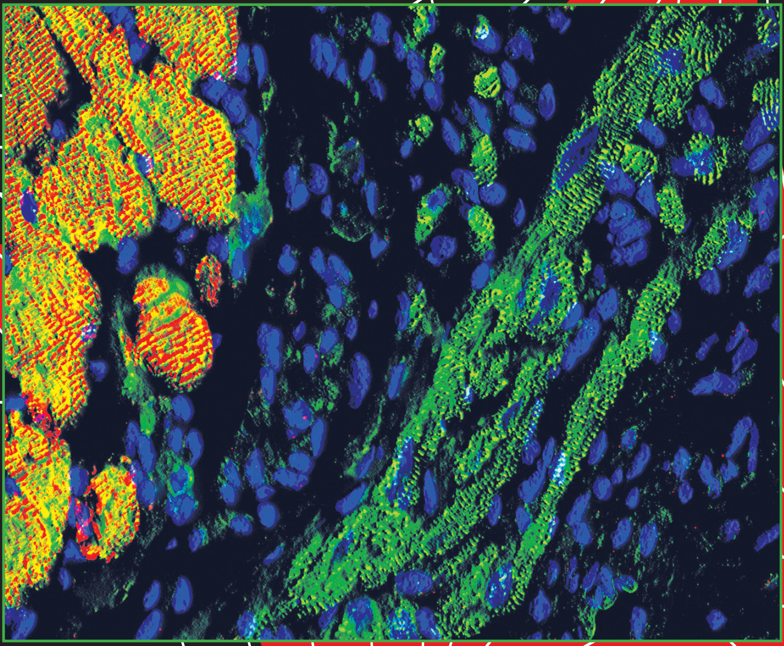
Mathematical Biosciences Institute
at The Ohio State University

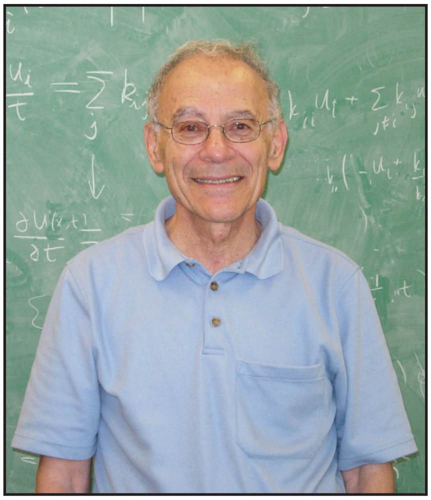
Mathematical Bioengineering

2007-2008



The MBI Receives funding from the National Science Foundation Division of Mathematical Sciences and is supported by The Ohio State University. The MBI 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 five emphasis years were Mathematical Neurosciences; Mathematical Modeling of Cell Processes; Genomics, Proteomics, and Bioinformatics; Ecology and Evolution; and Systems Physiology. This year was devoted to Mathematical Bioengineering.

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 focused on seven workshops and two mini-workshops on topics such as Metabolic Engineering, Cell and Tissue Engineering, Neuroengineering, Brain Imaging, Neuromechanics, Microfluids, and Systems Biology of Decision Making. While omitting large areas, these workshops provided examples of the central subject matter, and they highlighted two key modes of operation of bioengineering: (i) as a conduit for experimental methods, modeling and analytical tools from the physical sciences and mathematics into biology, and (ii) as a conduit for biological inspiration to the applied sciences and engineering, e.g., 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 nine 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.

The annual program included a series of tutorials to help prepare students and postdoctoral fellows to the workshops. Included was also a series of five public lectures held in conjunction with some of the workshops.

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 14 postdoctoral fellows at the MBI, each having two mentors, one from the mathematical sciences and another from the biosciences. Their research interests include neuroscience, mitochondrial models, immunology, tissue engineering, tumor angiogenesis, adipogenesis, multiscale and hybrid modeling in computational biology, bioinformatics, ecology, wound healing, membrane proteins, biochemical networks, tuberculosis modeling, and statistical genetics.

The annual summer program included a two-week program for undergraduates followed by an REU program, and a three-week program for graduate students. Both programs had a one-week tutorial followed by research projects by teams of students.

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

Avner Friedman
Director

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Mission

The founders and governors of the MBI identified the need for an institute dedicated to the mathematical biosciences. Vigorous programs of research and education foster the growth of an international community of researchers in this new field.

This need stems from the revolutionary advances in basic science and technology including medical imaging, nanoscale bioengineering, and gene expression arrays. The resulting deluge of experimental data has challenged scientists to produce mathematical solutions to analyzing and structuring this data in a meaningful way.

The mission of the MBI is:

- To foster innovation in the development and application of mathematical, statistical, and computational methods for the solution of significant problems in the biosciences;
- To engage mathematical and biological scientists in the solution of these problems;
- To expand the community of scholars in mathematical biosciences through education, training, and support of students and researchers.

To support this mission, the MBI will reinforce and build upon existing research efforts in mathematical bioscience and encourage human and intellectual growth in this area. Emphasis year programs, current topics workshops, educational programs, and sponsored research projects are the structure under which these goals will be achieved.

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

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 welcomes the participation of other academic institutions and invites those interested to join the MBI Institute Partner Program. The program subsidizes the travel and local expenses of IP member faculty, postdoctoral fellows, and students, to allow their participation in research and education programs at the MBI.

Each IP institution commits annual funds to the MBI. These funds are credited to the IP member account and may roll over from one year to the next. Following authorization by the IP member's chair, travel and local expenses of up to twice the balance in the IP member account will be paid in full with 50 percent debited from the IP account and 50 percent debited from the MBI's account.

The MBI provides up to $15K annually to support conferences in mathematical biology held at IP institutions; for more details, contact the MBI Director.

IP chairs or representatives are invited to annual meetings to explore educational and research opportunities and provide input for future institute programs. IP members also receive MBI newsletters, proceedings, and annual reports.

Current Institute Partners
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 Houston
University of Iowa
University of Maryland, Baltimore County
University of Michigan
University of Minnesota
Vanderbilt University

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 the FDG meeting should be between six months and one year from the time of submission.

Coming up in the Fall Quarter, there will be two Focus Group Meetings:

Mathematical and Computational Models in Biological Networks (October 20-24, 2008)

Multiscale Methods in Biology
(November 2-4, 2008)

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;
- stand-along workshop;
- extended program, several months to a year; and
- 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.

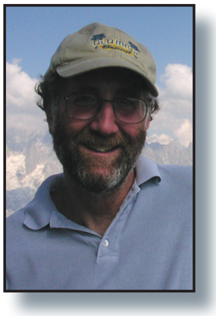
Please submit your ideas in the form of a few pages describing the background and motivation, and what the program is going to accomplish.

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.

Directors

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 Trustees.



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.

Staff

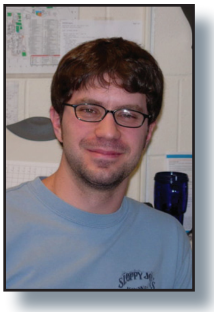
Nikki Betts, HR & Financial Manager
Nikki manages all human resources and financial activity in the MBI, including visa, travel, and reimbursement related activities. She also helps with program and reporting activities.

Stella Cornett, Program Assistant
Stella manages the web site; produces grant proposals and reports; creates and distributes brochures, flyers, and newsletters; 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.

Jared Hirsch, Systems Specialist
Jared provides support to users of MBI computer and presentation facilities, assists Michael with systems maintenance, and contributes to web programming projects.

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

Matt Thompson, Program Assistant
Matt assists in fiscal processing, registration, reimbursements, human resources, and event coordination; responsible for information given to all visitors.



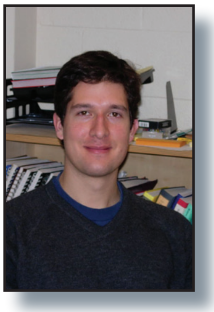
Michael Siroskey, Systems Manager
Michael is responsible for all technology aspects of the MBI, including maintaining and upgrading servers, desktop and laptop machines; handles hardware and software evaluation and procurement decisions; responsible for presentation and telecommunication facilities; provides support on space renovation project; and supervises web activity.

Dhruv Kaura, Student Worker
Dhruv provides critical logistic and clerical support for MBI events, including materials, advertising, and data management.

Postdocs

Cohort 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 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.

Cohort 2007

Huseyin Coskun (Department of Computational and Applied Mathematics, University of Iowa). Huseyin's research area is interdisciplinary: it is a combination of mathematics, biology and engineering. He is principally interested in applied mathematics, partial differential equations, and inverse problems.

He has developed models for cell movements which incorporate different components of the phenomena, such as mechanics and molecular dynamics that have been studied separately, into a single model. In that sense the models can be considered as 'systems biologic' approach. He has also formulated model based inverse problems for parameter and unknown function estimation. Neither this system biologic approach nor the inverse problem formulation have been studied previously in the area of cell motility.

Postdocs

Judy Day (Department of Mathematics, University of Pittsburgh). Judy's research interests are primarily focused on problems that have potential to translate directly to medicine in the care and treatment of the critically ill. In particular, she has worked to form and analyze mathematical models (systems of ordinary differential equations) to explore the non-linear interplay of the various components of inflammation. Inflammation is a complex process not well understood and many potential therapies to control inflammation have failed. Thus, in addition to developing models to understand the inflammatory response, she is also interested in using these models to explore potential therapies to correct immune dysfunction. Consequently, she has been investigating the use of nonlinear model predictive control as one method by which this might be accomplished.

Rasmus Hovmoller (Systematic Zoology, Stockholm University, Sweden). Rasmus's current research interest in phylogenetic studies of emergent infections disease with a focus on Influenza. By creating a genealogy over virus sequences, and mapping them geographically we can trace the events that enables a bird flu virus to infect humans. Influenza viruses have a segmented genome, consisting of 8 separate single-strand RNA fragments coding for 10 proteins.

Re-assortment between different strains of Influenza has been thought to cause the large pandemics. The Spanish flu of 1918 is believed to have originated as strain that jumped hosts directly bird to humans, while the Hong Kong flu of 1968 is thought to have passed through a genetic re-assortment between relatively benign bird flu and human flu viruses in pigs. These assumptions are based on the immunological characteristics of surface proteins: the Hong Kong strain appeared to have one protein from pig flu, and another from seasonal human flu. With new methods and computer implementations, we can examine possible genomic rearrangements in a rigorous phylogenetic context.

Committees

Scientific Advisory Committee

The Committee consists of up to 18 internationally ecognized mathematical scientists and bioscience researchers from academia and industry. The Committee meets annually to review the institute programs, to suggest and decide on new annual programs, and to give advice regarding programmatic goals.

Current 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)

Mark Chaplain, The SIMBIOS Centre, Division of Mathematics, University of Dundee
(1/1/08-12/31/11)

Mark Denny, Department of Biology, Stanford University
(1/1/08-12/31/11)

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
(1/1/03-12/31/08)

Suzanne Lenhart, Department of Mathematics, University of Tennessee
(1/1/08-12/31/11)

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)

Karl J. Niklas, Department of Plant Biology, Cornell University
(1/1/08-12/31/11)

Lior Pachter, Department of Mathematics, University of California, Berkeley
(1/1/08-12/31/11)

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

Stanislav Shvartsman, Department of Chemical Engineering, Princeton University
(1/1/08-12/31/11)

James Sneyd, Department of Mathematics, University of Auckland, New Zealand (1/1/08-12/31/11)

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

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

Lisa Fauci, Department of Mathematics, Tulane University

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

Jim Keener, Department of Mathematics, University of Utah

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

MBI Board of Trustees

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

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

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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

Board of Trustees

The Board consists of individuals with leadership experience in the public and private sectors, and of recognized scientists in fields related to the MBI activities. The Board meets annually to review the institute management and programs and to advise and approve the strategic priorities of the institute.

Committees

NSF sponsored Cyber-enabled Discovery and Innovation (CDI) Workshop at the MBI.

Rita R. Colwell (former director of National Science Foundation) Distinguished University Professor, Center for Bioinformatics and Computational Biology, University of Maryland, College Park (1/1/08)

Kirk E. Jordan (Chair of Industrial Advisory Committee) Emerging Solutions Executive IBM Strategic Growth Business/Deep Computing, Cambridge, MA (1/1/08)

Robb Krumlauf, Scientific Director, Stowers Institute for Medical Research, Kansas City, MO (1/1/08)

Barbara Kunz, President, Health and Life Science Global Business. Battelle Memorial Institute, Columbus, OH (1/1/08)

Mark Lewis (Representing the Scientific Advisory Committee) Department of Mathematical Sciences, University of Alberta, Canada (1/1/08)

Robert M. Miura (Representing the Institute Partners) Department of Mathematical Sciences, New Jersey Institute of Technology Newark, New Jersey (1/1/08)

Stephen J. Ruberg, Eli Lilly & Company Group Director, Global Medical Information Sciences, Medical Research & Development (1/1/08)

Emphasis Year External Advisory Committee

The Emphasis Year Scientific Advisory Committee reviews the Emphasis Year Proposals as they evolve and offers suggestions throughout the development of the Emphasis Year. A new Emphasis Year Scientific Advisory Committee is appointed for each Emphasis Year Program.

James Fallon, Department of Anatomy and Neurobiology, University of California

Eberhard Fetz, Professor of Physiology and Biophysics, University of Washington

James Collins, Professor of Biomedical Engineering, Co-Director, Center for BioDynamics Boston University

Joseph Pancrazio, Program Director, Extramural Research Program, NIH/NINDS

Andy Ruina, Theoretical and Applied Mechanics, Mechanical and Aerospace Engineering, Cornell University

Greg Stephanopoulos, Bayer Professor of Chemical Engineering, MIT

Robert Shapley, Center for Neural Science, New York University

Jerrold Vitek, Co-Chairman, Center for Neurological Restoration, The Cleveland Clinic Foundation

Jonathan Wolpaw, Laboratory of Nervous System Disorders, New York State Department of Health and State University of New York

Local Scientific Advisory Committee

Sudha Agarwal, Department of Oral Biology

Irina Artsimovitch, Department of Microbiology

Laura Bohn, Departments of Pharmacology & Psychiatry

John Buford, Department of Physical Therapy

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

Jonathan Bell

Greg Smith

Erich Grotewold

Long Term Visitors 2007-2008

Jonathan Bell
Department of Mathematics, University of Maryland, Baltimore County

Adela Comanici
Department of Mathematics, University of Houston

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

Bei Hu
Department of Mathematics, University of Notre Dame

Rune Kaasen
Department of Mathematics, Technical University of Denmark

Chih-Wen Shih
National Chiao Tung University, Taiwan

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Applied Science, The College of William and Mary

Yvonne Stokes
School of Mathematical Sciences, University of Adelaide

Anticipated Visitors 2008-2009

Yvonne Stokes

Khalid Boushaba
Department of Mathematics, Iowa State University

Shangbin Cui
Institute for Mathematics and its Applications, University of Minnesota

Chris Fall
Department of Anatomy and Cell Biology, University of Illinois at Chicago

Chih-Wen Shih

Bei Hu
Department of Mathematics, University of Notre Dame

Kota Ikeda
Mathematics Institute, Tohoku University, Japan

Tong Li
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Edward Lungu
Department of Mathematics, University of Botswana

Anna Marciniak-Czochra
Institute of Applied Mathematics, University of Heidelberg

Bei Hu

Bob Miura
Department of Mathematical Sciences, New Jersey Institute of Technology

Kevin Painter
Mathematical and Computer Sciences, Heriott-Watt University

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Applied Science, The College of William and Mary

Course Release 2007-2008

Department of Mathematics
Chiu-Yen Kao
Janet Best
Linda Chen
Greg Baker

Department of Statistics
Shili Lin
Jason Hsu
Joe Verducci
Tom Santner

Electrical & Computer Engineering
Aleix Martinez
Kevin Passino

Biomedical Engineering
Keith Gooch
Ronald Xu
Yi Zhao

Computer Science & Engineering
Hakan Ferhatosmanoglu
Raghu Machiraju

Anticipated Course Release 2008-2009

Department of Mathematics
Janet Best
Avner Friedman
Bo Guan
Chiu-Yen Kao
Yuan Lou

Department of Statistics
Shili Lin
Tom Santner
Joe Verducci
Xinyi Xu

Evolution, Ecology, and Organismal Biology
Ian Hamilton

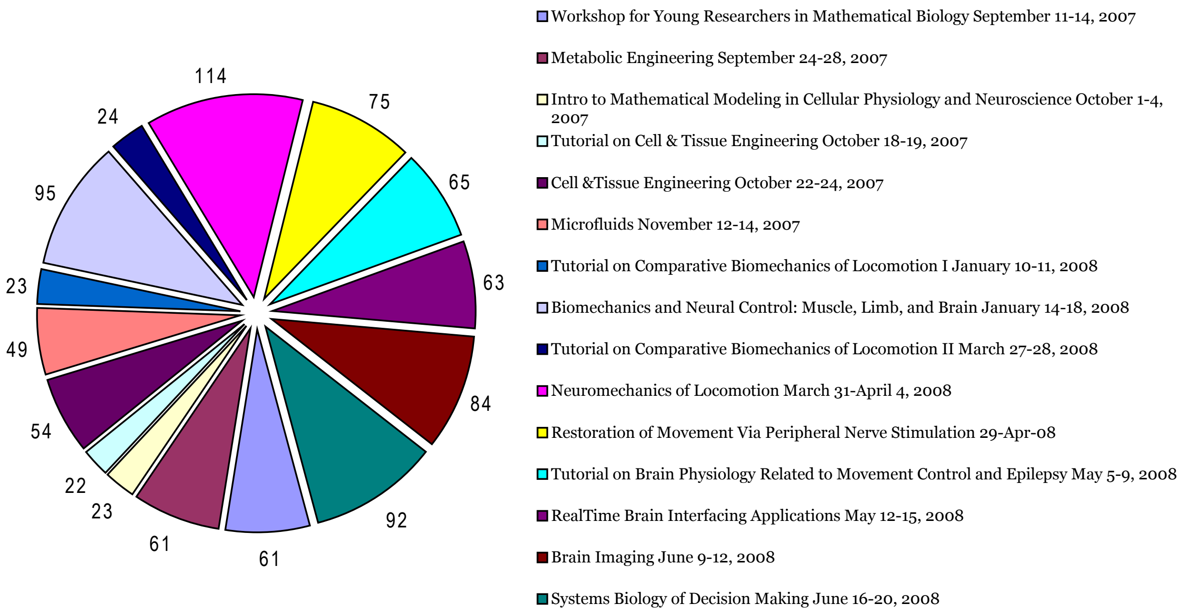
Electrical & Computer Engineering
Kevin Passino


Ian Hamilton


Shili Lin

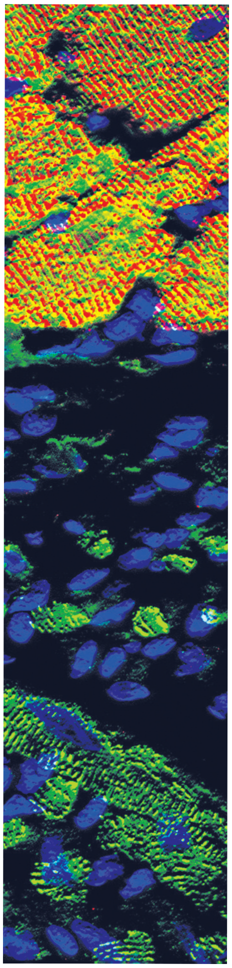

Aleix Martinez


Chiu-Yen Kao



Program Participation: total 805 participants

Workshops



Mathematical Bioengineering 2007-2008

Emphasis Year Organizing Committee:
Philip J. Holmes (Department of Mechanical and Aerospace Engineering, Princeton University)

Melissa Knothe Tate (Lerner Research Institute, Department of Biomedical Engineering, The Cleveland Clinic)

Art Kuo (Department of Mechanical Engineering, Department of Biomedical Engineering, Institute of Gerontology, University of Michigan)

Michael Savageau (Department of Biomedical Engineering, University of California, Davis)

Allen Tannenbaum (School of Electrical and Computer Engineering, Georgia Institute of Technology)

Dawn Taylor (Department of Biomedical Engineering, Case Western Reserve University)

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 focused around six workshops on Metabolic Engineering, Cell and Tissue Engineering, Neuroengineering, Brain Imaging, and Neuromechanics, the latter being covered in two linked workshops. Tutorials were offered to prepare participants, especially students and postdoctoral fellows interested in entering the field. While omitting large areas, these workshops provided examples of the central subject matter, and they highlighted 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, was 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 seven 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.

2007 Workshop for Young Researchers in Mathematical Biology, September 11-14, 2007

Organizers: MBI Postdoctoral Fellows

Overall Summary

The Fall 2007 Workshop for Young Researchers in Mathematical Biology (WYRMB) had phenomenal plenary talks from a wide variety of topics in mathematical biology. This year, the MBI postdoctoral fellows (organizers) changed several aspects of the workshop. A major change was in the timing of the workshop. We shifted it from the spring to the fall quarter in order to increase the visibility of those participants entering the job market. Additionally, we replaced small break-out groups with discussion panels led by senior mathematical biologists. In the spirit of trying to enhance young researchers' career opportunities, the discussion panels had the general theme of starting a career in mathematical biology. Lastly, we introduced a selection of short talks by MBI postdoctoral fellows to highlight MBI research projects, in accordance with survey comments from previous WYRMBs.

