mbi

Mathematical Biosciences Institute

MATHEMATICAL CHALLENGES IN DEVELOPMENTAL BIOLOGY

2008-2009

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

THE OHIO STATE UNIVERSITY

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Message from the Director: New Programs at MBI

MBI has two principal activities: MBI creates interdisciplinary scientific programs that attract visitors and MBI trains postdoctoral fellows. Both activities lead to research on the interface of the mathematical and biological sciences, but in quite different ways. Workshops lead to research through the transmission of new ideas and through new collaborations; post-doc training leads to research most frequently through the associations formed in the mentoring process. To complement the workshop and mentoring programs, MBI also has diversity and outreach activities.

During the past year these research activities have continued at their high level. The 2008-09 emphasis year on Developmental Biology, with its seven emphasis year workshops and four special workshops, was a huge success involving some 800 participants and a yet to be determined number of successful new collaborations. Detailed descriptions of these workshops are contained in this annual report. In addition, six MBI postdoctoral fellows completed their three years of training at MBI and have found new positions in the US and abroad. While at MBI, these post-docs collectively produced more than two dozen publications on a wide variety of topics from cancer to biomechanics to neuroscience.

During the past year, planning has also proceeded that will impact these research activities in ways we believe will be important to the math biology community.

First, research at the interface between the mathematical and biological sciences flows in both directions. On the one hand, the mathematical sciences provide tools for the biological sciences that enable models to be both created and analyzed. This math -> bio direction has been a staple of most MBI programs and it will continue to be a staple in the future. However, biology also offers the mathematical sciences new challenges and these challenges will surely lead to new mathematics and even to new fields in the mathematical sciences. MBI is planning to emphasize more bio -> math programs in the future and to do this

MBI is planning to increase the number of current topic workshops. So, in the future, the standard MBI portfolio will consist of six emphasis year workshops and six current topic workshops.

Second, MBI is working on ways in which the mathematical and biological sciences communities can be more significantly involved in creating programs at MBI. To begin, MBI welcomes suggestions from individuals and groups of individuals to organize workshops and/or emphasis years at MBI. In a more formal way, MBI has encouraged its Institute Partners (through the annual IP meeting) to play a greater role in the choice of future topics. MBI has also made changes to its Institute Partner program that will enable more MBI postdoctoral fellows to be mentored by researchers at IP institutions. The community has responded to these changes, and the number of MBI Institute Partners has nearly doubled (from 19 to 35) in the past year.

Third, during this past year, MBI has established a Diversity Committee that is helping to shape the MBI approach to diversity issues and to establish new activities. One activity that will soon be announced on the MBI website is a visiting lecturer program whereby MBI will help support undergraduate math biology lectures at institutions with large minority enrollments. MBI is planning additional ways to enhance community involvement, and your suggestions in this direction are always welcomed.

Marty Golubitsky
Director

MISSION AND GOALS

MISSION STATEMENT

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

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

The mission of MBI is

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

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

INSTITUTE PARTNERS

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

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

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

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

Current Institute Partners

Arizona State University
Boston University
Case Western Reserve University
Cornell University
Drexel University
Duke University
Florida State University
Howard University
Indiana University-Purdue University Indianapolis
Iowa State University
Legacy Good Samaritan Hospital
Michigan State University
New Jersey Institute of Technology
Ohio State University
Ohio University
Princeton University
University of California, Irvine
University of Cincinnati
University of Georgia
University of Houston
University of Iowa
University of Maryland, Baltimore County
University of Michigan
University of Minnesota
University Notre Dame
University of Nottingham
University of Oxford
University of Pittsburgh
University of Southern California
University of Utah
University of Washington
University of Waterloo
Vanderbilt University
Virginia Tech

Shuying Sun (Center) and her mentors Shili Lin & Albert de la Chapelle.

Avner Friedman and Marty Golubitsky (Director).

Mentoring Program

Researchers at MBI Institute Partners have the opportunity to mentor MBI postdocs. Postdocs who are mentored outside of OSU may spend significant time (up to a year) at the mentor's institution.

MBI postdocs mentor their areas of interest and then search the directory for potential mentors. MBI Directors then work with the postdocs to find successful matches.

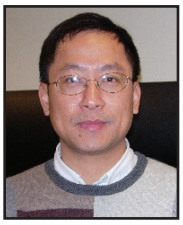
The directory of mentors can be found at the following web page:

http://mbi.osu.edu/postdoctoral/mentoring.html

DIRECTORS & STAFF

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

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



PROFESSOR YUAN LOU, ASSOCIATE DIRECTOR
Oversees the postdoctoral fellow mentoring program.

PROFESSOR LIBBY MARSCHALL, ASSOCIATE DIRECTOR
Works with the director of diversity issues.

PROFESSOR DENNIS PEARL, ASSOCIATE DIRECTOR
Responsible for the education programs, as well as the evaluation process.

PROFESSOR ANDREJ ROTTER, ASSOCIATE DIRECTOR
Provides leadership for relations between MBI and the Ohio State Medical Center.

PROFESSOR TONY NANCE, ASSISTANT DIRECTOR
A full time staff member with duties that include oversight of the day-to-day operation of the MBI offices and supervision of the institute staff.

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

STELLA CORNETT, WEB COMMUNICATIONS SPECIALIST
Manages the web site; handles all advertising including web and print; creates and distributes brochures, flyers, newsletters, posters, and annual report booklets; produces print series for technical reports and works with publishers and authors on MBI publications; and receives participant abstracts and presentation materials and places them on the web.

JARED HIRSCH, SYSTEMS SPECIALIST
Provides support to users of MBI computer and presentation facilities, assists Michael with systems maintenance, and contributes to web programming projects.

REBECCA MARTIN, OFFICE ASSOCIATE
Provides direct office support for the Director; serves as primary point of contact for people within and external to the MBI; sends letters of invitation to all workshop and tutorial participants.

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

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

STUDENT WORKERS
Our student workers provide critical logistic and clerical support for MBI events, including materials, advertising, and data management.

CASEY JACOBS

DHRUV KAURA

POSTDOCTORAL FELLOWS

COHORT 2006

Edward Green (Applied Mathematics, University of Nottingham). Ed's research is in tissue engineering, where biomedical engineers aim to grow new tissues in the laboratory to replace those which have become defective through injury or disease. The central question he and his colleagues consider is how do cells know what kind of tissue to make? They know some of the cues that can affect tissue architecture: nutrient levels, growth factors, mechanical forces and interactions with the extracellular cellular matrix (ECM). In the laboratory, cells are frequently grown in collagen gels, which have a fibrous microstructure.

When cells exert forces on these gels, the orientation of the fibres changes, which in turn changes the distribution of forces in the gel, and provides directional cues for cell migration. As a first step towards understanding the effect of cell-ECM interactions on tissue architecture, they are developing models for the response of collagen gels to prescribed forces, and trying to determine ways in which the parameters governing the rheology of the gels may be determined. They are also looking at cell-induced compaction of collagen gels. This work is carried out in collaboration with Dr. Keith Gooch in the Department of Biomedical Engineering.

Yangjin Kim (Mathematics, University of Minnesota). Yangjin Kim is interested in cell mechanics, tumor growth, tumor angiogenesis, wound healing, and gene control. At the MBI, he and colleagues (Prof. Friedman at the MBI and Prof. Ostrowski in the comprehensive cancer center at the OSU) developed a transwell model to understand the role of fibroblasts/myofibroblasts in early development of breast cancer. Tumor cells located in bottom of well were allowed to communicated with fibroblasts/myofibroblasts on top insert via growth factors (EGF and TGF-beta) through the holes of size 0.4\micron on membrane between two cell cultures. A mathematical model of density of tumor cells, fibroblasts/myofibroblasts, and concentration of EGF, TGF-beta was used to explore the interaction between tumor cells and fibroblasts/myofibroblasts. The model would be generalized to a multi-scale model where genetic control is taken into account. By knocking out some specific important genes such as SMAD, he will test the hypothesis and generate prediction based on experiments on mice. He is also developing a cell-based model for better understanding of this dynamics between these cells in this direction.

He is also working with Dr. Chiocca's group in neurosurgery department at the OSU in order to develop a mathematical model that can predict the different patterns generated by different glioma cells in collagen gel. Cell migration in brain cancer is important because of cell invasion into surrounding tissue and high recurrence rate after treatment. This model would help to identify the basic mechanism and point to the right direction. His active other research includes hybrid approaches for tumor spheroid growth in vitro and vascular tumor growth in vivo. Gene-controlled growth and therapies in colon cancer are under investigation as well.

Andrew Oster (Mathematics, University of Utah). Andrew's research interests primarily lie in the fields of mathematical neuroscience and computational cell biology, in particular using mathematical models to understand: 1) mitochondrial function and its role in calcium signaling and 2) the development of the visual cortex. Mitochondria have long been known to sequester cytosolic calcium and even to shape intracellular patterns of endoplasmic reticulum-based calcium signaling. Accumulating evidence suggests that the mitochondrial network is an excitable medium which can demonstrate calcium induced calcium release via the mitochondrial permeability transition. The role of this excitability remains unclear, but mitochondrial calcium handling appears to be a crucial element in diverse diseases as diabetes, neurodegeneration and cardiac dysfunction.

In collaboration with Dr. David Terman (Mathematics, The Ohio State University) and Dr. Christopher Fall (Dept. of Bioengineering, University of Illinois at Chicago), they demonstrate both excitability and calcium wave propagation that is accompanied by depolarizations similar to those reported in cell preparations. These waves depend on the energy state of the mitochondria, as well as other elements of mitochondrial physiology. Their results support the concept that mitochondria can transmit state dependent signals about their function in a spatially extended fashion. Beyond this work, he is continuing past work in collaboration with Dr. Paul Bressloff (Dept of Mathematics, University of Utah) on the development of the visual system, specifically the joint formation of ocular dominance (OD) columns and cytochrome oxidase (CO) blobs. It is a pattern formation problem that arises due to Hebbian competition for OD in cortex and involves a system of integro-differential equations and perturbation expansions.

Michael Rempe (Engineering Sciences & Applied Mathematics, Northwestern University). Michael works in collaboration with David Terman and Janet Best on sleep in the human brain. While sleep is a daily process for most of us, compared to other physiologic processes it is relatively misunderstood. Through both animal and human studies several of the important brain regions have been identified, but it's still not entirely clear how they each interact to achieve the separate stages of sleep and wakefulness. An important conceptual model for understanding the sleep/wake cycle is called the flip-flop model. It has been determined experimentally that the regions of the brain that cause wakefulness oppose those that cause sleepiness so the system is stable in either state, but does not spend much time in-between sleep and wakefulness.

This is called a flip-flop because the system quickly "flips" from one state into another, instead of gradually changing from one to another. It has also been found that there is a similar system for REM and NREM sleep. We use relaxation oscillators to model the activity of four groups of brain cells: one that is active only during sleep, one that is active only during wakefulness, one that is active only during REM sleep, and one that is active only during NREM sleep. Taking this approach, we can analyze the dynamics of the system using phase plane analysis. Our model does a good job of matching many of the important features of the human sleep-wake cycle including the timing of sleep and the dynamics of REM sleep. This type of analysis allows us to make predictions about some of the possible underlying mechanisms for the sleep-wake system, including disorders like narcolepsy where there are frequent unwanted transitions between sleep and wake.

Shuying Sun (Statistics, University of Toronto). Shuying Sun's research interest is DNA methylation microarray data analysis. Currently, she is working on pre-processing and analyzing the 244k Agilent CpG island methylation microarray data. In particular, her research focuses on the following four areas:
(1) preprocessing DNA methylation microarray using known negative control probes provided by Agilent and the internal control probes selected based on the experimental protocol.
(2) identifying the commonly methylated genes or CpG islands among all breast cancer cell lines using quantile regression.
(3) identifying differentially methylated genes or CpG islands between two tumor subtypes or racial groups using mixed effect and generalized least square regression models.
(4) integrating the DNA methylation and gene expression microarray data for all breast cancer cell lines using some known biological knowledge such as pathway information.

POSTDOCTORAL FELLOWS

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

COHORT 2007

Huseyin Coskun (Computational and Applied Mathematics, University of Iowa). Huseyin's research area is interdisciplinary: it is a combination of mathematics, biology and engineering. He is principally interested in applied mathematics, partial differential equations, and inverse problems. He developed models for cell movements which incorporate different components of the phenomena, such as mechanics and molecular dynamics that have been studied separately, into a single model. In that sense the models can be considered as 'systems biologic' approach. He also formulated model based inverse problems for parameter and unknown function estimation. Neither this system biologic approach nor the inverse problem formulation have been studied previously, in the area of cell motility.

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

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

Reassortment between different strains of Influenza has been thought to cause the large pandemics. The Spanish flu of 1918 is believed to have originated as strain that jumped hosts directly bird to humans, while the Hong Konf flu of 1968 is though to have passed through a genetic reassortment between relatively benign bird flu and human flu viruses in pigs. These assumptions are based on the immunological characteristics of surface proteins: the Hong Kong strain appeared to have one protein from pig flu, and another from seasonal human flu. With new methods and computer implementations, we can examine possible genomic rearrangements in a rigorous phylogenetic context. He will also be working on insect molecular phylogeny, focusing on bluet damselflies, with a group at the Department of Entomology.

COHORT 2008

Paula Federico (Ecology and Evolutionary Biology, University of Tennessee). Paula Federico is working with Libby Marschall (EEOB, OSU), Yuan Lou (Math, OSU) and Stuart Ludsin (EEOB, OSU) on using a multi-modeling approach to describe fish movement behavior in response to seasonal hypoxia (low dissolved oxygen availability) and other habitat attributes (e.g., temperature, prey availability).

Deena Schmidt (Applied Mathematics, Cornell University). Deena's interests are in applying probability to problems in population and evolutionary genetics and molecular biology. Her Ph.D. research focused on stochastic models of DNA regulatory sequence evolution in organisms of different population sized. She's currently working on a gene regulatory network model of an experimental system derived from the lambda switch (bacteriophage lambda) and looking for noise-induced oscillations due to a small number of molecules in the system. This is in collaboration with Timothy Newman (Arizona State University) and Vincent Noireaux (University of Minnesota). Thus far at the MBI, she is working on two projects: stochastic models for the evolution of gene expression, and the relationship between stochastic models and their corresponding mean-field approximations which is important in describing various biological systems.

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

Chuan Xue (Applied Mathematics, University of Minnesota Twin Cities). Chuan Xue's research involves multi-scale modeling in bacterial pattern formation and wound healing. She received her Ph.D. in mathematics from the University of Minnesota in Aug. 2008 under the direction of Hans G. Othmer. In her thesis, she focused on unveiling the mechanism of spatial pattern formation in the bacterial colonies found in her collaborator's lab. She developed a hybrid cell-based model which incorporated intracellular signal transduction, cell movement and extracellular signal dynamics. The model yields biologically-based explanations to radial and spiral stream formation in P. mirabilis colonies. To reduce the computational cost due to large number of cells, she lifted the cell-based model to a continuum model by deriving macroscopic chemotaxis equations of cell density using perturbation techniques and moment closure methods. She is also working on mathematical models for ischemic wound healing. The goal is to understand how the supply of oxygen affects the wound healing process and how hyperbaric treatment helps with chronic wound closure in patients with circulation diseases.

COMMITTEES

BOARD OF TRUSTEES (BOT)

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

Current Members

- **Rita R. Colwell**, Distinguished University Professor, Center for Bioinformatics and Computational Biology, University of Maryland, College Park (12/31/10)
- **John Guckenheimer**, Mathematics, Cornell University (12/31/11)
- **Kirk E. Jordan**, Emerging Solutions Executive, Computational Science, IBM T.J. Watson Research Center (12/31/11)
- **Robb Krumlauf**, Scientific Director, Stowers Institute for Medical Research, Kansas City, MO (12/31/10)
- **Barbara Kunz**, President, Health and Life Science Global Business, Battelle Memorial Institute, Columbus, OH (12/31/09)
- **Mark Lewis**, Mathematical Sciences, University of Alberta, Canada (12/31/11)
- **Robert M. Miura** (Chair, 2009-2010), Mathematical Sciences, New Jersey Institute of Technology, Newark, New Jersey (12/31/11)

SCIENTIFIC ADVISORY COMMITTEE (SAC)

SAC reviews MBI programs and suggests and decides on annual programs and organizers. The Committee consists of internationally recognized mathematical scientists and bioscience researchers from academia and industry. SAC meets annually to review the institute programs, to suggest and decide on new annual programs, and to give advice regarding programmatic goals.

Current Members

- **Linda Allen**, Mathematics and Statistics, Texas Tech University (12/31/11)
- **Adam Arkin**, Howard Hughes, Medical Institute, Bioengineering, University of California, Berkeley (1/1/07-12/31/09)
- **Mark Chaplain**, The SIMBIOS Centre, Mathematics, University of Dundee (1/1/08-12/31/10)
- **Mark Denny**, Biology, Stanford University (1/1/08-12/31/10)
- **Bard Ermentrout**, Mathematics, University of Pittsburgh (12/31/11)
- **Nicholas P. Jewell**, Biostatistics and Statistics, University of California, Berkeley, (1/1/07-12/31/09)
- **Suzanne Lenhart**, Mathematics, University of Tennessee (1/1/08-12/31/10)
- **Naomi Leonard**, Mechanical Engineering, Princeton University (12/31/11)
- **Mark Lewis** (Chair 2009-10), Mathematical and Statistical Sciences, University of Alberta (1/1/07-12/31/09)
- **Paul Magwene**, Biology, Duke University (1/1/09-12/31/11)
- **Karl J. Niklas**, Plant Biology, Cornell University (1/1/08-12/31/10)

- **Lior Pachter**, Mathematics, University of California, Berkeley (1/1/08-12/31/10)
- **Linda Petzold**, Mechanical and Environmental Engineering, Computer Science, University of California, Santa Barbara (1/1/07-12/31/09)
- **Steven Rust**, Battelle Memorial Institute, Columbus, OH (12/31/11)
- **Stanislav Shvartsman**, Chemical Engineering, Princeton University (1/1/08-12/31/10)
- **James Sneyd**, Mathematics, University of Auckland, New Zealand (1/1/08-12/31/10)
- **Steven Vogel**, Biology, Duke University (1/1/07-12/31/09)

Past Members

- **Reka Albert**, Physics and Biology, Pennsylvania State University
- **Herb Bresler**, Health and Life Sciences, Battelle Memorial Institute, Columbus, OH
- **Leah Edelstein-Keshet**, Mathematics, University of British Columbia
- **Lisa Fauci**, Mathematics, Tulane University
- **Louis Gross**, The Institute for Environmental Modeling, Ecology & Evolutionary Biology, Mathematics, The University of Tennessee
- **Sorin Istrail**, Center for Computational Molecular Biology, Computer Science Department, Brown University
- **Kirk Jordan**, IBM Computational Biology Center, Yorktown Heights, NY
- **Jim Keener**, Mathematics, University of Utah
- **Douglas Lauffenburger**, Biological Engineering, Chemical Engineering, Biology, Massachusetts Institute of Technology
- **Gregory Mack**, Environmental Monitoring and Assessment, Battelle Memorial Institute, Columbus OH
- **Philip Maini**, Centre for Mathematical Biology, Mathematical Institute, University of Oxford
- **Claudia Neuhauser**, Ecology, Evolution, and Behavior, University of Minnesota
- **Alan Perelson**, Theoretical Biology and Biophysics Group, Los Alamos National Laboratory
- **Mike Reed**, Mathematics, Duke University
- **John Rinzel**, Center for Neural Science and the Courant Institute of Mathematical Sciences, New York University
- **Stephen Ruberg**, Clinical Data Technology and Services, Eli Lilly and Company, Indianapolis
- **Terrence Speed**, Statistics, University of California, Berkeley
- **John Taulbee**, Epidemiology and Biometrics Division, Procter & Gamble Company, Cincinnati
- **Terry Therneau**, Biostatistics, Mayo Clinic College of Medicine, Rochester, MN
- **Frank Tobin**, Scientific Computing & Mathematical Modeling, GlaxoSmithKline
- **John Tyson**, Biology, Virginia Polytechnic Institute and State University
- **Michael S. Waterman**, Mathematics, University of Southern California
- **Raimond L. Winslow**, Center for Cardiovascular Bioinformatics & Modeling, Whitaker Biomedical Engineering Institute, and Biomedical Engineering, The Johns Hopkins University School of Medicine and Whiting School of Engineering

LOCAL SCIENTIFIC ADVISORY COMMITTEE (LSAC)

The LSAC consists of members of The Ohio State University community. It helps identify current topics workshops, suggest ideas for future emphasis programs and organizers, and potential mentors for postdoctoral fellows.

