



Mathematical Biosciences Institute
at The Ohio State University



Mathematical Modeling of Cell Processes 2003-2004

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Director's Letter

In order to fully utilize the potential opportunities for the mathematical sciences to accelerate progress in the biosciences, the following challenges must be met: (1) Learn the scientists' language; (2) Develop new mathematical/statistical models and techniques; and (3) Increase the community's size.

The Mathematical Biosciences Institute at the Ohio State University, funded by the National Science Foundation (NSF), was created in 2002 to provide a national forum for mathematical biosciences that can address these challenges. 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 approximately six 1-week workshops preceded by tutorials. In the summer, the MBI runs an educational program based on tutorials and team projects led by MBI postdoctoral fellows. Occasional "Current Topics" workshops introduce mathematical scientists to new opportunities for research. In this second year, the program focused on Mathematical Modeling of Cell Processes.

In the last few years the importance of mathematical models in the study of cellular processes has become widely accepted. There are already many instances of how experimentalists and theoreticians, working together, can make discoveries that would be difficult, if not impossible, for each working independently. Take, for example, the following areas where mathematical models have already played an important role: the phenomenon of electrical excitability and the propagation of action potentials; how oscillations in the cell cycle lead to regular cell divisions; how intercellular calcium waves coordinate cellular responses over large areas; and how tumors grow and respond to chemotherapy. With ever-increasing levels of computing power available to modelers, such collaborations will have an ever-increasing importance. Indeed, it is no exaggeration to say that biology is the new frontier of mathematics; it will have profound effects on the kinds of mathematics that are studied decades from now and, in return, mathematics will be an essential contributor to advances in biological knowledge.

The second year at the MBI explored a selection of topics, ranging from cell growth and death, to intercellular communication, to the behaviors of large populations of cells as found in the immune system. Thus, although the spatial and temporal scales vary widely, the topics all shared a common theme, based around the study of how cells respond to and influence their environment. Obviously, there was time for the study of only a small selection of topics in this general area, and we chose topics in which the theoretical and experimental work are closely intertwined.

Our goals were twofold: First, by bringing theoreticians and experimentalists together, we aimed to catalyze the production of good science, but just as important as the science is the fostering of interdisciplinary links, which was our second goal. Despite the clear importance of biology for the future of mathematics, it is still not a trivial matter for a mathematician to make the switch to working in this area. Vocabulary is different, the methods may seem strange, and the criteria by which one's work is judged can be radically different. Workshops, such as those which took place this year, play an important role; they are, in es-



sence, role models for those mathematicians interested in broadening their research interests; they provide examples of how interdisciplinary work is done, and how to work with experimental colleagues; and, with the provision of extensive tutorials, they provide a gentle introduction to the field of cell processes.

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

Avner Friedman
Director



MBI Mission

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

The mission of the MBI is:

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

Institute Partners

The MBI Institute Partner Program subsidizes the travel and local expenses of IP members and faculty, postdoctoral fellows, and students to allow their participation in research and education programs at the MBI; for details see the MBI web site <http://mbi.osu.edu>.

Current Institute Partners

Case Western Reserve University
Iowa State University
Michigan State University
Ohio University
University of Cincinnati
University of Georgia
University of Iowa
University of Maryland, Baltimore County
University of Minnesota
Vanderbilt University

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;
- ♦ Membership on Industrial Advisory Committee; and
- ♦ Invitation to present industrial challenges and problems to MBI audiences and to participate in MBI programs and workshops.

Current Corporate Members:

- ♦ Pfizer
- ♦ Eli Lilly
- ♦ GlaxoSmithKline



MBI Postdoctoral Fellows

Postdoctoral fellows fall into two support categories: Supported at 100 percent by the MBI or split 50/50 percent by the MBI and another specific program. Postdoctoral fellows sponsored by a specific organization spend 50 percent of their time on research suggested by the sponsor. All postdocs are provided with two mentors: one from the mathematical and statistical sciences, and another from one of the biosciences departments at The Ohio State University. Long-term visitors may also serve as mentors. More details are available in the *MBI Postdoctoral Research Program Handbook* on the MBI website.

MBI Postdocs

- ◆ Janet Best - Department of Mathematics, Cornell University
- ◆ Alla Borisyuk - Courant Institute of Mathematical Sciences, New York University
- ◆ Gheorghe Craciun - Department of Mathematics, The Ohio State University
- ◆ Sanjay Danthi - Department of Pharmacology, The Ohio State University
- ◆ Daniel Dougherty - Department of Statistics, North Carolina State
- ◆ Pranay Goel - Department of Mathematics, University of Pittsburgh
- ◆ Sookkyung Lim - Courant Institute of Mathematical Sciences, New York University
- ◆ Katarzyna Rejniak - Department of Mathematics, Tulane University
- ◆ Martin Wechselberger - Mathematics Department, Vienna University of Technology
- ◆ Geraldine Wright - Department of Entomology, Oxford University

A Brief Summary of the Year in Mathematical Modeling of Cell Processes 2003-2004

(Detailed description starts on page 9)

In the past few years, the importance of mathematical models in the study of cellular processes has become widely accepted. Mathematical models have played an important role, for example, in understanding how oscillations in cell cycles lead to regular cell division, and how intercellular calcium waves coordinate cellular response over large areas. This year, we explored topics from cell growth and death, to intercellular communications, and to the behaviors of large populations of cells such as those found in the immune system. These topics have been dealt with in a series of in-depth workshops. The program included tutorial sessions which provided important background information in preparation for the workshops.

Workshop 1 *Control of Cell Growth, Division, and Death*

This 5-day workshop tackled the following general themes: 1) basic molecular machinery of the cell cycle engine, from yeast to mammals; 2) models and modeling platforms; 3) mechanism of apoptosis; and 4) signal transduction and other pathways relevant to cell division and death. The workshop attracted biologists, mathematicians, physicists, and computer scientists.



The daily schedule typically consisted of two 1-hour lectures in the morning and one 1-hour lecture in the afternoon. There was a lot of time for informal discussions. A 1-hour meeting was scheduled on Thursday when the participants discussed grand challenges in the field, and how mathematicians and molecular biologists can synergize to bring the field to the status of a predictive science based on mechanistic modeling.

Organizing Committee for 2003-2004

- ◆ Jessie Au - College of Pharmacy, The Ohio State University
- ◆ Marek Kimmel - Department of Statistics, Rice University
- ◆ Denise Kirschner - Department of Microbiology and Immunology, University of Michigan Medical School
- ◆ James Sneyd - Department of Mathematics, University of Auckland, New Zealand
- ◆ John Tyson - Department of Biology, Virginia Polytechnic Institute

Workshop 2

Mathematical Models of Cell Proliferation and Cancer Chemotherapy

The aim of Workshop 2 was to address the state of the art and future directions in Mathematical Cancer Research. The philosophy of the meeting was to confront the thinking of modern cancer biologists and therapists, who employ the cutting-edge biological techniques to solve real-life problems, with the thinking of mathematicians and modelers, who sometimes apply high-level analytical tools to models, which are far idealizations. The outcome was very satisfying: The workshop was filled with discussions and even controversies, which promoted understanding on both sides.

Typically, each of the 5 days consisted either of four 1-hour talks, or of a large number of shorter talks. There was plenty of room for informal discussion. A structured discussion took place on Thursday afternoon.

Miniworkshop

Mathematical Challenges Arising in Cancer Models

The miniworkshop took place immediately following the workshop on cell proliferation, cancer, and cancer therapy. The main purpose of the workshop was to describe mathematical and statistical models and methods, which arise in cancer and in cancer therapy. At the opening of the miniworkshop, Marek Kimmel presented a summary of the discussion that took place in the previous week, regarding areas of research opportunities for the mathematical sciences community.



Workshop 3

Signal Transduction I: Calcium Dynamics, Phototransduction, and Olfaction and

Workshop 4

Signal Transduction II: Muscles and Synapse

Both of these workshops were organized around a common theme; the study of cells that convert one type of signal into another. For example, cells that convert light to electricity (photoreceptors), cells that convert an electrical signal to a force (muscle), or cellular regions that convert an electrical signal in one cell to an electrical signal in another (synapses). Since calcium is a crucial second messenger in practically all such processes, the workshops were further designed to focus on the essential role of calcium. The chosen physiological topics were all ones in which mathematical modeling has played an important role, and thus both workshops were an effective mix of theoreticians and experimentalists. Each workshop was preceded by a tutorial of eight 1-hour lectures.

Workshop 5

Immunology Models: Cell Signaling and Immune Dynamics

The aims of Workshop 5 were to bring together prominent researchers, postdoctoral fellows, and graduate students in the areas of experimental immunology, computer science, and applied mathematics, and address the major problems and future directions in mathematical modeling of immunological processes. The workshop emphasized the role of cell signaling in determining the dynamic patterns of immune responses.

Local Scientific Advisory Committee

The Local Scientific Advisory Committee helps identify current topics workshop, future emphasis programs and organizers, and potential mentors for postdoctoral fellows.

- ◆ Michael Beattie - Department of Neuroscience
- ◆ Albert de la Chapelle - Human Cancer Genetics
- ◆ Martin Feinberg - Department of Chemical Engineering
- ◆ Paul Fuerst - Department of Evolution, Ecology, and Organismal Biology
- ◆ Erich Grotewold - Department of Plant Biology
- ◆ Fernand Hayot - Department of Physics
- ◆ Charles R. Hille - Department of Molecular and Cellular Biochemistry
- ◆ Lee Johnson - Department of Molecular Genetics
- ◆ Doug Kniss - Department of Obstetrics and Gynecology
- ◆ Stanley Lemeshow - Center for Biostatistics
- ◆ Charles Orosz - Department of Surgery
- ◆ Dennis Pearl - Department of Statistics
- ◆ John Reeve - Department of Microbiology
- ◆ Andrej Rotter - Department of Pharmacology
- ◆ Wolfgang Sadée - Department of Pharmacology
- ◆ Joel Saltz - Department of Biomedical Informatics
- ◆ Larry S. Schlesinger - Division of Infectious Diseases and Center for Microbial Interface Biology
- ◆ Brian Smith - Department of Entomology
- ◆ David Terman - Department of Mathematics
- ◆ Deliang Wang - Department of Computer and Information Science



The specific objectives were to: (a) expose the biomathematical modeling community to current major questions and needs of immunologists involved in clinical and laboratory research; (b) present recently developed analytical and computer models and discuss the future directions for these modeling efforts; (c) provide the stage for open discussions between experimentalists and theoreticians; and (d) enhance the effectiveness of collaborative efforts in immunological research.

Emphasis Year Scientific Advisory Committee 2003-2004

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 committee is appointed for each emphasis year program.

- ◆ Michael Andreeff - MD Anderson Cancer Center
- ◆ David Axelrod - Rutgers University
- ◆ James Broach - Molecular Biology Department, Princeton University
- ◆ Fred Cross - Molecular Genetics Department, Rockefeller University
- ◆ Zbigniew Darzynskiewicz - New York Medical College
- ◆ Victor Di Rita - Microbiology and Immunology, University of Michigan Medical School
- ◆ JoAnne Flynn - Immunology Department, University of Pittsburgh School of Medicine
- ◆ Albert Goldbeter - Universite Libre de Bruxelles
- ◆ Michael Sanderson - Physiology Department, University of Massachusetts Medical School
- ◆ Elise F. Stanley - Physiology Department, University of Toronto

The workshop lasted 5 days, with each day corresponding to a specific area of interest. At the beginning of each day, one of the organizers provided a brief introduction to the subject (s) of discussions and gave concise descriptions of the major problems to be discussed during that day. A typical day consisted of three to four long (45 minute) talks and two to three short (20 minute) talks. Poster presentations were held on the evening of Day 1. An additional presentation of an online software package (Virtual Cell) was held during lunchtime on the fourth day. Informal discussions were held at the end of each day.

The workshop provided an open atmosphere for discussions, which were ample. Some of the discussions were concerned with major controversial issues, and the discussions were largely successful in promoting understanding between different schools of thought.

Workshop 6

Disease Models: Host-Pathogen Interactions

The goal of this workshop was to initiate discussions between outstanding researchers, postdoctoral fellows, and graduate students in the biological areas of microbiology, immunology, and virology together with computational areas such as applied mathematics, statistics, and computer science. The workshop focused on host-pathogen interactions and how mathematical approaches can contribute to our understanding of these biological areas.

The specific aims of the workshop were to: (1) initiate dialog between experimental and theoretical scientists on the topic of host-pathogen interactions; (2) expose experimental scientists to computational techniques available for studying specific questions in this area;



and (3) expose members of the biomathematics community to major questions and topics in host-pathogen systems.

The workshop lasted 4 days and was broken into two key topic areas: Days 1 and 2 focused on viral-host interactions, and Days 3 and 4 focused on bacterial and fungal-host interactions. At the beginning of each day, the organizers gave a brief introduction to the days' topics, and then the day was organized such that the morning talks (3-4, 40 minutes each) were given by experimentalists working on the particular topic area for the day. The afternoons consisted of 4-5 shorter talks (25 minutes each) where theoretical scientists presented their models and computational tools that focused on the same topic areas. During lunch on 2 of the days, two spontaneous and informal talks of 30 minutes each were given to go deeper into a particular topic area: One discussed the usefulness between simple, linear models versus complex, non-linear models, and the other gave a presentation on PATHSIM to individuals who wanted more details after the initial presentation. Finally, each afternoon provided 30 minutes or more for discussion time beyond the discussions that took place after each talk. These were lively and thoughtful (sometimes controversial) discussions that kept the meeting stimulating while promoting successful understanding of topics for all participants. The first evening of the workshop included a reception and poster session, and on the fourth evening there was a banquet. Both of these events, which occur in every MBI workshop, were vital aspects for promoting collegiality and discussions between participants.