The workshop participants (tenure-track faculty, postdoctoral researchers, and advanced graduate students) represented colleges, universities, and research institutes from around the world. Each gave a preview of his/her work through a brief talk (1 – 2 minutes). Each poster was displayed for a full day, allowing additional time for discussions during lunch and coffee breaks. The posters illustrated the breadth of research that composes the field of mathematical biology and included topics such as calcium signaling, development, and population dynamics (to name but a few).

The workshop also featured the participation of seven leading researchers in the mathematical biosciences. Six of the researchers gave hour-long plenary talks, while one led a discussion panel on opportunities at the NIH. Additionally, two plenary speakers led discussion panels on applying for jobs and grant writing. Most of the speakers attended multiple days of the workshop, and ample time was allotted for interactions with the young researchers; this was accomplished through 30-minute coffee breaks, poster sessions, and social events such as the reception and banquet dinner.

Summary of Presentations

The meeting began with a plenary talk given by Michael Reed (Department of Mathematics, Duke University). Dr. Reed outlined a key problem of how the central nervous system can perform so accurately from integrating information from pools of unreliable neurons. In particular, he discussed how the convergence schemes of neural collections in effect sharpen the tuning process in the auditory cortex so that the system performs reliably.

Following the morning coffee break, Mark Lewis (Department of Mathematics, University of Alberta) led a discussion panel (consisting of Carlos Castillo-Chavez, Michael Reed, and Bruno Sobral) on applying for jobs and the interviewing process. The panel was lively

Workshops

and many of the participants were actively engaged in the discussion.

In the afternoon session, Carlos Castillo-Chavez (Department of Mathematics and Statistics, Arizona State University) highlighted some of the challenges that have been brought up by emergent and re-emergent diseases. He provided examples from tuberculosis, influenza, and other infectious diseases, which showed how useful and important mathematical analysis can be in determining strategies to reduce infection rates. Following the afternoon plenary talk, half of the participants introduced themselves and gave a preview of their work to be presented. We followed these introductions with the poster session and a reception in the MBI foyer.

The second morning began with Mark Lewis discussing recent interdisciplinary work on the dynamics of naturally occurring parasites on wild salmon, namely sea lice, and the role played by salmon farms in changing those dynamics for juvenile salmon. This work has made big news in the Canadian fish farming industry and demonstrated that mathematical biology can, in fact, impact biology and how we make use of our natural resources.

Next a discussion panel was held consisting of Carlos Castillo-Chavez, Mark Lewis, Michael Reed, and led by Bruno Sobral (Virginia Bioinformatics Institute, Virginia Tech). The panel addressed grant writing and what young researchers should know. Again the participants were actively engaged in the discussion.

The afternoon session began with short talks by postdoctoral fellows Brandilyn Stigler and Andrew Nevai. Brandilyn Stigler gave preliminary results from a project to infer a regulatory network in C. elegans muscle genes, using discrete algebraic models; this is joint work with OSU Associate Professor Helen Chamberlin (Department of Molecular Genetics, Ohio University). Andrew Nevai discussed joint work with Linda J.S. Allen (Department of Mathematics and Statistics, Texas Tech) and Yuan Lou (MBI and Department of Mathematics, OSU). He discussed an analysis of spatial patterns in a discrete-time epidemic patch model of the spread of rabies. They showed that when the disease-free equilibrium is unstable, there exists a unique endemic equilibrium. Beyond the formal proof and analysis, there results were supported with numerical simulations.

Following the MBI short talks were poster previews for the remaining participants and the final poster session.

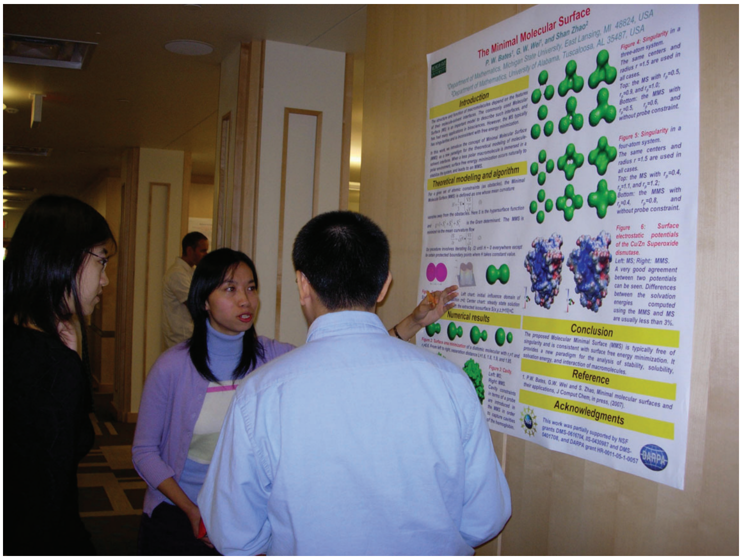
The opening talk of the day was given by Bruno Sobral discussing mathematics in transdisciplinary life sciences research. He stressed that multidisciplinary research projects with a common framework that spans the adopted disciplines may have greater impact in solving society's problems. He also provided examples of projects in which mathematics was essential for developing a transdisciplinary framework. Increasingly, mathematics is playing an integral role in the life sciences and at times communication between the communities can be a challenge. Beyond communication issues, we are moving into an age where there are very rich data sets that require modeling to paint a cohesive scientific theory that ties data to the correct model.

In the spirit of moving mathematics into the medical community, Arthur Sherman (Mathematical Research Branch in the National Institute of Diabetes, Digestive and Kidney Diseases of the National Institutes of Health) gave an overview on opportunities for young researchers at the NIH during the discussion panel. He outlined some of the funding options and gave a survey of the various NIH laboratories, while pointing out which ones had research requiring theoreticians.

In the afternoon session, Suzana Straus (Department of Chemistry, University of British Columbia) introduced mathematical tools used to solve membrane protein structures by solid state NMR (nuclear magnetic resonance spectroscopy). She explained how the NMR experiment PISEMA (Polarization Inversion Spin Exchange at the Magic Angle) can be used to extract data about the orientation of the peptide planes. She also outlined how this data is used in obtaining a minimal energy model for the protein structure. After the break, MBI postdoctoral fellows Paula Grajdeanu and Andrew Oster gave short talks. Paula Grajdeanu discussed a mathematical model that tracked the access failure to a graft, where growth factors due to surgical injury, oxidative stress, and turbulent flow can lead to access failure. Use of this model in a clinical setting could be integrated in order to prolong vascular access by targeting specific growth factors. Andrew Oster introduced the role of mitochondria in calcium signaling and focused on the surprising fact that mitochondria are excitable and exhibit calcium induced calcium release signaling, which could dampen or amplify intracellular calcium signals. This was joint work with Christopher Fall (Department of Anatomy and Cell Biology, University of Illinois at Chicago) and David Terman (MBI and Department of Mathematics, OSU).

The final day was comprised of two plenary talks with a coffee break in between. Angela Stevens (BioQuant/Applied Mathematics University of Heidelberg) discussed pattern and structure formation in biology due to local interactions, which differs from the classical diffusion-driven Turing instability often associated with pattern formation of diffusible morphogens. Development due to local interactions can give rise to unique structures not seen via the Turing-type instability.

The final plenary talk was given by Nancy Kopell (Department of Mathematics, Boston University). She described the interweaving of multiple rhythms that occur in the nervous system and how this may depend upon anatomy. Dynamical systems modeling can be used to explain how changes in the angle of a slice of cortex can change the power of the two frequencies, and how the cells producing the slower rhythm can coordinate the cells producing the faster one.



Conclusion

This workshop was well received by the participants and the speakers. Many positive remarks were made regarding the choices for plenary speakers, the focus on topics relevant to beginning a career as a mathematical

Workshops

biologist, and the new facilities at Jennings Hall. This was the first workshop in our new location, and the staff impressively was able to arrange for a smooth, problem-free workshop. 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 continue hosting the Workshops for Young Researchers in Mathematical Biology.

Workshop 1: Metabolic Engineering, September 24-28, 2007

Organizers: Michael Savageau (Department of Biomedical Engineering, University of California, Davis), David Gang (Department of Plant Sciences and BIO5 Institute, University of Arizona), and John Doyle (Division of Engineering and Applied Science, California Institute of Technology)

Overall Summary

The purpose of this workshop was to bring together mathematical modelers, computational scientists and experimental biologists working on various aspects of metabolic engineering. Although metabolic engineering of plants and microbes is a major scientific activity today, there are numerous biological and, increasingly, mathematical challenges in this rapidly expanding field. One can organize the challenges of metabolic engineering roughly into four areas: measurement technologies (sensing and quantification) for generating data and monitoring system performance, mathematical modeling (formulation, verification, and analysis) for systematic representation and characterization of the system, molecular tools (actuators and regulators) for altering the system in a controlled fashion, system integration (system [re]design, prediction, and control) for discovery of system design principles and rational optimization. Advances in one area are obviously dependent on those in the others. New developments in each of these areas formed the interrelated themes of this workshop. Examples from microbes and plants were emphasized.

Summary of Presentations

Erich Grotewold (Department of Plant Cellular and Molecular Biology, Plant Biotechnology Center, The Ohio State University) opened the workshop with an overview and historical perspective of the field of metabolic engineering from the biologist's perspective. Metabolic engineering has been defined as "the improvement of cellular activities by the manipulation of enzymatic, transport, and regulatory functions of the cell with the use of recombinant DNA technologies." The elucidation of the genome sequences for many microbes, fungi, animals and plants has provided a number of unique tools to tackle the challenge of engineering metabolic pathways as part of interdisciplinary efforts that integrate biology and chemistry with engineering and mathematics. However, fundamental issues remain, such as the adverse social reaction to the utilization of genetically modified organisms (GMO), the difficulties associated with predicting the effect of genetic manipulations on the metabolome, and the problems associated with targeting metabolites to the desired cellular or sub-cellular locations.

David Gang (Departments of Plant Sciences and Biochemistry and Molecular Biophysics, and BIO5 Institute, The University of Arizona) gave the second overview talk and discussed approaches used to produce metabolically engineered organisms. These include methods to mutagenize organisms, such as by biological (tDNA, transposons, retroviruses, etc.), radiological (Fast Neutron, cosmic radiation), and chemical (EMS, colchicine, other teratogenic agents), and to make transgenic organisms, such as by transfer of genes and production of specific gene knockouts. Recent developments in gene transfer technologies and in methods to alter gene expression in target organisms, such as by RNAi approaches, now allow for unprecedented advances in our ability to produce transgenic organisms across the tree of life. However, many challenges still remain and many important target plants, for example, still remain non-transformed.

Jay Keasling (Departments of Chemical Engineering and Bioengineering, University of California, Berkeley and Synthetic Biology Department, Physical Biosciences Division, Lawrence Berkeley National Laboratory, Berkeley) gave an example of metabolic engineering in practice. He spoke about his efforts to produce low-cost, effective anti-malarial drugs in microorganisms. Chloroquine-based drugs that were used widely in the past have lost effectiveness because the Plasmodium parasite, which causes malaria, has become resistant to them. Artemisinin-based drugs provide an alternative treatment means but are too expensive for large-scale use in the countries where they are most needed. Dr. Keasling has metabolically engineered E. coli to produce high levels of mono-, sesqui-, and diterpenes, most notably amorphadiene, the sesquiterpene precursor to artemisinin. The result of these studies is an E. coli host capable of producing 1,000,000-fold higher levels of amorphadiene than the strains and expression systems that had been available previously. The engineered strain contains a heterologous mevalonate-based terpene biosynthetic pathway and an amorphadiene cyclase gene resynthesized with the E. coli codon usage. He also cloned the final steps in the artemisinin biosynthetic pathway and engineered yeast to produce artemisinic acid at high levels. The goal of this technology is to reduce the cost of artemisinin-based combination therapies significantly below their current price, making them available to even the poorest of countries.

Genetically modified tomatoes.

Workshops

In the final session of the day, Larry Gold (SomaLogic) gave an excellent review of his use of SELEX experiments to provide aptamers (RNA antibodies) to study many different processes and features of organisms from bacteria to mammals, including the human plasma proteome. Dr. Gold discussed the possible value of in vitro and in vivo selections aimed at the discovery of novel biochemical systems. He also compared bacterial to mammalian evolution, and asked the question of whether certain groups of organisms are optimized or clunky. This led to a vigorous discussion, led by John Doyle, on how metabolic engineers should view their experiments in a larger evolutionary and ecological context, and whether "Rube Goldberg devices" really represent a metaphor that can be applied to biological systems. The consensus of the participants was that such devices are not reasonable comparisons to biological systems because they lack robustness and cannot be rationally explained - two properties that all biological systems appear to possess.

The second day's focus was on molecular approaches for metabolic engineering. Terry Hwa (Center for Theoretical Biological Physics and Department of Physics, University of California, San Diego) discussed the importance of small RNAs in biological systems and in metabolic engineering. An increasing number of small RNAs (sRNA) have been shown to regulate critical pathways in prokaryotes and eukaryotes. In bacteria, sRNA regulation is predominantly involved in coordinating intricate stress responses. The mechanisms by which sRNA modulate expression of its targets are diverse, and the level of a functional sRNA may be altered via its interaction with its targets. Aiming to understand the unique role played by sRNAs, Dr. Hwa studies quantitatively two classes of bacterial sRNAs in E. coli using a combination of experimental and theoretical approaches. These sRNAs provide a novel mode of gene regulation, with characteristics distinct from those of protein-mediated gene regulation. These include a threshold-linear response with a tuneable threshold, a robust noise resistance characteristic, and a built-in capability for hierarchical cross talk. Knowledge of these special features of sRNA-mediated regulation is crucial towards understanding the subtle functions that sRNAs play in coordinating various stress-relief pathways, and can help guide the design of synthetic genetic circuits with properties difficult to attain with protein regulators alone.

Christina Smolke (Division of Chemistry and Chemical Engineering, California Institute of Technology) then spoke about how recent progress in developing frameworks for the construction of integrated RNA devices is enabling rapid advances in cellular engineering applications. These devices provide scalable platforms for the construction of molecular communication and control systems for reporting on, responding to, and controlling intracellular components in living systems. Research that has demonstrated the modularity, portability, and specificity inherent in these molecules for cellular control was highlighted and its implications for synthetic and systems biology research were discussed. Specific applications discussed included non-invasive monitors of metabolite concentration, where xanthine levels could be monitored directly in specific cells, and integration of RNA devices with survival genes, which linked growth to metabolite concentration.

Mark Brynildsen (Department of Chemical and Biomolecular Engineering, University of California, Los Angeles) discussed the challenges associated with measuring gene expression in complex systems, and tools that are being developed to aid in this analysis. One of these is Network Component Analysis, which seeks to determine the topology of a network. Application of this approach to identify networks of transcription factors in single celled organisms such as E. coli and yeast was discussed.

The focus on Day 3 was on identifying and measuring system elements. Paul O'Maille (The Jack Skirball Chemical Biology and Proteomics Laboratory, The Salk Institute for Biological Studies) discussed how advances in structural and molecular biology have spurred the proliferation of protein engineering technologies, allowing fundamental questions about protein evolution to become approachable. The questions themselves, in turn, can be the drivers for the development of new tools. Dr. O'Maille described the development of structure-based combinatorial protein engineering (SCOPE); a tool for connecting evolutionary endpoints in local and global sequence space. He first discussed the inception of SCOPE as a homology-independent recombination method and its application to create multiple-crossover libraries from distantly-related DNA polymerases, and then described adaption of the technique for combinatorial mutagenesis to recapitulate the more recent functional divergence of closely-related terpene cyclases. This sparked a lively discussion on the evolution of enzymes and enzyme function, as well as of metabolic intermediates, and raised the question of whether a "perfect" enzyme could be produced with this technique, which would be very desirable from a chemical or metabolic engineering standpoint.

Oliver Fiehn (University of California, Davis Genome Center) then discussed application of metabolomics technologies to study stress responses in unicellular green alga Chlamydomonas reinhardtii, under nitrogen depletion time courses using different levels of N-supply and different time points. Metabolite profiles were analyzed first by an automated database approach using classic univariate and multivariate statistics, and then by analyzing metabolic networks using Likelynet, a Bayesian likelihood method that is geared towards unbiased detection and verification of linear relationships in metabolic datasets, taking into account the technical error estimates for each variable. The dominant effect on metabolic variance in Chlamydomonas was found to depend on cell cycle. Challenges in dealing with large datasets and approaches to overcome these challenges were discussed.

Elmar Heinzle (Biochemical Engineering Institute, Saarland University, Germany) briefly reviewed relevant methods for metabolic flux analysis. This includes metabolite balancing and flux analysis using labeled substrates with necessary experimental and computational methods. Dr. Heinzle then discussed two recent case studies. The first involved measurement of metabolic fluxes in a plant specialized (secondary) metabolite pathway, where dynamic labeling experiments were used to elucidate pathway fluxes in native potato and after addition of an elucidator. In the second case, regulation of central metabolic fluxes in Bacillus subtilis was investigated by determining fluxes in various mutants of B. subtilis using different substrate combinations after model based experimental planning.

The final speaker of the day, Brian Tjaden (Computer Science Department, Wellesley College) returned to the discussion of small noncoding RNAs, which are genes for which RNA rather than protein is the functional end product. In bacteria, many small RNA genes (sRNAs) appear to act as post-transcriptional regulators by basepairing with target messenger RNAs. In his talk, Dr. Tjaden described computational and experimental approaches to characterize these sRNA genes in bacteria. First, he described high-throughput approaches for identifying sRNA genes in a bacterial genome, where he outlined use of probabilistic model that combines heterogeneous data sources (including primary sequence data, comparative genomics information, and microarray expression data) for the purpose of predicting sRNA genes throughout a genome. Dr. Tjaden then discussed methods, both computational and experimental, for characterizing regulatory targets of sRNA action and how these high-throughput approaches are used to elucidate the roles of specific sRNA genes, such as RyhB, and the pathways in which the genes are involved.

The fourth day focused on the use of mathematical modeling in metabolic engineering. Armindo Salvador (Molecular Systems Biology Group, Centre for Neuroscience and Cell Biology, Chemistry Department, The University of Coimbra, Portugal) described design principles of moiety supply units in metabolic networks. Metabolic networks have bowtie architecture: a wide diversity of nutrients is disassembled into a few molecular currencies, which are then reassembled into a large variety of other molecules. At the “knot” of this bowtie lie cycles whereby a set of reactions transfer a molecular group (moiety) from various donor metabolites to a common carrier (metabolic currency) from which another set of reactions transfers the moiety to various accepting metabolites. These circuits couple moiety supply to demand. Their role and the performance criteria they should fulfill are akin to those of a power-supply unit in an electronic circuit. Dr. Salvador explored the design principles enabling this general class of metabolic circuits to operate effectively as “moiety-supply units”, and then examined quantitative aspects of the design of concrete biological realizations of these circuits. For example, many enzymes in core metabolic cycles are over-designed and have large substrate concentration tolerances, which are side effects of mechanistic constraints for selection of other aspects of performance.

Eberhard Voit (Department of Biomedical Engineering at Georgia Tech and Emory University) discussed estimation of metabolic model parameters from time series data. Stoichiometric approaches have been tremendously successful as mathematical models in metabolic engineering. Their linearity permits an unparalleled repertoire of mathematical and computational tools, and the combination of stoichiometric models with experimental data has yielded valuable insights into flux distributions under different conditions. However, as we strive to understand the details of control and regulation in vivo at a deeper level, refined models are needed, and these must be nonlinear. While simulations with nonlinear metabolic models are no longer a significant computational hurdle, the estimation of suitable parameter values continues to be a major challenge. In his presentation Dr. Voit reviewed current approaches to metabolic parameter estimation, especially for time series data, and demonstrated why it is important to obtain fast solutions on standard computers. As an example for many aspects of his presentation, Dr. Voit used the regulation of glucose utilization in Lactococcus lactis, for which high-precision in vivo data are available describing the dynamics of intracellular metabolite pools. He also compared advantages and use of bottom up and top-down modeling in biology and their application to metabolic engineering.

Ying Xu (Biochemistry and Molecular Biology, University of Georgia) presented methods to infer natural gene circuits in bacteria. He described how orthologous gene mapping, one of the most fundamental operations in comparative genome analysis, can be used in bacterial systems to predict pathways. For example, pairs of homologous genes to increase in probability if neighboring genes also exist as pairs across genomes. It is possible to predict functional linkage relationships by using co-occurrence relationships, co-evolutionary relationships, and functional relatedness defined in terms of GO classification. Dr. Xu described how these approaches were used to investigate nitrogen assimilation across bacterial taxa.