- **Sudha Agarwal**, Oral Biology
- **Irina Artsimovitch**, Microbiology
- **John Buford**, Physical Therapy
- **Ralf Bundschuh**, Physics
- **Helen Chamberlin**, Molecular Genetics
- **James Cogdell**, Mathematics
- **Meg Daly**, Evolution, Ecology, and Organismal Biology
- **Andrea Doseff**, Heart and Lung Research Institute, Molecular Genetics, and Internal Medicine
- **Avner Friedman**, Mathematics
- **Martin Feinberg**, Chemical Engineering
- **Paul Fuerst**, Evolution, Ecology and Organismal Biology
- **Erich Grotewold**, Plant Biology
- **Richard Hart**, Biomedical Engineering
- **Tim Huang**, Center for Integrative Cancer Biol-

COMMITTEES

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- **Daniel Janies**, Biomedical Informatics
- **Doug Kniss**, Obstetrics and Gynecology
- **Stanley Lemeshow**, School of Public Health, Center for Biostatistics
- **Gustavo Leone**, Molecular Virology, Immunology, and Medical Genetics
- **Shili Lin**, Statistics
- **Stuart Mangel**, Neuroscience
- **Elizabeth Marschall**, Evolution, Ecology,and Organismal Biology
- **Deborah Parris**, Molecular Virology
- **Dennis Pearl**, Statistics
- **John Reeve**, Microbiology
- **Andrej Rotter**, Pharmacology
- **Wolfgang Sadee**, Pharmacology
- **Larry S. Schlesinger**, Division of Infectious Diseases and Center for Microbial Interface Biology
- **Petra Schmalbrock**, Radiology
- **Chandan Sen**, Surgery
- **Amanda Simcox**, Molecular Genetics
- **Parthasarathy Srinivasan**, Computer Science and Engineering and Biomedical Informatics
- **Don Stredney**, Biomedical Applications, Ohio Supercomputer Center

EXTERNAL SCIENTIFIC ADVISORY COMMITTEE FOR THE EMPHASIS YEAR (ESACEY)

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

- **Paul Bressloff**, Mathematics, University of Utah
- **Helen Byrne**, Centre for Mathematical Medicine, Applied Mathematics, School of Mathematical Sciences, University of Nottingham
- **Mark A.J. Chaplain**, Society for Mathematical Biology, The SIMBIOS Centre, Mathematics, University of Dundee
- **Dirk Drasdo**, Mathematical Institute and Center for Systems Biology, Warwick University
- **Aron B. Fisher**, Institute for Environmental Medicine, University of Pennsylvania Medical Center
- **Robert A. Gatenby**, Radiology and Applied Mathematics, University of Arizona
- **Thomas B. Kornberg**, Biochemistry and Biophysics, University of California, San Francisco
- **Alex Mogilner**, Mathematics and Centre for Genetics and Development, University of California, Davis
- **Ken Muneoka**, Cell and Molecular Biology, Tulane University
- **George Oster**, Molecular and Cellular Biology and ESPM, University of California, Berkeley
- **Jonathan A. Sherratt**, Mathematics, Heriot-Watt University
- **Stephen Small**, Margaret and Herman Sokol Associate Professor
- **Angela Stevens**, Max Planck Institute for Mathematics in the Sciences

DIVERSITY PLAN

The MBI diversity mission is to help shape the mathematical biology community in a way that represents the diversity of our society. MBI will work towards this goal on two levels. First, it is MBI policy that each of its programs should actively seek diversity among its participants in gender and ethnicity. Second, MBI will sponsor activities that promote mathematical biology and its opportunities in the academic community.

Specifically, MBI will build and maintain diversity by the following.

1. Boards and Advisors: Ensure representation of underrepresented groups among the MBI standing committees.
2. Scientific Workshops and Emphasis Programs: Include members of underrepresented groups as members of emphasis year and workshop organizing committees and ensure broad representation among workshop participants.
3. Training of Younger Scientists: Ensure broad representation among postdoctoral fellows and build exposure of younger scientists to mathematical biology.
4. Awareness Workshops: Periodically host workshops on Opportunities in Mathematical Biology for Underrepresented Groups.

In addition, MBI will pursue the following strategies:

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

Diversity Committee

- **Carlos Castillo-Chavez**, Department of Mathematics and Statistics, Arizona State University
- **Joan Herbers**, Department of Evolution, Ecology, & Organismal Biology, The Ohio State University; President Elect AWIS
- **Trachette Jackson**, Department of Mathematics, University of Michigan
- **Yi Li**, Chair, Department of Mathematics, University of Iowa
- **Elizabeth Marschall**, Department of Ecology, Evolution, Organismal Biology, The Ohio State University (ex officio)
- **Maeve McCarthy**, Department of Mathematics & Statistics, Murray State University; Executive Director AWM
- **Aziz Yakubu**, Chair, Department of Mathematics, Howard University

VISITORS

LONG TERM VISITORS 2008-2009

- **Chris Fall**, Anatomy and Cell Biology, University of Illinois, Chicago
- **Bei Hu**, Mathematics, University of Notre Dame
- **Edward Lungu**, Mathematics, University of Botswana
- **Kevin Painter**, Mathematical and Computer Science, Heriott-Watt University
- **Anna Marciniak-Czochra**, Institute of Applied Mathematics, University of Heidelberg
- **Tong Li**, Mathematics, University of Iowa
- **Kota Ikeda**, Mathematics Institute, Tohuka University, Japan
- **Robert Miura**, Mathematical Sciences, New Jersey Institute of Technology
- **Khalid Boushaba**, Mathematics, Iowa State University
- **Rich Schugart**, Mathematics, Western Kentucky University
- **Chirove Faraimunashe**, University of Botswana
- **Najat Ziyadi**, Cadi Ayyad University, Morocco
- **Shangbin Cui**, Institute of Mathematics, Sun Yat-Sen University, China
- **Jianfu Ma**, Mathematics, University of Houston
- **Greg Smith**, Applied Science, College of William and Mary

ANTICIPATED VISITORS 2009-2010

- **Chang-Hong Wu**, Mathematics, National Taiwan Normal University
- **Lisle Gibbs**, EEOB, The Ohio State University
- **Matthew Miller**, Mathematics, University of South Carolina
- **David Romano**, Mathematics, Grinnell University
- **Ian Stewart**, Mathematics, University of Warwick, UK
- **Martin Wechselberger**, Mathematics and Statistics, University of Sydney
- **Dieter Armbruster**, Mathematics, Arizona State University

COURSE RELEASE 2008-2009

Mathematics

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

Statistics

- Shili Lin
- Tom Santner
- Joe Verducci
- Xinyi Xu

Evolution, Ecology, and Organismal Biology

- Ian Hamilton

Electrical and Computer Engineering

- Kevin Passino

ANTICIPATED COURSE RELEASE 2009-2010

Mathematics

- Janet Best
- Ching-Shan Chou
- Avner Friedman
- Chiu-Yen Kao
- Yuan Lou
- Boris Pittel
- Akos Seress
- Joe Tien

Statistics

- Laura Kubatko
- Shili Lin
- Tao Shi
- Joe Verducci

Biomedical Engineering

- Samir Ghadiali
- Yi Zhao

Evolution, Ecology, and Organismal Biology

- Ian Hamilton

Electrical and Computer Engineering

- Kevin Passino

Biochemistry

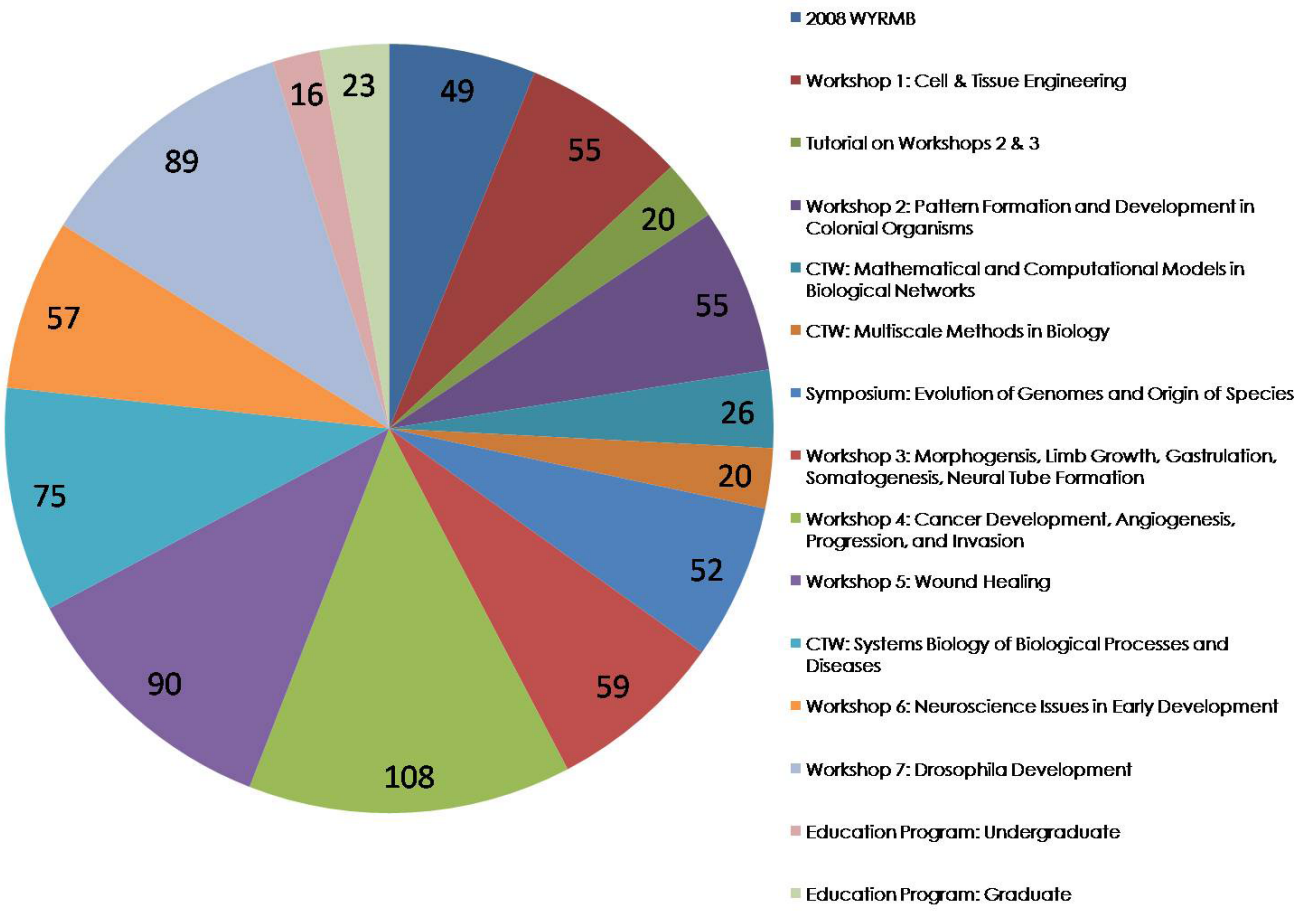
- Mark Foster

Medicinal Chemistry

- Chenglong Li

PROGRAM PARTICIPATION

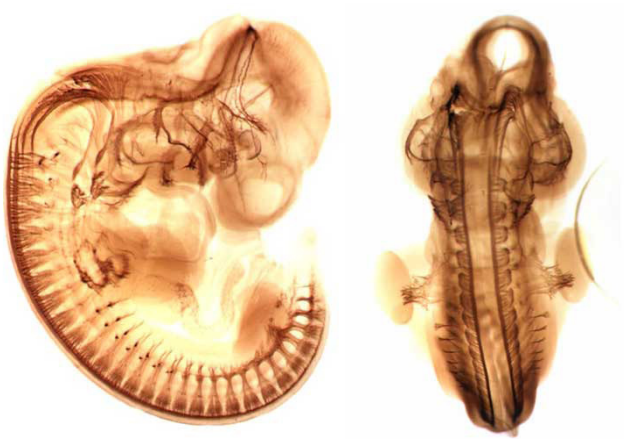
The chart below shows the total number of participants for each MBI event during the 2008-2009 Emphasis year. **The total number of participants this year was 794**.



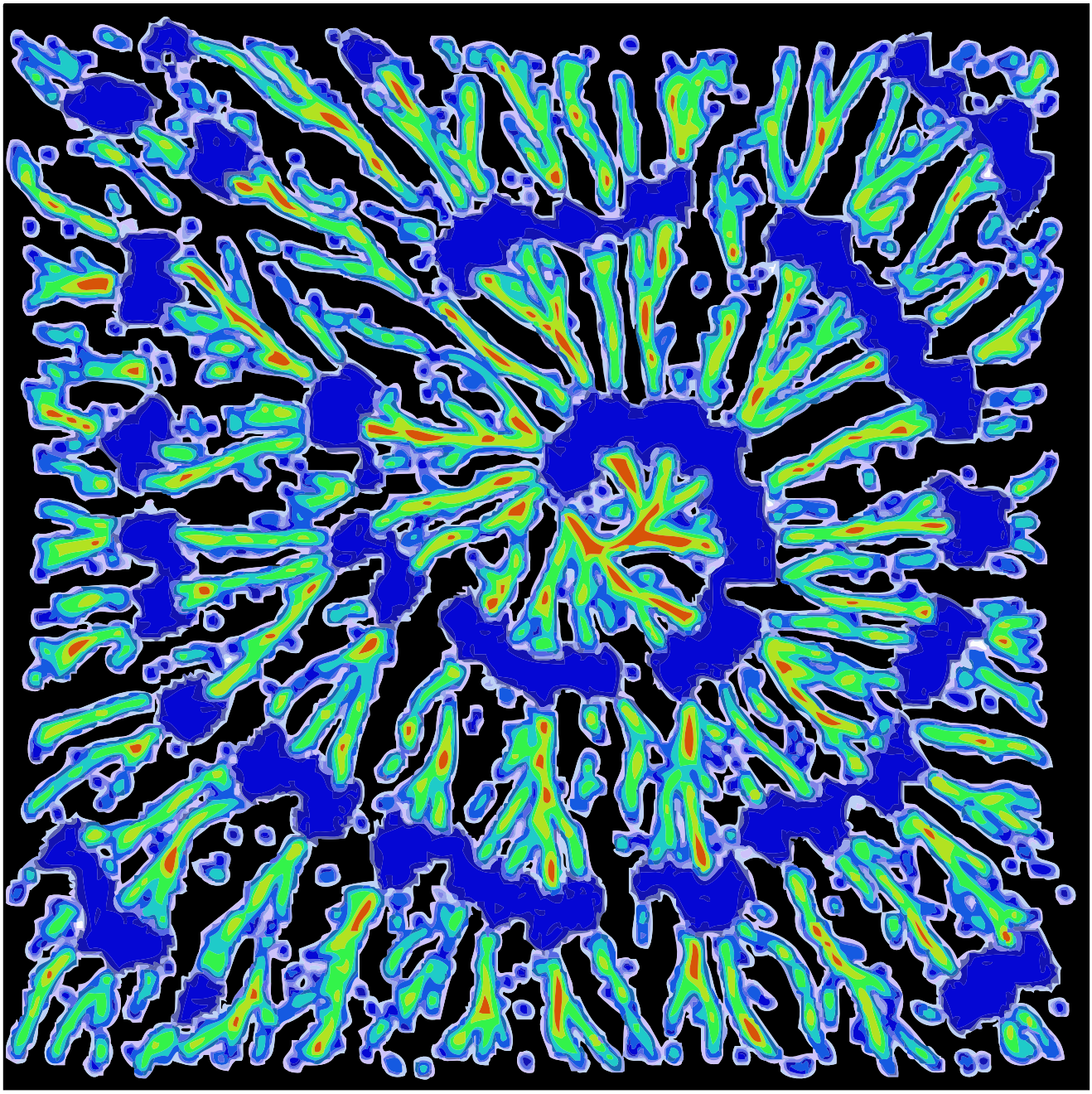
WORKSHOPS

MBI EMPHASIS YEAR ON MATHEMATICAL CHALLENGES IN DEVELOPMENTAL BIOLOGY SEPTEMBER 2008 - AUGUST 2009

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



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



Organizing Committee

- **Robert Dillon** (Department of Mathematics, Washington State University)
- **Leah Edelstein-Keshet** (Mathematics Department, University of British Columbia, Vancouver)
- **Michael Levine** (Department of Molecular and Cell Biology, University of California, Berkeley)
- **Philip K. Maini** (Centre for Mathematical Biology, Mathematical Institute, University of Oxford)
- **Ken Miller** (Department of Molecular Biology, Cell Biology, & Biochemistry, Brown University)
- **Hans G. Othmer** (School of Mathematics, University of Minnesota)
- **Kristin Rae Swanson** (Department of Pathology, University of Washington)
- **Fred Wolf** (Bernstein Center for Computational Neuroscience, Max-Planck-Institut für Dynamik und Selbstorganisation)

WORKSHOPS

2008 WORKSHOP FOR YOUNG RESEARCHERS IN MATHEMATICAL BIOLOGY (SEPTEMBER 2-4, 2008)

Organizers

- **MBI Postdoctoral Fellows**

Overall Summary

The Fall 2008 Workshop for Young Researchers in Mathematical Biology (WYRMB) had exceptional plenary talks from a wide variety of topics in mathematical biology. This year, the MBI postdoctoral fellows (organizers) changed the workshop from 3 ½ days to 3 full days. This format helped to achieve maximum attendance by participants during the entire workshop. In those three days, other than plenary lectures, we had two discussion panels, a series of short talks given by the MBI postdoctoral fellows, and the participant poster sessions.