Current Topics Workshop

Statistical and Mathematical Modeling of fMRI Data

This 2-1/2 day workshop brought together researchers from the statistical, imaging, and modeling communities. The goal was to integrate their knowledge to enhance the medical and basic biomedical sciences communities' understanding of the physiologic and physical mechanisms causing BOLD fMRI signal changes. This was accomplished successfully because members of each group were knowledgeable of the basic language used by each other and knew the limitations and promises of each group.

Board of Governors

- ◆ Louis Gross - Professor of Ecology and Evolutionary Biology, The University of Tennessee
- ◆ Jim Keener - Departments of Mathematics, University of Utah
- ◆ Gregory Mack - Vice President of Environmental Monitoring and Assessment, Battelle Memorial Institute
- ◆ Claudia Neuhauser - Professor and Director of Graduate Studies, University of Minnesota
- ◆ Sharon Nunes - IBM Computational Biology Center
- ◆ Alan Perelson - Head, Theoretical Biology and Biophysics Group, Los Alamos National Laboratory
- ◆ John Rinzel - Professor of Neural Science and Mathematics, Center for Neural Science and the Courant Institute of Mathematical Sciences, New York University
- ◆ Stephen Ruberg - Director, Clinical Data Technology and Services, Eli Lilly and Company
- ◆ Terrence Speed - Professor of Statistics, University of California, Berkeley
- ◆ John Taulbee - Epidemiology and Biometrics Division, Proctor and Gamble Company
- ◆ Terry Therneau - Division of Biostatistics, Mayo Clinic College of Medicine, Rochester
- ◆ John Tyson - Professor of Biology, Virginia Polytechnic Institute and State University
- ◆ Michael S. Waterman - University Professor, University of Southern California
- ◆ Raimond L. Winslow - Center for Cardiovascular Bioinformatics and Modeling, Whitaker Biomedical Engineering Institute, Department of Biomedical Engineering, The Johns Hopkins University School of Medicine and Whiting School of Engineering



Program Details

Workshop 1

Control of Cell Growth, Division, and Death: September 29-October 3, 2003

Organizers:

Jessie Au - College of Pharmacy, The Ohio State University

Baltazar Aguda - Departments of Genetics and Genomics and Biomedical Engineering,
Boston University School of Medicine

Summary of Talks

John Tyson (Virginia Tech) opened the workshop with a gentle introduction to the molecular biology of the eukaryotic cell cycle, summarizing the essential molecular pathways in the activation and deactivation of cyclin-dependent kinases (CDKs). A modular construction of a kinetic model of the cell cycle engine in budding yeast was described, and the mathematical analysis of the model using standard tools of dynamical systems theory was illustrated. Along similar lines, the second speaker, Bela Novak (Hungary), continued with details of the fission yeast cell cycle and presented an impressive bifurcation diagram of CDK activity as a function of mass. He discussed how this diagram could explain various size-control mutants. Jill Sible (Virginia Tech) gave an introduction to the molecular and developmental biology of the frog *Xenopus laevis*. She discussed how embryonic cell cycles are studied experimentally in free cell extracts from frog eggs, and how the cell cycle is remodeled during embryogenesis. Inspired by predictions of a Novak-Tyson model published in 1993, Jill presented convincing experimental evidence that supports the existence of a hysteresis loop in the activation/deactivation of cyclin B/Cdc2.

On Day 2, Joseph Pomerening (Stanford) presented his experiments - using frog eggs and slightly different protocols from Jill Sible's - that confirm hysteresis in Cdc2 activation/deactivation and that the system is bistable for a certain range of conditions. He also presented some mathematical modeling and computer simulations of the system. Mandri Obeyesekere (MD Anderson Cancer Center) started her talk with general concepts in modeling complex biochemical networks. She then discussed a detailed model that accounts for the role of the oncogene *mdm2* in the observed polyploidy in mice. She also presented detailed models that focus on specific phases of the cell cycle. The afternoon's speaker, Dennis Thron, discussed the relationship between reaction order and bistability, the repressor-repressor switch, a minimal mitotic switch model, and the role of polo-like kinase in Cdc2 activation.

Martin Feinberg (Ohio State) began day 3 by illustrating how network structure can influence the capacity of a complex reaction mechanism to admit multiple steady states. He discussed graphical representation of networks (e.g., SR graphs) and certain theorems that can decide whether or not a network with mass-action kinetics, but regardless of parameter values, can have multiple steady states. Rengul Cetin-Atalay (Turkey) talked about the software PATIKA (Pathway Analysis Tool for Integration and Knowledge Acquisition) being developed by her group. The PATIKA ontology takes into account various levels of abstractions and certainty of knowledge in pathway representation. Such ontology is conducive to modeling. She also briefly mentioned the iCancer project utilizing the software. The final speaker of the day, Stephen Cooper (Michigan), passionately described a different way of



looking at the cell cycle via his 'Continuum Model'. His model makes the controversial claim that there are no G1 or G2-specific events, and that the cell cycle is a continuous, phase-independent mass accumulation process. He presented a critique of various experiments that claim the existence of cell cycle-specific events, including synchronization of cells at specific cell cycle phases.

On Day 4, Baltazar Aguda (Boston) discussed how one could partition complex mammalian regulatory networks into signaling, cell cycle and apoptosis modules, and how these modules interact to control the initiation of the cell cycle and of apoptosis. Jaroslav Stark (UK) talked about the dynamic balance between cell proliferation and death in homeostasis. He gave a brief overview of the immune system and then discussed a model of T-cell memory. Jean Wang (UC San Diego) provided a biologist's overview of the different fates of the cell, namely, proliferation, senescence, apoptosis, quiescence, and differentiation. She discussed perplexing examples of pathways that give opposite results, e.g., those involving the proteins Rb, Abl, and p73, all of which have both oncogenic and anti-oncogenic functions.

On the last day, Tomasz Lipniacki (Rice) discussed a two-feedback-loop regulatory model of NF-kappaB activation. NF-kappaB is a transcription factor that induces expression of various inhibitors of apoptosis. He presented simulations of the model using ODEs. Paul Dent's (Virginia) talk again reminded the audience how complex signaling pathways could be in determining the fate of a cell. He showed the regulation of certain signaling pathways by radiation and drugs, and how autocrine growth factors and receptors are involved. Last

Program Participation 2003-2004	# Participants
Tutorial on the Cell Cycle: <i>September 2-5, 2003</i>	25
Control of Cell Growth, Division, and Death: <i>September 29 - October 3, 2003</i>	56
Mathematical Models of Cell Proliferation and Cancer Chemotherapy: <i>November 10-14, 2003</i>	61
Mathematical Challenges Arising in Cancer Models: <i>November 17-19, 2003</i>	40
Tutorial on Cell Transduction: <i>January 5-9, 2004</i>	26
Signal Transduction I: Calcium Dynamics, Phototransduction, Olfaction: <i>January 26-30, 2004</i>	67
Tutorial on Synapses and Muscles: <i>March 1-4, 2004</i>	25
Signal Transduction II: Muscles and Synapse: <i>March 8-12, 2004</i>	54
Statistical and Mathematical Modeling of fMRI Data: <i>March 18-20, 2004</i>	68
Tutorial on Immunology Models: <i>May 6-7, 2004</i>	21
Immunology Models: Cell Signaling and Immune Dynamics: <i>May 10-14, 2004</i>	70
Tutorial on Host-Pathogen Interactions: <i>June 15-16, 2004</i>	21
Disease Models: Host-Pathogen Interactions: <i>June 21-25, 2004</i>	68
Summer Program	25
Total	627
Long Term Visitors	
(a) 2-3 weeks	2
(b) 4 weeks - 3 months	12
(c) 3 months - 1 year	9
Total	23



but not least, Boris Kholodenko (Thomas Jefferson University) talked about quantification of control in regulatory networks and a novel strategy in unraveling the topology and the strength of network connections. As illustrations, he discussed EGFR signaling, MAPK cascade signaling, and endocytic trafficking.

Conclusion

This workshop brought together five speakers (Tyson, Novak, Obeyesekere, Thron, Aguda) who have considerable experience in mathematical modeling of the cell cycle; four speakers (Sible, Pomerening, Stark, Cooper) whose experimental work is inspired by mathematical models; three speakers (Feinberg, Cetin-Atalay, Kholodenko) whose network analysis tools are expected to be essential in future modeling of cellular networks; and three speakers (Wang, Dent, Lipniacki) whose talks on signaling pathways are important in understanding determination of cell fates. Thus, participants (speakers and audience) have benefited from the cross-disciplinary presentations of the complexity of cellular processes involved in cell growth, division, and death.

A 'roundtable' discussion was held on Thursday afternoon to get a sense of what the participants feel about the future of this research field. Some of the perceived grand challenges include bringing the status of the field to a predictive science based on mechanistic modeling, and how to further integrate all essential cellular processes relevant to growth, division, and death (multiscale modeling, biophysics, and use of high-throughput data). Practical issues as to how applied mathematicians and molecular biologists can help each other were discussed. Mathematical ideas such as bistability, hysteresis, robustness, and bifurcation are now increasingly recognized by biologists; in return, biologists can help generate new mathematics by posing new observations, problems, or questions that could be amenable to mathematical analysis. The group recognized that there are cultural differences between mathematicians and biologists, that these differences can be obstacles to collaboration, and discussed how they can be overcome.

Workshop 2

Mathematical Models of Cell Proliferation and Cancer Chemotherapy.

November 10-14, 2003

Organizers:

Jessie Au - College of Pharmacy, The Ohio State University

Marek Kimmel - Department of Statistics, Rice University

Summary of Talks

The first day of Workshop 2 was mostly devoted to "setting the stage" for more specific presentations to follow later. Jessie Au (OSU) opened the workshop with a review of new results on action and delivery of anticancer drugs. The stress was on new types of action, taking advantage of knowledge of molecular pathways specific to cancer cells, which increases efficiency and reduces side effects. Marek Kimmel (Rice U.) followed with a talk concerning modeling the natural history of lung cancer. The talk was focused on interaction between genetic susceptibility and environmental/behavioral exposure in lung cancer incidence and progression. It was followed by John Weinstein's (NCI) presentation of new bioinformatics tools for discovery of anticancer drugs. This talk reviewed a very wide array of



tools, which were used to analyze the NCI's project to employ 60 human cancer cell lines to screen more than 100,000 chemical compounds to find new drugs for cancer therapy. This was followed by Edison Liu (Genome Inst. Singapore), who discussed expression genomics and the cellular pharmacology of cancer therapeutics.

At first we thought the biology oriented talks, which do not contain much math, were not of interest to us, but then all the biological, medical, and pharmacological facts started coming together creating a background, which probably every mathematician who wants to seriously work in these kinds of applications should have. And what was absolutely unique was the atmosphere of the workshop. Participants were lively reacting to presentations. Discussions, sometimes heated, were filling the conference rooms and the hallways throughout the day. Mathematicians and biologists talked and interacted, and the "Grand Canyon", which someone mentioned separates both disciplines, was definitely getting smaller.

-Urszula Ledzewicz

Day 2 was a more detailed follow-up on the general theme of chemotherapy. Mike Grever (OSU) discussed the challenges of early cancer drug development. The goal is to identify strategically important molecules for treatment of cancer, to characterize the biological effects with assays for pharmacodynamics and pharmacogenomics while incorporating real time pharmacokinetics, and to complete early phase I (toxicity) and II (efficacy) and follow with expanded phase III (critical trials). He gave some examples of drug development, which inhibit enzymes. Here the specificity of inhibitor target and the selectivity of target expression needed to be identified, and this was accompanied by measuring the enzyme inhibitor in cells. He was followed by Steven Kern (U. Utah), who discussed modeling multiple-drug interactions with response surfaces. Drug delivery strategies that maximize positive effects and minimize side effects often employ drug combinations and for cancer chemotherapy, this approach represents the standard of care. The speaker discussed a classification of response surfaces, which accounts for modeling various types of interactions. A discussion ensued, which mostly concerned using models of drug kinetics to construct the surfaces. Another speaker, Olivier Hyrien (Rochester U.), proposed a method to analyze the effect of an anticancer drug on the proliferation of oligodendrocytes and O-2A progenitor cells in culture conditions. The dynamic of the cell population was represented by a multi-type Bellman-Harris branching process. The proposed methodologies were illustrated on a real data set. The discussion concerned mainly characterizations of cell colonies and verifiability of stochastic models.

An exceptionally interesting and heated discussion took place in the afternoon, following three presentations concerning application of optimal control methods to optimization of cell cycle-dependent chemotherapeutic agents. These presentations were started by Andrzej Swierniak (Silesian Tech), who reviewed models of cell cycle developed with the following in mind: (1) the inner structure of the cell cycle and the cell-cycle-phase specificity of chemotherapy agents; (2) the dynamics of emergence of resistance of cancer cells to chemotherapy; and (3) estimation of parameters of the cell cycle, drug action and cell mutation to resistance. This was followed by Jaroslaw Smieja (Silesian Tech), who discussed an infinitely dimensional model of evolution of drug resistance. The session was closed by Urszula Ledzewicz and Heinz Schaettler, who analyzed mathematically the impact of using quadratic versus linear penalty functions for optimization of chemotherapy protocols (quadratic being technically easier, but less helpful). There was an intense discussion,



which concerned the following topics: (1) including models of drug delivery and drug kinetics in chemotherapy models; (2) including models of action different from phase-specific killing and blocking; (3) explicit models for treatment toxicity; and (4) including correct models for development of drug resistance.

