriculum.

Day 2

We began early with Tim Comar (mathematician) following up on Ethel's presentation with a description of his BioCalculus sequence, supported by laboratory projects using software tools such as Excel, Stella, and Matlab. Lou Gross (mathematician/biologist) treated us to a thought- (and argument-) provoking description of a general biology course that encompasses mathematical and statistical tools. A recurring theme was the importance of actual data early on in such a course. Dr. Gross's presentation was followed by a panel discussion anchored by presenters with quite different perspectives on curriculum development. Joe Mahaffy (mathematician) discussed his calculus course at San Diego State which makes heavy use of Java Applets and other software, and is web available. Mike Martin represented the community college perspective and discussed the curriculum development, pedagogical and political problems unique to that environment. Finally Eric Klee and George Vasmatzis (engineers) described their Bioinformatics research at Mayo, to illustrate the kinds of skills -- mathematical, biological and communication -- that students will need, especially in a government or industrial setting. After lunch, Fred Adler (mathematician/biologist) described his Urban Ecology course as a model for broad interdisciplinary teaching. Significant discussion about the role of mathematics in this course ensued. Finally, Barry Robson (physician) from IBM followed up on Lou's earlier remarks about mathematical prerequisites of medical schools from a medical educator's point of view. Robson discussed the emerging need for Evidence Based Medicine and the variety of discrete mathematical tools that will be useful for that project.

> "A feature of this program is the plan to include students as early in their undergraduate careers as possible. This project has also entailed development of new courses and seminars."

The workshop ended with a lively discussion of "Where do we go from here?" The participants had many suggestions, ranging from an on-line journal to a Wiki site. The organizers agreed to summarize those suggestions and send them to the participants for further discussion and identification of action items. All agreed that a regular meeting at the MBI for discussion of undergraduate biomathematics education was very much in order!

Workshop 8: The Auditory System, June 25-28, 2007

Organizers: David Mountain, Department of Biomedical Engineering, Boston University; and James Sneyd, Department of Mathematics, University of Auckland, New Zealand

Introduction

The human auditory system from the inner ear to the auditory cortex is a complex multilevel pathway of sound information processing. One of the early stages of sound processing occurs in the cochlea, where the vibration pattern of the basilar membrane encodes the frequency and amplitude of incoming sound signals. Though well-known partial differential equations (PDEs) in classical mechanics provide a solid foundation for describing these mechanical activities, additional nonlinearities must be modeled to capture responses such as two-tone suppression and the observed level-dependent frequency selectivity. The workshop aimed to explore the mathematical models of the ear at a number of different levels, ranging from PDE models of the mechanics of the basilar membrane, to biophysical models of the outer hair cells, to signal processing applications in industry and health sciences.

Summary of Talks

The workshop began with an overview of auditory anatomy and physiology given by David Mountain followed by a presentation by Egbert de Boer on how to model waves in the cochlea. He described two types of fluid waves, compression waves, and surface waves. He further divided the waves into long and short waves; the region of the strongest response is that where short waves prevail. In theories of cochlear mechanics an amplification mechanism has been conceived which enhances the response and increases the sharpness of tuning. The same mechanism, being of physiological origin and thus extremely vulnerable, is also the (main) site of cochlear nonlinearity. A model of the cochlea that includes these types of waves and the physiological amplification mechanism can quantitatively replicate many of the linear and nonlinear phenomena that the real cochlea exhibits.

Robert M. Raphael discussed a computational model of ion transport in the inner ear. His model showed that transport of potassium by a network of transport protein from the stria vascularis into the endolymph generates a large positive endocochlear potential required for the normal function of the ear. He described an expanded model that can predict the results of altering expression levels of distinct ion transporters and channels, and can thus be used to understand the effects of gene mutations and drug interactions. Charles Steele described a computational approach to 3-dimensional fluid and elastic waves in the cochlea based on combining asymptotic and numerical methods. The computational results, which require little computer power, are in reasonable agreement with measurements.

The form and amplification of cochlear traveling waves are determined by quantities known as propagation and gain functions. The properties of these functions, and their variation along the length of the cochlea, are central to an understanding of cochlear mechanics. Christopher Shera outlined a method for deriving propagation and gain functions from estimates of basilar-membrane (BM) mechanical transfer functions. He then applied the method to derive and interpret propagation and gain functions throughout the cochlea. He concluded that cochlear amplification played and important role throughout the cochlea.

Jont Allen's talk dealt with the question of the cochlear amplifier. Understanding of the mechanism can be gained by consideration of power flux in an inhomogeneous transmission line (TL). However there is a lack of agreement on the TL's characteristic impedance. He analyzed the two commonly accepted ways to define the impedance, and showed how they can relate to one another.

Richard Chadwick talked about the whispering gallery effect in the mammalian cochlea which not only helps acoustic energy reach the apex of the cochlea, but also induces a radial pressure gradient that increases toward the outer wall. The resulting asymmetric loading of the cochlear partition boosts the sensitivity to low frequency sounds. The mathematics and physics of the effect are explained using wave propagation and wave tracing approaches. Marcel van der Heijden asked whether cochlear traveling waves are genuine waves, or whether they may be thought of as fluctuations described by group velocity. In a joint

work with Philip X. Joris he analyzed these fluctuations and the corresponding group delay along the cochlea.

Elizabeth Olson described experimental results for passive substrate for active cochlear tuning. The first example she cited was that Stapes vibration launches a traveling wave down the cochlear spiral. The traveling wave and peaking occur in both healthy (active) and dead (passive) cochleae. However, in an active cochlea, at locations where in a passive cochlea the traveling wave exhibits a broadly tuned peak, the wave instead continues to grow and attains a relatively sharp and much higher peak a short distance apical of the passive peak place. As she noted, the physical basis for even these very basic observations of cochlear tuning remains uncertain.