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

Summary of Presentations

Day 1

The meeting began with a plenary talk given by Jun Liu (Harvard University). This work was motivated by the epistasis detection problem in population-based genetic association studies. Epistasis is the interaction between genes that takes place when the action of one gene is modified by one or several other genes. He outlined a Bayesian approach, aided with MCMC (Markov Chain Monte Carlo) sampling techniques, to identify these interactions amongst the genetic markers for medical disorders.

Following the break, we had a series of MBI short talks by third year postdoctoral fellows: Shuying Sun, Barabara Szomolay, and Michael Rempe. Complimenting the work of Jun Liu, Shuying Sun displayed her strategies for analyzing methylation microarray data, which helps to identify problem CpG islands that could be targeted in gene therapies for tumor growth. Following this talk, Barbara Szomolay talked about dosing strategies for an immunotherapeuticagent (GM-CSF) that reduces tumor growth of breast cancer in mice. GM-CSF enhances the ability of macrophages to present antigen and initiate immune responses. Michael Rempe presented his and David Terman's work on modeling the sleep/wake cycle. Interactions between a circadian pacemaker and a sleep homeostat provide a biological basis for the two-process model for sleep regulation; in essence a flip-flop process balancing the effects of the pacemaker and the need for sleep.

The first talk of the afternoon was given by Markus Owen (University of Nottingham) on emergent vascular networks in simulated normal tissues and growing tumors. Vascular development and homeostasis are underpinned by two fundamental features: the generation of new vessels to meet metabolic demands of under-perfused regions and the elimination of vessels that do not sustain flow. He presented a multiscale model of vascular tissue growth that combined blood flow, angiogenesis, vascular remodeling with the subcellular and tissue scale dynamics.

After the break, MBI postdoctoral fellows Andrew Oster and Yangjin Kim gave short talks. Andrew Oster discussed the function of mitochondria and its role in calcium signaling. Previously it was thought that mitochondria solely sequestered calcium in a passive fashion. However, with the inclusion of the permeability transition pore, mitochondria ex-

hibit calcium induced calcium release excitability and, in an extended system of mitochondria suspended in a gel, can support traveling waves. Yangjin Kim showcased his mathematical model of brain tumor spread. He showed that by varying adhesion and other chemotactic parameters, brain tumor migration patterns exhibit a gradual shift from branching to dispersion, as observed experimentally. After the MBI postdoc talks, half of the participants introduced themselves and gave a preview of their work to be presented during the poster session, which followed with a reception in the MBI foyer.

Day 2

The second morning began with Stephen Coombes (University of Nottingham) discussing threshold models of intracellular calcium release. Calcium is a crucial cellular signal whose careful regulation is essential to cellular survival. A sequence of calcium release events can generate traveling waves of calcium across the cell. Various mathematical models of calcium signaling can be analyzed to shed light on naturally occurring waves due to calcium release such as those recently discovered in ventricular myocytes. In addition, he discussed a more realistic approach to modeling calcium signaling by looking at stochastic calcium release and propagation.

Next, a discussion panel was held on the topic of applying for jobs. The panel, which was led by Carson Chow (Laboratory of Biological Modeling, NIH) was comprised of plenary speakers Sally Blower, Stephen Coombes, Markus Owen, and John White as well as Janet Best (Assistant Professor, Department of Mathematics, OSU and former MBI postdoc). The panel addressed a variety of topics including (1) job opportunities that exist outside of academia, (2) gender issues in academia, (3) things that a search committee mostly focuses on in a candidate's application, (4) interviewing tips (5) how to negotiate once a job has been offered, and other career issues important to young researchers. The participants were actively engaged in the discussion and found the information helpful and insightful.

The afternoon session began with the fourth plenary talk by Sally Blower (University of California,

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Los Angeles). Her talk focused on the use of novel mathematical models to predict beneficial and detrimental effects of the use of vaginal microbicides designed to prevent HIV infection in women. The results showed some surprising results, including that the design of the clinical trial testing the microbicide could actually hide the true risk of drug resistance, potentially causing high-risk microbicides to be widely used. Another surprising result was the fact that although the microbicides are intended as a protection method for women, they may, in certain instances, benefit men more. Dr. Blower also showed how the results arising from these mathematical modeling studies could be presented in a way that can be very useful and relevant to public health officials as well as drug development entities, even if the results are not exactly what they want or expect to hear.

Following a break, brief talks were given by MBI postdoctoral fellows Richard Schugart and Edward Green. Richard Schugart presented results of his research on wound healing and angiogenesis, as related to tissue oxygen tension. He discussed how the mathematical model he developed could analyze strategies for improved healing and generate hypothesis for further experimental testing. Richard recently finished his third year at the MBI but agreed to give a talk for this workshop. He is now an assistant professor in the mathematics department of Western Kentucky University. Edward Green discussed modeling the mechanical behavior of collagen gels, a research area which can lead to a greater understanding of the remodeling of cells and tissues. This was joint work with the lab of Keith Gooch (OSU).

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

Day 3

The opening talk was given by Carson Chow discussing the dynamics of human body weight change. The analysis of the data and the mathematical models he discussed focused on understanding the balance between the exchanges of different sources of energy: those derived from food and those expended naturally or through physical work. He explained that this relationship has been typically difficult to analyze due to the heterogeneous makeup of the body in terms of fat versus lean mass. Results suggest that the food intake mass correlates with body mass index and imply that the body defends against eating too little rather than too much even with a highly variable diet. Further, he explained that to contain weight gain it might prove beneficial to monitor food mass intake over longer periods of time

(months) rather than day to day and to balance the energy content of food with intake mass. In addition, the models explained how children, deprived of necessary nutrition early in their development, experience "catch-up" growth once proper nutrition is restored.

Afterward, the last round of MBI postdoc talks took place. These were given by Judy Day (2nd year postdoc) and Paula Federico (1st year postdoc). Judy discussed the use of an engineering control methodology (nonlinear model predictive control) applied to modulating an inflammatory response with immunotherapy. The results showed that the use of such an algorithm to find optimal dosing strategies to control inflammation could potentially be a useful tool in the care of the critically ill. Paula discussed the use of optimal control strategies to limit or control the spread of a harmful species. Under certain circumstances, optimal control theory applied to an aggregated, analytic model can be used to effectively control a harmful species modeled by a simple IBM (individual based model). However, adding landscape heterogeneities in the IBM can limit the effectiveness of the control method derived from the analytic model. Thus, the need for developing optimal control methodology for IBMs was emphasize.

The afternoon session began with the second discussion panel led by Stephen Coombes (University of Nottingham) on "Habits of highly effective researchers." The panel was comprised of plenary speakers Carson Chow, Markus Owen, and John White. In addition, David Terman (Professor, Department of Mathematics, OSU and Senior Associate Director, MBI) joined the panel. The following topics were discussed:

What should a new assistant professor focus on during the pre-tenure years?

- Balancing Obligations: teaching, research, committees, students
- Identifying issues that arise from a multi-disciplinary career
- How to pick a good problem or know when to move on to something else
- Grant writing

Building and maintaining collaborations

- Clarifying roles and expectations
- Publishing: math vs. science publications

Publishing

- How to determine the best target audience (journal) in which to publish your "Math-Biology" research
- My paper was rejected, now what?
- Quantity vs. Quality

The last plenary talk of the day and the workshop was given by John White (University of Utah). John overviewed how the hippocampus is crucial for remembering episodes in one's life, and that synchronous activity appears to coincide with the encoding of information. The White laboratory studies the mechanisms behind this synchronicity using a combination of computational models and cellular electrophysiology. He explained techniques to "knock in" virtual ion channels that can be controlled with great mathematical precision, and to immerse biological neurons in real-time, virtual neuronal networks.

Conclusion

This workshop was well received by the participants and the speakers. Many positive remarks were made regarding the choices for plenary speakers, the focus on topics relevant to beginning a career as a mathematical biologist, and the MBI facilities and staff logistical support. Throughout the week, the young researchers were very pleased with the workshop structure, as there was time to meet the plenary speakers and interact with other participants. These interactions provided new insights into different areas and directions of research and opportunities to explore future research collaborations, as noted by many participants in the exit surveys. The overwhelmingly positive feedback from the participants has encouraged the organizers to continue hosting the Workshops for Young Researchers in Mathematical Biology.

WORKSHOPS

WORKSHOP 1: CELL AND TISSUE MOVEMENT (SEPTEMBER 15-19, 2008)

Organizers

- **Leah Edelstein-Keshet** (Mathematics, UBC)
- **Thomas Hillen** (Mathematics and Statistical Sciences, U. Alberta),
- **Stan Maree** (Bioinformatics Group, U. Utrecht)
- **Veronica Grieneisen** (Bioinformatics Group, U. Utrecht)

Overall Summary

Cell movement is fundamentally important in morphogenesis and formation of the organism but also plays a central role in wound healing, immune surveillance, and invasive malignant growth in cancer. The aim of this workshop was to bridge the scales between the subcellular molecular mechanisms implicated in cell motility, the motion and behavior of single eukaryotic and prokariotic, the repertoires of cell aggregates and clusters, and the level of multicellular tissue dynamics, morphogenesis, and mechanics.

The workshop showcased the experimental biology alongside recent advances in mathematical modeling and computational biology. Moving from the subcellular, microscopic scale to the macroscopic tissue level, the tutorial and lectures summarized the advances that have already been made, in both experimental and computational methods. They also illustrated the diversity of techniques that have been used to approach the underlying biological issues, including classical mathematics (partial and ordinary differential equations) as well as a variety of computational methods.

Summary of Presentations

Day 1

The workshop opened with an overview of research (both experimental and theoretical) on cell motility, given by Leah Keshet. She covered

phenomena at a wide range of scales, from the sub-cellular to the tissue level. On the microscopic scale researchers seek to understand how behavior such as chemotaxis is regulated biochemically. Others look at how the mechanical forces required for cell movement are generated; e.g., by actin polymerization. Moving to the cellular scale, there are questions such as how do cells become polarized? How do they move through complex environments (i.e., collagen gels)? And what affects cell shape and behavior such as blebbing? Finally, moving to the tissue level, one finds a range of questions concerned with how cells come together to form cohesive tissues. Cell sorting is a very important phenomenon here, which can involve a complex interplay between local and long-range effects. Packing constraints combined with cell proliferation can also have a profound effect on tissue architecture. The talk provided a taster of some of the topics which were covered in greater depth during the course of the workshop.

The next three talks formed the tutorial part of the

program. The first, by Thomas Hillen, was entitled "PDEs and cell movement." The theme of this talk was that a wide variety of the partial differential equations used in modeling cell movement (e.g., reaction-advection-diffusion equations, transport equations, and continuum mechanics equations) can be derived from stochastic processes. First to be considered were so-called "position-jump" processes, where one considers the probabilities of cells changing position by a discrete amount within a certain time interval. A master equation is obtained by considering the probability of finding a cell at each position. By taking appropriate limits one obtains a macroscopic advection-diffusion equation for the cell density, where the diffusion coefficient and drift speed can be related to the probabilities of a cell jumping in a particular direction. He then moved on to consider "velocity-jump" processes, which model movements such as "run and tumble" chemotaxis in bacteria, where cells periodically change their direction. In this case, one obtains a transport equation, which is analogous to the master equation in the previous case. Equations for macroscopic quantities such as mass density, pressure, and momentum can be derived from this equation in appropriate limits. However, there is a difficulty, known as the moment closure problem, in obtaining continuum equations in this case. In order to obtain a closed system of macroscopic equations, it is necessary to make some ad hoc assumptions about these quantities (*i.e.,* not based on the microscopic description).

The next tutorial speaker was Wayne Brodland (University of Waterloo), who spoke on the subject of finite element models in tissue mechanics. He began by considering the reasons for modeling a system, such as: to learn how components interact, to test hypotheses, to trace out causal pathways, and to help in understanding, or designing, experiments. Successful modeling involves first thinking carefully about a system: what it does, its key components, and how it might work. Then one writes down equations, chooses the geometry, validates the model and reports the results. He then went on to describe the finite element method, which is particularly suitable for continuum mechanics problems. In this method, the domain is divided up into small "blocks"; e.g., in one dimension, line segments. Shape functions are then used to relate how variables change within the element to their values at the boundaries. It is then essential to test for mesh-independence (i.e., to ensure that the solution obtained by the method is independent of the discretisation used). This is called the convergence test, and for time-dependent problems, similar testing must be carried out with varying timestep sizes. Dr. Brodland showed the results he had obtained using this method in a model for the development of an embryo.

The final tutorial was given by Stan Maree, on cellular based modeling. Here a variety of techniques are available, including cellular automata, agent-based models and the cellular Potts model. In the case of the latter, cells are discretised based on a grid, but a single cell may occupy many grid points. One very important application that can be studied using the cellular Potts model is cell sorting within tissues. This is hypothesized to occur due to differences in the strength of adhesion between cells of different types (the Steinberg hypothesis). The effect is similar to that seen in fluids, where liquids of low surface tension engulf drops of higher surface tension. The modeling can be made more realistic by having the cells minimize an energy made up of the interfacial energy, the difference from the cell's target volume, and the difference from the cell's target perimeter.

The final session of the day included the first research talk, given by Roseanne Ford (University of Virginia), on experimental studies of chemotactic bacteria in porous media. Here, the focus was on migration of chemotactic bacteria in porous media, with application to remediation of polluted

groundwater systems. A series of experimental approaches ranging from tracking individual cells or chemotactic bands in microfluidic devices to monitoring bacterial migration in a natural groundwater aquifer were presented. Interestingly, it turns out that when the pore size in the porous medium is small, the dispersion of the bacteria may actually be enhanced. This is because the small pore size restricts the angles through which the bacte-

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ria may turn in the "tumble" stage. As a result they tend to continue swimming in the same direction. This effect can be very significant in helping to ensure the bacteria reach a polluted site.

Day 2

The theme of the second day was *From the subcellular to the cellular*. The first talk was by Cecile Sykes, (Institut Curie / CNRS / Université Paris 6) on "Reconstitution of cytoskeletal dynamics at a liposome membrane." Cells move and divide by dynamically assembling and disassembling their cytoskeleton. In order to investigate generic mechanisms of cell movements, simplified stripped-down systems that reconstitute cellular behaviors have been developed. In the past, Listeria movements have been reconstituted by replacing the bacteria with beads that move by the same biochemical mechanism as the lamellipodium of cells. The advantage of such systems is that physical and mechanical properties of the load can be changed for a thorough study of the movement. The talk focused on how similar approaches could be applied to investigating the reorganization of Golgi membranes, the dynamics of the actin-myosin cortex in cells (leading to cell polarization and movement), and the effect of cytoskeletal structure on the membrane stiffness of red blood cells.

The next talk was on the subject of cancer cell invasion in 3D extracellular matrices, and was given by Katarina Wolf (University of Nijmegen Medical Centre). Tumor cell migration through extracellular matrix involves proteolytic cell-matrix interactions for matrix barrier removal. Studies of this phenomenon, using dynamic bright-field and confocal imaging of tumor cells invading 3D fibrillar collagen lattices were presented. These studies showed the topology of cell-matrix-interactions, structural matrix break-down, and related cell shape changes. One of the most striking observations is that, during migration, collagen fibers become aligned in parallel along the forward-moving cell body. The resulting tube-like matrix defects were further widened by following cells to give rise to multicellular invading strands. Proteolysis, path generation, and widening, as well as transition to collective invasion, were reduced by protease inhibition. These findings directly demonstrate how matrix breakdown results in cell and tissue patterning. However, cell migration is not prevented in the absence of matrix breakdown; cells can still move by "squeezing through" the matrix. This type of movement is strongly affected by the pore size of the matrix. Alexander Verkhovsky (Swiss Federal Institute of Technology) then talked about the organization and dynamics of motile machinery in keratocytes. The processes involved in cell motility include actin assembly, actin/myosin contraction, adhesion, and membrane tension. Force generation emerges from the events at molecular level. To find out how actin and myosin move in the cell, both were tracked over the entire cell. This showed that the front of the cell myosin moves forward with respect to actin, but at a velocity much smaller than the cell velocity. A finite element based approach was then used to determine force transmission to the substrate.

After lunch, Kevin Painter (Heriot-Watt University) spoke on the subject of "Modeling cell migration in the ECM." The ECM plays a key role in migration, providing cells with a scaffold for migration and providing guidance information to the cells through matrix fibre following (contact guidance). Individual cell migration in the ECM can be clas-

sified into two main groups: amoeboid and mesenchymal. In the former, cells move quickly and have a negligible effect on the structure of the surrounding ECM. Mesenchymal migration, however, is much slower and extensive matrix degradation takes place through the focused expression of specific matrix degrading proteins by the cells (pericellular proteolysis). A mesoscopic model (continuous formulation of the velocity jump formulation of individual cell movement) for these phenomena was presented, which retains some microscopic description of cell movement and admits a degree of analysis. Numerical simulations were used to illustrate how different structures of fibers can lead to different migration patterns, and might explain effects such as "fingering" in tumors.

In the final talk, Wayne Brodland presented more of his results on modeling the mechanics of amphibian neurulation, some of which had already been discussed during the tutorial the previous day. The model is based on a continuum mechanics formulation, using constitutive relations that capture the complex properties of the cells. It is necessary to make some assumptions concerning, e.g., the mechanical effect of the expression of certain genes in order to capture the behavior of the real embryo. However, due to refinements over a number of years, the computational model now reproduces the observed pattern of development very well. As well as the results of this work, more general problems arising from a lack of biological data and modeling geometrically complex situations were discussed.

Day 3

The theme was "Aspects of cell polarity in plants and animals." The proceedings kicked off with a talk from Veronica Grieneisen on modeling and experimental investigations of auxin transport (and its effects) in plants. Auxin is a hormone that determines cell differentiation and proliferation. Significantly, auxin is observed to be localized at the center of stem cell niche in the root, which leads to questions about how this arises, and its effect on morphogenesis. A modeling approach based on the cellular Potts model was presented in which an individual cell can grow and divide. Each cell can move vertically due to mitosis near the stem cell niche and is not allowed to migrate to the sides. Reaction-diffusion equations for auxin in each cell are solved with position-dependent permeability boundary conditions between cells. The results are in excellent agreement with experimental observations. Aspects of root architecture were also discussed. Roots are observed to branch at places where the root has been bent into a curve. In the model, very high concentration of auxin is observed along the outer edge of the curve, and this appears to explain the phenomenon.

The second talk was by Geoffrey Wasteneys (University of British Columbia) on "Polymer dynamics and the spatial organization of the cortical microtubule array in plant cells: implications for growth and morphology." Semi-rigid polysaccharide walls generally prevent plant cells from rapid movements. With the exception of pollen tubes and the motile sperm of certain taxa, plant cells do not migrate. Instead, plant cell movement occurs by expansion of the cell wall, which is driven by turgor pressure. Rather than expanding equally in all directions, cells within elongating plant organs expand along one major axis, which is generally perpendicular to the orientation of highly tensile cellulose microfibrils in the cell wall. The mechanical properties of cellulose microfibrils, in turn, are governed by dynamic microtubules (MT), which are self-organized into parallel arrays at the plant cell cortex. Cortical microtubules often have the same orientation as cellulose microfibrils. How spatial organization of the cortical array is achieved is one of the most enduring questions in plant cell biology.