Day 3 concerned modeling in pharmacokinetics, tumor growth and evolution, and genomic transformations in cancer. Cynthia Sung (OSU) discussed interspecies allometric modeling of the pharmacokinetics, biodistribution, and dosimetry of LymphoRad-131, a radiolabeled cytokine targeted to B cells. Unique binding profile suggests that LR131 may be a useful treatment for B cell neoplasias such as B cell lymphomas and multiple myeloma. One of the highlights of the talk was derivation of allometric relationships, which may allow scaling results of experiments on mice to humans. Jan Lankelma (VU Med. Ctr.) discussed the transport of small-molecule drugs, from injection site to the target. A mathematical model was developed describing doxorubicin transport by diffusion from the smallest blood capillaries into the tumor tissue. Using transport parameters measured in vitro for doxorubicin, the model could explain the observed gradients. The model showed that the radius of the islet and the width of the interstitium between the cells could have a significant influence on the steepness of the gradient. Guill Wientjes (OSU) talked about how to enhance drug delivery to a solid tumor. He illustrated his talk with experimental results in concentration of doxorubicin after infusion into prostate and into a rabbit tongue. He concluded that high tumor cell density is a barrier to penetration of protein-bound drugs in solid tumors, and reduction of tumor cell density results in enhanced delivery of protein-bound drugs to solid tumor. This reduction is accomplished by changing the treatment schedule to allow for induction and occurrence to apoptosis.

Paolo Ubezio (Mario Negri Inst.) discussed kinetics of cell cycle response of cancer cells to drug treatment. The authors used an ovarian carcinoma cell line (IGROV-1) growing in vitro and made measures at different drug concentrations and times with different techniques (particularly by flow cytometry), with a particular experimental design. Then a mathematical model of cellular proliferation kinetics was used to reconstruct the cell flows into the different phases of the cell cycle (G1, S and G2M) after a treatment. The aim of the analysis is to find a set, or sets, of descriptors coherent with the data, i.e., producing simulated measures in the range of precision of the real measures. Alexander Anderson (U. Dundee) presented a model of solid tumor invasion, with emphasis on the importance of adhesion. He presented a hybrid discrete/continuum mathematical model, describing the invasion of host tissue by tumor cells and examining how changes in key cell attributes (e.g., P53 mutation, cell-cell adhesion, and invasiveness) affect the tumor's growth. The continuous mathematical model consists of a system of partial differential equations for chemicals and discrete random processes for cell-level effects. This in turn allows examining the effects of micro-scale changes upon the overall tumor geometry and subsequently the potential for metastatic spread. Joe Gray (UCSF) discussed methodologies for determination of genomic deregulation in cancer, involving chromosomal translocations and similar effects.

Day 4 included more talks concerning chemotherapy and radiotherapy and tumor growth, but also a talk in modeling of carcinogenesis. Zvia Agur (Inst. Med. Biomath.) discussed the determination of the efficacy/toxicity tradeoff in cytotoxic and supportive cancer therapy: Thrombopoietin (TPO) has been developed as a therapeutic agent to attenuate thrombocytopenia in treatment of non-Hodgkin's lymphomas, but its immunogenicity is a serious impediment to further pharmaceutical development. To overcome this problem, a computer-



implemented mathematical model for thrombopoiesis has been employed, predicting platelet counts under different dose schedules. These predictions have been prospectively validated in preclinical trials. Gary Schwartz (Mem. Sloan-Kettering) talked about development of cell cycle inhibitors in combination with chemotherapy for the treatment of human malignancies. One approach that appears especially promising is to combine chemotherapy with small targeted molecules that enhance chemotherapy-induced apoptosis and result in an increased antitumor effect. Pre-clinical studies have been translated into



phase I clinical trials of sequential combination therapy, which have proven generally well tolerated and show promising antitumor activity. This class of drug may provide a completely new therapeutic strategy in the treatment of patients with advanced cancers. Leonid Hanin (U. Rochester) presented mathematical results concerning the classical problem of the distribution of the number of clonogenic tumor cells surviving fractionated radiation. Using theory of branching processes, he derived exact and asymptotic expressions, solving a long-standing open problem. A very animated discussion followed this group of talks: It was focused on finding appropriate mathematical tools for modeling of new chemotherapeutic modalities.

Mark Chaplain (U. Dundee) presented mathematical modeling of the spatio-temporal response of cytotoxic T-lymphocytes to a solid tumor. The mathematical model is focused upon the interaction of tumor cells with so-called tumor-infiltrating cytotoxic lymphocytes (TICLs), in a small, multicellular tumor, without central necrosis and at some stage prior to (tumor-induced) angiogenesis. Numerical simulations demonstrate the existence of cell distributions that are quasi-stationary in time but unstable and heterogeneous in space. Li Deng (Rice U.) discussed modeling the cell proliferation, and carcinogenesis in lung cancer, taking into account the interaction between genetic factors and smoking. This talk was an extension of Kimmel's talk from the first day. It made more specific assumptions concerning the gene-environment interaction by considering a modified Molgavkar's model and integrating the environmental exposure, namely cigarette smoking and genetic information into both mutation stages and the cell proliferation rate of intermediate cells. Simulated examples were presented.

The last day featured two speakers. Alberto Gandolfi (IASI, Rome) discussed modeling the regression and regrowth of tumor cords following cell killing. In some human and experimental tumors, cylindrical arrangements of tumor cells growing around central blood vessels have been observed. These structures are tumor cords. A mathematical model has been developed that describes the behavior of a cord under the influence of a cell killing treatment. The diffusion of a chemical critical for cell viability, assumed to be the oxygen, is taken into account. The model validates the existence of a transient phase of reoxygenation after treatment, in which the surviving cells should exhibit an increased sensitivity to a successive dose of the therapeutic agent. Nicola Bellomo (Torino Politechnic) discussed multiscale modeling of cellular systems in the competition between tumor and immune system.



The methodology involves mathematical description of the evolution of probability distributions of the states of interacting cells.

Summary of Discussion “State of the Art and Future Directions in Mathematical Cancer Research”

On Thursday (Day 4) afternoon, a joint discussion was carried out, the aim of which was, on one hand, to summarize the principal topics and results presented, and on the other, to review outstanding problems and new avenues of progress.

It was stated that new achievements in drug development and chemotherapy, involving drug delivery, pharmacokinetics, chemo-immunotherapy, radiation therapy, and others, create difficult challenges for modelers. Another area of challenge is using the genomics and proteomics data to produce gene networks and metabolic networks as well as models of signal transduction pathways and genetic susceptibility to cancer. In tumor growth modeling, a fusion of continuum mechanics, scaling methods such as homogenization and hybrid models is needed to describe such phenomena as angiogenesis, chemotaxis, and metastatic spread.

Much attention was paid to interactions between physicians, mathematicians, and biologists, and to the way biologists are treating models. The questions “what do we want from models?”, “will the model tell me something I do not already know?”, or “what is hot and what is passé?” are considered typical. On the other hand, it has to be realized that different measurements are needed for model building than for hypothesis-driven science. The problem of funding for mathematical cancer research was also discussed.

Another topic was the search of overarching principles, which would allow understanding complex phenomena in biology. The proposed approaches included recognition of modules in complex systems, development of new systems theory, and using evolutionary data to understand complexity.

From the viewpoint of mathematics, further development of models for cancer treatment, methods of analysis and optimization, nonlinear dynamics (bilinear systems), models for spatial phenomena, and new statistical procedures were used to interpret genomic and proteomic data.

A tentative list was assembled of achievements in mathematical modeling, which are likely to be of practical importance in cancer research, based mostly but not exclusively, on the Workshop’s proceedings. These included: Goldie and Coldman clonal resistance model, fractional irradiation theory, flow cytometry, and corresponding analytic tools; Molgavkar’s (and others) carcinogenesis models; Agur’s model of toxicity of chemotherapy; angiogenesis models of Preziosi, Arakelian, Chaplain, and others; drug delivery models (e.g., Lankelma’s Dox diffusion) and allometry, and extension of mouse molecular experiments to humans.



Conclusion

The Workshop provided a splendid opportunity to discuss the state of the art in modeling of chemotherapy, tumor growth and spread, carcinogenesis, genomic transformation in cancer, and some other topics. A lot of interesting new laboratory findings and mathematical methods were presented. Discussions exposed differences in approach and assumptions between mathematicians and biomedical researchers, these latter focusing on up-to-date approaches, even if they are mathematically simple and the former striving for excellence in analysis and generality of results. Most importantly, it demonstrated in what way both groups can be helpful to each other and jointly contribute to understanding and conquering cancer.

Miniworkshop

Mathematical Challenges Arising in Cancer Models.

November 17-19, 2003

Organizers:

Avner Friedman - Mathematical Biosciences Institute

Marek Kimmel - Department of Statistics, Rice University

Summary of Talks

Marek Kimmel gave the first talk describing the discussions that took place in the preceding workshop. The other talks in the first day were given by Antonio Fasano (University of Florence) and Howard Levine (Iowa State University). Fasano presented a model of tumor cord, surrounding a blood vessel. The model includes cell motion, oxygen diffusion, motion of extracellular fluid, and cell killing drugs, some residing in the extracellular matrix and some sequestered in cells, thereby raising the level of toxicity and causing apoptosis. The model is formulated as a system of PDEs with a free boundary. Fasano stated existence and uniqueness theorems and exhibited some numerical results.

Howard Levine proposed a mathematical model for the formation of an avascular tumor based on the loss of tumor suppressor function that ensues under p53 gene mutation. The p53 protein regulates apoptosis, cell expression of growth factor and matrix metalloproteinase, and regulatory functions, which many mutant p53 proteins do not possess. The central idea in his model, taken from the mathematical theory of dynamical systems, is to view the loss of p53 function in a few cells as a small instability in a rest state for an appropriate system of differential equations describing cell movement. This instability was shown (numerically) to lead to a second spatially inhomogeneous solution, which can be thought of as a solid tumor whose growth is nutrient diffusion limited. His model is stated in terms of a coupled system of four partial differential equations and five ordinary differential equations in time.

Both Fasano's and Levine's model suggest mathematical challenges of identifying all stable equilibrium states and of determining the asymptotic behavior of the solution of the PDE systems as time goes to infinity.

In the second day of the miniworkshop, Kevin Painter (Heriot-Watt University) presented a mathematical model of brain tumor by a system of PDEs. The model takes into account cellular mutations and demonstrates how mutation leads to a highly heterogeneous and ma-



lignant tumor. He discussed the model in light of the development of astrocytic tumors of the brain and employed the model to understand the effectiveness of biopsy sampling. In both Levine's and Painter's models, the problems of well posed systems are yet to be addressed.

Qing Nie (University of California, Riverside) presented numerical results of classical solid tumor models with two parameters: one accounting for proliferation and apoptosis, and another expressing cell-to-cell adhesion. He demonstrated that critical conditions exist for which the tumor evolves to non-trivial dormant states or grows self-similarly. Away from these critical conditions, evolution may be unstable leading to invasive fingering and topological transitions such as the capture of healthy tissue by the tumor.

The remaining two talks in the second day dealt with topics that are not cancer specific but have the potential to apply to cancer therapy. Marit Nilsen-Hamilton (Iowa State University) described the role which aptamers oligonucleotides are playing in biochemistry: Aptamers are fragments of DNA or RNA that bind to specific molecules. Nilsen-Hamilton described several types of aptamers. The possibility of using aptamers for facilitating drug penetration into cancer cells presents an exciting challenge not yet explored.

Andrzej Swierniak (Silesian University of Technology) described how support vector machines can be used for analysis classification and selection of gene expression data from DNA microarrays. This can be applied, for example, in medical diagnosis and in choosing proper medical therapy. One of the first papers dealing with classification was the article by Golub et al. (1999). In this paper, samples of two types, acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL), were classified and clustered. Swierniak compared several methods, RFR, RFE, NA and pure Sebestyen using data sets from the Golub et al., for tumor/normal colon and thyroid. This last set of data comes from experiments in the MCS Institute of Oncology collaborating with Swierniak's group.

The third day included presentations by Avner Friedman, Marek Kimmel, and Jacek Blaze-wicz (Inst. of Computing Science). Friedman presented mathematical results and open problems related to models of cancer and cancer therapy. The models are based on conservation of mass of cell densities and assume porous medium consistency of the tumor region. He stated existence and uniqueness theorems for the systems of PDEs, which describe the models, including existence of non-radially symmetric solutions, and stated open problems regarding the asymptotic behavior of the tumor shape. He also considered a model of tumor injected with virus, which destroys tumor cells, and raised questions of optimally administering this type of therapy.

Kimmel dealt with the models of dynamics of expansion and contraction of repeat DNA sequences in the genome and their relationship with human disease, including cancer. The first example was telomere shortening: Telomeres are endings of chromosomes, which are composed of short DNA repeat sequences. They provide protection from damage of chromosome endings, which leads to chromosomal abnormalities and sometimes to cancerous transformation. Another example was provided by the so-called trinucleotide diseases, which are caused by rapid expansions, from one human generation to another of DNA triplet repeats located in target gene regions. Kimmel showed stochastic models employing the theory of branching processes and computer simulations, which allow reconciling molecular-level mechanisms with macroscopic observations in test tube and in disease individuals.