Karl Grosh's talk was concerned with electromotility and electrical conduction in the cochlea. He hypothesized that the cells and structures of the organ of Corti to act in an electromechanical feedback system boosting the mechanical response of cochlea, such as the basilar membrane, to low-level acoustic input. Based on this hypothesis he developed a physiological model which predicts key aspects of the electromechanical cochlear response to both acoustical and electrical stimulation. The model explicitly couples mechanical, electrical, and fluidic domains, including a piezoelectric model of the OHC soma. A method for including hair bundle motility was also presented. Outer hair cells are critical to the amplification and sharp frequency selectivity of the mammalian cochlea. Outer hair cell has a unique form of motility (electromotility) driven by changes in the cell's transmembrane potential. The major features of the electromotile cell are length changes, active force production, and electric charge transfer. Alexander A. Spector discussed the modeling of these three interrelated phenomena at the molecular, cellular, and organ levels with a particular focus on high-frequency conditions. He presented a mathematical model describing the transfer of an electric charge across a portion of the membrane and showed how the outer hair cell can overcome the mechanical and electrical high-frequency filtering in the cochlear environment to produce an active force significant to the cochlear amplification.

The next few talks dealt with auditory processing. Li Deng talked about the role of auditory processing in computer speech recognition. He described a statistical model for the human speech which embeds a richer structure than the Hidden Markov Model (HMM) currently used. One main challenge is the computationally intractable inference for decoding with confidence measure on the posterior probability of the hidden states. He suggested that variational techniques developed for a general Bayesian network can be used as an efficient approximate algorithm for decoding.

James M. Harte talked about models he developed on the role of compression in the auditory system. The models, although simple and phenomenological, produce level curves that are similar to those measured on the mechanical response of the basilinear membrane.

Auditory pathway from sound to perception is a multi-level information processing system. It is often modeled as a transform with uniform and fine frequency resolution at low frequencies, yet nonuniform and coarse frequency resolution towards higher frequencies. Such a transform can be built using the discrete Fourier transform with characteristics derived from auditory experiments. This auditory transform is invertible perceptually. Inversion from perception to sounds is non-unique and involves optimization. Jack Xin described a frequency and a time domain method to address the inversion problem.

Johan Frijns and Robert Shannon talked about recent progress in cochlear implants. Frijns explain how his group has been developing electro-anatomical models of the cochlea and how these models can be used to predict the responses of auditory nerve fibers stimulation from cochlear implants. He then presented examples of how these models are used in a clinical setting. Shannon showed data illustrating the steady increase in cochlear implant patient performance over the years as the technology has improved and then went on to discuss differences in performance between patients with cochlear implants and with brainstem implants. His work with brainstem implants has led him to hypothesize that there may be pathway originating in

the cochlear nucleus that specialized for processing amplitude modulation and that this pathway plays a crucial role in speech perception.

The workshop presentations included also talks on the role of hair bundle motility, hair cell somatic motility, and signal processing in auditory cortex.

Conclusion

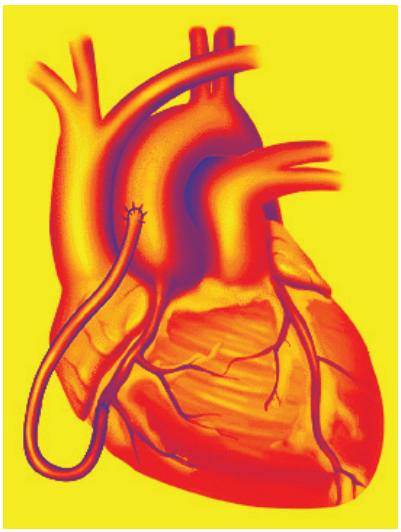
The workshop participants agreed that although much progress has been made, many questions remain to be answered. In the area of cochlear modeling questions remain such as how best to deal with the multi-scale and multi-physics nature of the cochlea. Models of hair cell function that involve state changes in ion channels and motor molecules must be integrated with large scale models of ion flow, solid mechanics and fluid mechanics. New experimental methods are needed to characterize the nonlinear nature of cochlear responses and to estimate the parameters needed for the computational models and very fundamental questions such as how are the inner hair cells stimulated unanswered.

"Many questions remain related to the problem of determining which statistical features in speech and in music acoustic waveforms are used by the human brain to decode these culturally important signals. Workshop participants agreed that mathematical techniques such as nonlinear systems theory and group theory will play an important role in this effort."

In the area of central auditory processing, the relative roles of envelop processing and fine-structure processing are still not well understood. Many questions remain related to the problem of determining which statistical features in speech and in music acoustic waveforms are used by the human brain to decode these culturally important signals. New experimental techniques are needed to study these high level questions such as better stimuli as well as corresponding analysis methods. Workshop participants agreed that mathematical techniques such as nonlinear systems theory and group theory will play an important role in this effort.

In the long run, efforts to answer these basic science questions will help advance the development of better hearing aids and cochlear implants and may also lead to advances in other areas such as automatic speech recognition.