Mustafa Khammash (Department of Mechanical Engineering, University of California, Santa Barbara) described stochastic gene expression and its implications for metabolic engineering. The cellular environment is abuzz with noise. Generated by random molecular events, cellular noise not only results in random fluctuations within individual cells but it is also a source of phenotypic variability among clonal cellular populations. In some instances fluctuations are suppressed downstream through an intricate dynamical network that acts to filter the noise. Yet in other instances, noise induced fluctuations are exploited to the cell's advantage. Intriguing mechanisms that rely on noise include stochastic switches, coherence resonance in oscillators, and stochastic focusing. While mathematical models of genetic networks often represent gene expression and regulation as deterministic processes with continuous variables, the stochastic nature of cellular noise necessitates an approach that models these variables as discrete and stochastic. In this framework, probability densities of the system states evolve according to a (usually infinite dimensional) Chemical Master Equation (CME). Until recently, sample trajectories have been computed almost exclusively with Kinetic Monte Carlo methods, such as Gillespie's Stochastic Simulation Algorithm. Dr.

Khammash described a new direct approach for computing the relevant statistics, which involves the projection of the solution of the CME onto finite subsets. He illustrated the algorithm underlying his Finite State Projection approach and introduced a variety of systems theory based modifications and enhancements that enable large reductions and increased efficiency with little to no loss in accuracy.

The focus of the last day was on principles of systems organization and integration. Drew Endy (Department of Biological Engineering, Massachusetts Institute of Technology) discussed engineering design principles and how these should be applied to metabolic engineering questions. He gave the example of an undergraduate research competition, the iGEM (international Genetically Engineered Machine Competition), where the goal of student teams is to construct and implement an original biological system using standardized, off-the-shelf genetic parts. He also returned to the topic of stochastic effects in biological systems. Biological systems appear to be noisy, but Dr. Endy argued that this might be apparent noise, due to how the measurements are being made. He outlined very interesting results from Lambda phage. He set up an experiment to test for cell size dependence of lysis vs. lysogeny and found that small cells go lysogenic, whereas large cells go lytic. This led to a very lively discussion on the role of stochastic vs. deterministic functions and properties in biological systems. Just how noisy are they really? Or, is this noise really a result of our approaches and way of thinking and experimental design?

Howard Salis (Chris Voigt's lab, Department of Pharmaceutical Chemistry, University of California, San Francisco) described approaches to rationally program bacteria. He gave the example of creating photographic bacteria and using them to make an edge detector. The edge detector system worked. It used AHL production in dark, and repressor of betaGal in dark, but expression of betaGal in light to produce a photographic negative of an image. Production of this edge detector system involved integration of components from different biological systems and suggested that metabolic engineering efforts in the future would likely take a similar approach.

In the final presentation of the workshop, John Doyle (Control & Dynamical Systems, Electrical Engineering, and BioEngineering, California Institute of Technology) talked about the application of the theory of robust design and control, which he described as robust yet fragile, to biological networks, and compared this to similar network problems in electrical engineering and computer networking. He returned to the concept of bow-ties in such networks and provided a framework for why they are essential for such networks to exist and function as they do. He also described how architectures can be structured to allow variation to allow for large changes in evolution. This led to the concepts of structured variation and "Evolving evolvability". This again led to an excellent discussion on the evolution of metabolic pathways and how these concepts must be kept in mind in efforts to metabolically engineer specific organisms.

Conclusion

In terms of stimulating scientific discourse, the workshop was a great success. The structure of the workshop, with a limited number of invited lecturers and ample time for informal discussions, allowed participants excellent opportunities to discuss the rapidly expanding field of metabolic engineering and gain a better understanding of the very diverse topics integral to this field. Broad discussions were started on the first day and continued through lunches and dinners to the end of the week.

The administrative support provided by MBI was first rate. Many participants stated that this was an exceptionally useful and enjoyable conference.

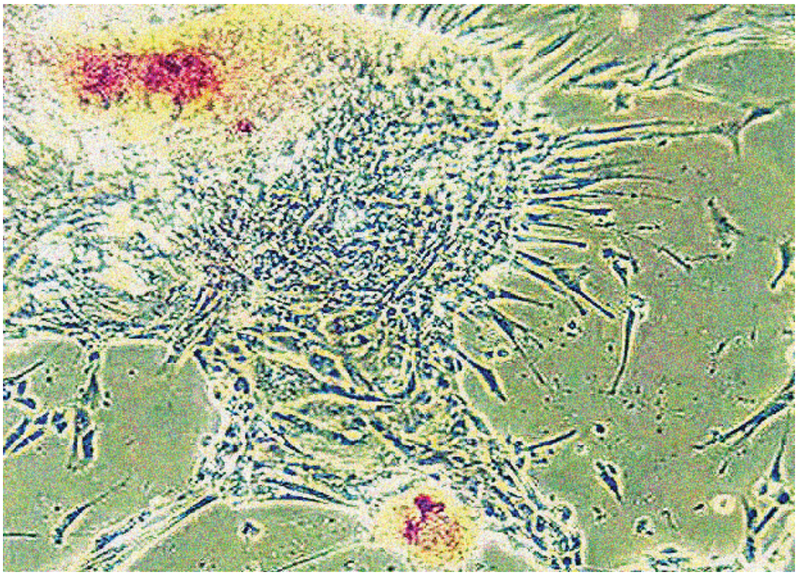
Workshop 2: Cell and Tissue Engineering, October 22-24, 2007

Organizers: Melissa L. Knothe Tate (Department of Biomedical Engineering, Case Western Reserve University) and Stanislav Shvartsman (Department of Chemical Engineering, Princeton University)

Overall Summary

The goal of the Workshop on Cell and Tissue Engineering was to bring developmental biologists, cell and tissue engineers, as well as computational modelers together at a joint forum, bridging across specific cell and tissue types as well as model platforms, to recognize common challenges and relevant strategies for addressing these challenges in tissues from diverse organisms, including plants, drosophila, planaria, salamanders, zebrafish, mice, rats, sheep and humans. Particular emphasis was placed on the promise of predictive modeling to accelerate advances in the field of tissue engineering.

In nature, tissues, organs and organisms self assemble from a pluripotent cell population deriving from the gametes (animal egg and sperm, plant pollen and ovules). In natural formation of tissues, organs and organisms, the formation of molecular patterns (patterning) allows for the subsequent specification of cell lineage (differentiation) and the formation of specialized tissues that form the template of organs and organisms (morphogenesis). The first segment of the MBI workshop addressed patterning in tissue development, and was followed by segments exploring morphogenesis as well as tissue growth and regeneration. Having explored nature's approach to building tissues, organs and organisms, in the final segment of the workshop, bioengineering approaches, to program the development of cells and tissues in the lab and in situ (replacing defective or pathologic tissues in the organism), were explored.



Summary of Presentations

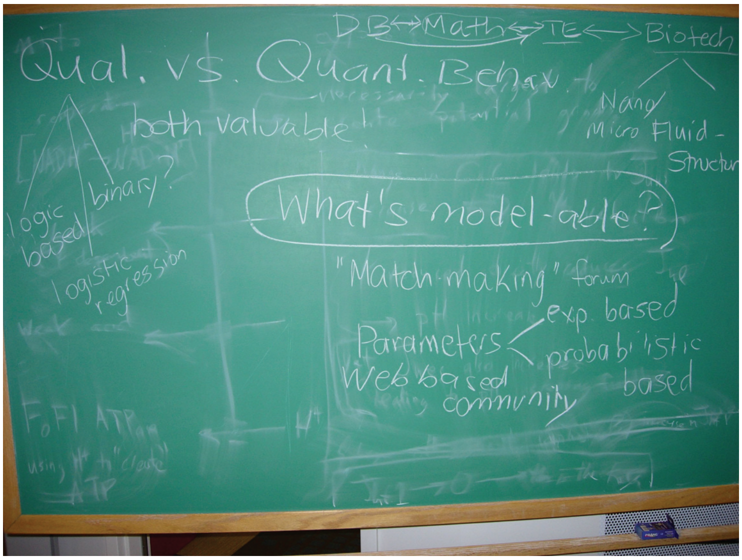
The first segment of the workshop addressed molecular patterning, which provides positional information to uncommitted cells, and allows for specification of cell fate (lineage commitment) and later tissue morphology. First, Stanislav Shvartsman, Ph.D. (Professor of Chemical Engineering, Princeton University) demonstrated the power of computational modeling in the elucidation of development pathways in his talk entitled "Engineering models of epithelial patterning in Drosophila oogenesis." The talk described the synergistic combination of imaging, genetic, and computational approaches to analyze morphogen gradients. Thereafter David Arnosti, Ph.D. and Chichia Chiu, Ph.D. (Professors of Biochemistry and Molecular Biology at Michigan State University) teamed up to present their collaborative work on "Identification of transcriptional cis-regulatory grammar in the Drosophila embryo by quantitative modeling". Arnosti and Chiu are developing a quantitative model to predict and explore how regulatory sequences in DNA control gene expression, in particular with regard to patterning of the embryo but with far reaching implications for population and evolu-

Workshops

tionary studies. Switching from Drosophila to botanical (Arabidopsis) models, Siobhan Brady, Ph.D. (Postdoctoral Fellow in the Center for Systems Biology at Duke University directed by Philip Benfey, Ph.D.) elucidated the complex, four-dimensional (space, time) transcriptional programs comprising Arabidopsis root development using a combination of experimental (microarray expression profiles) and computational approaches.

The second segment of the workshop addressed morphogenesis, or how cells form the structure of tissues and organs, ultimately providing the template of the organism. As detailed in his presentation, “Cytomechanics of polarization and morphogenesis in early embryos”, Edwin Munro, Ph.D. (University of Washington, Center for Cell Dynamics) combined experimental analyses of cell and sub-cellular dynamics with predictive computational models of virtual cells to explore how local force generating behaviors of groups of cells result in cellular rearrangements and tissue deformations that modulate morphogenesis of tissue and organism templates. Celeste Berg, Ph.D. (Professor of Genome Sciences, University of Washington) discussed the formation of three dimensional structures such as tubes from two dimensional epithelial sheets, a process fundamental to the formation of organs including the lungs, kidneys, gut, and neural tube in her talk on “Setting up and interacting across boundaries: Tube formation in Drosophila egg chambers.” Nathalia Glickman Holtzman, Ph.D. (Professor of Developmental, Cell and Molecular Biology, Queens College, City University of New York) followed this theme in her presentation on organogenesis of the heart, which develops via tube formation. Holzman’s presentation on “Endocardial-myocardial interactions direct cell migration during heart tube formation” described the use of in vivo time lapse microscopy to track cardiomyocyte migration in the embryo of the zebrafish. Dany Spencer Adams, Ph.D. (Forsyth Center for Regenerative and Developmental Biology & Department of Developmental Biology, Harvard School of Dental Medicine) addressed “Biophysical regulation of morphogenesis in development and regeneration: a new target for clinical intervention and the need for modeling”, by illuminating the underappreciated role of ion flux mediated signaling pathways in patterning of vertebrate embryos, regulation of planarian stem cells and regeneration of tadpole tails. Taken together, the use of experimental models as diverse as Drosophila, zebrafish, tadpoles, and planaria further underscored the common strategies found across diverse species in development of tissues and organs.

Once the template of a tissue, organ or organism is formed, processes of growth and regeneration are critical to the respective tissue, organ, or organism's survival. This topic was first expanded upon by Lars Hufnagel, Ph.D. (Kavil Institute for Theoretical Physics, University of California), who addressed the fundamental open question of how animal tissue knows to stop growing at appropriate times in the lifespan of the organism. By studying the spatiotemporal dynamics of morphogen distribution in the developing imaginal disk of the Drosophila wing, Hufnagel showed that growth is not arrested by the flattening out of morphogen gradients alone and presented an alternative model for control of cell proliferation and tissue growth. Showing that similar principles apply to the growth and maturation of gametes, Yvonne Stokes, Ph.D. (Applied Mathematics, School of Mathematical Sciences, University of Adelaide) presented "Mathematical modeling towards successful in vitro maturation of mammalian oocytes." Taking the concept one step further, Young Jik Kwon tackled the problem of engineering cells, modeling retrovirus delivery and binding at cell surfaces in his talk entitled "Quantitative analysis of retroviral gene delivery."



The final session of the workshop was dedicated to integrating nature's approaches to engineer cells and tissues. In his talk, "Functional tissue engineering: the role of biomechanics in cartilage repair" Farshid Guilak (Departments of Surgery and Biomedical Engineering, Duke University Medical Center) presented new technologies that enable three dimensional weaving of cell-extracellular matrix constructs from biocompatible fibres similar to those woven naturally during development. Rocky Tuan, Ph.D. (Cartilage Biology and Orthopaedics Branch, National Institute of Arthritis, and Musculoskeletal & Skin Diseases, National Institutes of Health) addressed the use of nanoscale materials comprising cells and their subunits in engineering materials to repair, replace or regenerate failing tissues. In his talk, "Application of adult stem cells and nanomaterials for skeletal tissue engineering," Tuan described the solution of tissue engineering problems as a "natural platform for life scientists, engineers, and clinicians working together to advance regenerative medicine." Finally, Melissa Knothe Tate, Ph.D. (Depts. of Mechanical & Aerospace Engineering and Biomedical Engineering, Case Western Reserve University) presented her work on "Taking cues from nature's paradigm to build tissues in the lab and the O.R. ," using the ecosystem of bone and its inhabitant cells as an example from which tissue engineers and technology developers can exploit nature's paradigms at multiple length and time scales to engineer not only tissues but also novel mechanoactive materials.

Conclusion

Integrated within the workshop program, research trainees were given the opportunity to present their work in short presentations followed by poster sessions during program breaks, providing ample time to interact with leaders from the field. Insights from the workshop will be further disseminated in a dedicated volume of the journal Tissue Engineering, providing a platform for peer-reviewed manuscripts from speakers at the workshop to be presented in a common platform (to be published summer 2008).

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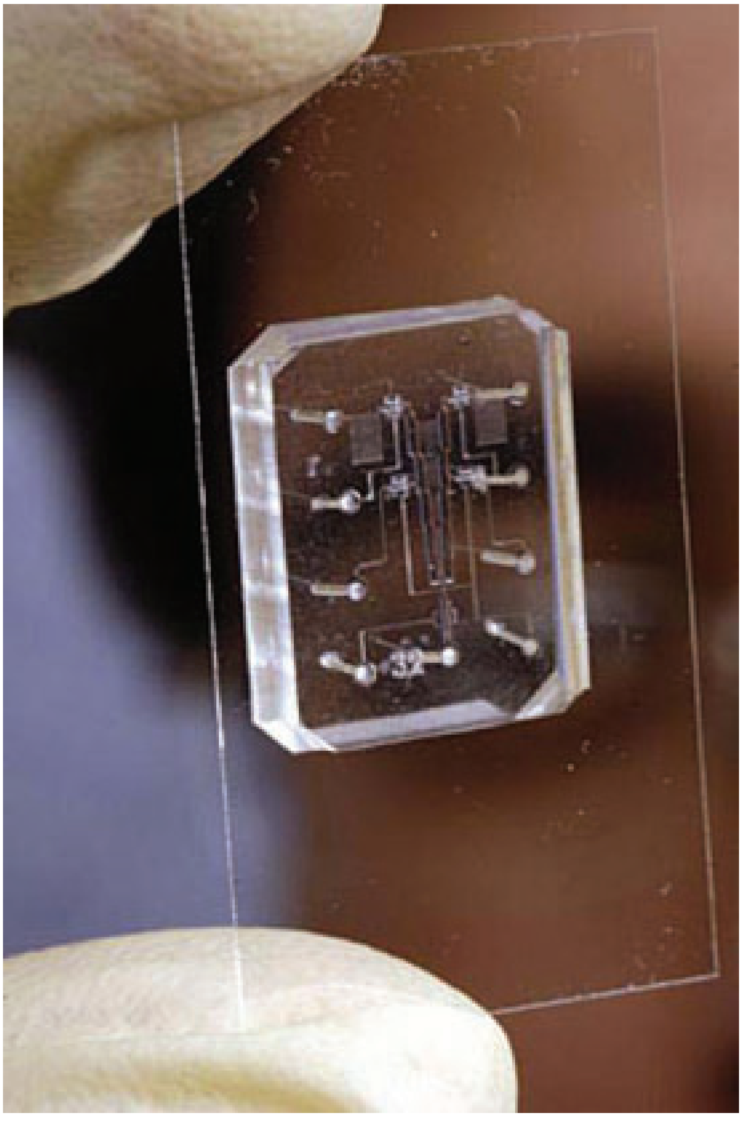
Mini-workshop on Microfluids: November 12-14, 2008

Organizer: Andre Levchenko (Biomedical Engineering, Johns Hopkins University)

Recent developments in micro- and nano-technology occurring in the fields of electronics and material sciences have created an opportunity to allow for significantly more control in definition of the micro-environment of single cells and cell ensembles. As a result, the applications of microfludics in the analysis of live cells have sky-rocketed, creating fertile ground for renewed interest in tight integration of mathematical and experimental biology.



This workshop was designed to introduce the community of mathematical biologists to the promise and recent developments in the microfluidic analysis of live cells and tissues. It was also aimed at allowing the experimentalists working in development of microfluidic applications to biological research to be exposed to the power of mathematical treatment in biology. Thus it was envisioned that the workshop, by way of examples of exciting and timely research, may provide a bridge between the communities, and a platform for discussion of possible future interactions.

The first day was devoted to the topic of spatial control of cell microenvironment. Mark Alber (University of Notre Dame) presented a multiscale model of thrombus development. At the macroscale level one deals with incompressible viscous blood plasma using the Navier-Stokes equation, and at the microscale level one has to deal with cell-cell adhesion, cell flow, and cell-vessel wall interaction described by a stochastic discrete cellular Potts model. Chih-Ming Ho (University of California, Los Angeles) addressed the multiscale problem which arises from the presence of macro complex molecules commonly found in biofluids in medical diagnoses and drug development. Azadeh Samadani (Brandeis University) talked about aspects of DNA repair at the single cell level; he described measurements that will be used to formulate a predictive mathematical model of the repair process.

The second day dealt with control and interfacing of microfluid devices. Robert H. Austin (Princeton University) introduced the concept of microfluidic metamaterial which could be used in on-chip continuous flow manipulation and analysis of cells. Ravi Desai (University of Pennsylvania) described efforts aimed to define cellular microenvironments that are dynamically complex compared with conventional in vitro culture platforms, yet still permit the manipulations and data collection necessary to gain insight into biologic processes.

The talk by Albert Folch (University of Washington) was concerned with efforts by his laboratory in the development of cell-based microdevices for neurobiology studies, such as neuromuscular synaptogenesis, axon guidance, and olfaction. Rafael Gomez-Sjoberg (Stanford University) presented a highly automated platform for culturing and studying mammalian cells, built around a microfluidic device that contains hundreds of micromechanical valves. He then presented results on the study of the motility and differentiation of human mesechymal stem cells, on the culturing of human colon cancer stem cells, and on the study of NFkB dynamics in mouse fibroblasts. Jagesh Shah (Harvard Institute of Medicine) talked about dynamic screening of single cell physiology by microfluidics, and how he monitors, for different cell lines, cell division at high resolution in an array of antimitotic agents similar to those used in cancer chemotherapy.

Shuichi Takayama (University of Michigan) spoke, as did other speakers, of the gap that exists between the cellular microenvironment in vivo and in vitro. One of the reasons for this gap is because the fluidic environment of mammalian cells in vivo is microscale and dynamic whereas typical in vitro cultures are macroscopic and static. He described his efforts to develop programmable microfluidic systems that enable spatio-temporal control of both the chemical and fluid mechanical environment of cells, and thus close the physiology gap to provide biological information otherwise unobtainable.

The last day began with a talk by John P. Wikswo (Vanderbilt University). He talked about devices that address the limitations of conventional in vitro cell culture, and enable, for example, the study of paracrine signaling dynamics in T cells; cellular haptotaxis in response to gradients of surface-bound proteins; cell migration and differentiation in wound healing, tissue remodeling, angiogenesis, and metastasis; the role of various genes in cardiac electromechanical activity; and cellular metabolic responses to toxins and drugs. The last talk, by Ali Khademhosseini (Harvard-MIT), was concerned with microengineering the cellular environment for tissue engineering and drug discovery. He presented his work in controlling the cell-microenvironment interactions in 2D and 3D using a variety of microscale technologies, and then explained how it is used in microfluidics for generating tissue-like structures with biometric microvasculature, and in emerging medical application.

Conclusion

In the exit surveys, participants commented that the fact the workshop was small enabled deeper communication between people and, in particular, between experimentalists and theoreticians.

Workshop 3: Muscle, Limb, and Brain, January 14 – 18, 2008

Organizers: Arthur D. Kuo (Departments of Biomedical & Mechanical Engineering, University of Michigan), Lena Ting (Department of Bioengineering, Georgia Institute of Technology), John Guckenheimer (Department of Mathematics, Cornell University), Tony Bloch (Department of Mathematics, University of Michigan)

Overall Summary

This workshop was designed to explore the intersection between three interlinked fields studying various aspects of human movement: muscle physiology, movement biomechanics, and sensorimotor neuroscience. Investigators in these fields address neuromuscular conditions such as stroke or spinal cord injury, and employ a variety of analytical and computational techniques to complement a plethora of experimental methods. Each having a scientific community of its own, it is rare for more than two of these fields to be represented at a typical scientific conference. Cross-fertilization is important, because no condition affects one system in isolation. For example, spinal cord injury often leads to altered muscle fibers and change in the mechanical characteristics of the muscle and limb in addition to deficits in neural motor activity. There are also unresolved scientific issues that can be addressed through interdisciplinary collaboration, as well as important conceptual problems that can be addressed through mathematical techniques. The workshop brought together both junior and senior researchers, all of whom have made significant contributions to their respective fields, and have technical interest and ability to use mathematical tools in their inquiries.