Dr. Wasteneys explored how the dynamic properties of cortical microtubules determine the spatial organization of microtubule arrays and how these arrays control the growth, morphology, and performance of plants. Comparing the dynamic behaviour of microtubules in mutant lines that have defective versions of the important MOR1, CLASP or ARK proteins permits the testing of models of the molecular mechanisms that drive microtubule

organization. This knowledge is being used to investigate the role microtubules play in the mechanical properties of the cell wall, the chirality of elongating organs, and the transport of the hormone auxin.

The next talk, continuing the botanical theme, was by Jose Feijo (University of Lisbon) on the dynamics of pollen tubes. Pollen is the male gametophyte of plants. From a dehydrated, quiescent organ in the atmosphere, pollen grains take up water from the

female tissues in a matter of seconds, and in minutes develop a unique form of cellular outgrowth, the pollen tube which is among the fastest growing structures in nature. How this growth is regulated, however, remains poorly understood. Theoretical modeling shows that just two processes— wall surface and cytoplasmic volume growth —are sufficient to generate the observed apical growth. Spatial and temporal integration of extended biochemical and biophysical processes is necessary, and it has been shown that "ion dynamics" (the regulation of ion membrane fluxes and cytostolic free ion concentration) are extremely important. These processes are being investigated experimentally by producing GFP-expressing versions of the putative genes involved in ion dynamics, and the results compared with the model predictions.

After lunch, we reconvened to hear a talk by Pablo Iglesias (Johns Hopkins University) on "Theoretical and experimental analysis of chemotactic systems in biology." This talk concerned models, based on biochemical data, of the regulation of chemotactic behavior in the slime mold Dictyostelium. Gradient sensors are localized on the cell boundary and PI3K and Pten are important regulators. The model has two important features: inhibition and excitation. The response depends on ratio of local excitation to local inhibition, and the model predicts that cells can detect multiple sources simultaneously. Experiments used to test these models were discussed. Finally, the problem of how a finite number of chemical sensors on a cell should be positioned to give the cell the best possible ability to follow the gradient was considered, using some ideas from information theory.

The day was rounded off by four short talks: "A mathematical model for mesenchymal and chemosensitive cell dynamics in tissue networks" was presented by Anita Kettemann (University of Stuttgart); "A 'Go or Rest' model for cell migration. A step forward toward the 'Go or Grow' modeling" by Arnaud Chauviere (Technische Universitat Dresden); "Collagen gel formation model in 3D" by Andy Stein from (University of Minnesota); and "Turning cells into Bits" by Jop van Rooij (Utrecht University).

Day 4

Thursday's talks were on cellular interactions and tissue formation. The first talk, given by Kristin Sherrard (University of Washington), was titled "Ascidian endoderm invagination occurs by apically constrained rounding of endoderm cells." Ascidians begin to gastrulate at only 64 cells, each largely relative to embryo size, providing an unparalleled window into the cellular basis of morphogenesis. The approach here was to use computational simulation to test their hypothesis that the invagination occurs in two steps: (1) apical contraction forms a placode and (2) apically

constrained basolateral contraction shortens the endoderm causing it to sink inwards. Wide-ranging searches of parameter space largely confirmed the hypothesized invagination mechanism: most placodes formed with conditions of strong apical contraction, and invaginations invariably required elevated basolateral contractility on the invaginating endoderm cells. A rather surprising finding of the study was that apical contraction was insufficient to drive invagination while basolateral contractility was essential, which has implications for invaginations with similar kinematics such as *Drosophila* ventralfurrow ingression.

The second speaker, Luigi Preziosi (Politecnico di Torino), devoted his talk mainly to tumor formation around the blood vessels. He introduced a recently popularized shear rate formulation from the literature including some relaxation and material tests for the tissue, Herschel-Bulkley's model, and Faty's reorganization test. He discussed cell and extracellular matrix interactions and introduced a cellular Potts model for angiogenesis. He concluded with sharing some thoughts on surface tension phenomena, and the applicability of the concept to cell aggregates.

Next, Ray Keller (University of Virginia) discussed "Unsolved mysteries of tissue shape change by cell intercalation." Cell intercalation has emerged as a major mechanism of transducing local cell behavior into massive changes in tissue shape. He discussed the players and processes essential for cell intercalation and the resulting tissue shape changes unveiled by recent molecular and genetic studies. He explained the types of cell intercalation induced by the convergent extension, and discussed the known theories and explanations as well as open problems about cellular, molecular and biomechanical aspects of cell intercalation-driven tissue shape change.

In the afternoon, Matthew Gibson (Stowers Institute) gave a talk on "Cell topology and spindle geometry in proliferating *Drosophila* epithelia." The capacity to organize cells into epithelial sheets is a defining feature of all metazoans, and the ability of cells to adhere and polarize is, in turn, central to nearly every aspect of organ morphogenesis and physiology. He described a combination of experimental and theoretical approaches to understand the effect of cell proliferation on the dynamic spatial relationships between cells in *Drosophila* epithelia. He also explained epithelial cell organization and a theoretical distribution of the number of cell sides for the epithelial cell topology. He concluded that proliferation mechanisms alone appear sufficient to explain much of the data.

Day 5

The talks on the last day of the workshop were grouped under the umbrella topic of morphogenesis. The first was given by Mark Miodownik (King's College London) on the effect of biomechanics on the robustness of ventral furrow invagination in the *Drosophila* embryo. Ventral furrow formation in *Drosophila* is the first large-scale morphogenetic movement during the life of the embryo, and is driven by co-ordinated changes in the shape of individual epithelial cells. He then introduced the computer model they developed to analyze the mechanics of invagination, and to investigate the ability of different combinations of independent active cell shape changes to bring about invagination. He explained that although many of the genes involved have been identified, the mechanical processes that convert local changes in gene expression into changes in embryonic form remain unknown. They concluded that qualitatively similar morphogenetic changes can be brought about by different combinations of active cell shape changes. Thus, different combinations of force generating mechanisms could underlie epithelial in-folding in different biological systems, instead of a single force or single active shape change. He compared the results of the model with the previously described effects of mutations in the morphogenetic regulators, Twist and Snail. Their studies also suggest that ectodermal pushing could well play an important role in gastrulation movements in other systems.

Kasia Rejniak (Moffit Cancer Center) ended the workshop with her talk entitled "Normal and malignant remodeling of epithelial tissues: an integra-

tive IBCell model." She discussed the application of the immersed boundary method to problems in tumor growth. This can be used as a computational tool for the investigation of genotypic and molecular abnormalities associated with epithelial cancers. The particular case considered was a 3-dimensional experimental model of epithelial acini. The effects of different rules governing cell behavior were discussed and in particular, she focused on the dynamics of cell membrane receptors that drive interactions between neighboring cells and between cells and their immediate microenvironment. The computational results were used to gain more insight into experimental data.

Conclusion

The meeting was very successful and enjoyable. There was a good mixing of experimental and theoretical contributors, and participants did not feel inhibited about asking questions during the talks and discussion sessions. A number of the attendees are looking at opportunities for new collaborations where their research interests overlap. The mixture of theoreticians and experimentalists was very stimulating for all participants. Theoreticians learned a lot about the underlying biology and biologists were quite impressed by the theoretical interest in their work. Important new contacts have been established and a number of collaborative research projects have been started. Since theory and real world were so close in this workshop it will have a large impact on future research. Even more, the organizers consider this workshop to be a "milestone" in the systematic study of cell and tissue movement.

TUTORIAL ON WORKSHOPS 2 AND 3 (OCTOBER 9-10, 2008)

Organizer

- **Hans Othmer** (Mathematics, U. Minnesota)

The tutorial was divided into several parts. In the *Introduction to Mathematical Models in Development* we learned that the basic problem in development is how the 250 types of human cells were generated during embryogenesis. To model cell development, simple model systems are used; for example, a frog native to Africa (*Xenopus*). The question of symmetry arises here— how to decide about the axis during cell division. In the early stages of development cell division is uniform; later it is not. An overview was given of other important mechanisms involved in development such as cell-cell signaling (biofilms), coordinated cell movement, pattern formation, differentiation, and morphogenesis (change in shape). Interestingly, there is no cell movement in plants.

Bacteria can sense a wide range of environmental signals- including temperature and pH changes, nutrient concentrations, osmolarity and oxygen tension- and they integrate this information to gen-

erate the pathogenic response. Chemotaxis and motility are essential for pathogenicity. Chemotaxis is the biasing of movement towards regions that contain higher concentrations of beneficial or lower concentrations of toxic, chemicals. For a cell to move, a force has to be generated— ATP (Adenosine triphosphate) is the most significant "energy molecule." Motility is of two types: gliding and free swimming. The Reynolds number for a free swimming bacterium is 10^{-6}, which means that bacteria experience high viscosity and almost no inertia, so when bacteria stop they stop immediately. Gliding bacteria secrete slime to move, and this movement is very slow (1μm min^{-1}) compared to free-swimming bacteria.

G-proteins are important signal transducing molecules in cells. More precisely, G-proteins function as "molecular switches," alternating between and inactive GDP and active GTP bound state, ultimately going on to regulate downstream cell processes. In modeling, the question of time scales often arises. It was shown in 1977 by Thomas Kinetz that stochastic models approach deterministic ones (the infinite molecule limit).

In the *Basic Mechanism of Pattern Formation* as a motivational example, the phenomenon Rayleigh-Benard convection in fluids was discussed. The first profound paper on pattern formation titled "The chemical basis of morphogenesis" by Turing was published in 1952 and it reported that pattern can emerge spontaneously through the interaction of reaction and diffusion. Another paper by Wolpert ("Positional information at the spatial pattern of cellular differentiation," 1969) showed that cells read their position and activate gene expression and other processes accordingly. A simple mathematical example of Turing's theory is two diffusing chemicals with concentrations *A* and *B*, where *A* is the activator and *B* is the inhibitor.

The standard Turing model in dimensionless form is given by a system of reaction-diffusion equations

$$\partial c/\partial t = vD\Delta c+R(c,p) \text{ in } \Omega,$$

where *c* is a vector of chemical concentrations and *p* is a vector of parameters. The boundary conditions are, typically, Dirichlet or Neumann on $\partial\Omega$. The dimensionless quantity *v* is the ratio of a kinetic relaxation time to a relaxation time for diffusion, in fact it is expected that for $v>>1$ all solutions will converge to spatially uniform solutions. The rigorous proof of this theorem was also analyzed.

In the *Bacterial Chemotaxis* the motility of E. coli was discussed. This bacterium moves according to a "run-and-tumble strategy"— runs counterclockwise in a favorable situation and tumbles clockwise in an unfavorable situation. In homogeneous environments swimming bacteria change direction about once a second, which produces random movement. In non-homogeneous environments the frequency of direction changing is controlled by positive or negative stimuli to bias the overall direction of movement.

The second day of the tutorial focused more on amoeboid cell movement, in particular the slime mold *Dictyostelium*. Under conditions of limited food supply, some of the cells of this organism begin to secrete a chemical known as cAMP, and chemotactic streaming occurs in response to the cAMP signal. This results in the formation of multicellular aggregates. The cell aggregates form themselves into a migrating slug, which in turn eventually reforms into a fruiting body, allowing the spores of the organism to be dispersed into a more favorable environment.

Unlike the "run-and-tumble" chemotaxis discussed the previous day, *Dictyostelium* cells must orient themselves by sensing differences in the cAMP signal between the front and back of the cell. The tutorial session concentrated on the process of signal transduction. The key ingredients for successful transduction are that there must be a positive feedback loop, to amplify small gradients and allow the cell to polarize, and adaptation to the ambient signal level, so the cell is not "swamped" at high chemical concentrations. Interestingly, it is not necessary for the cell to be able to sense the direction of the chemical gradient with great accuracy; provided in moves within a cone of 270° around the correct direction, aggregation will still occur (albeit more slowly for less accurate sensing). The signaling pathway is activated by cAMP binding to G-protein coupled receptors, which are uniformly distributed on the cell membrane. This triggers a complex cascade of further reactions within the cell, the details of which were discussed by the group after reading a recent review by Janetopoulos and Firtel.

The tutorial also introduced mathematical models for the migration of the *Dictyostelium* slug. Unlike for bacteria, mechanical effects are important here, as the cells are in close contact with each other as they migrate. An interesting result of experimental research into this phenomenon is that it appears the force exerted by the slug scales with the total

number of cells within it. However, modeling work suggests the force should scale with the surface area (as only cells in contact with the substrate can exert traction to move the slug forwards). Two possible explanations of this were discussed. The first, known as the "bedspring model" is that, at each point in time, some subset of the cells within the slug holds rigid, so the surrounding cells can exert traction on them. The second notes that the slugs studied experimentally all have a fixed aspect ratio; if this fact is used when interpreting the data, it appears that the force does scale with the slug surface area. Further experiments are in progress to verify if this is, in fact, the case.

WORKSHOP 2: PATTERN FORMATION AND DEVELOPMENT IN COLONIAL ORGANISMS (OCTOBER 13-17, 2008)

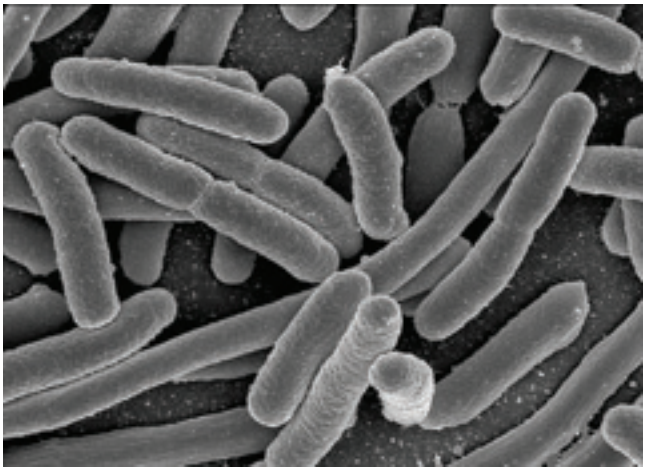
Organizers

- **Philip Maini** (Center for Mathematical Biology, U. Oxford)
- **Hans Othmer** (Mathematics, U. Minnesota)

Summary of Presentations

Day 1

The first talk was by James Shapiro (University of Chicago). The title was "What do colony patterns mean?" In the talk, Shapiro gave an overview of bacterial patterns formed in *E. coli, P. mirabilis,* and *B. subtilis* colonies. The aim of the talk was to show that although bacteria are single cell organisms, communication between different cells can lead to very complicated population structures. On hard medium, *E. coli* colony formed concentric ring patterns after a couple days of growth. New rings can also form from a wedge of the colony. On hard medium, a *P. mirabilis* colony grows, vegetative swimmer cells differentiate into long swarmer cells and form highly motile rafts. Therefore the colony not only grows but also actively propagates. During colony growth, periodic front movement and spatially concentric ring patterns were observed. During pattern formation, swarming phases and consolidation phases were identified. When two or more inocula were introduced on the medium at the same or different time, the periodic clocks of each colony do not interfere with each other. A mathematical model by Esipov and Shapiro was developed to describe the periodic colony front movement. Ayati also simplified the model and studied the spatial ring formation later. Depending on the hardness of the medium (concentration of agar) and nutrient abundance, *B. subtilis* colony can form uniform or fractal growth patterns.



E. Coli bacteria.

The second and fourth talks were two different models of *E. coli* chemotactic response to attractants. The aim was to understand how signals are processed inside the cells. The *E. coli* chemotaxis pathway has been studied for a long time both biologically and mathematically. However, there are still open questions regarding how receptors cooperate to achieve the large gain of the system, which means how the cells detect different scales of signal changes and react correspondingly, and how the cell buffers out the background noise and react correctly. The second talk was given by Yuhai Tu (IBM T. J. Watson Research Center). A mean-field approach was presented without explicitly modeling the molecular details. They used a two-state model of the ligand binding and reproduced some experimental results. The fourth

talk was given by Xiangrong Xin (University of Minnesota). A detailed model that takes care of almost all possible chemical reactions inside the cell was presented. This model could also reproduce many experimental observations.

The third talk was given by Roseanne Ford (University of Virginia). The aim of the study was to understand the attachment of individual bacteria to surfaces which happens as the onset of biofilm formation. Specific questions that need to be addressed include how swimming bacteria swim close to a surface or in a porous medium. ME experiments showed that cells swim in circles because of flagella and cell body rotation. Mutants that have no flagella or can not switch their flagella were analyzed to see how flagella rotation is important for cells to attach to the surface.

Day 2

Mark Alber (University of Notre Dame) began the second day with a talk about Myxobacteria swarming. *Myxococcus* is a bacterium which has two types of motility patterns, pili-based *S* motility and slime-based *A* motility. The aim of the talk was to see if cell-cell interactions were sufficient to explain the swarming patterns of *Myxococcus* instead of introducing chemotaxis as in previous works. A cell-based model (off-lattice model), which is rule-based, was presented. Each cell was modeled by N nodes. The configuration of the nodes was represented by an energy function. The simulation yields a constant rate of colony expansion.

In the second talk by Isaac Klapper (Montana State University) it was shown that biofilms can be viewed as living, growing fluids with a surprising ability to respond to and defend against their environments. In this talk a general overview of efforts to characterize and model biofilms on a continuum macroscale was presented, and an application related to bacterial-induced mineralization was also discussed. In the sense of fluids, the biofilm structure is influenced by

- the substrate concentration: $\Delta C = Gr(C)$, where C-substrate, $G^{-1/2}$-active layer depth (how far the biocide diffuses before depleted by reactions), r(C)-substrate usage function
- biofilm deformation: $u = -\lambda \nabla p$
- growth stress: $\Delta p = -\lambda 1 \nabla$. $u = -g(r(C))$, where g is the biofilm growth function
- interface motion: $u = -\lambda dp/dn$

Then a simple 1-D biofilm model with top at $z = h(t)$ is given by

$$\mathring{u} = -pz\,(h(t),t) = \int_0^t g(C(s,t))ds.$$

Growth of the biofilm takes place in the active layer of depth $O(G^{-1/2})$. Note that for small h (thin biofilm) the RHS of the equation is $O(h)$, so that there is exponential growth. For large h, the RHS is constant; there is a front moving at constant speed.

The last talk in the morning session was given by Chuan Xue (MBI Postdoc). She presented new experimental cell density patterns found in *P. mirabilis* colonies, e.g., radial and spiral streams, and a hybrid cell-based model with the aim of explaining these patterns. The model incorporated detailed descriptions of single cell signal transduction and movement, which were the content of several talks on the first day, and explained the counter-clockwise spiral cell densities by microscopic swimming bias of single cells. Because of the large computational cost of the cell-based model, chemotaxis equations were also derived in the diffusion limit from the cell-based model.

The first talk in the afternoon was given by Harry Swinney (University of Texas at Austin). The title of the talk was "Deadly competition between sibling bacterial colonies." In this talk the presenter reported findings on Paenibacillus pattern formation. The similarity of Paenibacillus, *Myxococcus* and Proteus is that all these bacteria move with the assistance of slime or wetting layer. In this study the cells secrete some compound that can kill sibling cells. When one colony was grown in the medium, the colony grows and expands with a dendritic pattern. When two colonies were grown on the same plate, competition between two sibling colonies results in no growth at the midline of the two inoculation sites. This was explained by a model that incorporated an inhibitor produced by the prespore cells of each colony. The question of why a single colony does not commit suicide is still to be understood.