Tutorials



Tutorial on the Heart, September 18-20, 2006

Organizers: Jim Keener (Mathematics Department, University of Utah) and Raimond Winslow (Institute for Computational Medicine Center for Cardiovascular Bioinformatics and Modeling & The Whitaker Biomedical Engineering Institute Johns Hopkins University School of Medicine and Whiting School of Engineering)

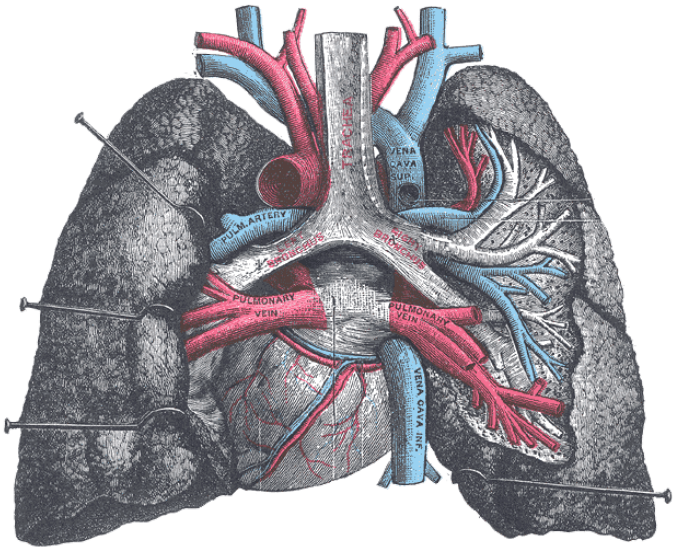
The tutorials described cells' basic concepts including cell membrane, ion channels, cell nucleus, and went on to describe the three types of cells the heart possesses: pacemaker cells, conductive cells, and myocytes. Subsequent talks included the topics of action potential and the ECG, conduction system of the heart, excitable media, modeling membrane electrical activity, ionic currents and action potential, the Hodgkin-Huxley equation, calcium dynamics, ryodine receptor, the cable equation, modeling cardiac tissue and the biodomain model, spiral waves, cardiac scroll waves, and ventricular fibrillation.

Another series of talks included anatomy and physiology of the heart, models of cardiac electromechanics, the cardiac cycle, the physiological basis of Starling's law, the sarcomere in skeletal muscle, cellular cardiac mechanics, and ventricular geometry.

Tutorial on the Lung, October 18, 2006

Organizer: Jason Bates (Vermont Lung Center University of Vermont College of Medicine)

Lung mechanics embody the dynamic relationships between pressure, flow, and volume in the lung. The ultimate goal is to link lung mechanical function to lung structure. This requires a mathematical model of lung mechanics. To assess lung mechanics, we need to measure pressure, flow, and volume of gas. Clinical tests of lung function are mostly based on forced expired flow and body plethysmography.



The basic model of lung mechanics is the single-compartment linear model. The static behavior of this model over the vital capacity range is described by the pressure-volume curve. The dynamic behavior model is accounted for by resistance (R) and elastance (E). The single-compartment linear model may be made nonlinear by making R depend on flow or E depend on volume R and E increase during bronchoconstriction; R and E depend on frequency. Lund resistance and elastance depend on frequency; Impedance is a complex quantity that characterizes mechanical behavior over a range of frequency. The constant phase model describes the impedance of normal lung tissue accurately.

In the final part of the tutorial, a mouse model of acute respiratory distress syndrome was described.

Tutorial on Microcirculation, January 19, 2007

Organizer: Tim Secomb (Department of Physiology, University of Arizona)

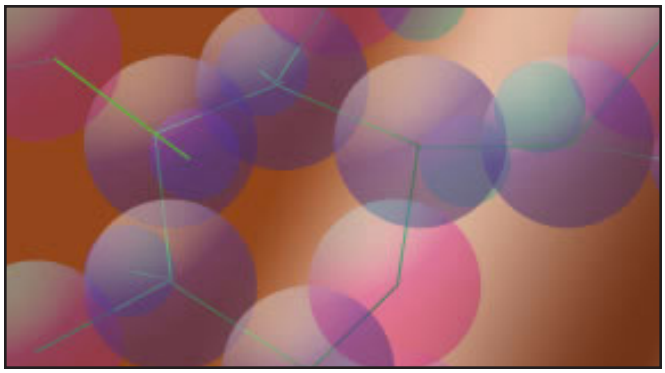
The function of the circulatory system is to transport materials throughout the body. Blood flows through an extensive branching network of tubes, driven by the pumping action of the heart. Transport of oxygen from the lungs to other parts of the body is a crucial task of the circulatory system.

The circulatory system is a dynamic structure. Blood vessels grow or regress during development and in a variety of normal and disease states, over time scales of hours, days and longer. Under normal conditions, these structural changes ensure that all parts of the tissue are supplied with blood, and that the network structure is well organized and efficient with regard both to the volume of blood needed and the energy required to drive the flow. In the arteries and arterioles, the relationship between blood flow rate and vessel diameter is found experimentally to be approximately cubic on average.

The circulatory system is capable of rapidly controlling blood flow, on time scales of seconds, minutes and longer, by active contraction and dilation of smooth muscle cells in vessel walls, particularly in the arterioles. This allows localized short-term flow regulation in response to changing conditions and tissue needs.

Tutorial on Cellular and Organism Models for Glucose Homeostasis and Diabetes, May 18, 2007

Organizers: Richard Bertram (Department of Mathematics, Florida State University) and Arthur Sherman (N.I.H.-N.I.D.D.K.-M.R.B.)



This tutorial reviewed the biological background on insulin secretion and insulin action and their relation to Type 2 Diabetes, highlighting past successes and current issues. Models for electrical activity of pancreatic beta-cells (ion channels/calcium stores/metabolism), insulin signaling (receptor kinetics/signaling cascades), and whole-body glucose homeostasis (compartmental models/diagnostic tools for beta-cell function and insulin resistance) were discussed.