Summary of Presentations

What determines muscle's function in movement?

This session was organized to present new considerations in muscle physiology that are relevant to movement. Speakers were asked to propose significant issues, unresolved questions, or new hypotheses drawn from their own expertise in physiology, and to present these to a broad audience of investigators from other fields who may be unaware of the most recent developments in muscle physiology. Peter Huijing (Free University of Amsterdam) opened the session with a presentation on epimuscular force transmission. This refers to tissues that transmit force across and between both muscle fibers and even neighboring muscles or structures. These elements have traditionally been ignored as important to movement, but Dr. Huijing presented data showing how muscle fascia and other tissues can substantially alter the overall forces produced by muscle, greatly affecting movement. Another macroscopic behavior of muscle was addressed by Sharon Bullimore (McGill University). Muscle fibers undergoing stretch have been found to change length inhomogeneously. The sarcomere constituents of muscle are arranged in series, and stretch of an overall fiber results in different amounts of stretch distributed across sarcomeres. Dr. Bullimore demonstrated how this behavior is relevant to whole body movement, and discussed some potential explanations for the phenomenon. Thomas Roberts (Brown University) presented how the three-dimensional geometry changes as a consequence of muscle contraction, altering the forces and displacements that the fibers undergo. Many studies of movement assume that muscle has uni-dimensional behavior, and this assumption can lead to errors for many muscles. Glen Lichtwark (Griffith University) discussed the stretch-shortening cycle of muscle, a phenomenon where muscle can produce enhanced forces following stretch. This has expected to have effect on energetic efficiency that have not yet been quantified. Dr. Lichtwark used a computational model of muscle to show how efficiency can be improved under appropriate stretch-shortening conditions. The session highlighted several major issues in muscle physiology, and indicated how study of movement can be sensitive to several phenomena if they are not properly accounted for. The session also highlighted the importance of integrative studies that combine state-of-the-art knowledge regarding muscles in macroscopic models of movement.

What biomechanical degrees of freedom does the nervous system control?

This session addressed the manner in which the nervous system selects between a highly redundant set of muscles to perform motor tasks. A major organizing principle for motor control is the motor synergy, in which multiple muscles share common activation commands to reduce the dimensionality and simplify control. Matthew Tresch (Northwestern University) presented evidence that optimization principles can be used to predict motor synergies, and showed how movement determined purely from optimization without constraints can resemble those produced by fixed synergies. Lena Ting (George Institute of Technology) showed how closer examination of behavior reveals the possibility that synergies may be numerous, and in fact more numerous than the individual muscles. These two presentations therefore questioned whether synergies are actually helpful for dimensionality reduction. Jason Kutch (University of Michigan and Northwestern University) followed up this theme with evidence that motor synergies are quite flexible, recruiting different muscles as a function of task direction. This indicates that the conventional view of synergies as relatively fixed groupings of muscle is not supported. The session ended with an extensive discussion, in which several participants argued that the synergy framework needs to be reconsidered.

Is locomotion a matter of neural control or just mechanics?

This session was concerned with the role of dynamics in the generation of locomotion. Manoj Srinivasan (Princeton University) presented computational studies on bipedal gaits, examining optimal locomotory strategies based on minimization of mechanical work. Previous researchers have thought that running gaits were optimal for fast speeds because they utilize elastic energy storage, whereas Dr. Srivasan’s studies show how running can be optimal even for systems with no elasticity. Andy Ruina (Cornell University) elaborated on this theme, showing how previously-held explanations for gait, based on

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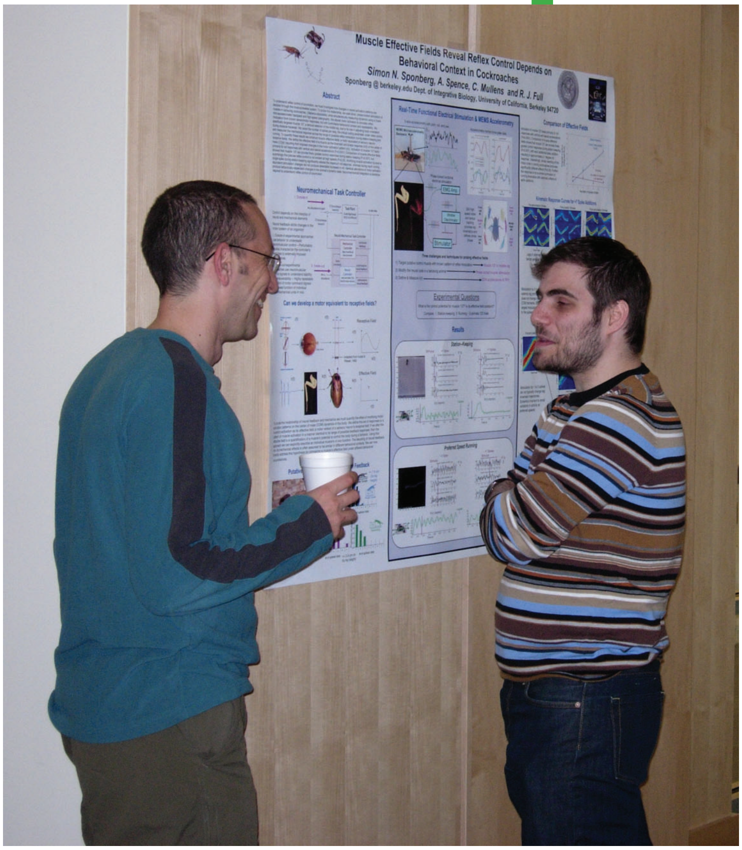

neural or mechanical properties, are in fact not necessary; work considerations alone can explain many features of gait. Ton van den Bogert (Cleveland Clinic) presented a complex, multi-degree of freedom model of human walking. He used his model to test for alternative hypotheses regarding optimality of gait, and showed how current complex models do not incorporate sufficient physiological characteristics to predict healthy and impaired gait based on optimization, implying that either the models or the optimization strategies are inadequate. Max Donelan (Simon Fraser University) presented evidence that the energetics of human gait are consistent with a few basic mechanical principles such as the work performed during step-to-step transitions. He showed how simple models currently have better predictive ability than complex ones. Art Kuo (University of Michigan) addressed the issue of central nervous system control, which has traditionally viewed as using a central pattern generator to set the limbs into motion. He promoted an alternative view, in which the limbs are allowed to generate the motion themselves, with the central nervous system gently shaping that motion for economy. As a whole, the session indicated the important role of limb dynamics, and the flexibility of the nervous system in harnessing those dynamics, in the energetics and control of gait.

How is stability achieved in musculoskeletal systems?

The afternoon session dealt with stabilization of locomotion, and considered the roles of the nervous system and the body in producing stability. Andrew Biewener (Harvard University) presented experimental measurements of muscle and tendon function in vivo, showing that muscle groups in different locations can have different mechanical functions. Proximal muscles appear to perform much of the work for gait, and distal muscles appear to perform little work and act more like springs, with stabilization properties. A. J. van Soest (Free University of Amsterdam) showed how the mechanical properties of body sensors place limitations on how stability can be performed, and demonstrated the minimal requirements of the central nervous system for making use of those sensors. Robert Peterka (Oregon Health Sciences University) demonstrated an extensive set of studies, each examining one sensory component of postural control, and found that integration of the individual sensory components requires a relatively simple but structured feedback scheme from the central nervous system. Daniel Merfeld (Massachusetts Eye and Ear Institute) elaborated on that structure in his presentation, providing evidence that the structure is akin to an internal model of the dynamics of the head, body and sensors, and that the nervous system appears to optimize its sensory integration to make best use of this knowledge. The session highlighted the interplay between musculoskeletal mechanics and nervous system in stabilization of movement.

What computations does the nervous system perform for control?

Continuing the exploration of central nervous system control, the sessions on Day 3 were concerned with computational models of control and adaptation. John Guckenheimer (Cornell University) opened the session with a presentation on the dynamics of neurons and of networks of neurons, and how they can interact to produce complex bursting behaviors. Michael Paulin (University of Otago) then presented a vision for how computations at the neuronal level can lead to apparently complex sensorimotor integration behavior, using the particle filter as a possible organizing principle for the cerebellum. Stefan Schaal (University of Southern California) then provided a theoretical framework for how pattern generating networks can actually perform optimal control. This was followed by Konrad Koerding (Northwestern University), who presented the hypothesis that sensorimotor integration based on internal models also presents a means of improving rehabilitation, due to the ways that the central nervous system appears to decode sensory information. By taking advantage of the types of errors that induce the greatest adaptation, it may be possible to accelerate the neural rehabilitation process. This session highlighted how mathematical models can drive a wide variety of hypotheses, from behaviors of single neurons, to rehabilitation applications for the entire body and nervous system.

Does the nervous system perform optimal control?

From the morning's emphasis on theoretical frameworks, the remainder of the day followed on with stronger ties to experimental neuroscience. Stephen Scott (Queen's University) presented work on direct recording of neural activity in the primary motor cortex, and showed how his experiments can be interpreted in terms of optimal feedback control. Emanuel Todorov (University of California, San Diego) then presented work on stochastic optimal control, expanding the concept of control to include uncertainty and variability. He argued that uncertainty is important for learning and adaptation, and that control can be constructed so as to minimize the variability resulting from uncertainty. Continuing this theme, Kurt Thoroughman (Washington University in St. Louis) presented experimental work on voluntary reaching motions, and showed how motor adaptations can take place on a trial by trial basis, with relatively simple neural transformations able to explain many aspects of real-time learning. Up to this point, most presentations have been concerned with free motions of the upper limb, but the frameworks described have not considered motor tasks where the body is in contact with the external environment. Sandro Mussa-Ivaldi (Northwestern University) proposed that optimal control frameworks can be made compatible with combined force and motion tasks, where some components of the task involve application of controlled force and others a controlled movement. His work indicates that such hybrid tasks are a frontier for continuing research in motor control. The session as a whole summarized the state of the art in computational approaches to motor control, and their interface to experimental neuroscience.

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Can musculoskeletal mechanics simplify neural control?

After devoting an entire workshop day to computational neuroscience research, the workshop returned to the roles of muscle and limb mechanics in movement. The morning session was opened by Richard Lieber (University of California San Diego). He presented studies showing how the architecture of skeletal muscle can provide mechanical behaviors that drastically simplify motor control, reducing the burden on the nervous system for stabilization. T.

Richard Nichols (George Institute of Technology) expanded on this theme, showing how the musculoskeletal geometry of multiple muscles can contribute to motor coordination, not only at the level of single muscle, but also for groups of muscles with appropriate mechanical behaviors. These first two presentations directed attention back towards muscle mechanics, indicating the utility of integrating reductionist approaches into the exploration of movement. Steven Lehman (University of California at Berkeley) presented a summary of research at the molecular level, showing how proteins can serve as motors to drive muscle and supply the same mechanical behaviors that appear important for whole body movements. He demonstrated how studies on a macroscopic scale can take advantage of findings at the microscopic scale. Walter Herzog (University of Calgary) then followed up with a discussion of the mechanics of sarcomeres, and showed how much of the scientific attention on contracting muscle has left a void in understanding of lengthening behavior, a critical issue since it is important in half of movement. Dr. Herzog showed how individual proteins can contribute to lengthening behaviors, and listed several gaps in current knowledge. This session was helpful in demonstrating that even highly conceptual approaches to neuroscience can benefit from recent findings at the molecular level of muscle physiology.

Manipulation: The brain really does something!?

Complementing previous sessions on reaching movements, this session focused on manipulation. Francisco Valero-Cuevas (University of Southern California) presented an overview of the problems of manipulation, and showed how the mechanics of the hand and the finger tendons can influence the stability of postures. He also presented experimental studies of highly unstable tasks, showing how the central nervous system detects the boundary of instability and regulates posture near the boundary, thus simplifying active control demands. Robert Howe (Harvard University) demonstrated a hardware device, a robotic hand gripper, having very few controllable degrees of freedom but which can actually perform remarkably

dexterous manipulation. This performance is gained from a design that reproduces some of the mechanical characteristics of human tendons, demonstrating how the biological architecture aids control and can contribute to hardware applications. Roland Johnasson (Umea University) presented studies of human hand coordination during object manipulation. He showed how sensors of the muscles and skin contribute to detection of object shape and mass, and how an internal model of hand biomechanics, embedded in the nervous system, can best use that information to perceive object properties. Randy Flanagan (Queen's University) continued this theme, showing how objects with unusual geometric or inertial properties are perceived through a combination of vision, touch, and prior expectation. Experience with highly regular or irregular objects can also cause the expectation to change over time. The session summarized highly integrative views of movement, where biomechanics and neural control acted in complementary ways to perform manipulation tasks.

Integrated approaches to control
The final session of the workshop considered integrative approaches in which human experimentation was combined with robotic design and testing to investigate motor control. Andre Seyfarth (University of Jena) showed how robots can be constructed based on principles of human motion, and then tested with experiments that are difficult to perform on humans. The results of these experiments then improve insight regarding human biomechanics. Brent Gillespie (University of Michigan) presented a series of haptics studies, in which a simple robotic device interacts with the human for experimental study of object manipulation. He showed how dynamical interactions lead to perceptions of object properties and improved control. Kevin Lynch (Northwestern University) demonstrated how robots can also take advantage of dynamics to improve coordination tasks, much as a highly skilled human can with a tool or in many sports. Knowledge of these dynamics can allow for fast and dexterous movements. Mitra Hartmann (Northwestern University) then presented her work on touch sensing, not with the hand, but with whiskers. Her studies of the role of rat whiskers in sensing and mapping was then applied to the construction of artificial whiskers that are able to sense object shape and location from touch. This session showed how the field of robotics can contribute to human movement control, and vice versa, through the interplay between science and engineering.

Conclusion

Participants found the workshop to provide a valuable and rare opportunity to meet with and learn from investigators from neighboring relevant fields. The integration of muscle, limb, and brain covered a wide spectrum of approaches to a common goal of understanding human movement. One unique aspect of this particular workshop was that a substantial amount of time was reserved for discussions. This time was used very well, with lively questions posed to the speakers and healthy debate among all participants. Key to the successful outcome of the workshop was the ability to invite the strongest investigators from throughout the world, the financial support to make this possible, and the administrative support of the MBI. Most participants rated the meeting as a tremendous success.

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Workshop 4: Neuromechanics of Locomotion, March 31-April 4, 2008

Organizers: Philip Holmes (Department of Mechanical and Aerospace Engineering, Program in Applied and Computational Mathematics and Neuroscience Institute, Princeton University), Ansgar Büschges (Zoological Institute, University of Cologne), and Robert J. Full (Department of Integrative Biology, University of California at Berkeley)

Overall Summary

Workshop planning and invitation of participants was driven by the following simplified summary of current approaches to locomotion:

(1) Neurobiology has successfully studied the role of central pattern generators (CPGs). CPGs are networks of neurons that can generate the signals that drive muscular activity in the absence of sensory feedback (fictive locomotion). CPGs represent the way by which the nervous system tells the muscles what to do and muscles pass the message on to limbs, which move the body.

(2) A related neurobiological approach concentrates on proprioceptive feedback in intra- and inter-limb coordination for shaping locomotory patterns. Thus, what the limbs are doing now, tells them what to do next; in this view the role of feedback is to control and coordinate the feedforward, clock-driven signals in the generation of the motor output for locomotion.

(3) In contrast, biomechanical studies often focus on body-limb-environment dynamics and ignore neural detail; some being purely passive (e.g. McGeer's and Ruina's passive dynamic walkers). Thus, Newtonian mechanics, with passively-generated forces, tell the body what it must do.

These approaches have generated vast amounts of data, and some mathematical models of individual neurons and motor circuits, sensory pathways, state estimators, and body-limb-environment mechanics. The organizers hoped to further the development of integrated models of locomotive behavior.

With this in mind, workshop participants were drawn from several fields of science and engineering, specifically: biomechanics, neuroscience, control theory and robotics, and applied mathematics. Participants spanned the range from laboratory and field station experimentalists through robot builders, to theoreticians and computational modelers, but many of the key invitees had already partially bridged the experiment/theory divide. The primary goals were to kindle discussions, strengthen current research collaborations, promote future interactions, and inform young scientists (including MBI postdoctoral fellows and OSU graduate students and faculty) of an exciting interdisciplinary research area.

Two other 2007-2008 MBI workshops (#3: Biomechanics and Neural Control, and #5: Real time brain interfacing applications), and the mini-workshop on Restoration of Movement Via Peripheral Nerve Stimulation address topics that compliment those of Workshop 4.

Summary of Presentations

Introduction to the phenomena and mathematical models

The workshop began with a linked pair of lectures by Ansgar Büschges (University of Cologne) and Keir G. Pearson (University of Alberta) on neural controllers for insect and cat legs, and on tracking and avoiding obstacles in locomotion. The former focused on the organization and functioning of local thoracic and spinal circuits for pattern generation, emphasizing common organizational and functional principles that allow the suggestion of a general neural controller architecture for stepping, and the latter on supervisory control and short term memory involving cortical circuits and visual input (cat hind legs can "remember" an obstacle that the front legs have stepped over for several minutes). Robert Full (UC, Berkeley) then introduced a key set of hypotheses that drive much of his work, and that of collaborations including Guckenheimer, Koditschek and Holmes, namely, that (H1) locomotive behaviors are stabilized (passively or actively) around a periodic cycle; (H2) the resulting motions can be characterized by many fewer states than describe the entire behavioral repertoire; (H3) tunable CPGs are coupled to mechanical units, such as passively-spring legs; (H4) within-cycle mechanical feedback and neural reflexes maintain posture, while task level reflexes control cycle-to-cycle behavior; and (H5) neuromechanical control architectures (coupled to the environment) can be situated in a 2-parameter space ranging from centralized to decentralized and feedforward to feedback driven. Örjan Ekeberg (School of Computer Science and Communications) then described a relatively detailed, feedback-driven multiple muscle model of cat hindquarters, ending with preliminary work on incorporation of a CPG.

The afternoon session featured lectures by Philip Holmes (Princeton University), reviewing feedforward models of insect locomotion including purely passive spring mass mechanics, a CPG with reduction of bursting neurons to phase oscillators, and A.V. Hill type muscle models, and by Noah Cowan (Johns Hopkins University), on cockroach steering via antennal input and motion sensing and adjustment in electric fish using control theoretic approaches. These were followed by Andy Ruina's (Cornell University) discussion of predictive theories of coordination and design rules for robots, in which he appealed to the limiting cases of passive dynamics without nerves, and "perfect" neural feedback. The day ended with Dan Koditschek's (University of Pennsylvania) review of control strategies for climbing robots, which drew on Full's hy-

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potheses (especially H3 and H5) and stressed the importance of understanding state space topologies and "repellor dynamics" in avoiding critical regions that correspond to failure (e.g., falling 4 stories).

Swimming

Sten Grillner (Nobel Institute for Neurophysiology) opened with an extensive review of data and modeling of lamprey swimming, including (hemi-) segmental oscillators and the CPG, edge cell and visual feedback, body actuation and hydrodynamics, showing that behaviors including turning and backward swimming can be reproduced based on current understanding of spinal network activity. His group has simulated spinal CPG models with 10,000 neurons and ~800,000 synapses in order to test current concepts of descending control and intersegmental coordination. In contrast, Thelma Williams (University of London) and Tyler McMillen (California State University, Fullerton) presented a relatively simple neuromechanical model featuring feedforward activation of muscles, passive body viscoelasticity and simplified (lift/drag) hydrodynamic reaction forces that allows one to determine the sources of speed differences between waves of neural activation and curvature passing down the lamprey body. Lisa Fauci (Tulane University) then described the immersed boundary method (of Peskin, Fauci, McQueen) for computing unsteady Navier-Stokes-based coupled body-fluid velocity fields, and illustrated with simulations of leech (medium Reynolds number) and sperm and bacterial flagellae (low Reynolds number). She and Chia-Yu Hsu (Tulane University) are currently developing a lamprey simulation. Keith Sillar (University of St. Andrews) then described development of axial and limb-based locomotion in the clawed frog, explaining how a contralaterally-inhibited traveling wave transforms into in-phase hind leg kicking. Many neurobiological details that determine the developmental switches have been identified.

Ted Iwasaki (University of Virginia) then reviewed his work with Otto Friesen on the CPG for leech swimming, concluding with a simple mechanical model for body motions with linearised hydrodynamic forces. Eric Tytell (University of Maryland) described spine bending experiments on lamprey: effectively an open loop experiment on edge cell feedback that reveals frequency ranges of CPG entrainment in response to inputs at different locations on the spinal cord. The session ended with Avis Cohen's presentations of a series of challenges for mathematicians on control in motor systems, via multiple examples, including locust flight, cat walking and lamprey swimming.