The final talk of the workshop dealt with computational approaches to DNA sequencing by hybridization (SBH). The topic is connected with the design of microarrays that may be important in testing cancer related issues. The basic SBH problem with isometric (equal length I-mers) libraries has been demonstrated to be equivalent to the Prize Collecting Traveling Salesmen Problem. Efficient heuristic approaches solving it have been given. A new approach based on isothermic (equal melting temperature I-mers) libraries has been presented and its practical usefulness demonstrated.

Conclusion

Most of the talks presented mathematical analysis of models of cancer and cancer therapy and raised many questions that need to be explored. Other talks addressed less specific topics in biochemistry, computer science, and statistics that may relate to cancer. On the whole, it was a relatively small workshop but with many lively and informative discussions.

Workshop 3

Signal Transduction I: Calcium Dynamics, Phototransduction, and Olfaction: January 26-30, 2004

Organizers:

James Sneyd - Department of Mathematics, University of Auckland, New Zealand

Mike Sanderson - Physiology Department, University of Massachusetts Medical School

Summary of Talks

The first day was devoted to calcium dynamics, beginning with a talk by Trevor Shuttleworth (University of Auckland), who presented evidence that channels are regulated by arachidonic acid. Shuttleworth is part of an experimental/theoretical team that includes David Yule (University of Rochester) and James Sneyd, and his results were presented in a suitable quantitative manner. The other experimental member of the team, David Yule, gave the third talk of the first day, devoting his talk to more technical aspects of the development of an IPR hybrid. The second talk, by Thomas Hofer (Humboldt University, Berlin), was the

An excellent meeting—successfully accomplished what is often a very difficult task, i.e., blending modelers with experimentalists. Well organized, well run, and a big success.

-Trevor Shuttleworth

first of the purely theoretical talks; Hofer presented a mathematical model of the IP₃/calcium signaling network which extended his previous models by inclusion of IP₃ dynamics. This was the modeling counterpart of the talk given by Andrew Thomas (New Jersey Medical School)

on Day 3 who discussed the experimental evidence that oscillations in IP₃ underlie calcium oscillations in hepatocytes. Back on Day 1, Yule's talk was followed by a short presentation by Krasimira Tsaneva-Atanasova (a Ph.D. student of James Sneyd). After lunch, Ian Parker (UC, Irvine) talked about the effects of different buffers on calcium waves in *Xenopus* oocytes, followed by a theoretical presentation by Stefan Schuster (Jena University), which focused on aspects of the bifurcation theory of calcium oscillators. The next talk, by Pablo d'Alcantara (National Inst. for Medical Research) was devoted to synaptic plasticity and Ca²⁺ dynamics in dendritic spines during back-propagating action potentials. This was followed by a presentation by Greg Smith (College of William and Mary) which dealt with nonexcitable cells, in which he presented his analysis of Markov models of stochastic calcium excitability.



Calcium dynamics was the major topic of Day 2 also, with the first talk by David Friel (CWRU) presenting a typically meticulous analysis of the modeling of calcium transport processes, in a manner analogous to the development of the Hodgkin-Huxley model of the action potential. The next talk, by Genevieve Dupont (University Libre de Bruxelles), presented a point of view rather different from that given by Andrew Thomas and Thomas Hofer. According to Dupont, who used a combination of modeling prediction and experi-

The workshop exceeded my already high expectations. Congratulations.

-Leslie Loew

mental confirmation, oscillations in IP_3 are not necessary for calcium oscillations in hepatocytes. It is not yet clear how the conflicting experimental results can be reconciled, or even if they are actually conflicting; this physiological controversy depends heavily on associ-

ated modeling work. Kevin Fogarty (UMass. Med. School) and Larry Lifshitz (UMass. Med. School) then presented a pair of talks on the experimental and theoretical aspects of their joint work, followed, after lunch, by Michael Sanderson's (UMass. Med. School) demonstration of how intercellular calcium waves can change people into vampires, or maybe cure them. He also showed his latest results on calcium oscillations in lung arteriole smooth muscle. Les Loew (University of Connecticut Health Ctr.) presented some elegant computations from a Virtual Cell model, to show how morphological effects can be extremely important in the study of the post-synaptic response. Next, Antonio Politi (Humboldt University, Berlin) next presented his theoretical analysis of the effects of feedback in calcium oscillation models, and the day ended with Jean-Francois Dufour's (University of Bern) data on the properties of IP_3 receptors from a liver with cirrhosis.

Day 3 began with yet more calcium dynamics, with the stochastic models of Martin Falcke (Hahn Meitner Inst.) followed by Andrew Thomas, as discussed above, and the theoretical approach of Marko Marhl. However, it soon switched to olfaction, with talks by

Karl-Ernst Kaissling (Max-Planck Inst.) and Stuart Firestein (Columbia University). Firestein gave a particularly interesting discussion of how both pharmacology and genomics can provide insights into how the brain perceives a world of innumerable and complex chemical odors.

This was one of the most productive and enjoyable meetings I've attended in some time. I want to thank the MBI for the opportunity to participate.

-David Friel

The final two talks were back to calcium dynamics, with Baruch Minke (Hebrew University) and Donald Gill (University of Maryland) both talking about TRP channels in their wonderful and intimidating variety.

Day 4 was devoted to phototransduction and olfaction. Daniel Tranchina (NYU) gave the first talk and discussed experimental evidence and mathematical theory for the role calcium in Single-Photon-Response reproducibility. Although evidence to support the calcium hypothesis seemed compelling, other experimental results and mathematical theory cast grave doubt on this hypothesis. Evidence on both sides can now be understood with the aid of a detailed stochastic biochemical kinetic model for rod phototransduction. Hugh Matthews (University of Cambridge) continued in a similar theme with a discussion of the interplay between theoretical prediction and experiment in his work on phototransduction. The next speaker, Dan Dougherty (an MBI postdoc), discussed a simple mathematical model for the G-protein coupled transduction machinery of olfactory receptor neurons, and then



Maarten Kamermans (Netherlands Ophthalmic Research Inst.) presented the evidence for ephaptic communication in the retina, in which the extracellular potential instead of the intracellular potential is modulated. Barry Ache (University of Florida) then argued that phosphoinositide signaling can inhibit cyclic nucleotide-dependent excitation of primary olfactory neurons, and that the interaction of these two signaling pathways is important in odorant coding by mediating opponent inputs into the receptor cell.

The fifth and last day of the workshop began with Steve Kleene (University of Cincinnati) who talked about the signal/noise ratio in olfactory transduction, followed by Jean-Pierre Rospars (INRA) who presented his investigations into how the intensive

I would like to thank you and your colleagues for organizing an interesting workshop of high quality, which was very useful for me. The most exciting part of the workshop was the possibility to meet and listen to people that I usually do not meet in regular professional meetings. I especially enjoyed my long discussions with David Holcman, whom I met for the first time in this workshop. Following these discussions we have decided to collaborate in the near future.

-Baruch Minke

properties of odors, measured by their odorant concentration in the air, are encoded in the spike trains delivered by olfactory receptor neurons. Johannes Reisert (Johns Hopkins) gave the very last talk. He brought the various parts of the workshop together with his presentation on the importance of the calcium-activated chloride channel in rat olfactory receptor neurons.

Conclusion

At the beginning of the workshop there were three rather separate groups of researchers, but by the end there was a lot more interaction between the various disciplines. One particularly noteworthy feature was the animated discussions between the modelers and the experimentalists, particularly in the field of calcium dynamics. There were at least three different groups there, each consisting of both experimentalists and modelers; it was highly gratifying to see how closely mathematicians now work with experimentalists in this area.

Back from my USA trip, I would like to thank you and James Sneyd so much for inviting me to the interesting meeting last January on Calcium and its role in Sensory Transduction. For me, it was most rewarding and also enjoyable. You created a perfect atmosphere for discussion and meeting with old and new friends and colleagues.

-Karl-Earnst Kaissling

For instance, Thomas Hofer (mathematician) and Andrew Thomas (experimentalist) both gave talks about their joint work, Genevieve Dupont talked about some recent experimental work she did based on her theoretical calculations, while Trevor Shuttleworth, David Yule, and Michael Sanderson (all experimental colleagues of James Sneyd) discussed some of their collaborative work.

Martin Falcke (modeler) and Ian Parker (experimentalist) contributed some joint insights, while Greg Smith also talked about work closely associated with Parker's experiments. Discussions across the experimental/theoretical divide were heated and ongoing; the divisions are no longer between mathematician and physiologist, but rather between collaborative research groups, each of which includes both modelers and experimentalists.



Phototransduction was relatively lightly represented, but the olfaction part of the meeting was a great success, due in large part to the efforts of some of the MBI postdocs and associated faculty. Geri Wright, Dan Dougherty, and Alice Yew went to great lengths to talk to the olfaction crowd, ask them questions about their experiments, and generally learn as much as they could in the time available. These initial contacts have now grown into substantial research collaborations. There is no doubt that the workshop played a crucial role in bringing the MBI members in contact with important experimentalists, and in stimulating lasting research connections.

Workshop 4

Signal Transduction II: Muscles and Synapse.

March 8-12, 2004

Organizers:

James Sneyd - Department of Mathematics, University of Auckland, New Zealand

Ed Pate - Mathematics Department, Washington State University

Summary of Talks

The workshop began with Don Bers (Loyola University), who gave an excellent overview of the field of cardiac calcium dynamics, and set the stage for much of what followed. He was followed by Christian Soeller (University of Auckland) who talked about a very detailed model of calcium movement and gradients in the diad. His model, using a Monte Carlo approach on a realistic geometry, suggested that there is an optimal DHPR gating time that maximizes responsivity of the RyRs while minimizing Ca^{2+} entry. After lunch, Jeremy Rice (IBM) talked about cooperative mechanisms in an ODE-based model of the myofilaments, followed by Josh Baker (University of Vermont), who presented some of his recent work in crossbridge mechanics.



Day 2 continued with Saleet Jafri (George Mason University) talking about a computational model of calcium sparks, followed by Julio Vergara's (UCLA) talk on calcium microdomains in the presynaptic terminal of a neuromuscular junction. Next, Alexandra Zahradnikova (Slovak Academy) presented detailed modeling work and experimental results addressing the connection between DHPR openings and RyR activation. Their analysis suggests that solitary DHPR openings have surprisingly low potency to activate RyRs and trigger calcium release. The potency is dramatically increased if DHPR openings are clustered due to the potentiating effect of the preceding openings on the subsequent openings, which may occur by increasing the basal calcium level and/or prolonging the duration of Ca^{2+} signals at the RyR sensing sites. The next speaker was Tim Elston (University of North Carolina) who talked about stochastic approaches to the modeling of biochemical networks, and the day ended with Tom Shannon (Rush University) presenting a four-compartment ODE model of the cardiac calcium transient.



The third day began with Mark Cannell (University of Auckland) who described a detailed model that was fitted to experimental data to determine the time course of SR calcium release from the measurement of calcium sparks. By evoking repeated Ca sparks from a single source identified within the cell, signal averaging could be applied to improve noise statistics, and calculations suggested that peak fluxes were somewhat larger than previously supposed. Cannell's talk was followed by Sasha Panfilov's (University of Dundee) presentation of his large-scale electrophysiological model for action potential in the heart. He discussed how the models used for large scale computational projects in electrophysiology

The talks were excellent, and I had many significant discussions with new contacts, as well as with colleagues I already knew. Combining E/C coupling and muscle mechanics in one small workshop was a great idea.

- Steve Lehman

have changed over the years, and he presented recent work on developing models for human cardiac cells for anatomically based models of human heart. Next was Jose Puglisi (Loyola University) with a show and a talk about his LabView implementation of a model for the

cardiac action potential. After lunch Nick Smith (University of Auckland) talked about a model of muscle contraction, concentrating on a computationally efficient model of cellular tension generation which is suitable for embedding in tissue models to predict cardiac mechanical behaviour. Earl Homsher (UCLA) followed with a similar theme, but focused on the effects of regulatory proteins on crossbridge mechanics. The day ended with Jim Keener's (University of Utah) talk about how flagella and suchlike things are built.

Crossbridge mechanics was the major focus of the fourth day. It began with Roger Cooke's (UCSF) talk on the energetics of motor proteins, connecting the free energy released by the binding cycle to the mechanical force produced by the proteins. Daniel Benteil (University of Vermont) spoke next, on the results obtained from laser trap experiments and his Langevin-type model of them. Next was Ed Pate (Washington State University), who presented his molecular dynamics simulations based on x-ray crystallographic structures of myosin. Hong Qian (University of Washington) then talked about a unifying stochastic model for single motor protein movements and cytoskeletal filament polymerizations, followed by Bryant Chase's (Florida State University) discussion of how calcium dynamics and the regulation of the calcium transient are connected to the mechanical aspects of the response.

The fifth and final day saw a change in topic to synapse modeling. Elise Stanley (Toronto Western Research Inst.) began this with a presentation of experimental data of some of the presynaptic structures and how they relate to calcium release. This was followed by Richard Bertram's (Florida State University) discussion of recent models of autoinhibition of neurotransmitter release, including models that ranged from very simple to much more complex. Finally, Victor Matveev (New Jersey Inst. Of Technology) talked about a model of synaptic facilitation through saturation of calcium buffers, comparing the modeling results to experimental data from the crayfish neuromuscular junction.