Summer Programs

Summer Program in Mathematical Biology for Undergraduates, July 9-20, 2007

The summer of 2007 marked the MBI's second annual summer program for undergraduates which included a two-week active survey of mathematical biology followed by a six-week Research Experience for Undergraduates (REU) program.

The first week of the program involved tutorials and hands-on computer labs in mathematical bioscience topics. The first day saw **David Terman** leading a tutorial on the principles of mathematical neuroscience while **Robert McDougal** gave participants experience with the XPP program in the afternoon computer lab. On Tuesday, **Dennis Pearl** presented key issues in statistical phylogenetics – aligning molecular sequences and inferring evolutionary trees. In the afternoon, **Jeff Pan** led the computer lab, giving students a chance to try out the Clustal alignment program along with **Phylip** and **MrBayes** phylogenetics software. **Kate Calder** presented a lively tutorial on environmental statistics the following day while **Candace Berrett** led the afternoon computer lab using the R statistical package. On Thursday **Greg Singer** covered selected topics in bioinformatics and had the students trying out some web-based bioinformatics software in the computer lab that afternoon. The week concluded with **Joe Verducci** and **Paul Blower** presenting morning lectures on issues in the quantitative analysis of chemogenomic and pharmacogenomic data, while **Li Yu** supervised the afternoon computer lab using the R package.

Dividing into teams, the first four days of the second week gave the students a chance to study a real problem in their chosen topic area. The two-week survey concluded with each of five teams participating in a mini-conference, making both poster and oral presentations on their projects. The mathematical neuroscience team (Einat Bergman and Jonathan Bonchak) presented their studies of the mechanisms underlying the beneficial affects of deep brain stimulation, a surgical treatment for patients with Parkinson's disease. The phylogenetics project team (Oana Carja and Stephen Swihart) presented an analysis of the evolution of the bird flu virus and testing its relation to geography, time, and host population. Next, the environmental statistics group (John Christensen and Jimin Ha) described their study of ice core-derived records of precipitation accumulation across Greenland to examine historical patterns in the North Atlantic Oscillation, a climatic phenomenon that influences inter-annual climate variability over large portions of Europe and North America. The bioinformatics project, presented by Nikko Demerite, explored database techniques to find human genes that are not present in other mammalian genomes with an eye toward attempting to characterize these human-specific genes. Finally, the chemogenomics team of Felicia Gibson and Eric Wohleb examined correlational methods to relate mRNA expression to drug activity over the NCI-60 panel of cancer cell lines. The collaborative nature of all of these efforts was illustrated as each student presented a substantial part of their group's work.

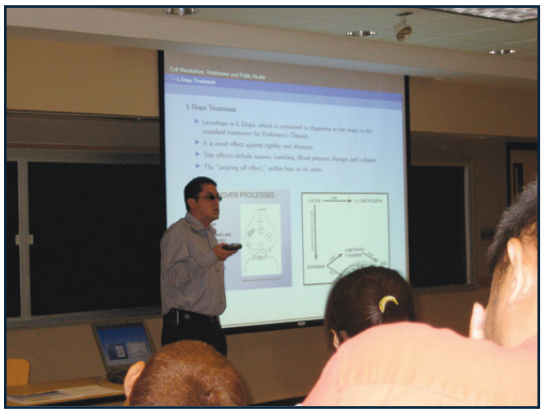
During this two-week program, the students also toured labs that use quantitative methods in the biological and medical sciences. This included tours of the labs of neuroscientist Joe Travers who studies how neuronal circuitry processes sensory information, and the epigenetics lab of Pearlly Yan in the Center for Integrative Cancer Biology (CICB). John Wenzel gave the group a tour of Ohio State's Museum of Biological Diversity with its major acarology and plant (more that a half million specimens each), insect (over 3.5 million specimens), fish (1.5 million specimens), and mollusk (150,000 specimens) collections that are available for both teaching and research. MBI Associate Director Libby Marschall and her team of graduate students showed off their work on the many projects in the Aquatic Ecology Laboratory. In the fifth tour, students traveled to Ohio State's Wetlands Research Park to view the work of Bill Mitsch's research group in understanding how wetlands function and how they can be created or restored.

At the conclusion of the two-week program, the REU component of the summer program then chose four students to spend six weeks going into much more depth in a research project in their chosen area. This work was highlighted in a second mini-conference on the last day of the program. To start the mini-conference, Einat Bergman presented her work in modeling the thalamic response to multiple inhibitory signals from the basal ganglia combined with an external stimulatory signal. By adding increased realistic assumptions, including stochasticity to the input signals, she used simulation techniques to demonstrate how the system produces output signals congruent with specific phenomena seen in either normal subjects or in those with Parkinson's disease.

Next Stephen Swihart presented his work studying the phylogenetics of the West Nile virus showing a clear evolutionary separation of the viruses in different host species and between human sequences from different continents. He also presented results on a novel method for examining the statistical issue of leverage (the influence of a single data point on the estimated model) in phylogenetics. John Christensen then presented his analyses of satellite remote sensing data from two measurement systems used in climate and vegetation research, MODIS and MISR. Focusing on data from southeast Asia, he showed that the two systems were generally well calibrated but found a number of factors that explained important differences including the effect of the rainy season. Finally, Eric Wohleb presented his reanalysis of chemogenomic data from several research studies. He demonstrated how a simple correlational method based on Kendall's tau statistic gave new insights not seen in the original publications.

All of the students taking part in the MBI undergraduate summer program were exposed to new areas of scholarship and appeared to gain an increased appreciation for the mathematical biosciences. The PowerPoint presentations from both the tutorials and mini-conferences are viewable on the MBI web site.