The last talk on Tuesday was given by Angela Stevens (University of Heidelberg). In contrast to previous talks, this talk was very mathematical. The aim was also to understand how *Myxococcus* swarm, but the approach was very different from the first talk in the morning.

WORKSHOPS

Day 3

The first talk was by Richard Firtel (University of California, San Diego), on the subject of "Ras control of chemotaxis." The aim was to understand how *Dictyostelium* cells detect and orient themselves in response to chemoattractant gradients. As has been noted previously, key elements are the amplification of the signal, and adaptation to the ambient level of cAMP. This occurs through a complex cascade of interactions within the cell. The biochemical pathway focused on in this talk was that involving PI3K. This protein is found at the leading edge of cells, and regulates chemotaxis and cell polarity through control over actin and myosin. It was noted that amplification of the cAMP signal must take place upstream from PI3K. A candidate for this role is Ras, a small G-protein which activates the PI3K pathway, as well as the TOR complex 2 (which regulates cell polarity and cAMP production). The main part of the talk concerned an investigation into the mechanism by which Ras is spatially and temporally controlled and the pathways that are regulated by Ras and by which Ras is regulated. This was achieved by studying the effects of its mis-regulation. The results show that strict regulation of Ras is essential for gradient sensing directed motion of the cells. Following the break, Wouter Rappel (University of California, San Diego) gave a talk entitled "At the interface of modeling and experiments in eukaryotic chemotaxis." Once again, the focus here was on understanding how cells are able to detect chemoattractant gradients, this time using a combination of modeling and experiments. The basic problem for the cell is how to compare the cAMP signals at the "front" and "back" of the cell, and respond accordingly. Since cAMP diffuses quickly, the intercellular processes must be rapid. One possible explanation, known as the "first hit model," was put forward. Here, it is postulated that, in response to a signal at the front of the cell, an inhibitor is produced which diffuses within the cell. However, two difficulties arise with this model - firstly, that the inhibitor must diffuse more quickly than cAMP, and secondly, that the cell would find it difficult to change direction using this mechanism. An alternative model of "balanced inactivation" was then introduced, the key ingredients of which are a membrane-bound activator and an inhibitor which has both cytostolic and membrane-bound forms. The success of this model depends on having equal production rates for the activator and inhibitor, which may be biologically plausible if, for example, they both depend on the same G-protein. The talk then moved on to the subject of the formation of Turing-like patterns of signaling proteins in the cell membrane. This occurs in response to a large uniform dose of chemoattractant. An interesting feature of the model presented is that instabilities can occur even when the diffusion coefficients for the two species are the same, unlike the classical case.

The next talk was by Peter Thomas (Case Western Reserve University) on "Stochastic phenomena in chemotaxis," and continued the day's signal transduction theme. During gradient sensing, a cell estimates the direction of a source of diffusing chemoattractant molecules based on the spatiotemporal sequence of ligand-receptor binding events at the cell membrane. The local directional signal results from a combination of diffusion of signaling molecules from nearby cells and interactions between these molecules and receptor proteins on the cellular surface. Cells are able to sense even shallow gradients and low concentrations of signaling molecules, and in such situations

stochastic effects arise due to the diffusive motions of the signaling molecules and the stochastic nature of the ligand-receptor binding interaction. The talk explored several aspects of the problem, including estimates of the optimal gradient detection accuracy within a maximum likelihood framework, and exploration of the information capacity of purely diffusion-mediated signaling processes. For shallow gradients, perturbation theory was used to obtain analytical results. An interesting result of the modeling was the finding that the cell experiences the greatest information gain in the first 1-2 seconds after the signal is turned on; this compares well with experimental results on how quickly cells polarize in response to exposure to chemoattractant from a pipette.

After lunch, the session resumed with a talk on "Modelling cell-cell interactions and motion with discrete viscoelastic ellipsoids," given by John Dallon (Brigham Young University). Mathematical and computational modeling of cell motion was the theme here. Cell motion is crucial to many diverse processes including morphogenesis, embryonic development, wound healing, angiogenesis and cancer. In all these processes local interactions of moving cells with one another are key. The talk introduced a computational model for aggregate cell motion which focuses on the local cell-cell interactions. The cells were treated as viscoelastic ellipsoids and force equations used to determine their motion. The model was applied to collective cell motion in *Dictyostelium* and wound healing. In the case of *Dictyostelium*, an additional factor ("counting factor") must be introduced to regulate the size of the fruiting body, in order to recreate experimental observations. Improvements to the model, such as replacing the viscoelastic ellipsoid representation of the cells with a cortical shell model, were also discussed.

Day 4

The fourth day began with a talk by Radek Erban (University of Oxford) entitled "Connecting single cell level and population level descriptions of colonial organisms." The focus here was on determining how the individual-cell-level behavior of an organism affects the collective behavior of the population. Three basic approaches can be used. Probably the most obvious is direct simulation of the stochastic processes (e.g., Monte Carlo simulations, molecular dynamics), but these are computationally expensive, and often do not give much insight into the behavior observed. An alternative is to derive macroscopic equations for cell density *etc.*, from the underlying stochastic process. The third is to use computer assisted methods of analysis (such as "equation free" methods). The talk initially focused on the second approach to deriving macroscopic equations for the movement of *Dictyostelium*, using methods similar to those previously described by Hans Othmer and Chuan Xue. However, as mechanical effects are significant in *Dictyostelium* (unlike bacteria), the resulting system is much more complex. It then moved on to equation-free methods, where it is supposed that a closed (but unknown) system of macroscopic equations exist. It is assumed that short-time simulations of the process can be undertaken, but the problem is to answer questions about steady-state or long-time behaviors. Short bursts of these simulations are used to estimate the parameters in the underlying macroscopic equations (the form of which must be assumed). The methods used were illustrated with examples from chemical reaction processes, and some difficulties with grid-based simulation methods were discussed.

Tony Romeo (Emory University School of Medicine) gave a talk on "Identification and regulation of an adhesin that influences cell organization during *Escherichia coli* biofilm formation." Biofilms are "cities of microbes" which exhibit complex architectures that provide a sheltered environment for cells. The first part of the talk dealt with the role of the CsrA gene (carbon storage regulator A) in regulating biofilm development. It appears that this gene is a repressor of biofilm formation and an activator of cell motility; its effects have been carefully investigated by looking at the behavior of mutants. This effect on biofilm development seems to be due to its role in regulating the production of a polysaccharide adhesin. The second part of the talk looked at the formation of periodic patterns during biofilm development. This involves an initial reversible interaction with a surface via a cell pole followed by conversion of the temporary

attachment to "permanent" adhesion, and continued growth of the biofilm via cell-surface and cell-cell interactions. Using fast Fourier transform analysis, it was determined that the patterns have a wavelength of around 12μm, and it is postulated that the clumps secrete an inhibitor that prevents another clump forming close to it. Interestingly, cell motility does not appear necessary for pattern formation, but the production of an adhesion protein is.

The next talk was by Thomas Hillen (University of Alberta) on "Merging and emerging patterns in chemotaxis." The literature contains a large number of chemotaxis models, and this talk considered the properties of each formulation. The best-known model is the Patlak-Keller-Segel model, which exhibits the phenomenon of blow-up. However, the model has been adapted in various ways to allow for global existence of solutions. This has been done by including additional physical processes, such as volume filling or including more detailed models of receptors and signaling. These modifications can give rise to interesting new pattern formation processes.

Across a wide range of modified models, it is observed that local maxima form and show "merging" (two local maxima coagulate) or "emerging" (a new maximum is formed) behavior. These dynamics can lead to steady states, periodic solutions or possibly to chaotic behavior. The talk was illustrated with a variety of examples of the results from the different models.

The goal of the talk by John King (University of Nottingham) was to illustrate the role of spatial effects in influencing quorum-sensing behavior. Asymptotic methods were applied to investigate growth and upregulation in a simple macroscopic model that encompasses biofilm deformation. In the simple one-dimensional case the cell population (n) is assumed to consist of downregulated (n_d) and upregulated (n_u) o phenotypes, where $n_d + n_u = n$, $n_u = Q(a)n$, $n_d = (1-Q(a))n$ and $Q(a) = ka^p/1+ka^p$.

The quorum sensing molecule concentration a is given by the ODE

$$da/dt=((ap/1 + ap)+\epsilon) n-a,\ p > 1.$$

For $\epsilon \longrightarrow 0$ a QS phenomenon is observed and the QS level a against the population n increases approximately linearly for $n > 1$. The relationship between the dimensionless n and dimensional size of the population N is given by $n = \epsilon$-p-$1/p\ N$, so that N has to be large. For $p > 1$ bistability occurs.

Spatial effects on upregulation are modeled by the reaction-diffusion equation

$$\partial a/\partial t = \partial 2a/\partial x2 + (ap/1+ap + \epsilon)\ n-a.$$

Upregulation is initially localized, spreading via a wavefront. By contrast, for $p = 1$ the population upregulates together.

In the talk by David Chopp (Northwestern University) an overview was given of several modeling efforts including studies on cell-to-cell communication, mechanical stresses due to fluid pressure and shear, and so-called "fuzzy layering" of some multi-species biofilms. The talk is based on the paper of D. Chopp "A Multi-Component, Multi-Species Biofilm Model" with co-authors B. V. Merkey and B. E. Rittmann, where they studied the interaction between species in a more complex biofilm model (compared to earlier studies). One of the most important results presented was that high flow rates prevent quorum sensing for a single colony biofilm. An interesting experiment was also mentioned - the Parsek lab observed that substrate affects surface morphology. When a biofilm was treated with succinate it grew flat, covering the substratum uniformly; however, when it was treated with glucose, it grew into a mushroom shape with a non-uniform coverage. It is suspected that the biofilm bacteria are more motile when treated with succinate. They aim to investigate this further, but this experiment also points to the importance of dealing with motility and reproduc-

tion rates of bacteria modeling-wise.

Day 5

The last day of the workshop began with a talk by Timothy Newman (Arizona State University) on "Using many-body theory to describe statistical correlations in self-organizing populations." In this talk, a stochastic model for chemotaxis was introduced, written in the form of a Langevin equation. In general it is difficult to make much analytical progress, but for small chemical gradients, perturbation methods can be used. It was shown that, in the limit where cells do not influence themselves, the stochastic model corresponds to the Keller- Segel model for the population-level behavior. However, the self-interactions can have an effect on the behavior of the cells, e.g., at first order, chemotaxis reduces the effective diffusion coefficient. The second part of the talk focused on subcellular element models where each cell is composed of interconnected elements: the behavior of each of which obeys a Langevin equation. These models allow, for example, cell shape deformation to be taken into account. Cell growth and division can also be incorporated. One of the advantages of this method is that it is efficient to implement computationally. The technique was illustrated with a couple of examples, including growth of a tumor-like ball of cells, and of an epithelial sheet, both of which showed good qualitative agreement with observations. A further test of the approach was to simulate cell rheology experiments, where it recreated the appropriate visco-elastic behavior, and was found to give semi-quantitative agreement with experimental results.

In the final talk, Jack Dockery (Montana State University) discussed persister cells. It has been known for many years that small fractions of persister cells resist killing in many bacterial colony-antimicrobial confrontations. These persisters are not mutants. Rather it has been hypothesized that they are phenotypic variants. Current models allow cells to switch in and out of the persister phenotype. A different explanation was suggested, namely senescence, for persister formation. Using several mathematical models including age structure, it was shown that senescence provides a natural explanation for persister-related phenomena including the observations that persister fraction depends on growth phase in batch culture and dilution rate in continuous culture.

WORKSHOP 3: MORPHOGENESIS, LIMB GROWTH, GASTRULATION, SOMITOGENESIS, NEURAL TUBE FORMATION (NOVEMBER 17-21, 2008)

Organizers

- **Robert Dillon** (Mathematics, Washington State)
- **Hans Othmer** (Mathematics, U. Minnesota)

Summary of Presentations

Day 1

The meeting commenced with a welcome to the MBI and followed with Ray Keller (University of Virginia) giving an experimentally driven talk on gastrulation in the Xenopus. The central question being how does a collection of cells arranged in a stable spherical organization escape from this state to an elongated form with a polarity that differentiates the eventual head and tail? Ray Keller introduced how a torus formation within the sphere folds in upon itself (at the blastopore), and sets up the ventral-dorsal differentiation, which can be blocked by shining light on the blastopore. The convergence due to cinching can be transferred to a combination of thickening and elongation (depending upon the system). The convergent thickening can be eliminated with the application of MHCIIB dorsally. The hypothesis is that changes in surface tension of the mesoderm drive convergent thickening. After elongation, the induction of polarity is postulated to occur due to gradients of molecular markers, (e.g., TGFß, Xbra, Chordin, C-cadherin) with some increasing and other decreasing along the elongated axis, which will be the anterior-posterior axis. There are pharmacological methods, which can block polarization in the frog. This opening talk provided a large amount of background to the problem of gastrulation.

WORKSHOPS

The following talk was by James A. Glazier (Indiana University) on understanding a complex developmental process and considered a multiscale model for somitogenesis. Growth occurs along the midline structure within the tip of the tail region, and segmentation follows behind. The segmented regions are referred to as somites, and the undifferentiated area in the tail makes up the pre-somatic mesoderm (PSM). An interplay of several processes takes place to set up such a rich, dynamic example of pattern formation. There are somitic clocks that set up a periodic pattern of genes (delta/notch) and there are long range chemical gradients (of FGF) that determine whether segmentation occurs. The system has multiple scales: within the cells are gene networks, cell-cell signaling and mechanical interactions between cells, and on the largest space scale are tissue morphology and chemical gradients. Using the software package Compucell 3d, Glazier modeled the system as cells arranged on a lattice, with cell movement and differentiation taking place following energy constraints. The internal segmentation clock in a single cell (using a model from Goldbeter, Pourquie, and Lewis) found that oscillations arise within the networks of delta/notch, FGF8 and WNT. How the phases vary determines how the cells differentiate. The work of James Glazier expands the individual cell model to include interactions between neighboring cells and also tail-bud growth. The model reproduces the experimental finding of traveling waves up the tail towards the head with segmentation at the anterior. The model interestingly improved going from a two-dimensional to three-dimensional because of the increase in neighbor-neighbor interactions that helps coordinate behavior.

The concluding talk of the morning session was by Lance Davidson (University of Pittsburgh) on reverse engineering the physical mechanics of morphogenesis. Two central questions are: what are the cell's behaviors and what are the forces acting upon them within embryos? Lance further discussed the convergence and extension during gastrulation introduced earlier by Ray Keller. Additionally, he examined which structures, both super-cellular and molecular, are responsible for these mechanics. He found that by manipulating the amount integrin (substrate being used on a glass slide preparation) affects the cell's protusive activity. With a reduction of integrin, cells protusive activity increases seemingly because cells are searching for substrate. With increased integrin, the amount of protusion decreases and becomes more directed. He went on to examine how cells interact with their environment and moreover how cell's themselves affect the extracellular matrix (ECM). Cells produce fibonectin, which is the building material of the ECM. Moreover, the matrix deforms with cell movement, demonstrating that the cell migration does not occur on a static scaffold. This raises the question: what are the roles of actin dynamics and contractions in the coordination of forces for cell arrangement?

After the lunch break, Dr. Christopher Wylie (Cincinnati Children's Hospital Research Foundation) gave a talk on the control of actin assembly during morphogenesis. Using Xenopus blastula as a model system, the Wylie lab studies C-cadherins and their role in controlling cortical actin assembly. C-cadherin expressed on the cell surface controls the amount of actin assembly in the cortex, with

the amount of C-cadherin being controlled by intercellular signaling through at least two G protein-coupled receptors. He showed that by blocking caterin Beta, it disrupts the WNK pathway and ventral/dorsal formation is lost. Depletion of plakoglobin causes depletion of actin and the embryo deforms to be larger round: squat cylinder instead of spherical. As the blastula turns into a gastrula, and then a neurula, new cadherins are expressed in tissue-restricted patterns, and the tissues undergo different types of morphogenetic movement. After the conclusion of Dr. Wylie's talk, the poster session and social took place.

Day 2

The second morning began with David J. Odde (University of Minnesota) giving a talk entitled "Traction dynamics of filopodia on compliant substrates." Filopodia are long, slender, tapering pseudopodia that act as feelers for a neuronal axonal growth cones. The way they traverse through the environment is best explained by the motor-clutch

hypothesis whereby the F-actin bundle protrudes with myosin motors inducing an intracellular retrograde flow. When the clutch engages, it transmits a force to the substrate resulting in a forward motion. Through the use of Monte Carlo simulation on load and fail dynamics on soft substrates, they found that the frequency of load and fail increases with stiffness, retrograde flow rate is slower on soft substrate, and that traction forces are higher on softer substrates. They went on to experimentally confirm the experimental predictions using chick forebrain. During growth cone migration, the Odde laboratory can track the traction force on the substrate at very fine resolutions using fluorescent nanoparticles. Leads to the ability to estimate the traction force for a single filopodium. Their work demonstrated that the motor-clutch system inherently senses and responds to the mechanical stiffness of the local environment.

The next talk by Paul M. Kulesa (Stowers Institute for Medical Research) was on the neural development of the sympathetic ganglia (SG), which regulates the autonomic system (e.g., breathing and blood flow). Defects in its development can lead to birth defects and pediatric cancer. Dr. Kulesa has been working on identifying molecular mechanisms of sympathetic ganglia formation. There is interplay of different molecular families that guide neural crest cells to form the primary and secondary SG. Paul Kulesa and his lab developed a novel sagittal slice explant and with it performed a series of time lapse analysis to show that multiple behaviors and processes occur. By introducing multiple color markers, enhances their ability to track cell migration patterns. By blocking N-cadherin, they found increases in the length and area of SG where as manipulating Eph and ephrin pathways affect the formation of the primary SG. His work suggests that migration of neural crest cells to sympathetic ganglia target involves interplay of multiple molecular cues.

The following talk by Kyle Miller (Michigan State University) dealt with developing biophysical models of axonal elongation. Mitochondria are generally thought of as the energy producers of the cell, but these organelles are not fixed entities. They are trafficked along the axon and dock for a period of time then travel retrogradely back to the body for recycling. The work that Kyle Miller presented made use of fluorescent dies that target the mitochondria and sense the potential that the mitochondria hold in comparison to the cytosol (this potential gradient is utilized to phosporylate ADP to ATP). The docked mitochondria are stationary in the proximal axon but travel at a low velocity in the distal region due to elongation of the axon. He sought to address the key idea that axonal lengthening is driven by stretching instead of mass addition through engorgement. The collected data on *Drosophila* larvae suggested mass addition along the length of the axon and preserves thickness of the axon. The data suggest a complex relationship between axonal length and mass production and that neurons may have an "axonal length sensor." In his analysis he also obtained estimates for mitochondrial half-life in the axon and how it varied from proximal to distal regions.