The day concluded with Robert Full's public lecture "Bipedal Bugs, Galloping Ghosts and Gripping Geckos: Bioinspired Computer Animation, Robotics, Artificial Muscles and Adhesives." Full articulated how we learn from nature by discussing: the difference between biology and human engineering, the need for reducing complexity by finding synergies and symmetries, how to select an organisms for inspiration by using the advantage of scale to discover principles, the Krogh Principle, the comparative method and extremes in design & key innovations. He showed an example of how to use the evolutionary history of organisms to discover novel principles and finished by presenting a model for mutualistic, interdisciplinary collaboration.

From swimming to walking and running
Jean-Marie Cabelguen (Institute National de la Sante et de la) and Auke Ijspeert (Swiss Federal Institute of Technology) opened with linked lectures on amphibian locomotion - transitions between walking and swimming - focusing on salamander experiments, their mathematical model, and an electromechanical realization as an amphibious robot. The CPG circuit was described in some detail: a notable feature being the addition of a second activation variable to the phase variable describing the state of each hemi-segmental oscillator. Anke Borgman (University of Cologne) resumed the stick insect neural controller discussion of Büschges, by describing experiments that reveal neural pathways and influences underlying intersegmental coordination among CPGs of the three thoracic segments, each driving a single front, middle or hind leg. Andrew Biewener (Harvard University) then described data and simple passive spring mass (SLIP) models of running guinea fowl subject to large perturbations (falling through a tissue paper `floor' to a lower surface, and recovering on the next stride). He showed that while SLIP captures mass center dynamics, redistribution of kinetic, elastic and gravitational energy is reduced from that predicted by SLIP by intrinsic muscle dynamics and EMG modulation. He proposed that differences in muscle-tendon architecture suggest that a proximo-distal gradient of neuromotor control may operate within the limbs of vertebrate animals, with proximal muscles hypothesized to operate under feedforward control and distal muscles via intrinsic and feedback control. He ended by discussing joint and limb compliance in the quadrupedal robot "big dog" (Boston Dynamics), noting that animal foot position and ground reaction force data had guided the robot design.

Josef Schmitz (University of Bielefeld) and Volker Duerr (University of Cologne) then returned to details of proprioceptive sensing and feedback in their talks on the WALKNET artificial neural network model of stick insect leg coordination and on "motor intelligence" in locust grooming movements. In contrast to the stereotypical centralized, feedforward control of legs in rapid cockroach running, Schmitz provided evidence suggesting that no (stick) insect gaits are produced by master clocks, that the six leg controllers are independent, and that cooperation is achieved by local feedback rules involving neighboring pairs of legs. Duerr used the somatotopic map involved in locust wing grooming to derive a nonlinear transform from target positions to joint angle space and argued that goal-directed movements can contain both "aimed" and "free" phases (e.g., swing in legged locomotion). Scott Hooper (Ohio University) and Jonas Buchli rounded out the day with talks on the importance of detail and differences (as a counter to general principles), and on simple oscillator models (e.g., for CPGs), with tunable frequencies. Hooper showed, for example, that parameter search by genetic algorithms can tune a complex multi ion channel (Hodgkin Huxley type)

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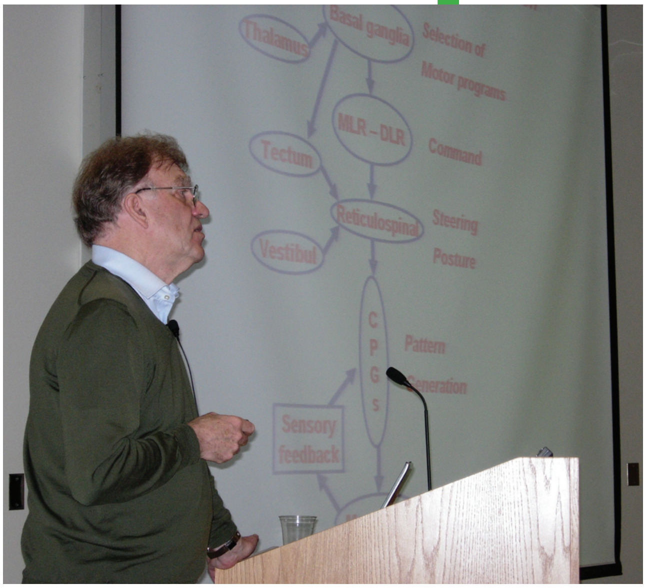


neuron model to recover a known parameter set. He also discussed slow muscle properties and the importance of scaling when thinking in terms of neural control for locomotor pattern generation. Buchli championed an extension of linear systems theory approaches using ideas from dynamical systems theory.

Walking, running and manipulating
Sasha Zill (Marshall University) opened with discussions of force sensing and feedback to muscles in insect legs, describing experiments in which animals were loaded with electromagnets while being otherwise free to move. Interestingly and relevant in terms of generating inter-leg coordination, local feedback signals on body load clearly depended on the phase of leg stepping of neighboring legs. Roy Ritzmann (Case Western Reserve University) followed by describing the role of descending control from the central complex in cockroach climbing and turning, showing that local proprioceptive pathways are modulated by descending CNS activities. Kiisa Nishikawa (Northern Arizona University) then described a new muscle model that accounts for storage and recovery of energy during ballistic motions, describing elastic recoil during the very fast mouth opening in a toad prior to prey capture. She closed by speculating on the role of such mechanisms in the CNS control of movement. Andre Seyfarth (Jena University) returned to spring mass models to describe the mechanical modulation of walking, running and hopping, ending by showing that a “hip torqued” model with feedback that directs its foot force through a virtual pivot point (near the shoulder) can produce periodic gaits with bounded pitch in a sagittal plane 3 degree of freedom model.

Matthias Gruhn (University of Cologne) returned to stick insects to discuss turning, showing that curve walking of a single leg can occur without intersegmental signals from neighboring legs, and that local (same leg) information and information from other legs both play roles in determining leg and joint kinematics, even in the absence of aspects of ground resistance (using a slippery oiled plate technique). Then Francisco Valero-Cuevas (Cornell University) reviewed his work on neuromanipulation: including detailed EMG and dynamic studies, with force measurements, at the limits of manipulative skill. He described both neuromotor redundancy and feasible force and motion regions in state space, and argued that anatomical complexity enables versative control. Finally, Reinhard Blickhan (Jena University) spoke on muscles, gearing and self-stability, revisiting Hill-type muscle models and simple spring mass body-limb and leg models, and proposing that human runners adjust to upcoming steps by preadapting muscle stiffness.

Flying, running, standing, simulating and optimizing

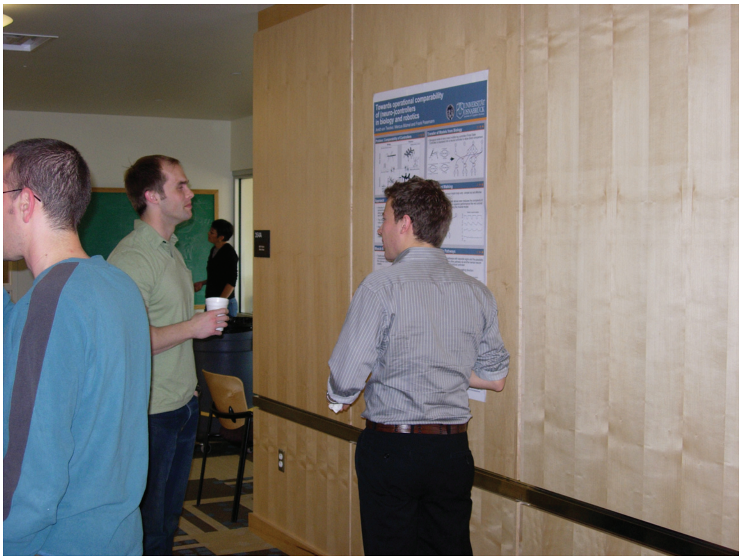
Jane Wang (Cornell University), our only pilot, described direct simulations of the Navier-Stokes equations in modeling unsteady aerodynamics of insect flight. Her models include single and multiple rigid wings moving on prescribed cyclical paths, and multiple flexible wings in both 2 and 3-dimensional geometries. She posed the question "Are wings optimal?" and described numerical experiments establishing that motions that minimize aerodynamic power to support a given body weight with a prespecified wing shape resemble observed wing motions in fruit flies, bumble bees and hawk moths. Shai Revzen (UC, Berkeley) and John Guckenheimer (Cornell University) then described the use of dynamical systems methods (phase reductions, Poincare maps and Floquet coordinates) and Grassmannian manifolds (for deriving statistical tests) in analyzing the stability and dimension reduction in cyclic locomotive motions. Lena Ting (Emory University and Georgia Tech) spoke on neuromechanics, dimensionality, redundancy, heirarchy and complexity in posture control, focusing on muscle synergies and feedforward/feedback tradeoffs, and John Miller (Royal College of Surgeons in Ireland Reserach Institute) explained a "preadaptive" numerical scheme for simulating multiple time scale (singularly perturbed) dynamical systems.

The closing formal talk was given by Manoj Srinivasan (Princeton University), who reviewed theoretical work on optimal gaits using a simple actuated bipedal point-mass model and a version with a biophysically-motivated muscle model. The former predicts a walk-run transition but overestimates energy costs; the latter underestimates costs, but together they suggest the generality of the notion that locomotive strategies minimize work.

Panel Discussion

First, a number of opening statements were given. John Guckenheimer argued from the perspective of a mathematician that he was intrigued by the use of mathematics in biological systems and by the mutual gain there is for mathematics and biology. In response to that, Andy Ruina and Noah Cowan emphasized the difference between robot systems in the 1980s and the hexapod systems today: instead of using high-level artificial intelligence, roboticists and other engineers who construct moving robots now use biologically inspired feedback control, thus better connecting robotics to the natural world. Ansgar Büschges argued that the interaction between biology and robotics were still biased in one direction: using biological findings for implementation and testing in robotics appeared to be more straightforward than in the other direction, i.e. than using approaches and results from robotics to develop testable hypotheses for biology and new experiments. He saw the main reason in the prominent differences in the "output stage properties" of robots as compared to biological systems. It was agreed in general that this, however, should not diminish the fact that decomposing engineering solutions could drive the development of new ideas for experiments in biology which, in turn, could give useful information to roboticists. Noah Cowan responded that an advantage of robotics could be, to offer an alternative to mathematical simulations. One example could be dealing with physical situations such as antennae-substrate interactions or ground contact – where a numerical simulation failed. He proposed that one may now be on the verge of being able to decide which approach might be the better one for a given

problem. (Subsequently, Phil Holmes noted that Lex Smits (Princeton), in collaboration with Avis Cohen's group, has constructed a robotic lamprey in order to study vortex shedding and unsteady fluid motions driven by an "exactly" time-periodic body, so that phase averaging methods may be used. Real lampreys rarely swim with sufficient regularity for this to be possible. This represents a use of robotics to support biological research.) Shai Revzen suggested that new boot-strapping methods were powerful tools to give a measure of statistical significance and that these methods should be used more often on the data collected.



In which direction(s) should the field move? With this comment, John Guckenheimer led the discussion into a new focus area, i.e. how much detail is needed to make general models and to serve the demands of theoretical approaches. He made a plea to make more quantitative data analysis in biology and robotics and also to make mathematical models of robots. Scott Hooper seconded that by emphasizing that more detail from available data is needed by mathematicians. In his opinion, one of the key issues and problems is, that a number of older electrophysiological experiments should be redone, given the fact that the amount of data collected at the time does not come up to today's demands on the level of analysis. In this respect, Shai Revzen saw the need for a more general use of numerical and statistical methods in data analysis which were presently largely absent. Volker Dürr raised the question whether one should start to build databases, to better access and exchange data between labs and within collaborations. Kiisa Nikishawa commented that one major problem with model templates were that real animals often behaved differently: she stressed the need to figure out the specifics of an animal much more thoroughly. André Seyfarth saw a major role in defining templates to show us that we usually understand neither mechanics and emergent behavior, nor how a system in question is sensing energy. Andy Ruina proposed that, based on the present available knowledge on the biological details and the available tools for performance analysis in biological systems, one could profit by attempting to take a robot and understand/analyze it like an animal. (The Koditshek and Full labs have begun such a program.) Örjan Ekeberg saw a need for mathematicians and control theorists to come up with mathematics that handle stability in situations with lots of variability within AND between steps in the area of modeling walking. In his opinion the trajectory didn't really matter because the boundaries were far away from it. He emphasized the need for hybrid systems with discrete and continuous elements. Neural activity would actually take place between the borders and not at the limit cycle. John Guckenheimer supported this notion as a strong proponent of "hybrid control" for understanding biological systems and designing robots.

Jean-Marie Cabelguen then moved the discussion towards future biological research and approaches. It is well known that sensitivity and gain of feedback were gated dependent on the present motor task and activity. Therefore, the "old" concept of sensory feedback not being influenced/modulated is irrelevant in today's biology. Homework for biologists would be to understand feedforward regulation of modulation in gain of sensory feedback. Ansgar Büschges saw a major problem with the biological data available on terrestrial locomotion. Aside from stating what kind régimes one is working on, being it slow walking or fast running, there appeared to be a need for biologists to explain the mechanisms that make an animal locomote "fast" or "slow." This would tell biologists and engineers what major differences there were, which are currently mostly inferred from theoretical considerations. It would also require new approaches that would allow one to look at transitions between the two forms of terrestrial locomotion.

Avis Cohen emphasized that, in her opinion, one should profit from this big advance of so many biologists and theoreticians coming together by preparing a major collaborative grant focusing on the most contemporary and pressing issues in the field, perhaps all working on the same "animal model" in order to work out all the details, and then serve as a model for other organisms. This was supported by Shai Revzen, who formulated the need for model organisms for studying swimming, walking and flying, but was opposed by Ansgar Büschges and others, who expressed the opinion that there is no single animal that can serve an "optimal model" in general. Instead contemporary advancement in approaches and techniques would allow us to choose the best suited animal for each question. "General applicability" of the insights could then be decided upon at a subsequent stage of research, when comparing the biological solutions different animals use for the same task or behavior. In fact the subsequent discussion showed that relatively few animals are used to study the mechanisms underlying locomotor behavior. These are stick insects, cockroaches, lampreys and lizards, some bipedal and quadrupedal birds and mammals, some legged and a swimming robot, and a very small number of flying insects.

Volker Dürr pointed out the complications of studying complex behaviors in general and asked for studying "well defined" aspects, like goal directed behavior. Noah Cowan also gave support to John Guckenheimer's approach (see above), but also emphasized the need for parallel approaches to look at goal directed behavior. Modeling would allow one to make predictions and to design appropriate biological experiments accordingly. When making predictions about the constraints one could question the underlying synergies and the number of degrees of freedom. Ansgar Büschges commented, that in order to analyze nervous system function in that respect, one needed to identify simple behavioral elements as some sort of "building blocks" and to analyze their neuronal bases. Based on that, one might then be able to work "from bottom up" to understand the neural control of goal directed behavior and subsequently even more complex behaviors. Simon Sponberg supported the approach to challenge an organism's performance and to profit from the insights gathered when the animal fails under certain

circumstances. Shai Revzen and Avis Cohen warned that very often one might be working on parameters and details of an animal that did not matter much for the generation of any given behavior and that the real problem might be to find those parameters that actually did matter. On top of that Kiisa Nishikawa warned that “description of behavior” might just be the easy part, and that prediction of behavior would tell us that we had understood its generation was much harder.

Some participants then commented on the communication conventions among scientists in different fields. Noah Cowan stated that he was amazed at the discourse and good communication despite the distant conceptual space. Andy Ruina asked for sharper ideas and more controversial discussions. In contrast Örjan Ekeberg saw no need for controversial issues at the moment. Instead, he argued that one should stress the importance of a common language and common semantics to be more efficient in doing collaborative work. According to Volker Dürr and Avis Cohen the knowledge about the different fields in the community was not big enough to have constructive arguments, yet. One suggestion for future workshops and discussions should therefore be to have a tutorial for all participants ahead of the workshop to allow more effective communication. Finally, there were many positive comments about the workshop and many notes of thanks to the organizers Phil Holmes, Bob Full and Ansgar Büschges.

Mini-workshop: Restoration of movement via peripheral nerve stimulation, April 29, 2008

Organizers: Dawn M. Taylor (Departments of Biomedical & Mechanical Engineering, Case Western Reserve University and The Cleveland VA Functional Electrical Stimulation Center of Excellence) and Dave Terman (Mathematical Biosciences Institute, Ohio State University)

Overall Summary

This focused one-day workshop was designed to bring together people working on modeling and implementing movement restoration strategies for people with motor disabilities. The workshop started with modeling at the resolution of the individual neuron and ended with modeling of the complete musculoskeletal system.

Summary of Presentations

Neuron Scale modeling

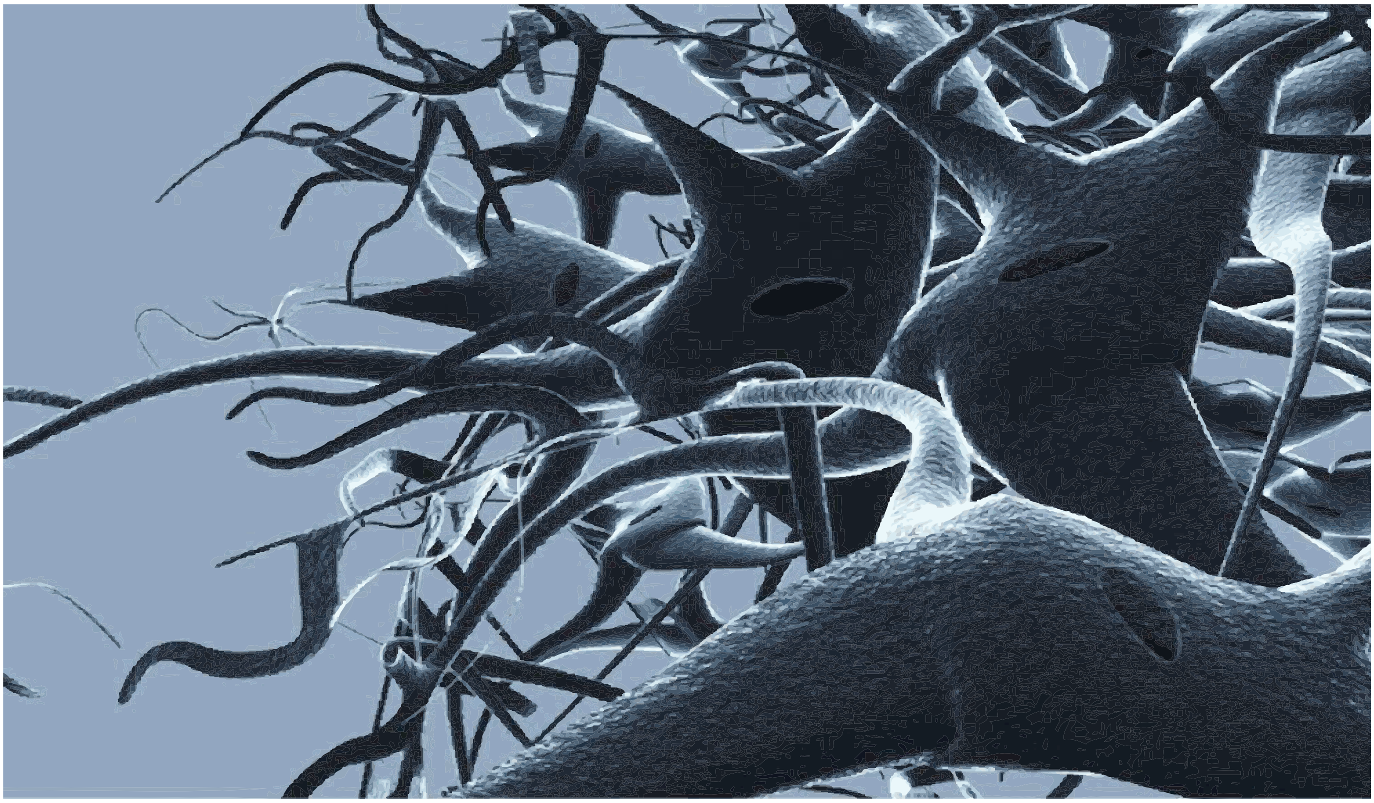
The morning session started with a short overview of the field of modeling peripheral nerve stimulation given by Cameron McIntyre (Cleveland Clinic). The field of peripheral nerve stimulation links models of the electric fields generated by stimulating electrodes with models of the neurons being stimulated. The keynote speaker for the morning session was Jay Rubenstein (University of Washington). Although Dr. Rubenstein’s work focuses on the auditory nerve instead of motor neurons, the fundamental properties of current-neuron interactions still applied, and cross fertilization between the auditory and motor neural stimulation fields benefits both fields. Dr. Rubenstein discussed how stimulation parameters can be modified to generate more naturalistic firing patterns in the target neurons via stochastic resonance. He also demonstrated the value of linking model-based research with in vivo experimentation by discussing experimental studies that are consistent with models and those that defy model-based explanation.