Summer Program in Systems Physiology, July 23 - August 10, 2007



A total of 21 graduate students participated in the program; they came from departments of mathematics, statistics, biology, and physics.

The first week of the program featured daily tutorial lectures by **James Keener** (9:00am-Noon) on introduction to cells and systems physiology. The topics included enzyme dynamics, the structure of cells, ion channels, biochemical reaction networks, calcium signaling, cell regulatory processes, excitable media, intracellular and intercellular communication, cell muscle, heart rhythm and classification of waves.

Each afternoon **Chiu-Yen Kao** gave a two-hour tutorial on computational methods for solving ODEs and PDEs.

At the end of the week the students were divided into six teams, each headed by an MBI postdoc or a long-term visitor. During the subsequent two weeks, each team worked on one project and then, on the last two days of the program, each team gave an hour long report on their results; each student made an oral presentation:

Miniconference: Group Project Reports, August 9-10, 2007

Project 1: Collagen Fiber Formation in Dermal Wound Healing
Project Leader: Richard Schugart
Participants: Richard Gejji, Humberto Perez-Gonzalez, and Ying Wang

Project 2: Modeling the Mechanical Interactions Between Cells and Biological Gels
Project Leader: Ed Green
Participants: Genevieve Brown, Ozge Ozcakir, Hyejin Park, and Zeynep Teymerglu

Project 3: TB Vaccine Strategies
Project Leader: Barbara Szomolay
Participants: Sungwoo Ahn, Aaron Brown, and Robert McDougal

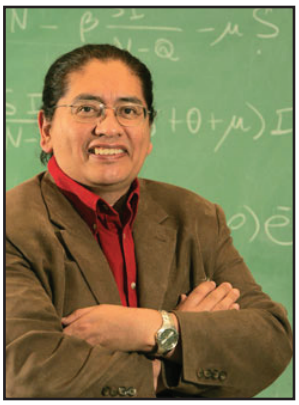
Project 4: Creating and Analyzing a Modular Model of Apoptosis
Project Leaders: Baltazar Aguda and Chiu-Yen Kao
Participants: Semik Ghosh, Heather Harrington, Ken Ho, and K.C. Tung

Project 5: Mathematics of Cell Metabolism and Public Health
Project Leader: Paula Grajdeanu
Participants: Han Han, James Sharpnack, and David Tello

Project 6: Modeling the Control of Solid Tumor Growth by Cytotoxic T-lymphocytes
Project Leader: Anastasios Matzavinos
Participants: Sayanti Banerjee, Badal Joshi, Haiyan Tian, and Xueying Wang

Public Lectures

Carlos Castillo-Chavez, Regents and Joaquin Bustoz Jr. Professor of Mathematics, Arizona State University; September 26, 2006
Title: Emergent Disease and the Challenges of Globalization



Our world is composed by a multitude of diverse communities tightly linked by economic interests and various associated factors typically collected in the word, globalization.

Mass and air transportation, immigration, and the integration of large heterogeneous economic communities (European Community, NAFTA, MercoSur, etc.) have dramatically altered the world. These "forces" have transformed the local and global, social and environmental landscapes where we live in today, and their impact is likely to grow.

In this lecture, Carlos addressed some of the challenges that we face in this new world order, particularly when dealing with global health challenges and public health policy. He illustrated some of these issues using recent and current experiences with tuberculosis, influenza, HIV, and drug use (alcohol and ecstasy).

Jim Keener, Departments of Mathematics and Bioengineering, University of Utah; October 3, 2006
Title: Heart Attacks can give you Mathematics

Heart attacks kill hundreds of people daily in the United States - many more than are killed by math anxiety!

A heart attack occurs when there is an occlusion of a coronary artery, leading to tissue damage. A heart attack is fatal when there is a subsequent disruption of the normal electrical signal of the heart, leading to fibrillation. There is very little understanding of why this occurs, and there are essentially no reliable predictors for the onset of fibrillation.

In this talk, Jim gave an overview of some of the ways that mathematics can help our understanding of cardiac arrhythmias, how they occur, what they are, and how they might be eliminated or prevented. The main emphasis was how mathematics can be used to give us insight and understanding that can not be obtained by other (non-mathematical) means.

Peter Macklem, Meakins-Christie Laboratories, McGill University; November 3, 2006
Title: A Physician's View of Complexity, the Origins of Order, Health and Disease

Two relatively unexplored features characterize physiologic systems: 1) They are complex, non-linear and dynamic which results in emergent phenomena that can neither be predicted nor explained by examining their component parts in isolation; 2) they become highly ordered during fetal development and throughout the course of Darwinian evolution in apparent violation of the second law of thermodynamics. It follows that interconnections among the parts must play a role in emergent phenomena and the origin of order. How this is accomplished through the nature and number of interconnections has been explored by Kauffman (1). Explanation of increasing order in spite of the second law was achieved by Prigogine (2) who showed that order can spontaneously appear in systems close to thermodynamic equilibrium if they are made to dissipate energy which increases order by displacing them far from equilibrium and decreasing entropy production rate. The approaches of Kauffman and Prigogine have not been combined or reconciled and this needs to be done in order to have a more complete understanding of health and how it breaks down in disease. If energy dissipation in a system is too little or too much and/or if the nature or number of a system's interconnections is altered malfunction results. Although how this occurs is rather obscure, fluctuations in time and space are

a common feature of complex systems. Many ways have been used to characterize these fluctuations but few have yet proven beneficial to medicine. Another common feature of complex systems is that, unlike many physical systems, the future can only be assessed by statistical probability. Physicians deal inadequately with uncertainty. Prognosis is part of the art of medicine and is the least scientific part of our profession. Yet the development of statistical mechanics to quantify probabilities in quantum mechanics has the potential of making prognosis more precise. Of the many ways to characterize fluctuations in complex systems, power laws are ubiquitous (3). They have powerful predictive properties; e.g., the Gutenberg Richter Law can predict the probability of an earthquake of any magnitude occurring over any region of the earth's surface over any given time interval with a high degree of certainty. Can power laws make prognosis quantitative? Although the future of physiology is uncertain, Peter predicted our understanding of health will depend on uncovering the secrets of energy-dissipating, interconnected complex biological systems. Precise knowledge of how abnormal interconnections and energy dissipation leads to dysfunction is essential in the understanding of disease and should lead to more precise prognostication.