After the lunch break, the talks continued with

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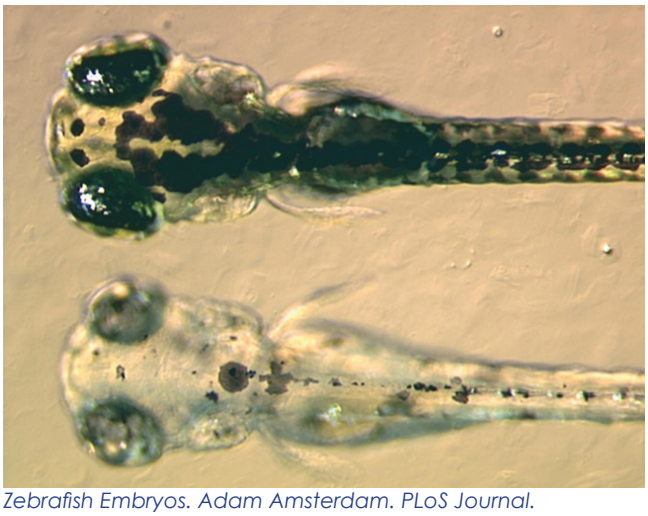
Shegiru Kondo (RIKEN Center for Developmental Biology) discussed stripe pattern generation in the zebrafish. The two dominant pigment cell types in the zebrafish are melanophores and xanthophores, which give the zebra-like skin a black and yellow color, respectively, in a stripe formation. Inspired by the work of Turing considering morphogens, Shegiru Kondo introduced a model for stripe formation due to the reaction and diffusion of the two varieties of pigment cells. It has been found that the xanthophores locally inhibit the melanophores and that there is long-range activation of the xanthophores to the melanophores. This sets up a system that has effective short-range excitation and long range negative feedback, akin to the one developed by Turing. The model can predict stripe formation, moreover the Kondo laboratory performed a series of experiments where they ablated the patterns and then observed the regenerated pattern. By setting initial conditions that mimic an ablation of a stripe pattern, their model then reproduced the experimentally observed regenerated patterns, which differed from the original, unmodified stripe pattern. The cohesion of the experimental results with the reaction-diffusion Turing instability theory suggests that the theory is, in fact, correct.

The penultimate talk of the day by David Parichy (University of Washington) was titled "Towards an integrative approach to studying development and evolution of adult form in danio fishes," where the danio is often referred to as the zebrafish. His laboratory performs gene knockout experiments to develop a variety of mutant strains. The mutational analyses reveal embryonic and metamorphic pigment cell populations. The metamorphic pigment cells were found to be responsible in the generation most pattern diversity, but have been found to be lost in one species. Zebrafish mutants identify candidate genes for pattern diversification, with distinct subpopulations allowing further pattern diversity. His work has showcased that inter-specific differences in pigment cells interactions are a rich source of variation.



Zebrafish Embryos. Adam Amsterdam. PLoS Journal.

The last talk of the day was given by Kevin Painter (Heriot-Watt University, Edinburgh). The title of the talk was "Modeling cell-cell adhesion and its role in morphogenesis." He started with a brief introduction of how adhesion was regulated inside and between cells and the role of adhesion in embryo development. Cell-cell and cell-substrate adhesion is important in maintaining the integrity of tissues and organisms. Cancer cells have abnormal adhesion functioning. Then he moved on with mathematical models on cell adhesion, which can be classified in two categories: discrete models and continuous models. Standard tests for models include aggregation formation and cell sorting due to adhesion of the same type of cells and different adhesion strength of a different type of cells. Discrete models include Cellular Potts model which were introduced by James Glazier the first day, cellular automaton models, deformable ellipsoids, lattice-free models, Voronoi tessellations, and models used in immersed boundary approaches by Robert Dillon (Washington State University). Discrete models can predict aggregation and cell sorting experiments. The second class of models uses PDE with nonlinear diffusion or surface tension, etc. These models could not predict biological experiments of cell sorting. Since different problems have different scales, discrete mod-

els are suitable for small scale problems with fewer cells, but PDE models are nicer computationally for large scale problems, e.g., cancer modeling. The natural question is how one derives the PDEs from the discrete models. It is shown that from position jump process and Cellular Potts model, reaction diffusion equations can be derived but these derived PDEs have finite time blow-up. To overcome the problem, a new phenomenological model with nonlocal sensing was introduced. The new model could prevent blowup and could regenerate the results similar to cell sorting experiments.

Day 3

The first talk was given by Claudio Stern (University College London), entitled "Gastrulation through a primitive streak: cellular mechanics and signals." Gastrulation is an important stage during embryo development, and during this time many cells become committed to their fates according positional information. Unlike sea urchin and *Drosophila*, animals and birds gastrulate through a primitive streak instead of a blastopore. The focus of this talk is the mechanism and signaling of gastrulation governed by primitive streak. One fundamental question is: what are the forces that drive cell movement during gastrulation? It is shown that cell division is not always along the elongation of the streak; therefore cell division is not the main reason. Trajectories of cells were recorded which shows that cells far from the streak move linearly towards the streak while cells on the midline move towards anterior or posterior ends. Movement of triangular elements were also recorded, and it turns out that triangles far from the stream translocate towards the midline, while triangles close to the midline get thinner and longer along the midline; however, the areas of the triangles are conserved. Then he proceeded to show that local cell intercalation is the key driving force for gastrulation and that this is controlled by the PCP pathway, independently from the induction of mesoderm. Inhibition of the Wnt-PCP pathway blocks primitive streak formation but not mesoderm ingression. Rotation of the hypoblast deviates (bends) the axis but does not change cell fates. Removal of the hypoblast generates embryos with multiple primitive streaks. He then presented a computer model of chick epiblast movement which generates the vortex pattern of movement shown in experiments. He also showed that during chick embryo gastrulation a small group of cells act as pioneers and induces ingression of other cells.

After the break, the second talk in the morning was given by Ruth Baker from (University of Oxford). The title was "Comparing deterministic and stochastic models for cell motility and domain growth." Morphorgen gradient has been shown to control cell motility and direct movement. There were both population-level models and individual-level models in the literature. Both types of models have pros and cons. Population models may not be accurate when the cell number is low but convenient to implement. Individual-based models are computationally expensive. The aim of the talk is to compare and find correspondence between models from the two different categories. The first case starts with biased diffusion modeled as chemical reactions between discrete spacial grid points. The master equation turns out to be that for a space jump process. A chemotaxis equation with a signal dependent diffusion rate was derived. Then the talk went on to a generalization that incorporates domain growth. Cell division is modeled by insertion of new daughter nodes and a random split of the number of particles between the daughter nodes. A convection-diffusion equation was derived from the master equation of the stochastic process. Finally for comparison, both models were applied to the example of stripe insertion of fish pigmentation.

The last talk in the morning session was given by Magdalena Stolarska (University of St. Thomas). The title of the talk was "Mathematical modeling of mechanical process in growth and movement." Cell motility is a very important process in gastrulation, angiogenesis, cancer development, and wound healing. The goal of the work is to model fully 3D single cell movement in a realistic matrix. The current work was done with movement of a 3D cell on a flat surface. The model describes the cell as a viscoelastic material which can actively generate force on substrate. The cell was assumed to be incompressible. The deformation gradient was decomposed into an active part and a passive part. The active part incorporates active movement and possible growth. Rather than including all the details of the intracellular signaling, a cartoon model was incorporated to the mechanical model so that the rate of change of active deformation depends on the density of actin, myosin, and their gradients. Numerical results with prespecified cell attachment sites were presented. Traction patterns on surface qualitatively agree with keratocyte movement. The model was then applied to chicken limb growth.

The next talk was given by Eric Dessaud (National Institute for Medical Research, London) titled

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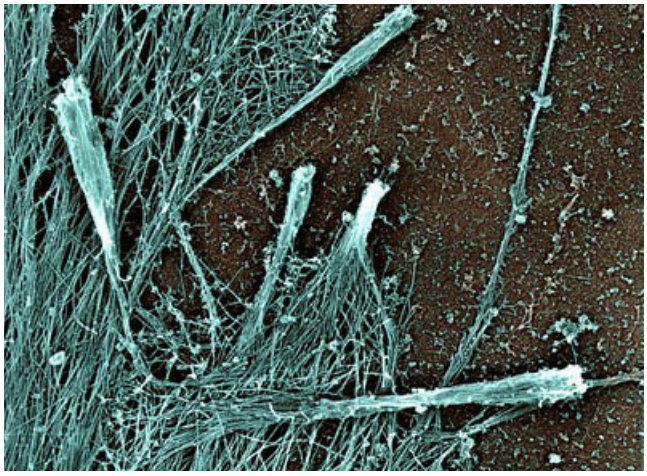


Filopodia. PLoS Biology Featured Image, Vol. 5(11).

"Neural tube patterning by Shh: interpretation of morphogen grating" on collaborative work with James Briscoe (National Institute for Medical Research, London). Different neuronal subtypes are generated from distinct domains of progenitor cells surrounding the lumen of the developing neural tube, with combinatorial expression of transcription factors determining each domain type. The secreted morphogen Sonic hedgehog (Shh) encodes the formation of the ventral regions of the neural tube. Progenitor cells to post-mitotic neurons were stereotyped by the organization of vertebrate neural tube formation where there is a graded Shh activity. The work of the Dessaud and Briscoe demonstrates that Shh controls progenitor cell fates in a concentration dependent manner, as well as depending upon duration. Cells appear to transform the strength of Shh signal into intracellular periods of signal transduction, the duration of which is proportional to the extracellular ligand concentration. The gradual de-sensitization of cells to ongoing Shh signal transduction accounts for cells sensitivity to duration of the Shh signal. So the cells are not merely passive recipients of the Shh gradients, but exhibit dynamic behavior and actively participate in fashioning the appropriate response. The dynamic behavior of the cells, leads to them adapting cell fate. Their data highlight the plasticity of the response to Shh and provide a mechanism to explain the robustness and reproducibility of neural tube patterning.

The last talk of the day was given by Santiago Schnell (University of Michigan). The title was "Investigating two mechanisms of neural crest cell migration." Neural crest cells migrate to form the dorsal root ganglia and sympathetic ganglia. They form follow-the-leader-chain-like arrays during migration, with nucleus of neighboring cells aligned. These structures were also observed in other tissues, e.g., cancer cell migration. The focus here was on understanding how do neural crest cells form and maintain chains during migration. Two hypotheses were tested using agent-based models. The first one is that leader cells form a channel in the extracellular matrix and other cells follow the path of least resistance in a follow the leader fashion, and the second one is that filopodia contacts between cells are responsible for providing a guidance mechanism directing cells to line up. Numerical results show that the second hypothesis is more appealing for the maintenance of the chain-like pattern, however the first hypothesis can not be ruled out.

Day 4

Lee Niswander (University of Colorado Denver) presented a talk on "Genetics and dynamic imaging of neural tube closure." The neural tube formation is the embryonic precursor of the central nervous system. Failure of the neural tube closure is the second common human birth defect. The goal of the research was to find genetic causes of neural tube defects and obtain mechanistic understanding of clinical therapies. Here, mouse was used as the model system. She showed that zippering of the neural folds occurs in the hindbrain region and along the spinal cord. In mid brain and forebrain regions, secondary closure sites are initiated by dynamic interactions between individual cells across the gap. Filapodia were observed to play an important role during the closure event. Then she showed studies on how cell behavior is disrupted in different mutants. As a second part

of the talk, she moved on to branching morphogenesis in lung development. Four stages can be identified during the branching process, namely, bud stage, flattening stage, splitting, and the final branched stage.

After the coffee break, two talks were given. The first one was given by Xin Sun (University of Wisconsin-Madison) who gave a talk on "Signaling interactions in limb and lung development." The first part of the talk was about signaling in limb development. FGFs in an apical ectodermal ridge are important in controlling the limb bud growth. FGFs are sufficient and necessary for limb bud growth, and their expression terminates towards the end of limb bud patterning; therefore, the limb stops growing. The aim here was to understand the regulation factors of the FGFs. She showed that there are interconnected positive and inhibitory loops of Shh, Grem BMP, and Fgfs. The signaling network executes an outgrowth program that, once initiated, can progress and self-terminate. Then she moved on to branching morphogenesis of lung development, where there are similar signaling structures.

The last talk in the morning session was given by James Sharpe (ICREA and EMBL-CRG Systems Biology Program, CRG, Barcelona). The title was "New tools to understand vertebrate limb morphogenesis: Combining 3D computer modeling with quantitative empirical data." The question to understand was how local cellular differences (e.g., spatially inhomogeneous growth) contribute to the limb bud growth with the correct shape. He presented a 3D computational model of mouse limb development using finite element methods. The results showed that heterogenity of cell division caused by a diffusing mitogen from AER could not explain the shape change of the limb bud.

In the afternoon, Robert Dillon (Washington State University) discussed "A cell-based model for vertebrate limb development." He started with a continuum model which describes the growing tissue as an incompressible fluid with a moving boundary, and solved it using an immerse boundary method. Then the model was coupled with reaction-diffusion equations of growth factors and morphogens and applied it to a different biological background, e.g., biofilm growth, swimming motility of sperm, and finally limb bud growth.

Day 5

On the last day David Umulis (Purdue University) gave a talk on "Organism-scale modeling of embryonic patterning in *Drosophila*." BMP is a subfamily of the TGF-beta family which has been shown to be tumor suppressor genes. The role of BMP in development has been studied extensively in *Drosophila* (the fruit fly). The topic of this talk is on modeling the role of BMP pathway in dorsal ventral patterning. A 3-D computational model using a finite element method was developed to analyze the interplay of different processes happening in the dorsal surface together with wet-lab experiments.

The last talk of this workshop was given by Hans Othmer (University of Minnesota). The title was "Patterning in development - the roles of growth and mechanics." The talk summarized the work done in several different biological background, from bacteria, to *Dictystelium*, to *Xenopus*, to animal pigmentation, and finally limb growth. The focus of the talk is to explain how growth, signaling, and mechanics are balanced in different organisms. This talk gave a nice summary of the whole workshop.

WORKSHOP 4: CANCER DEVELOPMENT, ANGIOGENESIS, PROGRESSION, AND INVASION (JANUARY 26-30, 2009)

Organizers

- **Kristin R. Swanson** (Pathology, U. Washington)
- **Alexander Anderson** (Mathematics, U. Dundee)

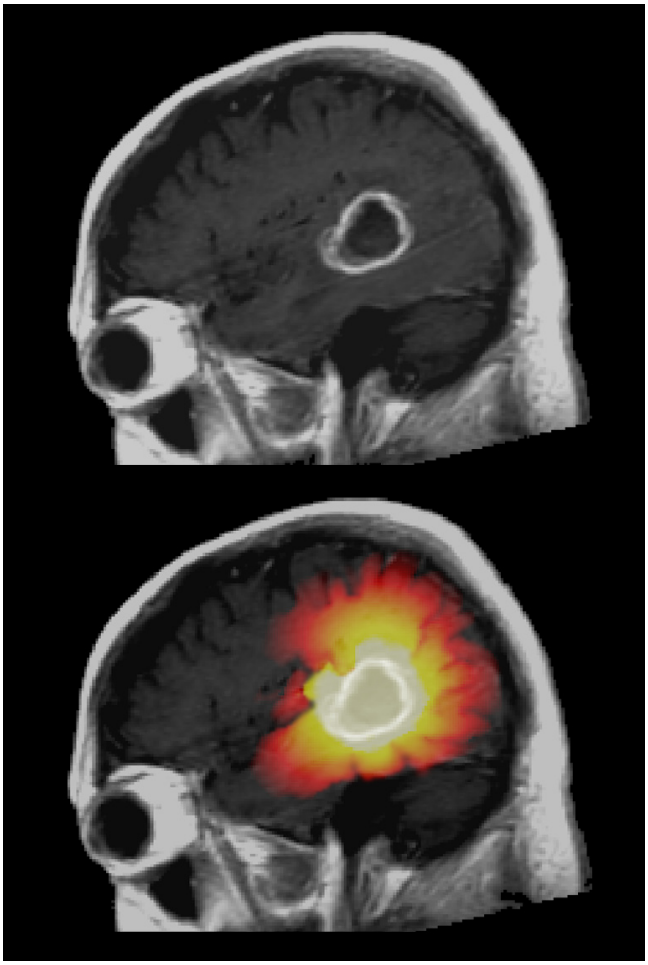
Overall Summary

Cancer and tumor-induced angiogenesis has a natural place in the MBI emphasis year on Developmental Biology as cancer is often thought of as a result of a faulty development process. Experimental and clinical oncology forms a massive literature aimed at understanding and treating cancer. Despite the enormity of the data available, clinical oncologists and tumor biologists proceed without a comprehensive theoretical model to help guide the organization and understanding of such data. To quote a recent Nature article on the topic: Heeding lessons from the physical sciences, one might expect to find oncology aggressively, almost desperately, pursuing quantitative methods to consolidate its vast body of data and integrate the rapidly accumulating new information. In fact, quite the contrary situation exists. Mathematical models are typically denounced as "too simplistic" for complex tumor-related phenomena (ignoring, of course, the fact that similar simplifying assumptions are required in most experimental designs). Articles in cancer journals rarely feature

equations. Clinical oncologists and those who are interested in the mathematical modeling of cancer seldom share the same conference platforms. -- Nature 421, 321 (2003).

Naturally, successful modeling approaches to cancer require scientists who are willing to communicate and interact extensively across disciplinary boundaries. This workshop aimed to do exactly this by having truly interdisciplinary scientists as well as giving a shared platform for both experienced modelers and state-of-the art experimentalists and clinician-scientists discussing their work covering every level of tumor growth.

Each day of the workshop consisted of three primary speakers including an experimentalist who laid out the biological problem, a mathematical modeler who described modeling approaches, and an imaging specialist who described the type of data (typically imaging) available for model validation and development. Additionally, other attendees were invited to present posters at the poster session. An expert panel comprised of leading modelers and experimentalists discussed current problems in the efficient translation of mathematical modeling techniques to the laboratory and the clinic.



Summary of Presentations

Day 1

The workshop began with a welcome by MBI director, Marty Golubitsky, and an overview by Dr. Kristen Swanson.

Dr. Dan Gallahan gave the first talk on the National Cancer Institute (NCI) effort to understand and manage the complexities of cancer: intersecting math and biology. Cancer is a leading cause of death worldwide and the total number of people who contract this disease is increasing. There are many contributing factors to cancer such as genes and genetics, a complex signaling network, multiple cellular processes, microenvironments, host systems environmental factors, and population factors. Beyond the microenvironment, there are other host systems, such as the immune system, that play critical roles and contribute to the overall complexity of the disease. Scale is another way to look at the issue of complexity. The complexity here is dealing with and integrating various components whether they are genetic mutations, signaling networks, or cellular processes. The complex nature of the disease has led to the view among many that cancer is an end result of a systems failure, and therefore a systems biology approach to studying cancer is needed. In an attempt to address this need, the NCI began

the Integrative Cancer Biology Program (ICBP). Mathematical modeling is necessary to get outcome from clinical mutational status through a black box. By quoting "all models are wrong, but some are useful," one could build a model to get useful information on cancer growth. This program is unique in its approach and use of predictive mathematical models of cancer. ICBP has been designed for linkage between systems biology for vast amount data and computational modeling and try to put both parts together. In addition, these mathematical and statistical approaches will be necessary to understand and integrate the vast amount of data being generated. An overview of the ICBP was presented along with other programs and potential funding opportunities of the NIH and the NCI.