Peripheral Nerve Electrode Technologies and Their Applications

The mid-day sessions covered new electrode technologies and how they can be applied in movement restoration applications. This section of the workshop started with a comprehensive survey of the field of applied peripheral nerve stimulation and the current state of the electrode technology given by Ron Triolo (Cleveland VA Medical Center). Two speakers then followed, each focusing on a different electrode technology.

Ken Yoshida (Indiana University-Purdue University Indianapolis) talked about a flexible, thin-film multi-channel, intra-fascicular neural prosthetic interface—the thin-film Longitudinal Intra-Fascicular Electrode (tfLIFE). His evaluation of the electrode ranged from computer simulations of electrode selectivity, electrode platform design and modifications, animal testing, and validation of the technique. He also compared and contrasted the tfLIFE with other available peripheral nerve stimulation strategies, such as multi-channel cuff electrodes, intra-muscular electrodes, and inter-fascicular approaches.

Richard Norman (University of Utah) talked about the Utah Slanted Electrode Array (USEA) and how this design can improve selective stimulation of individual nerve fascicles as well as provide fatigue resistant stimulation. His discussions also included practical issues such as automating characterization of the USEA nerve interface; measuring the kinematics of the sit-to-stand maneuver in the cat; achieving surgical access to the nerves innervating the muscles of the hip, knee, and ankle; automated mapping of implanted electrodes to specific muscles; automated evaluation of electrode-muscle stimulation selectivity; and stimulation strategies for producing tremor-free, fatigue resistant graded force in the muscles.



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Musculoskeletal Modeling

The afternoon session focused on using musculoskeletal models and virtual training environments to efficiently test and improve control strategies for generating functional movements in the disabled via neuroprosthetic technologies.

Robert Kirsch (Case Western Reserve University & Cleveland Functional Electrical Stimulation Center) gave a brief overview of the field of musculoskeletal modeling and how it can be used both online and offline to improve movement restoration via peripheral nerve stimulation. Offline, models enable us to efficiently run many hundreds or thousands of simulations to thoroughly evaluate different control strategies and to compare different electrode placement options. Online, models can be used in real time in conjunction with a virtual arm interface. This virtual simulation environment enables individuals to control a virtual arm that responds like their paralyzed arm would respond if activated via electrical stimulation. This real-time visual feedback enables us to test learning effects and ensures that the device control system is complementary to our own nature error correction movement strategies.

Rahman Davoodi (University of Southern California) expanded on this theme by talking about his parallel work on using real-time virtual simulation environments of prosthetic limbs to evaluate and refine prosthetic limb control system designs for amputees. Dr. Davoodi discussed the need for biomechanical modeling of neural prostheses and reviewed existing biomechanical modeling tools and their applications. He also discussed the challenges to accurate modeling and simulation of neural prostheses.

Conclusion

The workshop ended with an open discussion on what is needed to move the field forward. One consensus that came out of this discussion was the need for coordination and compatibility standards of the different modeling software packages designed to deal with modeling at the different scales (i.e. from the level of the individual neuron up to the whole musculoskeletal system). Standardizing model formats and implementation/analysis code as well as writing software to convert models between platforms would help develop cross-fertilization between labs and reduce redundant efforts. However it was also discussed how this coordination is unlikely to happen on its own without an initiative from one or more funding agencies to hire a dedicated team of engineers to work specifically on this issue.

Workshop 5: Real-time brain interfacing applications

May 12-15, 2008

Organizers: Dawn M. Taylor (Departments of Biomedical & Mechanical Engineering, Case Western Reserve University and The Cleveland VA Functional Electrical Stimulation Center of Excellence) and Dave Terman (Mathematical Biosciences Institute, Ohio State University)

Overall Summary

The field of neural engineering has been transformed by the growth in computer processing power over the last ten years. It is now possible to read in multiple neural signals, process those signals, and respond to that processed data in real time. The number of research articles published on 'Brain-computer or brain-machine interfaces (BCI/BMIs)' has been steadily increasing along with its mention in the popular media. There is something inherently fascinating about controlling various devices directly with one's brain. However, the capability to 'decode' and interact with the nervous system in real time has great potential for the development of new treatments and assistive devices for people with severe neurological disorders. This real-time interaction with the nervous system can also facilitate experimental studies to further our fundamental understanding of how the brain works, learns, and adapts.

This real-time interaction poses special challenges because device design requirements often include minimizing power consumption and device size for practical implantation. These design requirements necessitate implementing efficient algorithms and quantifying the tradeoffs between making algorithms more efficient versus more effective. Another issue common to most chronic neural engineering applications is non-stationarity of the neural interface and of the biological system itself.

Neural recording falls into two general categories: 1) 'unit' recordings where the action potentials from individual neurons are extracted from the signals, and 2) 'field potential' recordings which measure the summation of synaptic activity of many neurons together. Field potential based BCI/BMI systems were discussed on day one of the workshop. Days 2 & 3 focused on intracortical BCI/BMI technologies. Day 4 focused on a different aspect of real-time brain interfacing—epilepsy seizure detection and prevention.

Field-potential-based control of assistive devices

This session focused on BCI/BMIs that use extracortical recordings which range from scalp surface to brain surface and anywhere in between. Theresa M. Vaughn (New York State Department of Health) started off the session with an overview of the field. She provided a review of the clinical need in the different paralyzed populations (e.g. ALS, spinal cord injury, etc) and reviewed the applications in these populations. She also reviewed the aspects of extracortical signals that are modulated with various attempted movements or with different brain states.

BCI/BMIs are used to generate two distinct types of command signals for controlling assistive devices. Classifiers are used to select from a finite number of discrete choices (e.g. icon or letter selection) whereas continuous decoding of the brain signals allows for ongoing proportional control of a device such as controlling the X and Y position of a computer cursor or controlling the continuous movements of a prosthetic limb. The next two talks were designed to cover each of these areas. Charles Anderson (Colorado State University) discussed applying multistate classifier functions to EEG data. To correctly classify many different states from noisy EEG, Dr. Anderson described methods that make use of both spatial and temporal patterns in the EEG Gerwin Schalk (Washington Univ. in St. Louis) then covered decoding of ECoGs as well as EEGs. He compared the resolution benefits of ECoGs and discussed how attempted movements of different body parts can be differentially decoded. He showed that useful informa-

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tion is imbedded in the DC signals as well as in the frequency bands. He also showed how researchers from the Wadsworth Center have now been able to generate 3D cursor control with only surface EEGs.

Femke Nijboer (University of Tubingen) discussed problems and issues regarding moving EEG-based BCI/BMIs out of the lab and into the clinical or home environment. These issues include the effects of psychological factors on performance as well as how disease state may affect the ability to use different types of BCI/BMIs. Most BCI/BMIs rely on visual feedback, but the completely locked in person may have vision loss and new auditory-based interfaces may be more appropriate.

Spike sorting and tracking for real-time applications

Unlike EEGs or ECoGs, Intracortical recording technologies can detect the action potentials of individual neurons. Specific algorithms are needed for detecting (i.e. identifying if an action potential occurred) and sorting (i.e. identifying which of the neurons near the electrode made the voltage spike). Unfortunately, intracortical signals are often non-stationary over the course of days, so it is difficult to set up a spike detection/sorting system and just let it run as-is. Automated tracking and adjustment of sorting parameters is needed. Efficient and effective spike detection and sorting algorithms are critical for intracortical BCI/BMIs. Yet only a relatively small amount of effort is going into spike sorting and tracking compared to the efforts to decode the firing rates once they are received. Since many attendees working with field potentials were unfamiliar with the complex issues regarding spike sorting, the session started with an overview of the spike sorting process given by conference organizer Dawn Taylor (Case Western Reserve University & Cleveland VA Medical Center). She reviewed common spike sorting methods and problems as well as computational efficiency issues. In order to sort spikes, the signal must be sampled at a resolution an order of magnitude higher than the sampling rate needed for field potential analysis. On chip spike sorting is a necessity for intracortical recording technologies that are fully implanted. Developing and miniaturizing hardware to simultaneously process tens to hundreds of channels of data at a very high sampling rate is a challenge. Mohanasankar Sivaprakasam (University of California at Santa Cruz) talked about their work in efficient detection/sorting algorithm development and on-chip implementation.

Intracortical signals are non-stationary over days. In the lab, the signals are usually resorted daily before experiments are run. However, to integrate intracortical recording technologies into peoples' daily lives, this manual daily resorting must be replaced by a reliable automated process. Carlos Vargas-Irwin (Brown University) discussed their work in automating spike sorting as well as assessment of sorting algorithms using a large synthetic dataset incorporating realistic challenges faced during spike sorting (e.g. overlapping and phase-shifted spikes).

Multi-channel microelectrode-based control of Devices

Later on day 2, the discussions on analyzing intracortical signals for real-time applications transitioned from spike sorting algorithms and hardware to making sense of the signals once they are detected. To bridge these two topic areas, Karim Oweiss (Michigan State University) gave a talk on how we can conceptually design a Multiscale intra-Cortical Neural Interface System (MiCNIS) that extracts all the hypothesized constituents of the neural code in real time within the resource-constrained environment of an implanted system. He also described methods for inferring the cortical circuits underlying the observed spiking activity associated with specific behavioral tasks. This type of circuit-level analysis has the potential to enhance our understanding of single cell and population activity that encodes information relevant to Brain-Machine Interface systems. Lee E. Miller (Northwestern University) followed this up with a talk on decoding hand muscle activation levels from intracortical signals. Others have shown that limb kinematics can be decoded from the brain. Electrical stimulation of the peripheral nerves can be used to create these limb movements in paralyzed individuals. However, for decoded limb kinematic data to be used, the BCI control system itself would have to determine how much muscle activation is needed to generate the desired movements. By decoding muscle activations directly, this difficult transformation step can be bypassed and muscles activated directly based on the decoded brain activity.

Day 2 ended with a public lecture from Eberhard Fetz (University of Washington) who did some of the first work in real-time brain-machine interfacing back in the late Sixties. He gave a historical perspective on the field as well as showed some of his new cutting-edge work in which wearable circuits allow for continuous recording and stimulation of the nervous system in awake, behaving animals. Being able to link spike detection in one part of the nervous system with stimulation of another part of the system opens up many new avenues of research, especially in terms of evaluating plasticity and motor learning.

Multi-channel microelectrode-based control of Devices (Continued)

Within the last few years, intracortical BCIs have moved from the lab and into clinical testing in people with spinal cord injuries. Leigh Hochberg (Brown University/Harvard Medical School) started the day's session with an overview of intracortical BCIs that included a review of monkey work as well as a discussion of the ongoing pilot clinical trials where persons with high tetraplegia or other paralyzing conditions are chronically implanted with intracortical microelectrodes in the hand area of the motor cortex. His group is examining the use of intracortical activity for restoring communication, mobility, and independence to people with paralysis. Both local field potentials and unit activity can be acquired with intracortical microelectrodes. Useful information is contained in both types of signals and local field potentials (LFP) may be more robust over time. Daniel W. Moran (Washington University in St. Louis) shared his recent results in non-human primates suggesting that LFP spectral power in the 100-200 Hz range is well correlated with

single unit activity and may be used to obtain many of the same movement features. These results suggest that long-term unit stability is not necessary to get useful information from intracortical implants.

When brain activity is used to control an external device in real time, the user usually has visual feedback of the resulting movements generated by his or her brain activity. This visual feedback allows the user to learn through experience how to modulate their brain activity more effectively. To make use of these beneficial changes, the decoding function must also adapt. Dawn Taylor discussed the benefits of coadaptive decoding strategies and ways to optimize adaptation rates to the particular user. Whereas Dr. Taylor's discussion focused on ways to use an error vectors calculated at each time step to determine how to periodically refine the decoder, Justin Sanchez (University of Florida) talked about reinforcement learning—a form of adaptive decoding that provides more generalized feedback on the success or failure of a give action. This more general paradigm can be applied to many different types of BCI/BMIs including more abstract applications that do not have a movement or directional component.

Neural Analysis for real-time epilepsy interventions and neuromodulation

Another application of real-time brain signal analysis is in epilepsy prediction and intervention. Reliable identification of seizure precursors from the EEG of individuals with epilepsy could provide an early warning for the individuals and would enable the development of new real-time therapeutic interventions. Klaus Lehnertz (University of Bonn) presented an overview of the field of seizure prediction and detection, its history, accomplishments, recent controversies, and potential for future development, specifically with regard to real-time processing of multichannel EEG recordings. Clinical trials have already started with real-time detection and intervention of epileptic seizures. Robert B. Duckrow (Yale University School of Medicine) talked about an ongoing clinical trial of responsive neurostimulation for epilepsy. In this study, an implanted field potential recording system continuously monitors the brain signals and then triggers stimulation when it detects early indications of a seizure. Although it is difficult to prove that a seizure would have occurred but was stopped by any given stimulus event, large scale clinical trials with test and control populations will be able to determine overall efficacy of responsive stimulation for seizure suppression.

This early clinical trial is using simple algorithms for detecting seizures and for patterning stimulation. Improvements may be possible by developing more sophisticated algorithms that can predict and suppress seizures more effectively. Brian Litt (University of Pennsylvania) discussed how refinements to seizure prediction and intervention may be achieved by increasing the spatiotemporal resolution of the recorded signals. Fast ripples in the kHz range are seen in the field potentials of people with epilepsy when recording systems are set up with the appropriate sampling and filtering ranges. Fast ripples and other novel signal features may be able to further improve seizure prediction/detection in future systems.

Conclusions

This four-day workshop was well attended and brought together people working with extracortical and intracortical brain signals for applications that ranged from assistive communication devices, to neuroprosthetic limb control, to seizure prediction and suppression. Before the workshop, there were two days of tutorials given by leaders in these fields (Drs. Rachael Saidler, Andrew Schwartz, Paul Nunez, Julius Dewald, and William Stacey). These tutorials helped bring many of the attendees up to speed on the fundamentals of neurophysiology and neural recording in the areas in which those attendees were unfamiliar.

This workshop fostered lively but congenial discussions on key issues that cross applications and recording technologies. Discussions included: the challenges of moving these technologies out of the lab and into everyday use, the need to balance simplicity and ease-of-use with the performance of more complex hardware and software, and dealing with non-stationarities in the signals. New opportunities became apparent as people working with brain computer interfacing were made aware of the chronically implanted recording technologies already in clinical trials in the epilepsy studies. In addition, epilepsy research could be advanced by collecting continuous, long-term data from paralyzed but non-epileptic individuals to provide a range of ‘normals’ for comparison. More interactions between the brain-computer interface community and the epilepsy intervention community will inevitably advance both fields. The workshop provided opportunities for many attendees to give additional short talks and posters, which enhanced the diversity of discussions and interactions. Some of these additional talks, such as the one swarm intelligence and analog computing (which used a computer made with Jell-O as an example) challenged some traditional thinking and created quite a buzz. Overall, the workshop was very well received, and attendees left inspired and motivated from the cross-fertilization of ideas.

Workshop 6: Brain Imaging, June 9-13, 2008

Organizers: Allen Tannenbaum (Georgia Tech), Stefano Soatto (UCLA), Sylvain Bouix (Harvard), and Kaleem Siddiqi (MCGill)

Overall Summary

Medical imaging has been undergoing a revolution in the past decade with the advent of faster, more accurate, and cheaper imaging modalities. This powerful new hardware has driven the need for corresponding software development, which in turn has provided a major impetus for new algorithms in signal and image processing. Many of these algorithms are based on partial differential equations, curvature driven flows, geometry, and novel statistical techniques. The purpose of this workshop is to bring together researchers from all aspects of medical imaging with the emphasis on brain imaging for a multi-disciplinary workshop in which various views may be shared, and hopefully new research directions may be opened.

A key research area is to formulate biomedical engineering principles based on a rigorous mathematical foundation in order to develop general-purpose software methods that can be integrated into complete therapy delivery systems. Such systems support the more effective delivery of many image-guided procedures--biopsy, minimally invasive surgery, and radiation therapy, among others. Mathematical models form the basis of biomedical computing in general and medical imaging in particular. Basing those models on data extracted from images continues to be a fundamental technique for achieving scientific

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progress in experimental, clinical biomedical, and behavioral research. Images, acquired by a range of techniques across all biological scales, are central to understanding biological problems and their impacts on human health purely because images now encompass so many techniques beyond the visible light photographs and microscope images of biology's early years. Today, imaging is better thought of as geometrically arranged arrays of data samples measuring such diverse physical quantities as time-varying hemoglobin deoxygenation during neuronal metabolism or vector-valued measurments of water diffusion through and within tissue. The broadening scope of imaging as a way to organize our observations of the biophysical world has led to a dramatic increase in our ability to apply novel processing techniques and to combine multiple channels of data into sophisticated and complex mathematical models of physiological function and dysfunction.

The workshop brought together a diverse group of researchers from the medical imaging community with various backgrounds including radiology, psychiatry, signal and image processing, surgery, physics, mathematics, and neurophysiology.

The workshop focused on the following topics:

- Medical Imaging Modalities for Brain Imagery: MRI, fMRI, DTI, PET, SPECT, CT
- Medical Imaging Processing and Computation: Registration, segmentation, visualization, computer graphics, shape theory;
- Mathematical Algorithms: Statistical, geometric, partial differential equations;
- Applications: Image guided surgery (e.g., interventional magnetics), imaging for understanding pathology (Alzheimer's disease, Parkinson's, OCD, clinical depression), image processing and deep brain stimulation.

Summary of Presentations

Generalities in Brain Imaging and Neuroscience

After introductions by Professors Avner Friedman and Allen Tannenbaum, the first day began with a panel discussion on biological drivers and applications. Members of the panel were Mike Miller, Mike Vannier, and Zhuowen Tu. The day was dominated by two tutorial talks.

Jim Fallon (University of California, Irvine) gave an overview of brain imaging science and neuroanatomy. Behavior is assumed to emerge from specific circuits in the brain. These circuits are routinely inferred from functional brain imaging patterns. Differences in patterns of functional images between, for example, task conditions, drug conditions, and between control and pathological conditions are routinely used to inform researchers of basic biological mechanisms and pathophysiological processes in normal and abnormal brain function. There are, however, multiple levels and principles of organization of brain circuitry, often beyond the resolution and/or functional capabilities of imaging techniques such as PET, fMRI, and DTI. Furthermore, each neurological/psychiatric disorder differentially affects neuroanatomical modules and types of circuitry, and these must be borne in mind in the analyses and discussion of implied circuitry in imaging experiments.

Mike Vannier (University of Chicago Medical Center) gave a tutorial on imaging as a biomarker. Imaging as a biomarker of drug response is becoming an increasingly important field of research. Government, industry and academia have agreed to collaborate on improving the development of therapies and outcomes for common diseases, especially cancer, through biomarker development and evaluation. Biomarkers are biological indicators of disease or therapeutic effects that can be measured by in vivo biomedical imaging and molecular imaging in particular, as well as other in vitro or laboratory methods. Recent work has shown that biomedical imaging can provide an early indication of drug response by use of CT, MRI and PET/SPECT.

Many sources of uncertainty exist in imaging as a biomarker. Biological variability, for example, is a factor both drug- and patient-dependent and thus difficult to characterize or model. However, other uncertainties are associated with the image data collection platform and the robustness of software tools required for reliable, quantitative measurement of change over time, such as tumor volume, radioactive tracer activity, or contrast agent dynamics. All these sources of uncertainty significantly affect the statistical power of clinical drug or therapy trials.

The challenges and opportunities for imaging biomarkers are explored for brain imaging, especially brain traumatic injury and developmental disorders.

Issues in Brain Medical Image Processing
Zhuowen Tu (UCLA) gave a talk on a methodology for an automated whole brain image segmentation Segmenting cortical and subcortical structures from 3D brain images is of significant practical importance. In this talk, we will discuss a new statistical modeling/computing framework and show its application for whole brain segmentation. The notion of using context information for solving the medical imaging problem has been increasingly realized in the field. However, how to learn an effective and efficient context model, together with the image appearance, remains mostly unknown. The current literature using Markov Random Fields (MRFs) and Conditional Random Fields (CRFs) often involves specific algorithm design, in which the modeling and computing stages are studied in isolation. Medical images observe complex patterns, contributed by many factors such as textures (homogeneous, inhomogeneous, and structured) and machine parameters. This auto-context model is about a new attempt to push the appearance and context information in a seamless way by automatically incorporating a large number of short-range and long-

range features. The resulting algorithm has nearly the identical procedures in computing (testing) as in modeling (training), and thus, achieves rapid performance the holistic medical image segmentation task. Dr. Tu showed a variety of sub-cortical and cortical segmentation results using this model.

Marcel Prastawa (University of Utah) gave a talk on statistical and physical models for generating a brain tumor MR image validation database. Automatic segmentation of pathological brain MR images with tumors is crucial for analyzing tumor characteristics, efficacy of drug treatments, and surgical planning. Many segmentation schemes have been developed, yet validation and performance comparisons are difficult since there are no public brain tumor MRI databases with consistent, reliable ground truth. In his talk, he presented the practical use of statistical and physical modeling for generating synthetic brain tumor MR images with known, objective ground truth. He combined a physical deformation model and a physical infiltration model to generate anatomical data with pathological structures (tumor and edema). He then used a statistical image generation model to obtain synthetic multimodal brain tumor MR images that correspond to the generated anatomical data. The synthetic brain tumor MRI database has potential uses for validating different segmentation schemes, for surgical simulations, and for clinical training.