1. S. Kauffman. The Origins of Order: Self-Organization and Selection in Evolution. New York: Oxford University Press, 1993.
2. I. Prigogine and I Stengers. Order Out of Chaos: Man's New Dialogue with Nature. New York: Bantm Books, 1984
3. P. Bak. How Nature Works: The Science of Self-Organized Criticality. New York: Springer-Verlag, 1996.

Jay Hoying, Arizona Research Laboratories, Regenerative Medicine/ BIO5 Institute, University of Arizona; January 23, 2007
Title: Tissue Engineering and Repair: A Vascular Problem

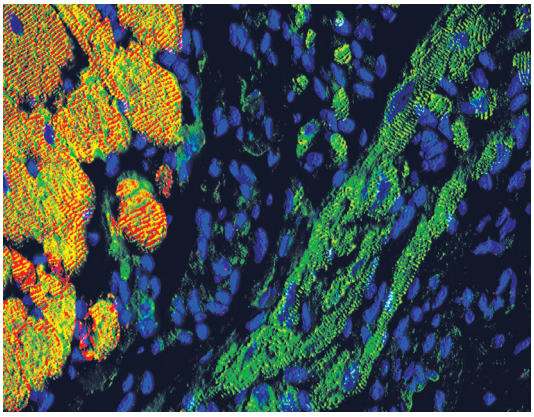
Tissue engineering and related cell-based therapies promise to not only facilitate tissue repair but also functionally replace damaged and diseased tissues. With tissue engineering, the goal is to fabricate tissue constructs, comprised of cells in a supportive environment, which mimic the function and/or architecture of the target tissue. The source of cells used in these constructs is the subject of considerable scientific discussion (and, in the case of stem cells, public discussion). However, regardless of the source and types of the cells incorporated into these engineered constructs, there remains a significant challenge in providing sufficient nutrients to the cells during fabrication and following implantation. Any tissue implant greater in dimension than a few millimeters is too big for nutrients to efficiently diffuse to the construct's cells from outside the construct. This is why the first successfully engineered tissues have been thin, sheets of cells (e.g. a simple skin). As advances give rise to more complicated, 3-dimensional tissue designs, the need for a strategy to support the health of these constructs becomes more urgent. In the body, the cardiovascular system serves to effectively deliver nutrients to any tissue. Therefore, the ability to form and incorporate blood vessels (particularly microvessels) into the constructs is critically important for construct health and function. Jay discussed the particular challenges related to providing proper nutrition to constructed tissues and the strategies being employed to build vessels and vessel networks in the laboratory.

Alan Perelson, Los Alamos National Laboratory; March 14, 2007
Title: HIV/AIDS: How Mathematics Has Saved Lives

Human immunodeficiency virus (HIV) causes AIDS but on a time scale that averages about 10 years. This suggested that HIV infection was a slow process and thus treatment could be delayed. Alan showed how using mathematical modeling to interpret changes in HIV level after drug therapy was initiated led to a revolution in thinking about HIV and formed the basis for combination therapy that has made HIV a treatable disease. During the lecture he discussed the basic biology of HIV, showed how mathematical analysis of clinical data uncovered many other features of HIV biology, gave an update on HIV vaccines and other unsolved problems in this field, and lastly showed how the lessons learned about HIV have been applied to improve the understanding and treatment of hepatitis C virus infection.

Future Programs

Mathematical Bioengineering
September 2007 – August 2008



Bioengineering lies at the interfaces of biology, the applied sciences and engineering. It combines the excitement of multi-disciplinary research with the promise of making improvements to society, especially in health care, e.g. in the diagnosis and treatments of degenerative diseases. However, it is a relatively new field that is still finding its way among the established engineering and biological disciplines. As a multi-discipline it presents particular problems for the seasoned researcher as much as for the new student: indeed, we are all new students when it comes to subfields in which we have not trained.

The 2007-2008 MBI Year in Mathematical Bioengineering will focus around six workshops on Metabolic Engineering, Cell and Tissue Engineering, Neuroengineering, Brain Imaging, and Neuromechanics, the latter being covered in two linked workshops. Tutorials will be offered to prepare participants, especially students and postdoctoral fellows interested in entering the field. While omitting large areas, these workshops provide examples of the central subject matter, and they highlight two key modes of operation of bioengineering: as a conduit for experimental methods, modeling and analytical tools from the physical sciences and mathematics into biology, and as a conduit for biological inspiration to the applied sciences and engineering, as in bio-inspired design of new devices and materials.

A common feature of the topics chosen, and indeed, of much of bioengineering, is their integrative nature. Biological systems are unavoidable complex, often containing many apparently redundant parts or pathways. In trying to understand, predict, control, change, or build such a complex system one must successfully reduce and combine a mass of detail. In this endeavor mathematical modeling and analysis offers a unifying language and set of principles that can draw together disparate ideas from genomics, molecular biology, neuroscience, biochemistry, physiology, imaging and signal processing (to name only topics germane to the six MBI workshops). Mathematics can also reveal common principles operating on different time and space scales, and guide the development of computational algorithms for simulation and data analysis.