The organizers gave an overview of modeling aspect of cancer. Kristen Swanson emphasized that it is important to carefully match the data available and scales of the questions being asked. A continuum model has been introduced to show how a mechanistic model fits the data well. A very simple diffusive model can still give good insight in glioma, a brain tumor that is fundamentally different from other tumors. How to assess clinical-scale data has been discussed in detail and an experimental model of PDGF producing retrovirus glioma cell motility and individual cell tracking was introduced. Proliferation-invasion (PI) model showed a good match with experimental data. Series of MRIs also allow estimation of some parameters, such as random motility constant and growth rate. Heterogeneity of GBMs can be characterized by some parameters and one can deduce that a high net proliferation rate implies increased response to XRT (i.e., effectiveness of radiotherapy). They also found that hypoxic burden increases with tumor aggressiveness and a grade map can be represented using random motility and growth rate. Overall, a mathematical model can say something very useful in terms of predicting the invasion behavior of gliomas.

In the afternoon, Alexander Anderson started the session by presenting a minimal modeling approach and misconceptions. Cancer is multiscale and modeling of cancer at a cellular level could be a good start to bridge lower level to higher level. After a brief introduction of cancer cells, general phases of solid tumor growth were represented: early avascular phase, angiogenesis and vascularization, and invasion and metastasis. In addition to a previous introduction of density continuum models, different kinds of cell-based models (hybrid, forcebased lattice-free, Potts, immbersed boundary methods) were introduced. An evolutionary hybrid CA model (EHCA) was introduced to explore spatial distribution of proliferating dead quiescent glycolytic cells and the evolution of phenotype and/or genotype over time. A different behavior of genotype/phenotype with a given oxygen rich and starved environment could suggest an important indicator for whole tumor growth dynamics. Immersed boundary methods can capture subcellular, cellular, and environmental factors, and has been applied to predict different patterns in mammary acini. A hybrid prostate model and Potts model were also introduced. In conclusion, a tumor microenvironment is critical for driving progression toward aggressive tumor cell phenotypes. Several future works were suggested, including a prediction of a model in an organ specific environment. The usefulness of this model was discussed in detail among the audience and the speaker.

Robert Gatenby gave a talk titled "Does cancer use 'spite' as an evolutionary strategy? Warburg revisited." Carcinogenesis as in vivo evolution is intuitively appealing and consistent with many empirical observations; however there are open questions. Properties of tumor cells are always the results of specific selection. It is generally accepted that carcinogenesis is formally analogous to Darwinian evolution as environmental selection forces act on new phenotypes that are continuously generated through accumulating genetic mutations and epigenetic changes. Those intracellular phenotypes that yield a proliferative advantage are rewarded by clonal expansion and persistence in the population. This process yields progressive fitter populations until a fitness maximum is reached and an invasive cancer emerges. Since the pioneering studies of Warburg, it has been consistently demonstrated that invasive cancers maintain a high rate of anaerobic glu-

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cose metabolism even in the presence of oxygen. Widespread application clinical of FDG-PET imaging has demonstrated the vast majority (perhaps all) clinical primary and metastatic cancers exhibit significantly increased glucose flux as a result of glycolytic metabolism. They investigated development of aerobic glycolysis using quantitative methods from evolutionary game theory. Even though cells are the players, environments set the rule of carcinogenesis. Darwinian dynamics (2DDEs) can predict that eventually tumor population growth is limited by substrate availability and lead to review of the environmental context of somatic evolution with new focus on the anatomy and physiology of epithelial surfaces. This led to a general cell-based model based on micro-environmental selection forces. Simulation showed two possible subsequent evolution paths because the cells are constrained by two selection forces (hypoxia and acidosis). Models predict additional benefit using drugs to reduce H+ production. This suggests that cancer cells use an evolutionary strategy previously described as "spite." That is, they reduce their own fitness through aerobic glycolysis, but by doing so reduce the fitness of their competitors even more.

Day 2

The theme of day two is genetics and molecular biology. Due to some unexpected changes, the second talk in the morning, MicroRNA by Carlo Croce, was canceled and replaced by two talks given by Drs. Simon Hayward and Georg Luebeck in the afternoon. Dr. Forrest White's talk, which was originally scheduled to be in the afternoon session, was moved to the morning.

Dr. Gustavo Ayala gave a talk entitled "From Biomarkers to Modeling." At first, he emphasized the importance of studying biomarkers by pointing out that the number of publications related to biomarkers in Pubmed is huge (431,452), though only a few are clinically used, such as ER, PR, Her2, Proliferation rate, and C-kit. He then introduced the five phases of biomarker development for early detection and discussed some research conducted in his lab: prostatic adenocarcinoma, gene profiling using tissue microarray, and the convenience cohorts versus longitudinal cohorts. In the last part of this talk he discussed some new research projects about the relations between nerve cells and cancer cells. He also showed the effect of nerves on three-dimensional caners.

Dr. Forrest White's presentation was entitled "Biological insights from quantitative analysis of signaling networks." He started his talk with the question: How does signaling regulate cellular response? He gave an answer using circuits as an analogy. His talk covers the following parts: 1) collect both phosphorylation data and phenotypic data and then do integrative data analysis (i.e., data-driven correlative analysis and quantitative mechanistic models) to study certain biological hypothesis, then come up with combinatorial inhibition strategies; 2) conduct quantitative signaling network analysis by mass spectrometry; 3) study ErbB receptor family signaling; that is, first, quantify the effect of HER2 expression and EGFR signaling, second, study the effect of HER2 over expression on EGFR signaling network and cell migration pathway, and third, compare Heregulin versus EGF simulation in Her2-expression cells; and 4) study EGFR receptor signaling pathway in the context of Glioblastoma.

In the afternoon, Simon W. Hayward (Vanderbilt University Medical Center) gave a talk entitled "Cellular interactions and prostate cancer progression." He mainly addressed the following two questions: 1) how does the stroma environment promote or facilitate tumor progression; and 2) can interactions between stroma cells inform and influence interactions with adjacent epithelial cells. With some specific examples and data, he explained that: 1) TGF-beta signaling elicits EMTs at the invading front of BPH1caftd1 tumors; and 2) stroma-epithelia interactions can be considered as a simple two-way combination.

The second afternoon talk was given by Georg Luebeck (Fred Hutchison Cancer Research Center). His talk title was "Temporal and spatial scales of premalignant clones." This talk mainly covers the research published in PNAS (September and October 2008). That is, 1) preneoplastic lesion growth driven by the death of adjacent normal stem cells, and 2) the age-specific incidence of cancer: phases transitions and biological implications. Using some mathematical and computational models, he addressed the questions related to these two topics. The main conclusions were that: 1) age-specific incidence exhibits four basic phases, and only two of which can be observed; 2) age-specific incidence is essentially linear (not log-log linear); 3) premalignant lesions may sojourn in tissue for decades; and 4) growth of premalignant lesions critically depends on tissue architecture and environment.

Day 3

The talks at MBI were cancelled due to a snow emergency. However, the participants arranged to hold the talks at the Holiday Inn. They were:

"Adaptation-driven Models of Cancer Invasion: Experimental Parameterization and Validation" by Vito Quaranta (Vanderbilt Integrative Cancer Biology Center)

"Modeling Tumor Cell Invasion" by Muhammed Zaman (The University of Texas at Austin)

"Imaging the Hallmarks of Cancer in the Tumor Microenvironment" by David Morse (H. Lee Moffitt Cancer Center & Research Institute)

"Industry perspectives on Mathematical Modeling of Cancer Therapeutics" by Dean Bottino (Novartis Pharmaceuticals Corporation) and Frank Tobin (Tobin Consulting LLC)

Day 4

The first talk was by A. S. Popel on "System Biology of Angiogenesis: From Molecules to Therapy." Angiogenesis starts mostly under hypoxia via VEGF activation by HIF1-Œ± (hypoxia-inducible factor-1Œ± protein). Major steps in angiogenesis are - migration of tip cells and proliferation of stalk cells. The ultimate goal of system biology is to bridge different scales (molecules, cells, tissues, organs, the whole body). VEGF was only discovered in 1989. Its effects on cells in vitro include - proliferation, chemotaxis, migration, survival; its effects on tissues in vivo include - angiogenic sprouting, neuronal and vascular guidance, inflammation, wound healing, vascular permeability, hematopoitic cell specification. Interestingly, even mechanical factors like shear stress, stretching, ultrasound can make EC secrete VEGF. A mathematical model of VEGF secretion in skeleton muscle was introduced (simulating moderate exercise under different PO2 levels). The model simulations suggest that there are sufficient VEGF gradients that can drive capillary sprouting. Up to date, there are about 10,000 publications on VEGF. Neuropilin is a protein receptor active in neurons. Blocking NRP blocks VEGFR-2 (major pro-angiogenic). However, the therapeutic response depends on tumor - for example, blocking VEGF-NRP binding is less effective than blocking VEGF-NRP coupling. Hence, understanding the complexity of microenvironments is important for human therapeutics.

A larger scale compartmental model of VEGF transport was also discussed (included tissue and blood compartment). Anti-VEGF therapies were simulated by introducing the anti-VEGF agent to plasma. A recent paper by Karaglannls and Popel (PNAS, 2008) deals with bioinformatics identification of novel anti-angiogenic peptides. They identified >120 endogenous peptide inhibitors of EC

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proliferation and migration. Interestingly, some of the peptides are derived from proteins known to be pro-angiogenic (CXC chemokines). A system biology approach raises some important questions like the error validation of multiscale models (how to validate in vitro against experimental data) and bridging the data (human and mice data are not the same).

The second talk was by L. L. Munn on "Multi-scale tumor physiology and blood vessel dynamics." Recent cancer therapies have targeted tumor blood vessels with inconsistent results. Some treatments show promise while others fail, underscoring a frustrating lack of understanding of the mechanisms that control blood vessel formation, destruction and function. A major difficulty lies in the fact that the mechanisms of vessel formation and remodeling operate at multiple scales, each with its own set of controls, and each critical to the overall function of the blood vessel network. Most importantly, "rare" events occurring at the single cell level can dominate overall vessel network function, and therefore, tumor growth. Analytical approaches--both experimental and computational - that span the size scale from single cells to the bulk tumor should incorporate the relevant parameters critical for understanding tumor growth. Experimentally, intravital microscopy allows determination of single-vessel hematocrit, blood velocity, permeability as well as vessel and network morphology over time. Mathematical models of blood-flow, vessel growth and remodeling, and tumor growth and invasion span the size scale from cells to tissue and elucidate the cellular events that influence tissue-scale physiology. These tools will provide a framework for studying the effects of anti-tumor therapies and improving their efficacy.

Day 5

Jason Rockhill gave a talk on "Current Challenges in Radiation Oncology." This was followed by Dr. Carl Panetta (St. Jude Children's Research Hospital) who spoke on An Introduction to Pharmacokinetic and Pharmacodynamic Modeling. The talk provided an introduction to the process of PK/PD modeling using examples from pediatric oncology. Pharmacokinetics (PK) is the study of the disposition of drugs (absorption, distribution, metabolism, and elimination) in the body and pharmacodynamics (PD) is the study of the effects of the drugs on the body. Over the last several decades PK/PD modeling has evolved into a complete mathematical / statistical subfield in pharmaceutical research and is now involved in all aspects of drug development from in vitro to clinical studies. There are several reasons why PK/PD models are developed. First, they are used to describe data such as plasma concentrations of a drug and/or its metabolite (PK) or the effect of the drug on a target such as a cell or receptor (PD). This descriptive information can be used to determine if effective concentrations are being obtained to cause the desired effect without causing excessive toxicity. In addition, PK/PD models are used to predict drug concentrations and/or effects. For example, the drug disposition for a multiple dosing regimen can be predicted given the data from just one dose. The PK/PD modeling process first involves model building, which is as much of an art as a science. This is followed by model parameter estimation using methods such as weighted least squares, maximum likelihood estimation, or maximum a posteriori probability estimation (Bayesian estimation).

WORKSHOP 5: WOUND HEALING (MARCH 9-13, 2009)

Organizers

- **Philip Maini** (Center for Mathematical Biology, U. Oxford)
- **Chandan Sen** (OSU Medical Center)

Overall Summary

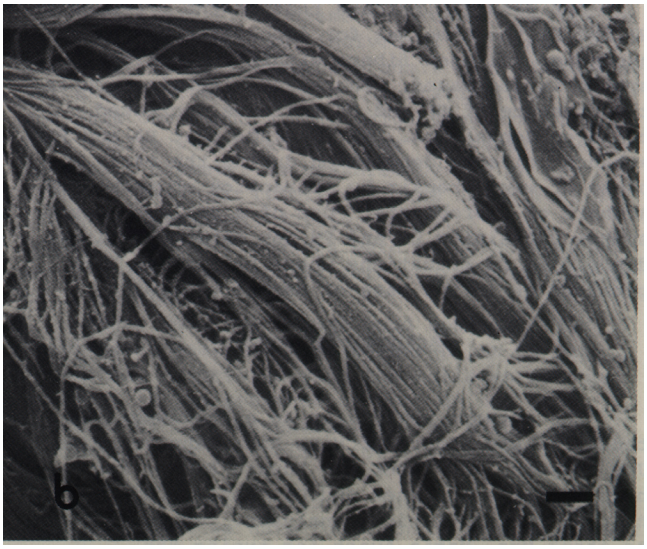
The major aim of this workshop was to combine the strength of experimentalists, theoreticians, and clinicians with the goal of initiating multi-disciplinary approaches to address key questions in normal and abnormal wound healing. Wound healing involves processes on very different spatial scales, and therefore presents challenges in developing modeling frameworks that take into account these disparate time and space scales. Abnormal healing of wounds in, for example, elderly patients or patients with diabetes has spurred research in the fundamental processes at work in wound healing.

Each of the first three days of the workshop focused on a different spatial scale involved in wound healing. The fourth day was aimed at deriving a more comprehensive model that spans these spatial scales. The last day of the workshop presented a number of future challenges for the field in the context of clinical case studies setting the stage for new collaborative efforts between participants.

Summary of Presentations

Day 1

Chandan Sen (The Ohio State University Medical Center) opened up the conference by presenting introductory remarks addressing the scope and purpose of the workshop. Robert Diegelmann (Virginia Commonwealth University Medical Center) started the first day's talks by giving an overview of the biology of wound healing in a generally digestable format. He highlighted that the healthy human body does a remarkable job of healing itself, especially in the young. He discussed mechanisms of healing with respect to different types of wounds. The first cells involved in the acute healing response include red blood cells, epithelial cells, and platelets. Fibrin clots help provide the framework onto which collagen is laid to strengthen the clot. The inflammatory phase includes the attraction of neutrophils to the wound site to clean up tissue debris and bacteria. To do this, the neutrophils must exit the blood flow and squeeze through the vascular endothelial layer



into tissue. He explained how sometimes this response can get out of control, where too many neutrophils have infiltrated the site. Macrophages are a critical part of the healing process that follows the work of neutrophils and helps the healing process to continue. Mast cells also play a role in this process and are responsible for the cardinal outward manifestations of inflammation: rubor, tumor, calor, and dolor. He presented data related to collagen deposition that might be proved useful to modelers. One set showed that during the regeneration of wounds the rate of collagen turnover is much higher than in normal skin. In normal wound healing, there are four distinct phases of healing: hemostasis, inflammation, proliferation, and remodeling. There are many local factors that modulate the healing response that need to be considered such as blood supply, denervation, hematoma, infection (which will markedly delay healing), irradiation, mechanical stress, dressing materials, and other local factors. Moist wound healing is an important factor and can promote healing. Age, anemia, anti-inflammatory drugs, cytotoxic and anti-metabolic drugs, diabetes mellitus, hormones, systemic infection, jaundice, malignant disease, malnutrition, obesity, temperature, trauma, uremia, vitamins A, C, and D, and trace metals are some of the general factors that can affect the process. Wound healing cannot happen properly when there is a disruption in the balance between degradation and synthesis. Too much synthesis (of collagen for instance) can result in excessive scarring and even contribute to keloids on the skin, even from the most minor injuries. Excessive contraction that pulls tissues together is another example of a complication that can arise when collagen synthesis is out of control. When degradation is out of balance wound healing is

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poor, as in diabetic ulcers that can lead to amputation or chronic pressure ulcers. He discussed some of the advances in addressing these problems by modulating various factors in the wound healing process. Many of the same signaling mechanisms are found also in embryonic development and cancer, implying that the various experimental models used in these areas could help in the wound healing area. He concluded with an overview of new strategies being used to modulate the wound healing response. Doxycycline (an antibiotic) inhibits a certain enzyme that causes the problems in pressure ulcers and enables abnormal wound healing to be corrected. Oxycytes are small molecules that are loaded with oxygen and help deliver massive amounts of oxygen to deprived sites. Oxygen producing bandages are another strategy being used to modulate the healing process. Androstenediol (AED) reverses some of the ill effects of anti-inflammatories, such as cortisol and steroids, so that necessary inflammation is restored to help healing progress. Lastly, the use of integrated systems biology analysis of critical illness and injury is used to determine how to better help the healing process in humans, a necessary approach due to the fact that there is a huge network of related interacting pieces of this very complex process.

The next talk was given by Luisa DiPietro (Center for Wound Healing & Tissue Regeneration, UIC College of Dentistry) who addressed the role of inflammation in the healing wound. Increased blood flow, increased vascular permeability, and cellular activation and infiltration are the major processes of the inflammatory response, which are modulated by many soluble molecules and factors released or produced at the site. Key players in inflammation include: platelets (circulating), mast cells, neutrophils (circulating), macrophages, lymphocytes (circulating), and epithelial cells. After platelets and mast cells infiltrate the wound area, neutrophils are the first major responders at the site of the wound, followed by an influx of macrophages, and then T lymphocytes. Neutrophils clear microbes as their primary function, while macrophages help to ingest dying neutrophils, cleaning up debris from the "battle field". The function of T lymphocytes is still poorly understood. She discussed methods by which experimentation can determine the functional significance of the inflammatory cells in wound healing and the acquired data on their behavior. Mast cells play a role in scar formation, but may be dispensable for wound closure. Neutrophils are important in clearing microbes and in reducing re-infection, but also produce a number of toxic mediators (i.e., excessive free radicals) that cause some tissue damage which may inhibit wound closure. Neutrophil depletion in some cases results in better healing in a diabetic setting. The macrophage, of which there are several phenotypes, can be an inflammatory mediator or a reparative cell involved in tissue repair. Disruption in the signaling cascade that promotes the infiltration of neutrophils to the wound site can also be a serious inhibitor of healing. There are more than 50 highly complex inflammatory mediators at the wound site. These are measurable entities: the levels of which change during the healing process. She then discussed the modulation of the cytokine cascades through the receptors on the surface of cells, which initiate various pathways inside the cells (i.e., Jak-Stat pathway). In addition, there are activators and inhibitors that also control the bind-

ing of a cytokine to a receptor. She brought out the fact that experimentally teasing out the role of specific mediators in wound healing is typically accomplished in one of three ways: studies with genetically modified mice lacking a specific pathway, utilizing blocking antibodies or other specific inhibitors to paralyze a specific component of a given pathway, or temporary attenuation of the function of a pathway using knock-down strategies. She pointed out caveats such as the issue of how informative is depletion of a single mediator for elucidating mechanisms on a systems level since the depletion of one inflammatory cytokine, for instance, influences the production of others. She described certain special circumstances in which inflammation is not necessary in wound healing, as in fetal wound healing, where no scarring or any distinguishing features are present after healing has taken place. In fetal wound healing, there is no inflammatory phase, but only proliferative and rapid remodeling phases. In addition, some mucosal (vs. cutaneous) wounds have better healing due to a difference in the presence of inflammatory cells, with fewer neutrophils present in mucosal wounds and a reduced inflammatory phase. However, there are other special circumstances in which the inflammatory response even when disrupted a little, can result in impaired healing. Thus, optimal inflammation is required for healing while excessive inflammation hurts the healing response. Dysregulated inflammatory response is noted in conditions such as diabetes.