Conclusion

Once again, it was gratifying to see how closely modeling and experimental work is intertwined in these areas. Experimentalists such as Christian Soeller or Alexandra Zharadnikova use mathematical models on an everyday basis to help them understand their experimental work, while Tim Elston, Saleet Jafri, and Ed Pate, although primarily modelers, are closely associated with experimental colleagues. In many respects, it is becoming almost impossible to classify many researchers as either theoretical or experimental, as the two approaches have become so closely intertwined.

Cardiac calcium dynamics and crossbridge models were both particularly well represented. Don Bers, one of the leading experimentalists in excitation-contraction coupling, gave the first talk, thus setting a high standard for the rest of the workshop. The connection from calcium transients to the activation of the actin/myosin complex was glossed over to some extent, but models for crossbridges were presented in great detail. This was a particularly educational part of the workshop.

The workshop ended with a series of talks about synapses, concentrating on the neuromuscular junction. These were interesting because of their connection to Workshop 3. Many of the models developed for calcium dynamics and buffering have played a crucial role for understanding calcium microdomains in synapse models. Thus, the two workshops were brought together when studying models of presynaptic facilitation.

As in Workshop 3, MBI postdocs benefited greatly from the chance to meet others in the field. Pranay Goel, an MBI postdoc interested in working on models of postsynaptic depression, was able to meet Richard Bertram, Elise Stanley, and Victor Matveev, some of the leaders in the field of synaptic modeling. Elise Stanley will be revisiting the MBI later on in 2004 to maintain this connection. In addition to the chance to meet the leaders in the field, the postdocs were also able to learn by observing some theoretical/experimental collaborations at close range. Both workshops were lively and informal, with a great deal of discussion

One of the best workshops I have attended. Very well organized with an ideal balance between focus and spread in the topics covered.

-Bill Gibson

and argument, and mathematics played an important role at all levels. The workshops were examples of how best to establish and maintain these sorts of collaborations, and could serve as role models for those more junior in the field.

In addition, the workshops stimulated a great deal of discussion and thought among the leaders in the respective fields. It is yet too early to give a complete list of research ideas and projects to have arisen from these workshops, but they have stimulated several people to think and work in different directions.



Workshop 5

Immunology Models: Cell Signaling and Immune Dynamics: May 10-14, 2004

Organizers:

Denise Kirschner - Department of Microbiology and Immunology, University of Michigan Medical School

Jennifer Linderman - Chemical Engineering, University of Michigan

Sergei Pilyugin - Department of Mathematics, University of Florida

Summary of Talks

Day 1 was devoted to the general topics in immune responses. Marc Jenkins (University of Minnesota) opened the workshop with a summary of experimental findings that concern the early events during the immune response. He described the recent experiments on mice that elucidate the time frame of interactions between dendritic cells and CD4⁺ T-helper cells in the draining lymph nodes. Carson Chow (University of Pittsburg and National Institutes of Health) proposed a simplified mathematical model to study the innate immunity and its role in developing acute inflammation (sepsis), which is a major medical problem in devel-

I truly enjoyed the opportunity to visit the institute and share my research and get some very insightful feedback and ideas. I am pleased to see the environment of research that you have there among postdocs and professors.

-Miriam Nuno

oped countries. Rustom Antia (Emory University) presented a mathematical framework for modeling the CD8⁺ arm of pathogen-specific immune response focusing on questions regarding generation, maintenance, and duration of immunological memory. Lee Segel (Weizmann Institute of Science, Israel) raised questions of the nature of global

interactions between various cell types during the immune response and discussed possible optimization schemes that may explain the observed dynamics of such responses. Sergei Pilyugin (University of Florida) gave a talk on analytical methods used for estimating kinetic parameters of lymphocyte turnover from the in vivo CFSE assay.

Posters presentations were held during the reception. Individual posters were presented by Vitaly Ganusov (Emory University), David Klink (Entelos Inc.), and Christian Ray (University of Michigan). Two group posters were presented by K. Duca, D. Bowman, R. Laughenbacher, C. North, N. F. Polys (Virginia Tech), T. L. Kinzer-Ursem, A. Waller, K. L. Sutton, A. Absood, G. M. Omann, and J. Linderman (University of Michigan).

The second day consisted of a detailed discussion of cell-to-cell signaling processes and their role in shaping the immune response. Arup Chakraborty (UC Berkeley) opened the discussion with his lecture on kinetic reactions involved in APC-to-T cell signal transduction through the immunological synapse. He discussed recent experimental results and presented a computer-based model for signal transduction. Ravi Ivengar (Mt. Sinai School of Medicine) spoke on formation of signaling networks in different cell types. He presented a graph-theory based approach to study large signaling networks and discussed the importance of gates and feedback loops for signal propagation in a network with applications to the regulation in T cell functions. Raibatak Das (Cornell University) presented the experimental results for mast cell signaling and degranulation and discussed the possible therapeutic consequences for treatment of allergies and other autoimmune malfunctions. Benoit



Morel (Carnegie Mellon University) gave a brief overview of dynamic complexity exhibited by the immune system and discussed new mathematical tools that may be required to study these complexities. Leslie Loew (University of Connecticut Health Center) gave an introduction to the Virtual Cell Project, a modeling software package that allows implementing

This was one of the very best meetings I have been to for a very long time. It really was exceptionally outstanding.

-Jaroslav Stark

various biochemical processes and their interactions in different subdomains of the cell membrane and cytoplasm. Jason Haugh (North Carolina State University) talked about the PDGF receptor-induced signaling pathway in fibroblasts. He discussed experimental and model-

ing efforts focusing signal integration and spatial regulation in response to PDGF gradients. Peter Woolf (MIT) gave a brief talk on modeling the signal transduction networks using Bayesian network representations.

Short talks were given by Simon Preston (University of Nottingham), Daniel Coombs (University of British Columbia), and Karen Duca (Virginia Tech).

Day 3 included discussions of two major topics. The morning talks focused on receptor-ligand interactions, and the afternoon talks were devoted to the role of B-cells and B-cell receptor diversity. Byron Goldstein (Los Alamos National Labs) set the tone for the day by presenting the theoretical framework for modeling specific signal recognition and signaling through cell surface receptors. He showed how simple modeling schemes, such as kinetic proofreading and serial engagement, provide significant insight into the signaling behavior of immune cells. Jaroslav Stark (Imperial College, London) followed with a lecture on the role of feedback mechanisms in signaling pathways. He presented a mathematical model that explains the existing trade-off between T cell specificity and sensitivity and provides a hysteresis mechanism for sustained T cell activation. Thomas

As a graduate student, I was excited to meet a number of people whose work I had read but whom I had never met or even heard give a talk. I also enjoyed meeting other graduate students working on projects of similar themes. Therefore, "coffee break" times were invaluable and should not be compromised in future workshops.

-Stewart Chang

Kepler (Duke University) discussed a new information-based statistical approach to studying the diversification mechanisms that shape the adaptive immune system of vertebrate hosts. Philip Hodgkin (The Walter and Elisa Hall Institute of Medical Research) gave a lecture on cellular calculus, which is a modeling framework for studying the role of various cytokines in regulating the lymphocyte stimulation, proliferation, and differentiation in vivo. He illustrated how cellular calculus can be used in conjunction with the CFSE labeling experiments to estimate kinetic parameters of cell division and apoptosis. Ramit Mehr (Bar-Ilan University) presented a cellular automata-based model for studying the role of lipid rafts in formation of the immunological synapse. Lindsay Cowell (Duke University) discussed how Markov chain models of mouse recombinant signals could be used to predict the efficiency of V(D)J recombination. Stephen Kleinstein (Princeton University) presented two modeling approaches to estimating the hypermutation rates and frequency of lethal mutations in B-cell lineages.



A specific discussion on T-cells was the topic for day 4. The morning session began with a talk by Gary Huffnagle (University of Michigan) who discussed the role of environmental factors that may play a role in increased incidence of inflammatory diseases in the western world. He presented an experimental mouse model of antibiotic-induced gastrointestinal microflora disruptions and demonstrated how antibiotic treatment may alter the regulatory mechanisms of immune response and induce allergic responses. Robin Callard (University College London) described the model of fractricide to study the homeostatic regulation of CD4 and CD8 T cell compartments. He also showed how this model can be used to investigate the loss of T cells during HIV infection. Ping Ye (John Hopkins University) talked about

My congratulations to all involved. It was one of the most interesting meetings I have attended.

-Philip Hodgkin

modeling thymic function in healthy individuals and proposed a way of estimating the loss of this function by using the TREC (T cell receptor excision circles) data. Rob De Boer (Utrecht University,

Netherlands) discussed the dynamics of CD4 and CD8 responses to acute LCMV infections in mice. He used simple mathematical models to estimate the kinetics of both responses during different phases (expansion, contraction, and memory) and provided interesting comparisons between CD4 and CD8 responses. Alan Perelson (Los Alamos National Labs) emphasized the importance of stochastic variability among the antigen-specific lymphocyte lineages and presented computer simulations of stochastic models for specific immune responses to acute infections. Charles Orosz (Ohio State University) gave a talk on the complexity of the immune system in which he argued that the commonly employed top-down analytic approaches may be futile in the struggle to understand such complexity. As an alternative, he presented a systems approach to studying immune interactions and demonstrated a computer-based cellular automata model of a generic immune response. Roland Regoes (Emory University) presented a mathematical model he used to estimate the killing rate of CTL (cytotoxic T lymphocytes) during the LCMV infection.

Day 5 concluded the workshop with a summary of cell-to-cell interactions in the immune system. Steven Kunkel (University of Michigan Medical School) summarized the roles of numerous cytokines in immune cell interactions focusing on chemokine activity in regulating Th1/Th2 immune response. Penelope Morel (Carnegie Mellon University) spoke on the role of DCs (dendritic cells) in Th1/Th2 regulation process. She presented experimental results for NOD (non-obese diabetic) mice and discussed the therapeutic potential of DCs. The last talk was given by Zvi Grossman (Tel-Aviv University) who elaborated on the role of feedback mechanisms for inhibition of autoimmune reactivity, control of immune responses, and homeostatic regulation of T cell numbers.

Conclusion

The workshop provided an excellent overview of recent experimental and theoretical advances in our understanding of complex cell interactions within the immune system. Both experimentalists and modelers have come to realize that there are differences of opinions and that there is a need for enhanced collaborative efforts. The workshop brought together prominent researchers, postdoctoral fellows, and graduate students and significantly increased the level of interaction between different research groups. Numerous private discussions were sparked by lectures on several controversial subjects. After the fact, many participants expressed the opinion that the intensity of the workshop program was overwhelming and that more time should have been allotted for group discussions.



Workshop 6

Disease Models: Host-Pathogen Interactions.

June 21-25, 2004

Organizers:

Denise Kirschner - Department of Microbiology and Immunology, The University of Michigan Medical School

Thomas Kepler - Computational Biology, Department of Biostatistics and Bioinformatics, Duke University

Summary of Talks

Day 1 began with a talk by Marry Carrington (National Cancer Institute) who discussed natural killer (NK) cells and their role in viral dynamics. A major group of receptors on NK cells are KIRs. These receptors regulate inhibition and activation of NK cell responses through recognition of HLA class I molecules on target cells. Given their receptor-ligand relationship, she hypothesized that KIR may be involved in many of the diseases for which an HLA influence has been identified. She applied these findings to two specific viruses, namely HIV and Hepatitis C. This was followed by a talk from Todd Reinhart (University of Pittsburgh) who studied the effects of *in vivo* infection with SIV on the immune environments within lymphoid tissues. He identified three key areas whereby changes observed are likely to be important in disease: (1) up-regulation of chemokines, which control constitutive and inflammatory cell trafficking; (2) altered tissue compositions of dendritic cells, which are potent antigen presenting cells controlling the nature and strength of immune responses; and (3) up-regulation of members of a group of receptors within the innate immune system, Toll-like receptors, which control rapidly-induced inflammatory responses. The final morning talk was by Georgia Tomaras (Duke University). She talked on the role of CD8⁺ T cells in HIV-1 infection. It has recently become evident that the virus can escape from noncytolytic suppression illustrating the ability of this antiviral activity to exert significant immune pressure *in vivo*.

Great intro to a field that is new to me. Fantastic line-up of speakers, both biological and mathematical. Learned an incredible amount in a short time. Met lots of interesting people! Chance to see live people who wrote the papers I read.

-Cliburn Chan

The molecules involved in this antiviral response and their precise mechanisms remain elusive. She presented studies of HIV variants harboring escape mutations that provide new insights into the identities of noncytolytic CD8⁺ suppression. After lunch, there were four short talks. The first was by Leor Weinberger (UC Berkeley) on the proviral reservoir in HIV infection. He presented the first evidence that an HIV-1 positive feedback regulatory pathway, implicated in the establishment of proviral latency (the HIV-1 Tat transactivation loop), may utilize stochastic molecular fluctuations. This was followed by Seema Bajaria (University of Michigan) who presented a model for the role of CD8⁺ T cells in HIV-1 infection. Her results indicated that CD4⁺ T cells as well as dendritic cells likely play a significant role in successful activation of CD8⁺ T cells into CTLs. Her model simulations correlated with clinical data confirming a quantitative relationship between CD4⁺ T cells and CD8⁺ T-cell effectiveness. Wai-Yuan Tan (University of Memphis) discussed a model for the assessment of treatment effects on HIV pathogenesis under HAART. To monitor the progression of therapy in HIV-infected individuals treated with antiviral drugs, he argued that it is critical to estimate and assess the efficiency of the drugs and to estimate the number of infectious and noninfectious HIV under treatment. He developed a method to



estimate these parameters and the state variables to assess effects of drugs on HIV pathogenesis. The day ended with a talk by Robert Stengel (Princeton) who uses optimal control theory as a means for specifying optimal therapeutic protocols given a satisfactory immune system model. For illustration, he presented results in two settings: the humoral response to extracellular bacteria and the cellular response to the human-immunodeficiency virus (HIV).