Tutorials

Introduction to mathematical modeling in cellular physiology and neuroscience: October 1-4, 2007

Tutorial for Workshop 2: October 18-19, 2007

Tutorial for Workshop 3, Introductory orientation on comparative biomechanics of locomotion I: January 10-11, 2008

Tutorial for Workshop 4, Introductory orientation on comparative biomechanics of locomotion II: March 27-28, 2008

Tutorial for Workshop 5, Brain physiology related to movement control and epilepsy: May 8-9, 2008

Tutorial for Workshop 6, Mathematics of Brain Imaging: June 6, 2008

Workshops

Fall 2007 Workshop for Young Researchers in Mathematical Biology (WYRMB) September 11 - 14, 2007
Organizers: MBI postdocs

Metabolic Engineering: September 24-28, 2007
Organizers: John Doyle (Department of Electrical Engineering, California Institute of Technology), David Gang (Department of Plant Sciences, University of Arizona), and Michael Savageau (Department of Biomedical Engineering, University of California, Davis)

Cell and Tissue Engineering: October 22-24, 2007
Organizer: Melissa L. Knothe Tate (Lerner Research Institute, Department of Biomedical Engineering, The Cleveland Clinic) and Stanislav Shvartsman (Department of Chemical Engineering, Princeton University)

Microfluids: November 12-14, 2007
Organizer: Andre Levchenko (The Whitaker Institute for Biomedical Engineering, Johns Hopkins University)

Biomechanics and Neural Control - Muscle, Limb, and Brain: January 14-18, 2008
Organizers: Art Kuo (Department of Mechanical Engineering, Department of Biomedical Engineering, Institute of Gerontology, University of Michigan) and Lena Ting (Laboratory for Neuroengineering, Georgia Tech)

Neuromechanics of Locomotion: March 31 - April 4, 2008
Organizers: Ansgar Bueschges (Biology Department, University of Cologne), Robert J. Full (IBIBI-Integrative Biology, University of California, Berkeley), and Philip J. Holmes (Department of Mechanical and Aerospace Engineering, Princeton University)

Restoration of Movement Via Peripheral Nerve Stimulation: April 29, 2008
Organizer: Dawn Taylor

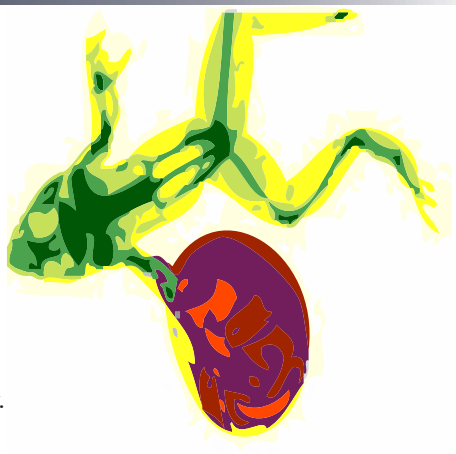
Real Time Brain Interfacing Applications: May 12-15, 2008
Organizers: Dawn Taylor (Department of Biomedical Engineering, Case Western Reserve University) and David Terman (Mathematical Biosciences Institute)

Brain Imaging: June 9-13, 2008
Organizers: Sylvain Bouix (Psychiatry Neuroimaging Laboratory, Brigham and Women's Hospital), Kaleem Siddiqi (Centre for Intelligent Machines, School of Computer Science, McGill University), Stefano Soatto (Department of Computer Science, University of California, Los Angeles), Allen Tannenbaum (School of Electrical and Computer Engineering, Georgia Institute of Technology)

Systems Biology of Decision Making: June 16-20, 2008
Organizers: Nigel Franks (Department of Biological Sciences, University of Bristol), Naomi Leonard (Department of Mechanical and Aerospace Engineering, Princeton University), Kevin Passino (Department of Electrical and Computer Engineering, Control Research Laboratory, The Ohio State University), Roger Ratcliff (Department of Psychology, The Ohio State University), Thomas Seeley (Department of Neurobiology & Behavior, Cornell University), and Thomas Waite (Department of Evolution, Ecology, and Organismal Biology)

Future Programs

Mathematical Challenges in Developmental Biology
September 2008 - August 2009



Growth, movement and differentiation of cells are three key processes involved in pattern formation and morphogenesis in developing systems. Pattern formation involves the expression of genes at the correct point in space at the correct time, and this in turn typically involves spatially- and temporally-varying signals, and mechanisms for signal transduction and activation or repression of gene expression. Gene expression during embryonic development is not a cell-autonomous process, because cell fate in a multicellular embryo usually depends on the cell's location. This fact led to the theory of positional information, which posits that a cell must 'know' its position relative to other cells in order to adopt the correct developmental pathway. Positional information is viewed as a necessary part of pattern formation. Frequently pattern formation results from the response of individual cells to a spatial pattern of chemicals called morphogens: molecules that move through a tissue by diffusion or other means, and regulate gene expression in a concentration-dependent manner. Morphogenesis refers to the processes that shape tissues, organs and organisms and necessarily involves both signaling and force generation for movement and cell rearrangement. While there are many variations on how the different processes are involved in different organisms, it is striking how conserved the basic processes are across the phyla. Also not surprisingly, these same processes are involved in various diseases such as cancer, and this unity and conservation of basic processes provides the rationale for studying various experimental model systems. This same unity and conservation also implies that mathematical models of the fundamental processes can have a wide-ranging impact across the spectrum of normal and pathological development.