Michael Miller (Johns Hopkins University) gave a general lecture on computational anatomy. Computational Anatomy is the study of the shape and structure of manifolds in human anatomy. In his talk, Professor Miller reviewed results from CA along these lines, including (i) embedding of shapes into a metric structure via flows of diffeomorphisms (ii) conservation laws for geodesics describing metric connection of shapes (iii) statistics on families of shapes encoded via these metrics. The emerging focus in Computational Functional Anatomy is the inclusion of the study of function in the curved coordinates of anatomical manifolds. Methods for performing inference in this setting were examined coupled to morphometric studies.

Steven Zucker (Yale University) described the human visual system and related issues in machine vision. He applied notions from Computer Vision and Perceptual Organization to the problem of modeling biological tissue structure in diffusion MRI data. The key ideas are to model white matter fibers as 3D space curves, to view diffusion MRI data as providing information about the tangent vectors of these curves, and to frame the problem as that of inferring 3D curve geometry from a discretized, incomplete, and potentially blurred and noisy field of tangent measurements. Inspired by notions used in Perceptual Organization in Computer Vision, he developed local geometrical constraints which guide the inference process and ultimately result in the recovery of the underlying fiber geometry.

In a very entertaining special seminar directed at a general audience Jim Fallon talked about the brain of the psychopathic murderer. Professor Fallon described the the effects of early and late brain lesions on behavior. In particular, he outlined the importance of inhibition and disinhibition, lesions associated with aggression and violence, and lesions associated with the psychopathic murderer. The impact of gene is also essential: mutations vs. single nucleotide polymorphisms (SNPs), gene SNPs associated with aggression, impulsivity, and violence, and the interactions of these factors with the environment. In short, he attempted to give the necessary and sufficient conditions for creating a psychopathic murderer.

Statistical Methods

The third day began with a lecture by Professor William Wells (Brigham and Women's Hospital) on a marginalized MAP approach and EM optimization for pair-wise registration. He formalized the pair-wise registration problem in a maximum a posteriori (MAP) framework that employs a multinomial model of joint intensities with parameters for which we only have a prior distribution. To obtain an MAP estimate of the aligning transformation alone, he treated the multinomial parameters as nuisance parameters, and marginalize them out. If the prior on those is uninformative, the marginalization leads to registration by minimization of joint entropy. With an informative prior, the marginalization leads to minimization of the entropy of the data pooled with pseudo observations from the prior. In addition, Wells showed that the marginalized objective function can be optimized by the Expectation-Maximization (EM) algorithm, which yields a simple and effective iteration for solving entropy-based registration problems. Experimentally, he demonstrated the effectiveness of the resulting EM iteration for rapidly solving a challenging intra-operative registration problem.

Ganesh Sundaramoorthi (UCLA) talked about tubular surface evolution for segmentation of tubular structures with applications to the cingulum bundle from DW-MRI. He provided a framework for extracting tubular structures from medical imagery. The general methodology was applied to modeling and extracting the cingulum bundle (CB) from diffusion-weighted imagery (DW-MRI) of the brain. The CB is a tube-like structure in the brain that is of major importance to clinicians since it may be helpful in diagnosing schizophrenia. This structure consists of a collection of fibers in the brain that have locally similar diffusion patterns, but vary globally. Standard region-based segmentation techniques adapted to DW-MRI are not suitable for this application because the diffusion pattern of the CB cannot be described by a few simple global statistics. Typical active surface models extended to DW-MRI allow for arbitrary deformations that give rise to unlikely shapes, which do not respect the tubular geometry of the CB. In his work, Sundaramoorthi explicitly modeled the CB as a tube-like surface and construct a general class of energies defined on tube-like surfaces. Modeling the CB as a tube-like surface is a natural shape prior. Since a tube is characterized by a center-line and a radius function, the method is reduced to a curve evolution that is computationally much less costly than an arbitrary surface evolution. The tubular model of the CB also has the advantage that computing shape statistics and functions defined on the CB are simplified.

Polina Golland (Computer Science and Artificial Intelligence Laboratory (CSAIL), Massachusetts Institute of Technology) gave a presentation on modeling anatomical heterogeneity in populations. She described iCluster, a fast and efficient algorithm that clusters a set of images while co-registering them using a parameterized, nonlinear transformation model. The output of the algorithm is a small number of template images that represent different modes in a population. This is in contrast with traditional, hypothesis-driven computational anatomy approaches that assume a single template to construct an atlas. She derived the algorithm based on a generative model of an image population as a mixture of deformable template images. The experimental results demonstrate that the algorithm can discover interesting sub-populations, suggesting applications in atlas-based segmentation and statistical analysis of anatomical differences in clinical studies.

Jim Duncan (Yale University) described his work on the model-based analysis of brain structure and function from MRI data. Quantitative analysis of brain structure and function is important in the study of many neurological and neuropsychiatric disorders. Professor Duncan presented work grounded in the use of spatial constraints and mathematical optimization to analyze neuroanatomical structure and function of the human brain from Magnetic Resonance Images (MRI). He described his approach to segmenting cortical gray matter using a coupled level set strategy. Then, he presented an approach to subcortical segmentation based on the use of both object self-shape and neighborhood spatial relationship priors, both embedded in a level set- parameterized, maximum a posteriori (MAP) estimation framework. Finally, he discussed very recent work aimed at incorporating prior knowledge of brain activation patterns and segmented anatomical information (gray matter/white matter) to provide improved estimates of activation strength in a functional MRI (fMRI) attention-modulation experiment, again using a MAP estimation approach.

Keith Worsley (Montreal Neurological Institute, Montreal, Canada) gave a talk on the statistical analysis of surface data. SurfStat is a Matlab toolbox for the statistical analysis of univariate and multivariate surface data using linear mixed effects models and random field theory. It is inspired by Jason Lerch's Thickness Statistics written in R, and Jonathan Taylor's BrainStat, part of NIPY, written in Python. It is intended for cortical thickness data on triangular meshes, either for the whole cortex or one for each hemisphere. It will handle any triangulated surface data, written in FreeSurfer or MNI object format. The only requirement is that the triangulation scheme must be the same for all surfaces, i.e. the data must be registered to a common surface. Its main engine fits fixed effects and mixed effects, univariate and multivariate, linear models and makes inference using T, F, Hotelling's T2 and Roy's maximum root statistics.

Diffusion Imaging and Psychophysics
Yogesh Rathi (Brigham and Women's Hospital, Harvard Medical School, Boston, MA) began the day with a talk about directional functions for orientation distribution function estimation in the context of Q-ball imaging. Orientation distribution functions (ODF) can be used to represent multiple fiber crossings in the brain as recorded by High Angular Resolution Diffusion Imaging (HARDI). Current state-of-the-art methods use spherical radial basis functions or spherical harmonics to represent the ODF. These methods however require many coefficients to represent each ODF and ambiguities can occur when the principal diffusion directions are to be extracted. In his work, Rathi proposed to use "directional functions" for representing the signal and provide closed form expressions to approximate the corresponding ODF. These functions require very few parameters (three) to represent the ODF and the principal diffusion directions are naturally obtained during the estimation process. He showed how to perform interpolation using these directional functions and propose 2 metrics, a Euclidean and a hybrid-Euclidean-

Riemannian, to compute geodesic distances between 2 ODFs.

John Melonakos (Georgia Institute of Technology) described his recent work on geodesic tractography segmentation for DW-MRI analysis. Many frameworks have been proposed for the analysis of brain DW-MRI imagery. The objective of these frameworks is to yield a greater understanding of structure and connectivity within the brain and the relation of these to function. In his research, he developed a framework for the analysis of DW-MRI datasets that consists of two components: 1) an optimal path connecting two regions of interest and 2) a volumetric fiber bundle segmentation, initialized on the optimal path. This framework has the advantage of providing both connectivity and structural information about fiber bundles. Also, in this talk, he discussed the pros/cons of this framework and challenges in the state-of-the-art of fiber bundle segmentation.

Allan C. Dobbins (University of Alabama at Birmingham) gave the final talk of the Workshop about binocular vision ranging from psychophysics to imaging. Binocular vision is central to both space and form perception and plays a critical role in visuomotor feedback control. He described his recent work that demonstrates a dissociation of perception from feedback control in a way that highlights the different computational requirements of these tasks. Attempts to look at the cortical loci of these processes were also elucidated.

Workshop 7: Systems Biology of Decision Making, June 16-20, 2008

Organizers: Kevin Passino (EEOB, OSU), Thomas Waite (EEOB, OSU), Roger Ratcliff (Department of Psychology, OSU), Thomas Seeley (Department of Neurobiology and Behaviour, Cornell University), Nigel Franks (School of Biological Sciences, University of Bristol), and Naomi Leonard (Mechanical and Aerospace Engineering, Princeton University)

Overall Summary

Experimental biology is uncovering the mechanisms supporting decision-making in individual animals (e.g., in monkeys) and social animal groups (e.g., bees and ants). Multiscale mathematical models are being developed and validated for several species, including those for the (i) neuron-to-behavioral levels in cognitive neuroscience (e.g., diffusion or decision field theory models), (ii) organism-to-group levels for social insects (e.g., differential equations and individual-oriented models), and (iii) individual/group-to-ecological levels in behavioral ecology (e.g., optimization or evolutionary game-theoretic models).

Several of these models and species share common features; hence there exists significant opportunities for cross-fertilization and progress toward an understanding mechanisms and whole-system emergent properties. Mathematical, statistical, and computational analyses are being to used to study (i) properties of the dynamics of decision making (e.g., feedback mechanisms, coupling, stability, and speed-accuracy trade-offs), (ii) cross-scale effects (e.g., impact of massively parallel mechanisms at one level on emergence of choice discrimination or distractor elimination abilities at a higher level), (iii) effects of context (e.g., similarity and attractivity effects),

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and (iv) Darwinian evolution of robustness or reliability in the presence of uncertainty (e.g., isolated failures at one level and environmental variations).

The goal of this workshop is to facilitate the development of an integrated "systems biology" of decision-making processes that spans multiple spatio-temporal scales and levels of biological organization, and accounts for the perspectives of biologists, psychologists, economists, mathematicians, and engineers.

Summary of Major Components

The workshop was broken into three parts: individual decision making, ecology and evolution of decision making, and group decision making. The topics naturally built on each other, yet the participants were from three very different areas (ones that normally do not overlap in conferences, or journal where they publish). Participants uniformly were pleased that these three groups were brought together for the first time and felt that they learned a lot from each other. Basically, researchers from each of the areas knew that the other areas existed, and that they were relevant to their own, but this was the first time that they had the opportunity to hear the top experts talk from these areas. Participants were quite pleased that this group was brought together and several expressed the desire to have a similar meeting in the future.

Below, the list of speakers is given for each of the three areas along with a summary report on what happened in each.

Summary on Individual Decision Making

Monday: Individual Decision Making I
Speakers: Roger Ratcliff (OSU), Phillip Holmes (Princeton), Hauke Heekeren (Max Planck), Sophie Deneve (Inst. Sci. Cog., France).

Tuesday: Individual Decision Making II
Speakers: Jeffrey Schall (Vanderbilt), Jochen Ditterich (UC Davis), Bill Newsome (Stanford), Marius Usher (U. London).

Panel discussion: Leader, Roger Ratcliff

The first two days of the workshop focused on mathematical models and experimental methods for discovering how individual decision making takes place in humans and animal models (primarily monkeys). Roger Ratcliff overviewed progress on use of diffusion models in representing a range of decision making tasks under a variety of conditions (e.g., human aging). Phillip Holmes talked about mathematical models of decision making, including optimality analyses. The talks by Hauke Heekeren and Sophie Deneve built on the work by Ratcliff and Holmes. On Tuesday, we started with talks by Jeff Schall and Jochen Ditterich. Schall talked about experiments and models of decision making for monkeys performing choice tasks, while Ditterich discussed fine details of the mathematical models and their accuracy. Bill Newsome and Marius Usher's talks discussed experiments with monkeys and mathematical models respectively. Ratcliff led a panel discussion where he tried to integrate the concepts and approaches and point to holes in the overall discussion.

The first two days were quite successful at overviewing the work on the neurobiology, behavior, and mathematical models of decision making. The focus was necessarily on relatively simple decision making since a high level of understanding was sought at the neuron or neuronal population level. While the main decision making tasks were ones of choice (e.g., indicating with an eye saccade the direction of movement of coherent dots moving in a field of random dots), it was felt that such types of choices were relevant to the interests of the workshop participants from the other two areas (ecology and evolution of decision making, and group decision making). In particular, many questions were asked by these other two groups and an integration of ideas began to occur on the first two days, which was later fulfilled after the next three days of the workshop.

Summary on Ecology and Evolution of Decision Making

Wednesday: Ecology and Evolution of Individual and Group Decision Making
Speakers: Thomas Waite (OSU), David Stephens (Minnesota), Luc-Alain Giraldeau (Montreal), Melissa Bateson (Newcastle).

Panel discussion: Leader, Ian Hamilton

Due to health reasons Thomas Waite was not present. David Stephens talked about foraging theory and its use in analyzing decision making by animals. Luc-Alain Giraldeau talked about social foraging theory and its use in the study of group decision making, particularly his study species was birds. Melisssa Bateson talked about context-dependent decision making in birds and other species. Ian Hamilton led a panel discussion where he facilitated the integration of the talks of the day, and the integration with the previous two days of discussions on individual decision making.

It was felt that there was a significant disconnect between the study of the ecology and evolution of decision making vs. the study of the neurobiology of decision making. Yet, several felt that there were potential bridges between the two fields that would lead to progress in both areas. First, it was felt that in individual decision making there needs to be an understanding of some of the well-studied decision making concepts from ecology and evolution (e.g., the marginal value theorem). Second, it was felt that more work needs to be done on understanding irrationality in animals (e.g., context dependent decision making as studied by M. Bateson). Third, it was felt that the neurobiologists should seek to understand the neural basis for context dependent decision making.

Summary on Group Decision Making

Thursday: Group Decision Making I
Speakers: Thomas Seeley (Cornell), Kevin Passino (OSU), Iain Couzin (Princeton), Naomi Leonard (Princeton).

Friday: Group Decision Making II
Speakers: Nigel Franks (U. Bristol), Stephen Pratt (Arizona State U.), Nick Britton (U. Bath), James Marshall (U. Bristol).

Panel discussion: Leader, Kevin Passino

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Thomas Seeley explained how he and his colleagues have conducted a long series of experiments over many years to understand how a hive of honey bees selects its new home. He also overviewed relationships between the choice of the new home and choice experiments in neurobiology. Kevin Passino overviewed the dynamics of nest-site selection by honey bees and introduced the notion of swarm cognition, the idea that the swarm acts as an information processing cognition system during choice tasks. He showed a wide range of similarities between swarm cognition and neurobiology. Iain Couzin talked about coordinated motion of animals, with a focus on social insects (e.g., locusts). Naomi Leonard talked about mathematical models of coordinated motion of agents (both animals and robots), specifically synchrony. Nigel Franks overviewed a range of experiments on ants performing the choice task of selecting a new home. Stephen Pratt continued this discussion on ants, and also covered his initial work on context dependent decision making for an ant colony (which meshed well with the earlier talk and discussions on Melissa Bateson's work). Nick Britton talked about mathematical models of ant colony decision making. James Marshall's talk integrated the diffusion models from individual decision making with, e.g., the mathematical models by Nick Britton of honey bee nest site selection. He discussed common features and optimality analyses. This was definitely a fine talk to integrate the various concepts and discussions held throughout the workshop.

Summary on Challenges for Each Field

Overall, we feel that the workshop made good progress in the direction of integrating three disparate fields of study. To help make the progress tangible Kevin Passino, in the final panel discussion, presented a set of challenges for each of the three groups. These were:

Challenges to Individual Decision Making Researchers (Neuroscientists):

1. Can you find the neural basis of the marginal value theorem?
2. Can you test monkeys with a "best of N, with N unknown" problem (like for bees and ants)?

Challenges to Ecology and Evolution of Decision Making Researchers:

1. Can you use the neuroscience models to help explain context-dependent choice in animals?

2. Are the optimality models/analyses from mathematical neuroscience useful in explaining animal behavior?
3. Is there such a thing as an evolutionarily stable diffusion model?

Challenges to Group Decision Making Researchers:

1. What do general models (i.e., ones that can represent both individual and group decision making) teach us?
2. Can choice experiments like the ones used in neuroscience be administered to animal groups?

Tutorials

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

Speakers: David Terman and Greg Smith

Topics covered included: membrane transport and diffusion, classical biophysics of the squid giant axon, Markov chain models of single channel gating, cell signal transduction, the buffered diffusion of intracellular calcium, intracellular calcium responses, and excitability, bistability, oscillations, and bursting in a physiological context. We also considered activity patterns in networks of synaptically coupled neurons, along with specific applications including models for sleep rhythms, Parkinsonian tremor and sensory processing.

Each topic was studied from the perspective of nonlinear dynamics (either deterministic or stochastic). Mathematical idealizations of each phenomena was constructed and then analyzed using computer simulation (numerical integration) and graphical techniques (phase- plane analysis).

Tutorial for Workshop 2, October 18-19, 2007

Speaker: Keith Gooch

The first session began with a brief history of cell, organ, and culture from the early 1900s to the present and its relationship to modern efforts in cell and tissue engineering. The focus of this hour was a survey of current and proposed applications of cell and tissue engineering. Using these applications as a starting point, the second hour was a survey of the recurring approaches to (paradigms) and methods evident in CTE applications. The third hour covered major challenges in CTE and some promising approaches to dealing with them.

Part 1. Tutorial for Workshop 3, January 10-11, 2008

Speakers: Kurt Thoroughman and Art Kuo

Topics included: muscle physiology; dynamics of multi-body systems, passive walking; and feedback control and state estimation.

Kurt Thoroughman spoke on the *Foundations of Neural Computation and Human Motor Behavior*. An initial consideration of quantification of the neural basis of human motor control can be quite attractive: people are easier to talk to than animals, people can perform motor tasks per the instructions of the scientist, and scientists can analyze the performance of people. The next steps, however, contain several conundrums, enigmas, paradoxes, and dilemmas. People dislike having electrodes driven into their brains; functional imaging techniques offer limited spatial and/or temporal resolution. Emergent observable human motor behavior integrates a motley stew of predictive and reactive cortical control, subcortical and spinal circuits, and musculoskeletal biomechanics. In this tutorial I will describe the origins of my prescription for addressing these issues via a computationally-intensive theoretically-and-neurophysiologically-inspired psychophysical approach. Wide-ranging retrospective, circumspective, and prospective questions and discussions are wholeheartedly encouraged.

Part 2. Tutorial for Workshop 4, March 27-28, 2008

Speakers: Ansgar Bueschges, Phil Holmes, and Shai Revzen

Shai Revzen:

- Experimental methods of video tracking -- some of the tracking and filtering tools that we used that biologists are less familiar with, such as Kalman filter variants.
- Phase estimation details, with a more "hands on" orientation.
- Application of phase estimation to control hypothesis testing.
- Details of the numerical methods - a "methods section" for the joint talk in the workshop.

Possible illustrations using SciPy.

Phil Holmes:

- Basic mathematical ideas: hoppers and hybrid dynamical systems.
- Piecewise holonomic constraints and partial asymptotic stability.
- Passive SLIP and LLS models.
- Muscle models.
- Bursting neurons and coupled oscillators as CPG models, phase reduction, phase response curves and averaging. Illustrated by some matlab simulation demos.

Ansgar Bueschges:

- Biological sensors and sensorimotor processing relevant for locomotion, organizational principles of CPG networks.

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

Speakers: Rachael Seidler, Andy Schwartz, Paul Nunez, Julius P.A. Dewald, and William Stacey

Topics included: intracortical unit recording studies of normal movement; field potential recording studies of normal movement; deep brain structures and movement disorders; and physiology and epilepsy.

Paul Nunez discussed *Fundamentals of the Relationships Between Brain Activity and EEG: Large Scale Brain Physics and Neocortical Dynamic Correlates of Conscious Experience*. Spatial-temporal patterns of scalp recorded potentials (electroencephalography or EEG) are determined by the dynamic behavior of current sources in cerebral cortex and volume conduction through head tissue. Volume conduction is governed by a macroscopic version of Poisson's equation, whereas cortical source dynamics originates with delay mechanisms characterized as "local" (e.g., postsynaptic potential rise times) or "global" (finite speed of action potential propagation in cortico-cortical fibers).

All measures of brain function (fMRI, PET, etc.) are highly selective, for example, electrophysiological data recorded from inside the skull are scale-dependent, sensitive to electrode size and location. Scalp potentials are

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dominated by “synchronized” (phase locked) cortical sources facilitated by cortical anatomy and physiology. Cortical sources of scalp potentials are most conveniently expressed at the mesoscopic spatial scale as current dipole moment per unit volume. The integrated product of this “meso-source” with the head Green’s function determines scalp potential.