Day 2 opened with a talk by an HIV-1 clinician, Dr. Sandro Cinti (University of Michigan Hospitals). Since most of the talks focused on HIV-1, Dr. Cinti provided an important perspective with epidemiological statistics as well as the latest information regarding treatment and prevention. This talk was followed by Miles Cloyd (University of Texas Medical Branch) who focused on pathogenic mechanisms of HIV-1. He showed data regarding a bystander effect of cells becoming infected that are not able to produce a virus, but die due to enhanced apoptotic mechanisms. The final morning talk was given by Garnett Kelsoe

(Duke University) who spoke on B cell dynamics in the lymph node. After lunch, there were four shorter talks. Jaroslav Stark (Imperial College) discussed the use of a simple mathematical model to provide insight into the different roles of evasion and resistance in the evolution of escape mechanisms to avoid cytotoxicity. He suggested experiments to validate the hypotheses of the model, and discussed the implications for immunotherapy against intracellular pathogens. Next, Zvi Grossman (NIH) discussed implications for different modeling approaches in HIV-1. After the Coffee break, Reinhard Laubenbacher (Virginia Tech) showed a



new tool known as *PathSim*. It is an example of an information-rich model with associated databases. The main goal of PathSim is to model a variety of viral agents in human and animal hosts, from initial infection to viral clearance. PathSim allows an end-user to explore the physiology and dynamics of infections and immune system response. As an interface to this system, they constructed and are evaluating information-rich virtual environments (IRVEs) for the PathSim project. This interface framework can also be applied to other similar information-rich databases in the life sciences that share these characteristics. The final speaker of the day was Ping Ye (Johns Hopkins) who spoke about a clinical study on HIV-1 whereby they attempted to define immune biomarkers for disease stage. These markers are the beta chemokines. She showed that, in blood, there is no correlation; however, she cannot rule them out for more local compartmental dynamics.

On Day 3 the topic switched from viral host-pathogen interactions to bacterial and fungi host interactions. The kick-off speaker was Vic DiRita (University of Michigan Medical School). He spoke on the relationship between *Vibrio cholerae* and M cells, which are the immune cell types located in the small intestine. He showed that complex regulatory networks are at work balancing this dynamic. His talk was followed by Arturo Casadevall (Albert Einstein School of Medicine) who spoke on a concept he has developed called “the damage-Framework of Microbial Pathogenesis”. He also has developed an algorithm for calculating



the biological weapons potential for a microbe. The final morning talk was by Amy Herring (University of Michigan Medical School). She described work on a specific fungus, namely, *C. neoformans*. She discussed the mechanisms of chronic fungal infections and how it depends on the interplay between innate and adaptive immunity. After lunch, there were five short talks. Jorge Velasco-Hernandez (Instituto Mexicano del Petroleo) spoke on biofilm formation. He studies three aspects of it: (1) spatial structure and its relation to coexistence

I liked the combination of talks and discussions and also modeling and experimental approach.

-Natasa Macura

of multispecies biofilms; (2) the role of mutations in the existence of colonial biofilms; and (3) the interaction between biofilms and the fluid environment in which they thrive. This talk perfectly preceded the next talk by John Ward

(Loughborough University) on the topic of quorum sensing, which biofilm formation relies on. He presented a spatio-temporal model of bacterial growth and QS in an infected burn wound situation incorporating the known microbiology. He used asymptotic and numerical techniques to highlight conflicting effects of QSM production in the infected regions and loss (via diffusion and degradation in the surrounding tissues). Regimes in which substantial up-regulation (and therefore virulence) can occur and on what timescale were determined in terms of the model parameters. Therapeutic implications were also discussed. After the coffee break, Tom Kepler (Duke University) presented work on a 3-D agent based model of immune responses to bacterial pathogens. John Tomfohr (Duke University), also from the Kepler group, convinced the audience that it is sometimes valuable to look at expression data at the level of groups of functionally related genes, such as those belonging to the same pathway or complex. This can reveal higher-level features not as apparent from the variations in the individual genes alone. He presented an approach to analyzing gene expression at a multigene level using a collection of about 400 predefined pathways and complexes, and made comparisons with to experimental data. The final talk of the day was given by Sergei Pilyugin (University of Florida). He presented a theoretical model with analysis, which involved backward bifurcations and the role of co-infection in multidisease dynamics.

The focus of most of the fourth day was on immunology and the pathogen *Mycobacterium tuberculosis* (*Mtb*). JoAnne Flynn (University of Pittsburgh) started the day by discussing the evolving immune response to *Mtb* infection. She focused specifically on the role of $CD8^+$ T cells (a now common theme at this meeting) and showed that both experimental data and mathematical modeling highlight their importance. This talk was followed by Dr. John Chan (Albert Einstein College of Medicine) who is a TB clinician and researcher. His talk focused on the role of a cytokine, TNF, as a pro-inflammatory modulator of the immune response to *Mtb*. Mary O'Riordan (University of Michigan Medical School) gave a talk on the interaction between host cells and bacterial pathogens that live within the cell. She found that macrophages, which are an important niche for many intracellular pathogens, can sense unique bacterial molecules within the cytosol. Triggering of this cytosolic surveillance pathway results in a characteristic pattern of gene expression that includes cytokines and other pro-inflammatory target genes. Using *Listeria monocytogenes* as a model pathogen, she is attempting to identify signaling molecules and transcriptional regulators that are specific to the cytosolic surveillance pathway. The final talk of the morning was given by Mark Miller (Washington University). Using two-photon microscopy, he showed real-time behavior of endogenous DCs and $CD4^+$ T cells in lymph node explants during a robust T cell response. His results suggest that naïve $CD4^+$ T cells encounter DCs at random and



not by following chemokine gradients emitted by DCs. Quantitative analysis of his imaging data suggests that random motility is a natural property of lymphocytes and that stochastic, multi-agent based models may best describe lymphocyte trafficking and behavior *in situ*. After lunch, three talks by postdoctoral fellows from Denise Kirschner's lab presented results of models exploring Mtb. First, Simeone Marino discussed a two-compartmental trafficking model of Mtb between the lung and lymph-node. Next, Jose Segovia-Juarez showed results from an agent-based model of granuloma formation in TB. Finally, Stewart Chang gave results of a model developed to study the inhibitory effects of Mtb on antigen processing in macrophages. Jun Lu (Duke University) gave the final talk on analyzing gene expression in the host-defense against Arabidopsis. This last talk was followed by over an hour discussion on important topics, questions, and controversies that arose during the meeting. This discussion continued over dinner at the banquet that evening.

Conclusion

This workshop provided an excellent forum for the presentation of ideas related to host-pathogen interactions. It allowed for scientists to present the most up-to-date data and approaches to problems in this area and opened up important lines of communication between both theoretical and experimental groups. An added feature was the presence of young investigators as well as more senior members adding to training aspects. Numerous informal discussions and eventual collaborations arose from this meeting and all participants commented that it was an invaluable experience enhancing their research programs.

Current Topics Workshop

Statistical and Mathematical Modeling of fMRI Data:

March 18-20, 2004

Organizers:

Thomas Santner - Department of Statistics, The Ohio State University

Petra Schmalbrock - Department of Radiology, The Ohio State University

Jay Zweier - Heart and Lung Institute, The Ohio State University

Summary of Talks

Blood Oxygen Level Dependent (BOLD) functional magnetic resonance imaging (fMRI) is the most prevalent and perhaps the most important method in use. Among the numerous neuro-functional applications of BOLD fMRI are assessments of the processing of motor, visual, auditory, and sensory tasks by the normal brain; the evaluation of various pathologies including neurological and psychiatric disorders; the presurgical determination of brain function; and cardiac imaging. The current practice in the majority of neuro-functional applications is the use of BOLD fMRI in a qualitative fashion followed by the employment of statistical analysis to extract the signal changes present in fMRI data. This statistical task is very difficult because of the highly spatially and temporally correlated nature of fMRI data and because of the small levels of the signal changes (1-4%). Used ad hoc empirical assumptions in modeling the fMRI signal intensity response; specifically, assumptions regarding the temporal change of the fMRI signal in response to the neural task and regarding the spatial relations between neural activation. A complete understanding of the BOLD effect and its relation to neuronal activation requires the understanding not only of where signal changes occur, but also the physiologic and physical mechanisms causing the signal



change. A number of studies have addressed these issues. However, many details regarding these physical and physiological mechanisms remain open questions.

In more detail, the physical modeling of fMRI data involves the description of MRI signal changes due to the diffusion of tissue water molecules in the locally variable magnetic fields produced by (paramagnetic) deoxyhemoglobin. These spatially variable magnetic fields, on a 10-100 micrometer scale, can be described mathematically. This knowledge can be used to estimate the signal from water proton diffusion in different tissue compartments (intra-, extra-vascular) and in different geometries (vascular and micro-vascular networks), as well as the amount and distribution of deoxyhemoglobin. Physiological models are needed to explain the altered amount of deoxyhemoglobin during neuronal activation and its dependence on blood oxygenation, cerebral metabolic rate, oxygen extraction fraction, cerebral blood volume, and cerebral blood flow. It needs to account for the interconnectedness of these different factors under normal or pathologically altered physiologic conditions. Using this knowledge, the statistical modeling of BOLD fMRI signal changes can be improved by better descriptions of the spatial and temporal correlations present in such data and the prior extent of activation. This will, in turn, lead to more accurate understanding of the physiologic and physical mechanisms causing the signal change.

The ordering of the presentations was intended to facilitate the mixture of talks describing the physics of the BOLD signal and its physiology with ones describing statistical approaches to the analysis of such data. The first day's schedule consisted of two 1-hour morning lectures (Joe Mandeville and Bill Eddy) and two invited 1-hour lectures in the afternoon (Mark Haacke and Jean-Francois Mangin) plus shorter topics and poster talks by workshop participants (Kary Myers, Tom Nichols, Stefan Posse and Ray Hoffman). On Day 2, the morning schedule had two 1-hour morning lectures (Harold M. Swartz and John Kornak) and a 1-hour lecture in the afternoon (Fahmeed Hyder). The rest of the afternoon was devoted to a discussion facilitated by (Seong-Gi Kim, Bill Eddy, and Dave Beversdorf) where participants discussed grand challenges in the field, and how mathematicians and molecular biologists can synergize to bring the field to the status of a predictive science based on mechanistic modeling. Day 3 consisted of a morning session with two more invited talks (John Mayhew and Keith Worsley) and a wrap-up session (Petra Schmalbrock and Tom Santner). Throughout the workshop, there was ample time for discussion after every lecture, and there was a lot of time for informal discussions and a tour of the OSU MRI facilities.

Day 1

Joseph B. Mandeville (Department of Radiology, Harvard Medical School)

Title: *CBV Contributions to BOLD: Implications for Modeling & Statistics.*

Dr. Mandeville opened the workshop with a discussion of the BOLD effect and its dependence on Cerebral Blood Flow. Perhaps the most significant point that he made was that modeling dynamic fMRI data, such as event-related studies, requires a detailed understanding of transient features of the fMRI response and non-linearities that arise between the stimulus design and the measured output. A temporal mismatch between flow and volume is one of the major sources of BOLD transients.



William Eddy (Department of Statistics, Carnegie Mellon University)

Title: *CBV Contributions to BOLD: Implications for Modeling & Statistics.*

Professor Eddy described the important sources of variability that effect the modeling of fMRI data that must be accounted for in any attempt to model such data. In Human Brain Mapping, these effects include variation addressed by registration, physiologic changes, and other effects that might be termed “noise” when compared with the experimental protocol being considered.

E. Mark Haacke (Department of Radiology, Wayne State University)

Title: *High Resolution SWI and Complex Analysis in fMRI*

The physics mechanisms underlying BOLD fMRI and susceptibility weighted imaging were explained. Using this mechanism for structural imaging produces exquisite displays of venous cerebral vasculature especially at high magnetic field strength. This helps in the diagnosis of brain tumors, infarct, and brain trauma. Optimal approaches for data acquisition and analysis and limits for detection of small sized vessels were discussed. The method was also applied for functional assessment of vascular changes with caffeine and for estimating oxygen saturation.

Jean-Francois Mangin (Paris, France)

Water molecule diffusion can be measured with MRI, and in the structured cellular environment, cellular and molecular boundaries determine the mobility of the water molecules. This fact can be used to track tissue fibers. In the brain, such axonal fiber tracks represent the connectivity of the brain. In this context, BOLD fMRI can be used to identify functional start-points for the tracking algorithm. Details of the algorithms and display techniques were discussed. In the future, diffusion fiber tracking will help understand human brain development, complex interconnections between different parts of the brain, and alterations thereof in disease.