In the last two decades much has been learned about the molecular components involved in signal transduction and gene expression in a number of systems, and the focus is now shifting to understanding how these components are integrated into networks, and how these networks transduce the inputs they receive and produce the desired pattern of gene expression. Several model systems, including Drosophila and limb development, will play a major role during the year. Development is a sequential process in which later stages build on earlier stages, but within stages there are often multiple feedback loops in signaling and gene control networks that may serve to buffer against perturbations caused by fluctuations in morphogen concentration and other components. This suggests two areas in which theoreticians can contribute: (i) the understanding of the relationship between network topology and functionality, and (ii) the development of computational tools for simulating growth, cell movement and differentiation in developing systems. The purpose of the year in Mathematical Challenges in Developmental Biology is to bring together theoreticians who have made significant contributions to various basic processes involved in development with experimentalists working on specific systems for which a quantitative approach has been or may be productive.

Tutorials

Tutorial on Cell Motility, Tissue Remodeling, and Signal Transductions

Tutorial on Cancer, Angiogenesis, and Wound Healing

Workshops

Cell and Tissue Movement: September 15-19, 2008
Organizers: Leah Edelstein-Keshet (Mathematics Department, University of British Columbia, Vancouver), Thomas Hillen (Department of Mathematical and Statistical Sciences, University of Alberta), and Stan Maree (Theoretical Biology/ Bioinformatics Group, Utrecht University)

Pattern Formation and Development in Colonial Organisma: October 13-17, 2008
Organizers: Philip Maini (Centre for Mathematical Biology, Mathematical Institute, University of Oxford) and Hans Othmer (School of Mathematics, University of Minnesota)

Morphogenesis, Limb Growth, Gastrulation, Somatogenesis, Neural Tube Formation: November 17-21, 2008
Organizers: Robert Dillon (Department of Mathematics, Washington State University) and Hans Othmer (School of Mathematics, University of Minnesota)

The API of Cancer: Angiogenesis, Progression, and Invasion: January 26-30, 2009
Organizers: Kristin R. Swanson (Department of Pathology, University of Washington) and Alexander Anderson (Department of Mathematics, University of Dundee)

Wound Healing: March 9-13, 2009
Organizers: Philip Maini (Centre for Mathematical Biology, Mathematical Institute, University of Oxford) and Chandan Sen (Departments of Surgery and Molecular and Cellular Biochemistry, The Ohio State University)

Neurosciences Issues in Early Development: April 27 – May 1, 2009
Organizers: Ken Miller (Molecular Biology, Cell Biology, and Biochemistry, Brown University) and Fred Wolf (Department of Nonlinear Dynamics, MPI für Strömungsforschung)

Drosophilia Development: June 8-12, 2009
Organizers: Michael Levine (Department of Molecular and Cell Biology, University of California, Berkeley) and Hans Othmer (School of Mathematics, University of Minnesota)

Publications

Technical Reports

Authors: Baltazar Aguda and Andrew B. Goryachev
Title: From pathways databases to network models
Date of Publication: September 2006

Authors: Abbas Khalili, Dustin Potter, Pearlly Yan, Lang Li, Joe Gray, Tim Huang, and Shili Lin
Title: Gamma-normal-gamma mixture model for detecting differentially methylated loci in three breast cancer cell lines
Date of Publication: September 2006

Authors: Linda J.S. Allen, Ben M. Bolker, Yuan Lou, and Andrew L. Nevai
Title: Asymptotic profiles of the steady states for an SIS epidemic patch model
Date of Publication: October 2006

Authors: Winfried Just and Andrew L. Nevai
Title: A Kolmogorov-type Competition Model with Multiple Coexistence States and its Applications to Plant Competition for Sunlight
Date of Publication: October 2006

Authors: Linda J.S. Allen, Ben M. Bolker, Yuan Lou, and Andrew Nevai
Title: Asymptotic profiles of the steady states for an SIS epidemic reaction-diffusion model
Date of Publication: January 2007

Authors: Yixin Guo, Jonathan E. Rubin, Cameron C. McIntyre, Jerrold L. Vitek, and David Terman
Title: Thalamocortical relay reliability varies across subthalamic nucleus deep brain stimulation protocols in a data-driven computational model
Date of Publication: April 2007

Authors: David Terman, Sungwoo Ahn, Xueying Wang, and Winfried Just
Title: Reducing neuronal networks to discrete dynamics
Date of Publication: April 2007

Author: Marko Djordjevic
Title: SELEX experiments: New prospects, applications and data analysis in inferring regulatory pathways
Date of Publication: May 2007

Authors: Marko Djordjevic, Ekaterina Semenova, Boris Shraiman, and Konstantin Severinov
Title: Quantitative analysis of a virulent bacteriophage transcription strategy
Date of Publication: May 2007

Authors: Marko Djordjevic and Anirvan M. Sengupta
Title: Quantitative modeling and data analysis of SELEX experiments
Date of Publication: May 2007

Authors: Anastasiya Sevostyanova, Marko Djordjevic, Konstantin Kuznedelov, Mikhail S. Gelfand, Konstantin Severinov, and Leonid Minakhin
Title: Transcription strategy of Thermus thermophilus bacteriophage YS40
Date of Publication: May 2007

MBI Newsletter

Autumn 2006, Volume 2, Issue 1
Winter 2007, Volume 2, Issue 2
Spring 2007, Volume 2, Issue 3

MBI Volumes

Friedman, A. (Ed.). (2007). *Tutorials in mathematical biosciences: Evolution and Ecology* (Vol. 4). Berlin, Heidelberg, New York: Springer-Verlag.