Human behavior and cognition are believed to originate with cell assemblies (neural networks) embedded in the synaptic source fields that generate EEG. Based on their apparent importance to EEG dynamics, healthy brains may require the following: non-local interactions via cortico-cortical fibers, nested hierarchical structure of cerebral cortex, resonant interactions between cell assemblies at multiple scales, and a proper “balance” between functional segregation and integration controlled by (chemical) neuromodulators.

Rachael Seidler focused on *Fundamentals of Motor Control Theory and Underlying Neuroanatomy*. She covered basic motor control theory and neuroanatomy of the motor system. She discussed methods for measurement of human movement and brain activity, with particular emphasis on techniques that are relevant for brain machine interfaces. Attendees gained a working understanding of forward and inverse motor control models, efferent copy, state estimation, and their underlying neural correlates. She then delved further into motor system neuroanatomy, including the motor cortical areas (parietal cortex, premotor, supplementary, and cingulate motor areas) as well as basal ganglia thalamocortical loops.

Finally, William Stacey presented his talk on *Bringing Clinical EEG into the 21st Century*. Clinical epileptology relies heavily on EEG for diagnosis and treatment. Current practice with EEG is based on 80 years of experience, and has derived from visual classification of the voltage patterns produced by patients with and without epilepsy. One interesting result of this method is that much of clinical EEG is based on recognition of patterns that are poorly understood physiologically. There are many EEG waveforms that have only recently been reconciled with physiology, and many more that are still unexplained. Paradoxically, epileptic seizures are one condition for which the physiology is still poorly understood. Seizure classification, therefore, is a subjective measure that relies on visual inspection and comparison with known patterns and with the patient’s “typical background.” A seizure is a waveform that a) deviates from the norm b) evolves in frequency and location and c) has clinical or electrical characteristics of a seizure. The subjective nature of this process, as well as the heterogeneity of seizures, makes automated seizure detection a difficult endeavor. An even more difficult problem is seizure prediction, in which early seizure biomarkers might be identified long before the actual seizure begins. Modern EEG equipment now is capable of performing complex analyses and sampling at much higher rates, opening new avenues for analysis that had never been accessible to clinicians. While clinical practice has only begun to utilize this new technology, there are tools from mathematics, engineering, and machine learning that provide intriguing new methods to tap in to this new information.

Summer Programs

Summer Undergraduate Program (June 23 - July 3, 2008)

The summer of 2008 marked the MBI's third annual Summer Program for Undergraduates that includes a two-week active survey of mathematical biology followed by a six-week Research Experience for Undergraduates (REU) program.

The first week of the program involved tutorials and hands-on computer labs in mathematical bioscience topics. The first day saw Dennis Pearl presenting key issues in statistical phylogenetics – aligning molecular sequences and inferring evolutionary trees. In the afternoon, Jeff Pan led a computer lab, giving students a chance to try out the Clustal alignment program along with Phylip and MrBayes phylogenetics software. On Tuesday Joe Verducci and Paul Blower presented 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. David Terman lead a tutorial on the principles of mathematical neuroscience on Wednesday morning, focusing on issues related to modeling sleep rhythms while Hyejin Park and Michael Rempe gave participants experience with the XPP and MatLab programs in the afternoon computer lab. Tao Shi presented a lively tutorial on statistical analysis of climate change data the following day while Jenny Brynjarsdottir led the afternoon computer lab using MatLab. The week concluded with Greg Singer covering selected topics in bioinformatics and had the students trying out some web-based bioinformatics software in the computer lab that afternoon.

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 (Kyle Lyman, Xiaoge Clare Tao, Brittny Major, and Harika Rayala) presented their studies of the mechanisms underlying sleep rhythms and the human sleep/wake cycle. The phylogenetics project team (Amrish Deshmukh, Stephanie Hayes, Ryan Starski, and Tim Wang) presented an analysis of the evolution of the bird flu virus and testing its relation to geography, time, and host population. Next, the Climate change group (Arjun Dasgupta, Mark Kilkert, and Lyda Urressta) described their study of temperature records over North America separating the pattern of long term changes from their natural short term variability. The bioinformatics project, presented by Vikas Choudhary, Valerie

Tiu, Michael Sharpnack, and Adam Jones, 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 Jack Enyeart and Hunter Rhodes examined correlational methods to relate micro RNA and 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 Byrd Polar Research Center where Ellen Mosley-Thompson, Lijia Wei and Victor Zagorodnov introduced the students to the workings of their ice-core paleoclimatology research.

At the conclusion of the two-week program, the REU component of the summer program then chose five students to spend six weeks going into much more depth in a research project in their chosen area. These projects are on-going at the time of this writing.

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 Programs

Summer Graduate Program (July 7-25, 2008)

In a series of tutorial lectures during the first week Richard Bertram discussed examples of how mathematical modeling is used in the areas of neuroscience and physiology. Topics included the dynamics of electrically excitable cells, calcium dynamics and waves, fast and slow time scales, bursting oscillations, phase oscillators, circadian gene oscillations, and synchronization of oscillators. A basic familiarity with ordinary and partial differential equations was assumed. Techniques for the analysis of nonlinear ordinary differential equations using phase plane and bifurcation diagrams were discussed throughout the series of lectures.

Monday: A description of neuron models and mean field models for neural populations; analysis of these models through phase plane and bifurcation analysis.

Tuesday: Biophysical mechanisms for and mathematical analysis of bursting oscillations; oscillations of this type are frequently observed in nerve and endocrine cells.

Wednesday: Mathematical descriptions of stochastic systems; stochastic ion channel fluctuations in nerve cells, and hybrid deterministic models that include noise; ways that noise itself can amplify a signal, such as stochastic resonance.

Thursday: A synapse is a tiny structure that is the center of many reactions that are key to short term and long term memory. Memory is stored in synaptic couplings between neurons. Mathematical models for the mechanisms of short and long term memory.

Friday: Synchronization as a widespread phenomenon in neural populations; synchronization analyzed mathematically, using the phase oscillator as a mathematical tool for the analysis.

Each afternoon David Terman gave a two-hour tutorial on computational methods for solving ODEs and PDEs.

At the end of the week the students were divided into five teams, each headed by and MBI postdoc or 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.

Mini-conference: Group Projects Reports (July 24-25, 2008)

Project 1: Dynamical properties of biochemical reaction networks
Project Leader: Gheorghe Craciun
Participants: Sayanti Banerjee, Badal Joshi, Dori Luli, and Caian Pantea

Project 2: Mathematical modeling in immunity
Project Leader: Judy Day
Participants: Jerome Goddard II, Jung Kim, Yanping Ma, Debra McGivney, and Kaitlin Sundling

Project 3: Microarrary data analysis
Project Leader: Shuying Sun
Participants: Robert Fitak and Morteza Haeri

Project 4: Development of the primary visual cortex: ocular dominance, competitions for neurotrophins, and the cortical laminae
Project Leader Andy Oster
Participants: Einat Bergman, Sam Hsiao, Robert McDougal, and Svitlana Zhuravytska

Project 5: An ODE/PDE model for tumor growth
Project Leader: Yangjin Kim
Participants: Joseph Isaacson, Orit Lavi, Hyejin Park, and Kara Pham

Public Lectures

Why do we walk the way we do?

Max Donelan, PhD CIHR New Investigator and MSFHR Scholar, Assistant Professor of Kinesiology and Associate Member of Engineering Science, Simon Fraser University; January 15, 2008

Max Donelan

Walking is much easier to do than understand. After all, we could put a man on the moon before we had a good idea as to how he would move once he got there. Our understanding of walking has been limited not by effort or creativity but by the complexity of the problem. This complexity is a consequence of the tight interactions between the mechanics of muscles and limbs, the control of the brain and spinal cord, and the constraints of the physical environment. While sometimes frustrating, it is also what makes the study of locomotion physiology so fascinating and is responsible for walking's many unsolved mysteries. For example, why does amputee walking requires more energy than able-bodied walking? And, are their advantages of bipedalim over quadrupedalism? The goal of this talk is to provide insight into some of the general principles that underlie walking as well as the interesting techniques that have elucidated these principles. Many of these principles were originally identified, or have since been expanded upon, by the participants in the ongoing MBI Workshop titled "Biomechanics and Neural Control: Muscle, Limb and Brain".

Robert Full

Bipedal Bugs, Galloping Ghosts and Gripping Geckos: Bioinspired Computer Animation, Robotics, Artificial Muscles and Adhesives

Robert Full, Ph.D., Professor, Poly-PEDAL Lab, Department of Integrative Biology, University of California, Berkeley; April 1, 2008

Integrative biology is providing inspiration to disciplines such as animatronics, animation, mathematics, medicine, robotics and space exploration. In return, these disciplines supply biologists with novel design hypotheses, algorithms and measurement devices. One example is in the area of BioMotion. Comparing the remarkable diversity in nature has lead to the discovery of general principles. Animals are amazing at legged locomotion because they have simple control systems, multifunction actuators and feet that allow no surface to be an obstacle. Extraordinarily diverse animals show the same dynamics - legged animals appear to bounce like people on pogo sticks. Force patterns produced by six-legged insects are the same as those produced by trotting eight-legged crabs, four-legged dogs and even running humans. Rapid running cockroaches can become bipedal as they take 50 steps in a single second and ghost crabs seem to glide with aerial phases. Yet, the advantage of many legs and a sprawled posture appears to be in stability. Mathematical models show that these designs self-stabilize to perturbations without the equivalent of a brain. Control algorithms appear embedded in the form of the animal itself. Muscles tune the system by acting as motors, springs, struts and shocks all in one. Amazing feet permit creatures such as geckos to climb up walls at over meter per second without using claws, glue or suction - just molecular forces. These fundamental principles of animal locomotion have inspired the design of creations in computer animation (A Bug's Life, Pixar), new control circuits, artificial muscles, self-clearing dry adhesives, and autonomous legged robots such as Ariel, Sprawl, Sitckybot and RHex will spawn the next generation of search-and-rescue robots.

Volitional control of neural activity and brain-computer interfaces

Eberhard E. Fetz, Ph.D., Professor, Physiology & Biophysics, Core Staff, University of Washington; May 13, 2008

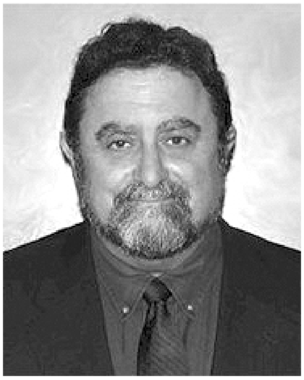
The conscious volitional self in our brain perceives and interacts with the world through sensory, motor and cognitive systems that involve largely subconscious neural mechanisms. Experimental manipulations of these mechanisms reveal the brain's remarkable ability to adapt to changed conditions. The volitional self can also be extended through artificial devices, such as brain-machine interfaces, which exploit the brain's ability to incorporate prosthetic extensions. Accurate control of brainmachine interfaces depends on a combination of effective decoding algorithms and the brain's ability to adaptively modify its neural activity. Recently developed implantable recurrent brain-computer interfaces provide artificial feedback connections that the brain can learn to incorporate and that can also modify the brain's neural connections. This talk will explore these issues in light of current advances in neuroscience and neuroprosthetics.

Imaging Nature and Nurture in the Human Brain: From Psychosis, Aggression and Murder to Politics and Free Will

James Fallon, Psychiatry and Human Behavior, University of California Irvine School of Medicine; June 10, 2008

Eberhard E. Fetz

Although it is presently not precisely known what causes a person to become aggressive, violent, or psychotic, new neuroscientific evidence from functional brain imaging and genetics in schizophrenics and psychopathic killers hint at a rare convergence of genetic, epigenetic, and environmental factors occurring at specific windows of time. And there may be little room open for 'free will' to mitigate this tragic convergence of factors.



James Fallon

Real democracy: How honey bees choose a home

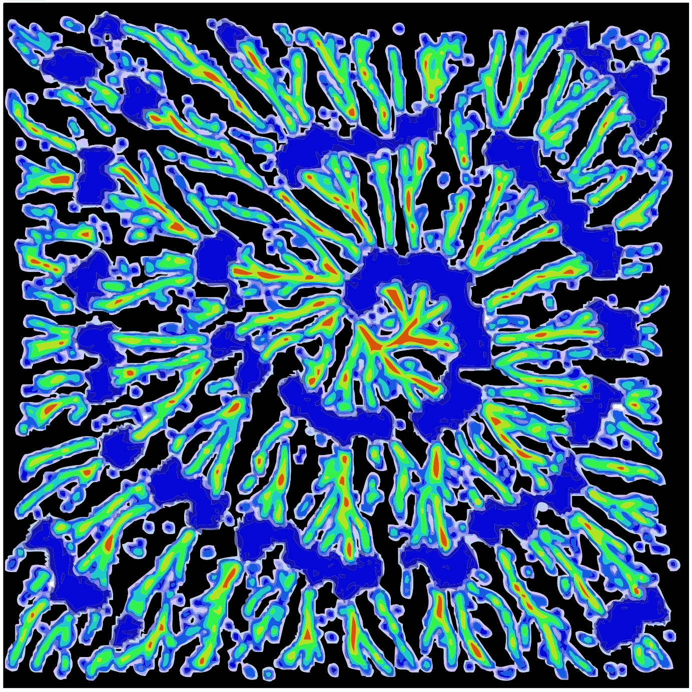
Thomas D. Seeley, Professor of Biology and Chairman, Department of Neurobiology and Behavior, Cornell University; June 17, 2008

Real democracy - when citizens meet in a face-to-face assembly and bind themselves under decisions they make themselves - has been practiced for some 2500 years by humans, but for more than 20 million years by honey bees. We will examine the remarkable democratic decision-making process of a honey bee swarm as it chooses a new home. We will see that bees have evolved sophisticated ways of working together to identify a dozen or more potential dwelling places, to choose the highest quality one for their new home site, and to make a decision without undue delay. We will conclude with some take-home lessons from the bees ("swarm smarts") on how to foster good decision making by democratic groups of humans.

Thomas D. Seeley

Future Programs

Mathematical Challenges in Developmental Biology
2008-2009



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.

Workshops

2008 Workshop for Young Researchers in Mathematical Biology (WYRMB)
September 2-5, 2008
Organizers: MBI Postdocs

Cell and Tissue Movement
September 15-19, 2008
Organizers: Leah Edelstein-Keshet, Thomas Hillen, Stan Maree, and Veronica Grieneisen

Pattern Formation and Development in Colonial Organisms
October 13-17, 2008
Organizers: Philip Maini and Hans Othmer

Focus Group for Discovery: Mathematical and Computational Models in Biological Networks
October 20-24, 2008
Organizers: Marty Feinberg, Eduardo Sontag, and Gheorghe Craciun

Focus Research Group: Multiscale Models in Biology
November 2-4, 2008
Organizers: Mark Alber

Symposium: Evolution of Genomes and Origin of Species
November 10, 2008
Organizers: Daniel Janies, Baltazar Aguda, Jeffrey Parvin, and Avner Friedman

Morphogenesis, Limb Growth, Gastrulation, Somitogenesis, Neural Tube Formation
November 17-21, 2008
Organizers: Robert Dillon and Hans Othmer

Cancer Development, Angiogenesis, Progression, and Invasion
January 26-30, 2009
Organizers: Kristin R. Swanson and Alexander Anderson

Wound Healing
March 9-13, 2009
Organizers: Philip Maini and Chandan Sen

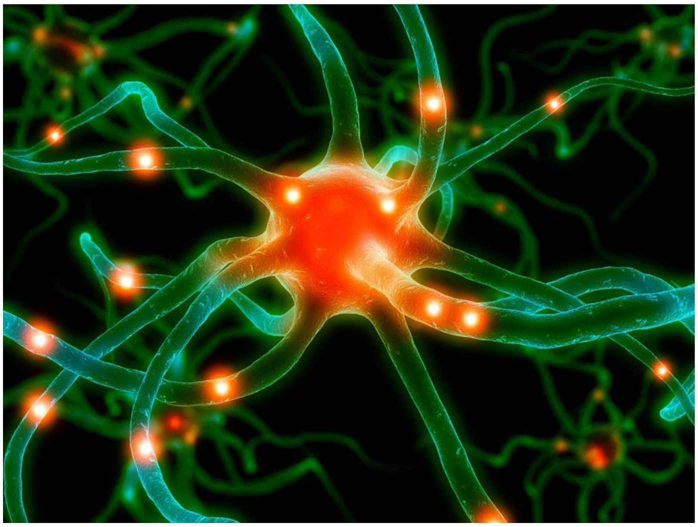
Current Topics Workshop: Systems Biology Processes and Diseases: Biological Problems and Statistical Solutions
April 16-17, 2009
Organizers: Hongzhe Li, Shili Lin, and Tim Huang

Neuroscience Issues in Early Development
April 27-May 1, 2009
Organizers: Ken Miller and Fred Wolf

Drosophila Development
June 8-12, 2009
Organizers: Michael Levine and Hans Othmer

Future Programs

Molecular interactions within the cell: Network, scale, and complexity 2009-2010



Biological processes can be characterized by different degrees of complexity at microscopic (genes, molecules), mesoscopic (protein-DNA complexes) and macroscopic (cells, organisms) levels. Historically, all biological systems have been studied at different levels. However, an increasing amount of experimental results and theoretical studies suggest that a more comprehensive system approach would tackle better biological problems. It would require a collaboration and intensive exchange between experimental and theoretical researchers from physics, chemistry, biology, mathematics, computer science, and engineering.

The proposed activity will answer the following fundamental questions: What are the properties of biological networks? How do they function? How do genes come together to form networks, and how can we use bioinformatics to discover such networks? Can our understanding of the fundamental mathematics inform the design of those bioinformatics methods? How is information transferred in cells? What role can synthetic biology perform in aiding our understanding of real life processes? How can different subjects of biological systems interact together to create effective dynamic systems?

Specific sub-areas of molecular and cellular biology generate their own sets of problems and mathematical challenges, to be addressed by individual workshops throughout the year. For example, how do cells develop, control, and regulate highly-efficient, highly-selective and robust biological transport? What are the algorithms and models that can help elucidate RNA structure and function? What are the basic pathways of cell-to-cell signaling? How can we design genetic regulatory networks with targeted function for synthetic biology? What are the mathematical principles behind DNA-protein interactions and the co-ordinated regulation of gene expression? The over-arching theme of the workshops bridges multiple scales, from the molecular to the cellular, in pursuit of the fundamental biological principles guiding the structure, evolution, and maintenance of these networks.

A unifying long-term goal of the proposed activities is to develop a unified approach to study the complexity of biological systems within cells. Such a comprehensive view of biology will require an application and development of new mathematical methods. Current approaches include hidden Markov processes, stochastic dynamics, graph theory, partial differential equations, discrete mathematics and other tools of probabilistic modeling, machine learning and computational analysis. As in the past, it is expected that new frontiers in biology will both benefit from and stimulate the development of novel mathematical techniques.

Workshops

Network Biology: Understanding metabolic and protein interactions
Organizers: Lazlo Barabasi and Eivind Almaas

Signal transduction and gene regulatory networks
Organizers: Reka Albert, Andre Levchenko, Alex Mogilner, and John Tyson

Synthetic Biology
Organizers: Ron Weiss and Jeff Hasty

Inference in stochastic models of sequence evolution
Organizers: Ian Holmes and Gerton Lunter

Mathematical and experimental approaches to dynamics of protein-DNA interactions
Organizers: Jane Kondev and Hao Li

Transport in a cell
Organizer: Anatoly Kolomeisky and Michael Diehl

Evolution: from molecules to cells
Organizers: Gil Bejerano, Istram Miklos, and Dan Weeinrich

Publications

Technical Reports

Integration of Ranked Lists via Cross Entropy Monte Carlo with Applications to mRNA and microRNA Studies
Shili Lin and Jie Ding
August 2007

Minimal attractors in digraph system models of neuronal networks
Winfried Just, Sungwoo Ahn, and David Terman
August 2007

The extensional flow of a thin sheet of incompressible, transversely isotropic fluid
J. Edward F. Green and Avner Friedman
August 2007

A Kolmogorov-type Competition Model with Finitely Supported Allocation Profiles and its Applications to Plant Competition for Sunlight
Winfried Just and Andrew Nevai
November 2007

Spatial Patterns in a Discrete-Time SIS Patch Model
Linda J.S. Allen, Yuan Lou, and Andrew Nevai
November 2007

A neurobiological model of the human sleep/wake cycle
Michael Rempe, Janet Best, and David Terman
January 2008

Irregular behavior in an excitatory - inhibitory neural network
Choongseok Park and David Terman
March 2008

A mathematical model of liver cell aggregation in vitro
J.E.F. Green, S.L. Waters, K.M. Shakesheff, H.M. Byrne
April 2008

On immunotherapies and cancer vaccination protocols: a mathematical modelling approach
Badal Joshi, Xueying Wang, Sayanti Banerjee, Haiyan Tian, Anastasios Matzavinos, and Mark A.J. Chaplain
June 2008

Newsletters

Autumn 2007, Volume 3, Issue 1
Winter 2008, Volume 3, Issue 2
Spring 2008, Volume 3, Issue 3