Short Presentations on Day 1

Kary Myers (Carnegie Mellon University)

Title: *The Billion Byte Brain: Toward Removing Physiological Effects from Gigabytes of Optical Imaging Data*

Methods for analysis of functional optical image data were described.

Thomas Nichols (Department of Biostatistics, University of Michigan)

Title: *Diagnosing Linear Model Fit in fMRI*

fMRI creates vast amounts of data with numerous ways for statistical analysis. It is thus of paramount importance to have intuitive interactive tools and comprehensive display methods. Temporal and spatial summaries and details were presented.

Stefan Posse (MIND Imaging Center, University of New Mexico)

Title: *TurboFIRE: Advances in Interactive Real-time fMRI*

For fMRI studies in brain regions near air spaces such as the paranasal sinus and temporal bones, magnetic susceptibility artifacts occur severely distorting the images. A new T2* measuring method (TURBOPEPSI) reduces these problems. Furthermore, for complex neural tasks, it is important to have immediate on-line data analysis available and even use it to provide feedback to the study subject. A new tool (TURBOFIRE) for fast online analysis was presented.



Poster Presentation on Day 1

Ray Hoffman (Department of Biostatistics, Medical College of Wisconsin)

Day 2

Harold M. Swartz (Dartmouth Medical School)

Title: *Integrating Data Obtained by In Vivo Spectroscopy and Imaging with Modeling of Oxygen Distribution in Tissues: Concept and Approach*

Dr. Swartz discussed the conceptualization of the complex physiology/pathophysiology that is involved in changes of oxygen in tissue. He then applied advanced computational methods to develop a comprehensive physiological model that describes the distribution and changes of oxygen in tissue and the metabolic and signaling events associated with oxygen. This was done using data from several different and complimentary methods for making measurements in vivo. Because the distribution of oxygen in tissues is very heterogeneous, even at cellular dimensions, such measurements and the resulting model are important but challenging tasks.

John Kornak (University of California, San Francisco, VA Medical Center)

Title: *Modeling Spatial Variation in the Shape of the BOLD Response*

Several statistical approaches exist to compensate for the temporal smoothing effect inherent when using the BOLD response as a proxy for neural activation. Commonly used BOLD correction methods, such as convolving a stimulus function with a hemodynamic response kernel, inevitably make assumptions restricting the possible shapes of the BOLD response. Furthermore, the BOLD response shape is typically restricted so that only the response magnitude can vary spatially. These assumptions were examined by fitting a range of parametric "shape" functions to voxel averaged BOLD response cycles using least squares estimation. The results imply that the shape of the BOLD response can vary spatially in a coherent fashion which, if ignored, could have implications on the detection and interpretation of activation patterns.

Fahmeed Hyder (Departments of Diagnostic Radiology and Biomedical Engineering, Yale University)

Title: *Neuroenergetic Basis of fMRI*

The conventional functional MRI (fMRI) map offers information indirectly about localized changes in neural activity because it reflects changes in blood oxygenation, not the actual neural activity. To provide neural basis of fMRI, researchers have combined electrophysiology and various optical methods to show correlations between fMRI and surrogate signals associated with neural activity. Such "calibrated fMRI" in animal models allows for simultaneous acquisition of electrophysiologic data, assessment of cerebral oxygen metabolism, and cerebral blood flow and blood volume in addition to BOLD fMRI. This in turn allows for quantitative assessments of various physiology models used in the interpretation of BOLD fMRI.



Day 3

John Mayhew (Department of Psychology, University of Sheffield)

Title: *The Hemodynamic Response to Increased Neural Activity in Brain: BOLD signals*

Dr. Mayhew presented the attempts of his group to build a 'forward' biophysical model whose purpose is to develop the 'inverse' analysis methodologies needed for the understanding of the BOLD (and OIS) response to activation.

Keith Worsley (Department of Mathematics and Statistics, McGill University)

Title: *A General Statistical Analysis of fMRI Data*

Dr Worsley presented a proposed method for the statistical analysis of fMRI data that seeks a compromise between validity, generality, simplicity, and execution speed. The method is based on linear models with local AR(p) errors. The AR(p) model is fitted via the Yule-Walker equations with a simple bias correction that is similar to the first step in the Fisher scoring algorithm for finding REML estimates. The resulting effects are then combined across runs in the same session, across sessions in the same subject, and across subjects within a population by a simple mixed effects model. The model is fitted by REML using the EM algorithm, after re-parameterization to reduce bias, at the expense of negative variance components. The residual degrees of freedom are boosted using a form of pooling by spatial smoothing. Activation is detected using Bonferroni, False Discovery Rate, and non-isotropic random field methods for local maxima and spatial extent. The talk examined briefly an alternative method based on conjunctions. Finally, a simple method is used to estimate and make inference about the delay of the hemodynamic response function at every voxel. The talk concluded with some suggestions for the optimal design of fMRI experiments.

Conclusion

This workshop has brought together five speakers and poster presenters (Eddy, Kornak, Nichols and Worsley, Hoffman) who have considerable experience in statistical analysis of BOLD fMRI, with seven speakers who have extensively modeled the physiology (Mandeville, Hyder, Mayhew) and physics (Haacke, Posse) of the BOLD effect. In addition, several speakers discussed the advantages of combining BOLD fMRI with other MRI methods (Mandeville: Perfusion MRI, Hyder: ^{13}C MR spectroscopy, Mangin: MRI Diffusion fiber tracking) and/or other imaging modalities (Mayhew, Meyers: optical imaging, Swartz: electron spin resonance). Thus, participants (speakers and audience) benefited from the cross-disciplinary presentations of the complexity of fMRI modeling and analysis.



Tutorials

Tutorial on the Cell Cycle:

September 2-5, 2003

Organizers and Speakers:

John Tyson - Department of Biology, Virginia Polytechnic Institute

Bela Novak - Agricultural Chemical Technology, Budapest University of Technology, Hungary

David Axelrod - Department of Genetics, Rutgers University



Tutorial on Signal Transduction:

January 5-9, 2004

Organizer:

James Sneyd - Department of Mathematics, University of Auckland, New Zealand

Speakers:

Johannes Reiser - Department of Neuroscience, Johns Hopkins University School of Medicine

Michael Sanderson - University of Massachusetts Medical School

James Sneyd - Department of Mathematics, University of Auckland, New Zealand

Dan Tranchina - Courant Institute, New York University



Tutorial on Synapses and Muscles:

March 1-4, 2004

Organizer:

James Sneyd - Department of Mathematics, University of Auckland, New Zealand

Speakers:

Richard Bertram - Florida State University

Ed Pate - Department of Mathematics, Washington State University, Vancouver

Thomas Shannon - Department of Molecular Physiology and Biophysics, Rush University Medical Center

Raimond L. Winslow - The Center for Computational Medicine and Biology and the Whitaker Biomedical Engineering Institute, The Johns Hopkins University School of Medicine and Whiting School of Engineering



Tutorial on Immunology Models:

May 6-7, 2004

Organizers:

Denise Kirschner - Department of Microbiology and Immunology, University of Michigan Medical School

Thomas Kepler - Computational Biology, Departments of Biostatistics and Bioinformatics, Duke University

Speaker:

Thomas Kepler - Computational Biology, Departments of Biostatistics and Bioinformatics, Duke University



Tutorial on Host-Pathogen Interactions:

June 15-16, 2004

Organizer and Speaker:

Denise Kirschner - Department of Microbiology and Immunology, University of Michigan Medical School

Summer Program

August 2-20, 2004:

Cell Processes

I thought the entire program was wonderful. I am really thankful that there are such programs available.

-Kyle Covington

This year, the program focused on Cell Processes. The program leader was Professor James Sneyd. After an introductory tutorial and discussion in the first 2 days, the participants were divided into teams of five, with each team led by an MBI postdoc. Teams worked on one project for the first 2 1/2 weeks, and there was a miniconference in the final 2 days.

During the 3-week period, there were also several general talks on cell cycle and proliferation by active researchers and visits to their bioscience labs.

Tutorials and Talks

August 2-6

James Sneyd Tutorials:

1. Enzyme Kinetics
2. How Cells Control Their Volume
3. Calcium Physiology
4. Cardiac Electrical Physiology

I liked the style of the tutorial instructor. His use of humor made the lecture very live. The instructor was very knowledgeable and helpful in answering questions. It was a great experience to work in a team. To meet people from different schools was very stimulating. I learned a lot during these 3 weeks.

-Taras Odushkin



Talks:

Martin Wechselberger - Introduction to Dynamical Systems: Phase Analysis and Bifurcation

Pranay Goel - Introduction to XPP

Talks and Lab Visits

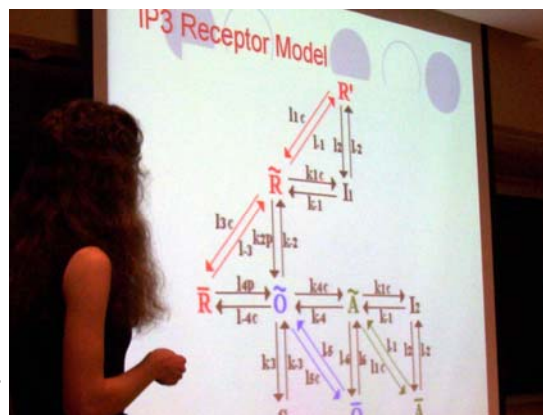
August 10-13

Talks:

Andrea Doseff - Apoptosis I and II

Berl Oakley - Gamma-Tubulin Functions in Microtubule Nucleation and Cell Cycle Regulation

Gustavo Leone - Cellular Differentiation and Cancer



During this period, there were afternoon visits to the labs of Andrea Doseff, Berl Oakley, and Gustavo Leone.

Miniconference:

Group Projects Report

August 19-20

Project 1: Calcium and Heart Failure

Team Leader: Pranay Goel

Project 2: Synaptic Transmission

Team Leader: Alla Borisyuk

I learned a lot of biology from my team members and the team leader. The combinations of participants (biology, math, undergrad, and grad) is great! Erin in my team was most helpful to me in programming.

-Yuan Lou

I really enjoyed working with Alla and also my teammates. It was a well picked group. Alla was extremely helpful and supportive. I would like to work with her again. I think this project was perfect for the program! The miniconference is a great idea; I enjoyed listening to what the other groups had done. They were well put together.

-Richard Yamada

Project 3: Cell Volume Control

Team Leader: Gheorghe Craciun

Project 4: Olfaction

Team Leader: Daniel Dougherty

Project 5: Calcium Oscillations

Team Leader: Martin Wechselberger



Future Programs

September 2004 - August 2005

Genomics, Proteomics, and Bioinformatics

GENOMICS was defined in the 1980s as the new discipline of mapping, sequencing, and analyzing genomes, that is, the study of genes and their function in organisms on a global rather than local scale. Proteomics, the study of the PROTEin complement to a genOME, emerged in the 1990s as the qualitative and quantitative comparison of proteomes under different conditions to further unravel biological processes. Both subject areas are at the forefront of the revolution taking place in biological and medical research, which is transforming them from data poor to data rich fields. While most biomedical research continues to be centered around single investigators or small groups of investigators, recording their experimental data in notebooks, increasing use is being made of novel technologies generating massive amounts of data, and requiring careful computational, mathematical, or statistical analyses. In the third year of the MBI, our focus is on these aspects of genomics and proteomics.

A major milestone in genomics was the completion of the mapping and sequencing of human and mouse genomes in the period 2001-2003. This followed the sequencing of many bacterial genomes, as well as those of numerous other species of biological or medical importance, such as yeast, the roundworm, and the malaria parasite and its associated mosquito vector. This massive amount of DNA sequence data brings with it the ability to make progress on the molecular mechanisms of disease, including the complex interplay of genetic and environmental factors, and to generate thousands of new biological targets for the development of drugs, vaccines, diagnostics, and therapies. Further, fundamental biological research is greatly aided by this wealth of data, permitting not only a genome-wide perspective in the study of particular organisms, but a greatly enhanced evolutionary perspective through the use of comparative genomics.

Tutorials

Tutorial on Microarrays:

September 13-17, 2004

Organizer:

Sashwati Roy - Department of Surgery, The Ohio State University

Chandan Sen - Molecular and Cellular Biochemistry, The Ohio State University

Tutorial on Statistical Methods:

September 20-24, 2004

Organizers:

Sandrine Dudoit - Department of Statistics, University of California, Berkeley

Nick Jewell - Department of Statistics, University of California, Berkeley



Workshops

Analysis of Gene Expression Data: Principles and Applications: October 11-15, 2004

Organizers:

Shili Lin - Department of Statistics, The Ohio State University

Terry Speed - Department of Statistics, University of California, Berkeley

Regulatory Networks: November 8-12, 2004

Organizer:

Ralf Bundschuh - Department of Physics, The Ohio State University

Jeff Hasty - Department of Bioengineering, University of California, San Diego

Fernand Hayot - Department of Physics, The Ohio State University

Quantitative Mathematical Modeling of Gene Regulatory Networks: December 2-4, 2004

Organizers:

Erik M. Boczko - Vanderbilt Medical Center School of Medicine

Tomas Gedeon - Department of Mathematical Sciences, Montana State University

Konstantin Mischaikow - Center for Dynamical Systems and Nonlinear Studies, School of Mathematics, Georgia Institute of Technology

Computational Proteomics and Mass Spectrometry: January 11-14, 2005

Organizers:

Vineet Bafna - The Center for the Advancement of Genomics, University of California, San Diego

Tim Ting Chen - Departments of Biology, Computer Science, and Mathematics, University of Southern California

Emerging Genomic Technologies and Data Integration Problems: February 21-24, 2005

Organizers:

Terry Speed - Department of Statistics, University of California, Berkeley

Hongyu Zhao - Division of Biostatistics, Yale University

First Young Researchers Workshop in Mathematical Biology: March 29 - April 1, 2005

Organizers:

MBI Postdoctoral Fellows

Biomarkers in HIV and Cancer Research: April 18-22, 2005

Organizers:

Victor De Grutolla - Department of Biostatistics, Harvard University

Alan Perelson - Los Alamos National Laboratory

Mark Seigal - Department of Biostatistics, University of California, San Francisco

Steve Skates - Department of Biostatistics, Massachusetts General Hospital

Jeremy Taylor - Department of Biostatistics, University of Michigan



Current Topics Workshop: *Enzyme Dynamics and Function*: May 19-21, 2005

Organizers:

Russ Hille - Department of Molecular and Cellular Biochemistry, The Ohio State University

Ming-Daw Tsai - Department of Chemistry, The Ohio State University

***Recombination: Hotspots and Haplotype Structure*: June 13-17, 2005**

Organizers:

Rick Durrett - Department of Mathematics, Cornell University

Paul Fuerst - Department of Molecular Genetics, The Ohio State University

Summer Program 2005

Microarray Gene Expression Data Analysis

Organizers:

Joseph Verducci - Department of Statistics, The Ohio State University

Shili Lin - Department of Statistics, The Ohio State University

September 2005– August 2006

Ecology and Evolution

Ecology and evolutionary biology have historically been two of the areas of biology which have most benefited from, and made use of, mathematical methods. Many distinguished mathematical biologists have contributed to these areas, and their efforts have illuminated much of ecological and evolutionary theory over the past century. An objective of this special year is to focus on specialized areas that offer particularly challenging mathematical problems, which are relatively unexplored and are of potentially great interest to observational biologists. Thus an underlying goal of the proposed activities is to maintain direct connections to observable biology.

One thread of connection between the various proposed activities concerns spatial aspects of natural systems. Central questions about the history and structure of biological systems are affected by spatial variation. Additionally, numerous problems, which have great public impact, necessarily involve the spatial heterogeneity of biological systems, both those occurring through natural processes and those deriving from human actions. Conservation biology, biodiversity, harvest planning, invasive species control, and wildlife management are just a few of the applications that utilize mathematical methods to address major public policy issues. These applied areas rely greatly upon general ecological and evolutionary genetics theory. Determining how natural systems are affected by interactions of space and time leads to problems that require mathematical approaches. Although a large body of mathematical literature has developed over the past several decades dealing with spatio-temporal interactions, there are still many biologically important questions that require new mathematical approaches and would benefit from close collaborations between ecologists, evolutionary biologists, and mathematicians.

Beyond emphasizing the spatio-temporal nature of natural systems and the mathematical approaches that are used to address them, the special year is intended to foster interactions between individuals working on problems at different spatial/temporal scales. While



the underlying biological questions may operate on quite different scales, the necessary mathematical approaches may be similar. Another theme for the year is linking between scales, for example, how might evolutionary models that account for the dynamics of spatial structure relate to ecological models, which operate on shorter time periods? How might genomic information that is rapidly becoming available assist in developing a theory for whole organism interactions with environment and the functioning of populations, communities, and ecosystems? What new mathematical approaches might contribute to better models for natural system response across the genome/organism/population interfaces? The proposed set of activities will enhance our ability to address these questions and hopefully lead to new collaborations between mathematicians and biologists that are beneficial to both fields.

Tutorials

Tree Reconstruction and Coalescence Theory:

September 7-9, 12-13, 2005

Organizers:

Dennis Pearl - Department of Statistics, Ohio State University

Paul Fuerst - Department of Molecular Genetics, Ohio State University

Reaction - Diffusion Models

March, 2006

Organizer:

Chris Cosner - Department of Mathematics, University of Miami

Workshops

Phylogeography and Phylogenetics: September 26-30, 2005

Organizers:

Craig Moritz - Department of Integrative Biology, University of California, Berkeley

Michael Hickerson - University of California, Berkeley

Dennis Pearl - Department of Statistics, The Ohio State University

Aspects of Self-Organization in Evolution: November 14-18, 2005

Organizers:

Chris Adami - California Institute of Technology

Claus O. Wilke - Computation and Neural Systems, California Institute of Technology

Spatial Heterogeneity in Biotic and Abiotic Environment: Effects on Species Ranges, Coevolution, and Speciation: February 6-10, 2006

Organizers:

Sergey Gavrilits - Departments of Ecology and Evolutionary Biology and Mathematics, University of Tennessee

Mark Kirkpatrick - Section of Integrative Biology, University of Texas at Austin

John Thompson - Earth and Marine Sciences, University of California, Santa Cruz



Spatial Ecology: March 13-17, 2006

Organizers:

Lou Gross - Departments of Ecology and Evolutionary Biology and Mathematics,
University of Tennessee

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

Chris Cosner - Department of Mathematics, University of Miami

Mark Kot - Department of Applied Mathematics, University of Washington

Uncertainty in Ecological Analysis: April 3-7, 2006

Organizers:

Catherine Calder - Department of Statistics, The Ohio State University

Jim Clark - Department of Electrical and Computer Engineering, McGill University

Noel Cressie - Department of Statistics, Ohio State University

Jay Ver Hoef - Alaska Department of Fish and Game

Chris Wikle - Department of Statistics, University of Missouri

Microbial Ecology: May 15-16, 2006

Organizers:

Frede Thingstad - Department of Microbiology, University of Bergen

George Jackson - Oceanography Department, Texas A&M University

Global Ecology: June 26-30, 2006

Organizers:

John Pastor - Department of Biology and Center for Water and the Environment, University
of Minnesota

John Harte - Department of Environmental Science, Policy, and Management, University of
California, Berkeley

David Schimel - National Center for Atmospheric Research

The workshop on the Auditory System was really great (also due to John) and I know it had a few rather interesting spin-offs.

-J. Leo van Hemmen

The following attachment is taken from the introduction to *Biological Cybernetics*, Vol. 89 (2004), November 28, 2003 Special Issue on the Auditory System:

The present issue exhibits a diversity and richness of problems that tie in with those found in nature. It is the aim of "Biological Cybernetics" to also pin down problems by providing theoretical analyses - and solutions. Many papers published herein constitute, in part, a review so as to allow a beginning graduate student to enter the field.

Part of the motivation of the authors and the initiative of the present editors is the result of an inspiring workshop on the auditory system at the Mathematical Biosciences Institute (MBI) at The Ohio State University in Columbus in early May 2003. We trust that our readers will obtain at least as much inspiration from papers presented herein as the authors had during their thought-provoking meeting in Columbus.

-J. Leo van Hemmen
John Rinzel



Publications

Technical Report No. 5

Authors: Joanna Pressley, Predrag-Peter Ilich, and Daniel Dougherty

Title: A contrast-based neural control system for ant navigation

Date of Publication: September 2003

Technical Report No. 6

Authors: Jonathan Bell and Gheorghe Craciun

Title: A distributed parameter identification problem in neuronal cable theory models

Date of Publication: October 2003

Technical Report No. 7

Authors: Marek Kimmel and Andrzej Swierniak

Title: Using control theory to make cancer chemotherapy beneficial from phase dependence and resistant to drug resistance

Date of Publication: November 2003

Technical Report No. 8

Authors: Adam Czornik and Andrzej Swierniak

Title: On direct controllability of discrete time jump linear system

Date of Publication: November 2003

Technical Report No. 9

Authors: Krzysztof Fujarewicz, Andrzej Swierniak, Barbara Jarzab, Malgorzata Wiench, and Marek Kimmel

Title: Using support vector machines for analysis of gene expression data from DNA microarrays

Date of Publication: November 2003

Technical Report No. 10

Authors: Howard Levine and Marit Nilsen Hamilton

Title: A mathematical feasibility argument for the use of aptamers in chemotherapy

Date of Publication: November 2003

Technical Report No. 11

Authors: Jacek Blazewicz, Piotr Formanowicz, Marta Kasprzak, Wojciech T. Markiewicz, and Aleksandra Swiercz

Title: Tabu search algorithm for DNA sequencing by hybridization with isothermic libraries

Date of Publication: November 2003

Technical Report No. 12

Authors: Howard Levine and Joanna Renclawowicz

Title: Singularity formation in chemotaxis - A conjecture of Nagai

Date of Publication: December 2003

**Technical Report No. 13**

Author: Martin Wechselberger

Title: Existence and bifurcation of canards in \mathbb{R}^3 in the case of a folded node

Date of Publication: December 2003

Technical Report No. 14

Authors: Gheorghe Craciun, Baltazar Aguda, and Avner Friedman

Title: A detailed mathematical analysis of a model that couples the cell cycle and apoptosis

Date of Publication: January 2004

Technical Report No. 15

Authors: Gheorghe Craciun and Martin Feinberg

Title: Multiple equalibria in complex chemical reaction networks: The injectivity property

Date of Publication: January 2004

Technical Report No. 16

Authors: Vivian Hutson, Yuan Lou, and Konstantin Mischaikow

Title: Convergence in competition models with small diffusion coefficients

Date of Publication: February 2004

Technical Report No. 17

Authors: Jonathan Rubin and Amitabha Bose

Title: Localized activity patterns in excitatory neuronal networks

Date of Publication: February 2004

Technical Report No. 18

Authors: Jeffrey Groff, Corrie Camalier, Cindy Chiu, Ian Miller, and Geraldine Wright

Title: Spatial and temporal coding in an olfaction-inspired network model

Date of Publication: February 2004

Technical Report No. 19

Author: Katarzyna Rejniak

Title: An immersed boundary model of the formation and growth of solid tumors

Date of Publication: May 2004

Technical Report No. 20

Authors: Robert D. Carr and Giuseppe Lancia

Title: A successful application of compact optimization. The protein contact map overlap problem

Date of Publication: May 2004

Technical Report No. 21

Authors: Yixin Guo and Carson Chow

Title: Existence and stability of standing pulses in neural networks: I. Existence

Date of Publication: July 2004



Technical Report No. 22

Authors: Yixin Guo and Carson Chow

Title: Existence and stability of standing pulses in neural networks: II. Stability

Date of Publication: July 2004

Technical Report No. 23

Authors: Gheorghe Craciun, Anthony Brown, and Avner Friedman

Title: A dynamical system model of transport of neurofilaments in axons

Date of Publication: July 2004

Technical Report No. 24

Authors: Avner Friedman and Georgios Lolas

Title: Analysis of a mathematical model of tumor lymphangiogenesis

Date of Publication: July 2004

MBI Volumes on Tutorials in Mathematical Biosciences**Published by Springer-Verlag**

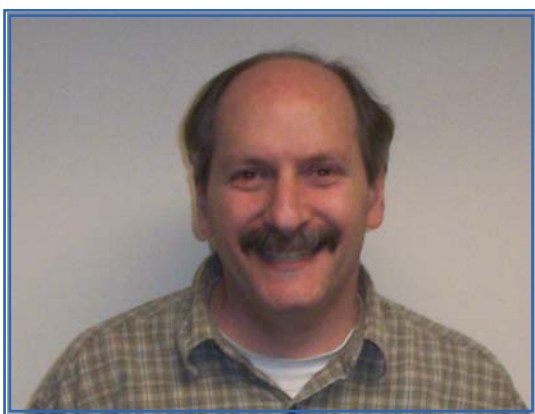
Volume 1: Mathematical Neuroscience (in press)



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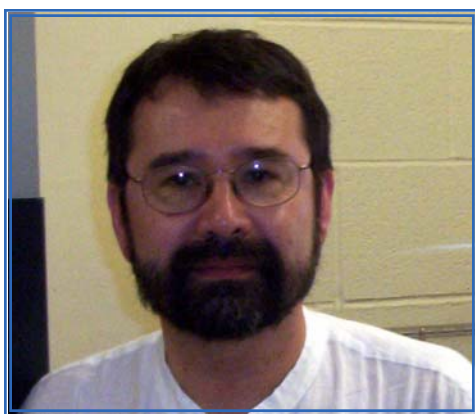
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Rebecca Martin
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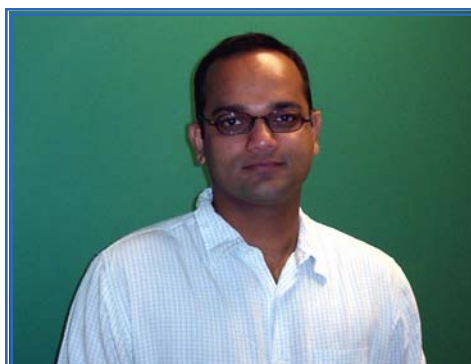
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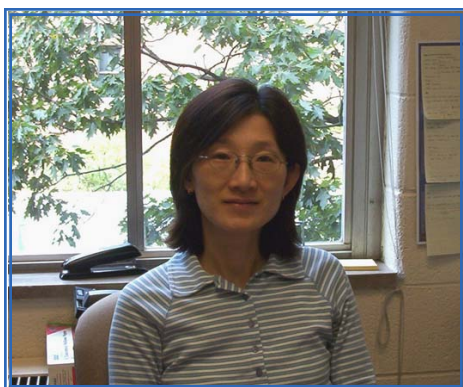


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