The third talk was given by John King (University of Nottingham) who spoke about various mathematical models related to tissue growth with a particular focus on "hole-closure." He started off describing a reaction-diffusion partial differential equations (PDE) model which tracks the wave front (Ia wave of healing, per se) with respect to a hole (wound) closing. The PDE describes the boundary moving along the direction of its normal at a constant rate for the purpose of covering the domain of rupture. He addressed the two-dimensional case for this class of models with respect to how various wound shapes close. He then moved on to the more realistic three-dimensional case, which has more degrees of freedom than the two-dimensional case. There are both bistable (two stable states: unhealed and healed wound states are stable) and monostable (wounded state is unstable, healed state stable) problems. The next "simplest" model deals with continuum mechanics and he explained some of the conservation laws that are used. He discussed the mathematical difficulty of assuming non-circular domains (realistic wound shapes) and showed some simulations of a very simple model of tissue growing coherently as a whole, closing the opening. Extensions can be made to this model, but the outcome is similar. The next was a description of a two-phase model, which takes into account cell creation, something that was left out in the continuum mechanics. A three-phase model includes cells, water, and a scaffold. He ended his talk by briefly discussing a new class of models known as "distilled PDE Problems" which leads to new mathematical formulations.

The next part of the program consisted of short talks by various participants. Richard Shugart (Western Kentucky University) presented a mathematical model describing wound healing in a hyperbaric oxygen chamber. He showed the importance of understanding the length and amount of oxygen exposure of the wound. Jianzhong Su (University of Texas at Arlington) talked about foreign body reaction processes during implantation. He focused on collagen formation due to the process by which fibroblasts dissolve the fibrin clot, replacing it with collagen. He presented a mathematical model that described the experimental data on collagen. Nicanor Moldovan (The Ohio State University) discussed a model of epithelial cells of the skin, and showed experimental data illustrating the reorganization of the extracellular matrix in healing wounds. The orientation of the blood vessels is restricted by the collagen fibers. Newly generated blood vessels are oriented not only by the wound but also by mechanical forces which play a significant role. He also discussed an agent-based model of inflammation and wound healing. Peter Sheehan (Mount Sinai School of Medicine) explained the problems associated with and issues involved in wound healing arising from diabetes (Type 2) and obesity. He described the

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differences between acute and chronic wounds. For chronic wounds, excessive inflammation plays a large role as well as neuropathy and this is especially true of foot ulcers. In fact, neuropathy is common in foot ulcers caused by non-diabetic conditions such as leprosy, implying that blood sugar levels and other characteristics specific to diabetics may not necessarily play a role in the improper healing of wounds.

Paul Liu (Roger Williams Medical Center) discussed the importance of blood supply at the wound site. He described "flap gene therapy" which is used to modify the supply of blood to a specific wound site. He lamented that the current paradigm of wound healing research is quite confusing and by and large, clinically irrelevant and suggested a "P4 Medicine" approach: personalized, predictive, preventive, and participatory. He noted the many systems biology centers that are focused on bringing this to reality because the complexity is so great and reductionist experimentation cannot accomplish everything. Because of the failure of the current paradigm, the importance of embracing systems biology approaches for wound healing problems is a crucial direction to take.

Raj Mani (Southampton University Hospitals Trust) discussed compression or suction methods in facilitating wound healing. He described the seriousness of venous ulcers and the current treatment available. Compression treatment and wound dressings, for instance, work; however, it is difficult to know exactly why or how they work. In addition, vacuum assisted drainage or suction also helps heal wounds. Thus, these two opposing physical effects aid healing but are difficult to understand. Modeling then becomes an important tool, especially since various clinical situations are not completely understood. However, he noted that although venous ulcers are well understood clinically, they are very difficult to model.

Day 2

To begin the second day, Sanjay Kumar, M.D.

Ph.D. (University of California, Berkeley) discussed cell-matrix mechanobiology. He described how the ability of a living cell to control its three-dimensional structure is critical to normal tissue physiology. An individual cell derives this morphological control from its cytoskeleton, the three-dimensional network of biopolymers whose collective dynamics and mechanics define cell shape and enable cells to sense, process, and respond to a variety of physical cues in the environment, including mechanical force and the geometry and stiffness of the extracellular matrix (ECM). Several experimental approaches were described to understand how cytoskeletal polymers contribute to cellular mechanics and biophysical crosstalk with the ECM, including the use of various micro/nanoscale technologies to probe the biophysical properties of contractile and adhesive structures within living cells. Finally, he discussed the determination of the role of cell-ECM mechanobiology in influencing the growth and invasion of tumors of the nervous system, and cell-ECM mechanobiology to engineer cell fate and assembly in bottom-up tissue engineering systems.

In the second talk John Ward (Loughborough University) introduced a free boundary mathematical model of normal and chronic wound development. The model was tractable to mathematical

analysis. It addressed, amongst other things, the role of bacteria and use of Maggot Debridement Therapy (MDT). In mathematical terms, the model is a reaction-diffusion system. Steady state analysis of the reduced ordinary differential equation (ODE) system was discussed and numerical solutions to the complete system were presented. A second and extended model of the proliferative phase was also introduced. This new model accounted for fibroblast activity, immune cell activity, angiogenesis, nutrients, and their effects. Numerical computations of the model were presented. Solution profiles for both normal healing and wound closure failure were discussed. It was predicted that application of growth factors can significantly boost healing and successful healing is sensitive to nutrient availability. The model predicts qualitatively what might be expected during the normal healing. Effects of bacterial infection and qualitative analysis of the model, such as traveling wave solutions and bifurcation analysis, are planned for future studies.

In the next presentation John Dallon (Brigham Young University) discussed collagen lattices. He described how Bell's introduction of the fibroblast populated collagen lattice (FPCL) has facilitated the study of collagen-cell interactions. In the first part of the talk, John presented the historical background and biological basis of the phenomena and in the second part a mathematical model was introduced and some preliminary results presented. The differences between fibroblasts and myofibroblasts were emphasized, together with their roles in wound healing and other pathologies. He discussed the three proposed mechanisms responsible for FPCL contraction, namely cell contraction, cell tractional forces related to cell locomotion, and initial cell elongation and spreading. The cells and collagen matrix are modeled using discrete elastic subunits. He used stochastic simulations to account for, amongst other things, biological differences between fibroblasts and myofibroblasts and between moving and stationary cells.

The final talk of the day was given by Pierre Coulombe (Johns Hopkins University School of Medicine) on intermediate filaments. Pierre gave a brief introduction to intermediate filaments and their molecular structure. He then addressed the structural support function of keratin filaments and other non-mechanical functions like the regulation of cell translation and cell growth. The keratin gene family was introduced at the beginning of the talk. They are mutated in genetic diseases but also dysregulated in several other pathologies without mutation. They polymerize and provide structural support in the form of intermediate filaments. They play a role in microfilament and microtubule interactions. In human epidermis it is shown that various types of keratin family genes have a non-homogeneous spatial expression. Experimental evidence indicates that these filaments provide structural support. Mutations in this gene family impact cellular network properties such as elasticity, thereby affecting mechanical stress. Particle tracking micro-rheology is used to ascertain the elasticity of live keratinocytes. Experiments show that keratin intermediate filaments are cross-linked. Other than mechanical support, cytoplasmic intermediate filaments are shown to play a role in many other processes, including apoptosis. He also addressed the paradox of keratin gene modulation soon after acute skin injury. Some conflicting results were presented, such as unchanged elastic properties between wild type and mutant cells, measured by laser tracking micro-rheology (LTM) methods. The role of binding proteins in regulation of the keratin family of genes was also addressed through experimental evidence and qualitative models. Finally, the role of intermediate filaments (IFs) in tissue repair, their redundancy, EBS and sulfuraphane (SF) as a therapeutic option for epidermolysis bullosa simplex (EBS), and SF treatments were discussed.

Day 3

The third day of the workshop began with a talk by Periannan Kuppusamy (The Ohio State University Medical Center) in which he discussed imaging methods for determining tissue oxygen tension. At the beginning of the talk Dr. Kuppusamy introduced the technology used for imaging tissue oxygen. He then discussed the effect of hyperbolic oxygenation on myocardial pO2 infract and non-infract cases. The results indicate that oxygenation, together with stem cell treatment, increases healing significantly, although oxygenation alone does not. The results also indicate that the oxygen level and wound healing are correlated. A recent study shows that oxygen tension in tumors reduces after the treatment. He then presented a novel oxygen-sensing device developed for clinical use in humans, called OxyChip. He is currently studying biodegradable/bioobservable oxygen sensing polymers for clinical oximetry with the goal of improving OxyChip technology. The advantage of this new study is that it will replace the crystal particles with molecules which can be degraded within the body.

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The second talk of the morning was given by Ronald Xu (Biomedical Engineering Department, The Ohio State University) who presented research on imaging techniques for wound assessment. He first introduced the clinical significance of wound healing as the motivation of his research. He showed that accurate characterization of structural, functional, and molecular changes at each phase of the wound healing process will help to quantitatively guide the therapeutic process and objectively assess the clinical outcome. He then presented the quantitative technique MEASURE, which he developed. This portable multimodal imaging system is for quantitative imaging of wounds, wound assessment, and to measure clinical parameters for chronic wound treatment. Many existing techniques and clinical procedures for wound assessment are classified as qualitative and subjective. The imaging system can be used for multiple clinical applications such as wound margin detection, hypoxia imaging, infection detection, perfusion assessment, and therapeutic guidance. He discussed current techniques for wound assessment together with their limitations such as structural imaging, functional imaging, and biochemical and chemicophysical changes. He also introduced light tissue interaction (absorption, scattering, etc). Using the idea of oxygen absorption, he described the techniques for multispectral and hyperspectral imaging of biological tissues and their limitations. The correlation between oxygen saturation and tension were discussed as well. The technology developed for an extension of hyperspectral methods (Ohio State Comprehensive Wound Center dual model wound imaging system) was introduced along with results on human subjects. He described the optical coherence tomography (OCT) technique which is based on light scattering, the types of this technique, and advantages and limitations. Finally, he discussed multimodal imaging techniques, including contrast agents, sensitivity, clinical efficiency, and safety. The model was proposed as integration between structural and functional imaging, and also between different imaging platforms. The speaker has also developed a biodegradable and biocompatible carrier for targeted delivery of multiple contrast enhancement agents and drugs. Some preliminary results and potential clinical applications were discussed.

The first speaker after lunch was Leonard Sander (University of Michigan) who takes a modeling approach to understanding wound healing. At the beginning of the talk he introduced discrete and continuum treatments of growing systems. The main purpose of the talk was to make a comparison between agent-based models and PDE models. In agent-based models cells are considered to be particles, and dynamics are replaced by Markov processes where the randomness plays a role. The advantages of agent-based models are the fact that they are more biological, easy to implement numerically, and able to provide quantitative information. One of the disadvantages is that they are slow for large concentrations. Based on an example of population fronts with and without cell-cell adhesion, the agent-based model was compared to a PDE approach. He introduced the analogy between the discrete model and Fisher-Kolmogorov (KPP) equation for low densities. He briefly mentioned the mathematical analysis of the KPP equation and its disadvantages, for ex-

ample, the formulation is not applicable to small densities, which is precisely the case at the wound front. He presented a discrete model with cell-cell adhesion and showed simulation results. Another continuum formulation to address the cell-cell adhesion component was formulated by the Cahn-Hilliard (CH) equation. To add the proliferation dynamics, the CH equation was modified to a generalized version (GCH).

In the second part of the talk, he introduced collagen mechanics within an agent-based discrete model where the fibers are modeled as beams. The model is then compared to elastic theory. He concluded that elastic theory does not work as the collagen network shows non-affine behavior. As a result of the analysis of these two examples, he mentioned that the discrete models can deal with smaller length scales better than continuum models.

The final talk of the day was given by Min Zhao (University of California, Davis) who discussed electric fields in wound healing. The main aim of Dr. Zhao's research is to achieve better wound healing and regeneration. Experimental data show a directional component to the growth of epithelial cells during wound healing, as well as the position of nerve fibers and blood vessels. The reasons of directional motion are listed to be chemotaxis, stress, population pressure, mechanical stimulation, among others. Recent experiments provide compelling evidence that the wound electric signal plays a predominant role in wound healing as a directional cue. Electric fields of the strength that can be measured in vivo override many well-accepted directional cues (such as contact inhibition release, population pressure and chemical gradients) and guide the migration of epithelial cells in wound healing. The theoretical molecular basis of the electrical potential is explained as Na+, K+ and Cl- dynamics across the skin. Experimental justification is provided for the hypothesis that electric field polarity determines whether wounds close or open and can override all other directional cues. A similar response is justified in the case of stratified epithelial wound healing. Later Dr. Zhao addressed the question of how the cells sense and relay the electrical signals into cellular responses. Some experiments show that some cells lose all chemotactic response but continue to respond to applied electric fields. To find the molecular basis of the phenomenon, the PI3K signaling pathway was examined. It was shown that PI3K null cells have impaired response to an electric signal. Continuous medium perfusion and genetic decoupling experiments also argue that the electric field-directed cell migration is not exclusively mediated by chemotaxis. It is concluded that PI3 kinase/Akt and Pten are essential molecules in the response and are activated asymmetrically by the electric field. The endogenous DC electric field thus may represent a fundamental signaling mechanism to give cells and tissues a direction to heal and to regenerate in wound healing. He presented some further examples of the relationship between electric fields and directed motility including angiogenesis, neuron migration and stem cell motion.

Day 4

The fourth day began with a talk by Sarah Waters (Oxford Centre for Industrial and Applied Mathematics, Mathematical Institute) on mathematical models of various tissue engineering processes. One of the main goals of tissue engineering is to be able to grow biological tissues and organs in a laboratory that can then be used to replace damaged tissue in a patient or to test new drugs. After presenting some background on different experimental approaches and challenges involved with growing tissue, Sarah presented three mathematical models of various processes involved in tissue engineering: stem cell proliferation in the gut, fluid flow and nutrient transport in a rotating bioreactor, and a model of a perfusion bioreactor. In the first case she looked at mechanical stresses that affect the proliferation and differentiation of stem cells. She presented a cell kinetic model and a tissue mechanic model and she indicated that future work will involve combining these two approaches. For the second case, she described a rotation bioreactor which is a common experimental set-up for growing bioengineering tissue. The rotation keeps the nutrients in motion and more accurately mimics the in vivo scenario. This case study involved simulating the fluid flow using the Navier-Stokes equations and taking into account nutrient transport. Finally, the last case study she presented was of a perfusion bioreactor. This is a more complicated set-up to grow tissue and the model was a multiphase model that accounted for cell-cell and cell-scaffold interactions. Each of her models produced results that agreed well with experimental observations and offered suggestions for improving experimental designs or providing insight into the physical mechanisms at work.

The second talk was given by Marc Basson MD, PhD (Michigan State University College of Human Medicine) on intestinal epithelial wound healing. Marc described how mucosal injury happens all

the time, even in healthy patients, as food moving through the intestines "injures" cells. However, in some diseases like Crohn's disease there is a higher than normal amount of damage being done to the cells. The mechanisms used to heal the ulceration depend on the size of the injury. Also, healing varies with the depth of the ulceration and length of time since the ulceration happened. Marc showed that physical forces like pressure and deformation play a key role in the wound healing process of intestinal epithelial wounds. His presentation was from an experimental/clinical perspective and it opened up a lot of discussion and ideas from the mathematical modelers in the audience.

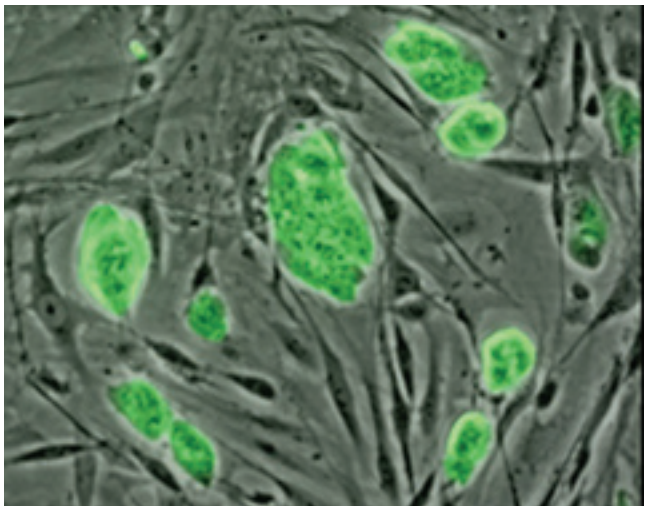
In the third talk Geoffrey Gurtner (Stanford University School of Medicine) discussed progenitor cell-mediated repair following injury. Geoffrey gave a background on regenerative medicine, and how it contrasts with healing with a scar. He discussed the role of stem and progenitor cells in tissue regeneration and gave a background on various methods of deriving stem cells before describing his own laboratory's method of deriving and characterizing adult stem cells. The process of finding useful adult stem cells was likened to finding a needle in a needle stack: you can get lots of cells, but maybe not too many of the ones you want. He described his laboratory's novel technique for characterizing putative stem cells as well as the expected benefits of using these kinds of cells.

After Geoffrey Gurtner's talk, Benjamin Yu (UCSD School of Medicine) presented his laboratory's work on models and mechanisms of organ regeneration. Two of the major questions in regeneration that he addressed are: Where do new cells come from and how is the appropriate pattern generated? He presented background on how the shape and function of organs is determined by "organizing centers." These groups of cells support patterned growth and are closely self-regulated: they prevent insufficient or overgrowth of tissue following injury or disease. He proposed negative feedback loops as a mechanism for regulation of these centers. He also demonstrated the importance of the RAS/MAPK pathway and proposed that using RAS/MAPK signaling to manipulate organizing centers could be used to restore normal amounts of tissue during wound repair.

The final speaker of the day was Anie Philip (McGill University) who presented research on the regulation of TGF-β signaling in skin cells. She presented background on how TGF-β plays an important role in wound healing, including the promotion of re-epithelialization, as well as tissue formation and remodeling. TGF-β is therefore an obvious target for manipulation by drugs that seek to improve wound healing. However, clinical trials in humans have yielded only modest results. Anie demonstrated her laboratory's alternative approach: They have identified a novel TGF- β co-receptor called CD109 that negatively regulates TGF-β signaling. CD109 may be an important molecular target for the treatment of wound healing and scarring.

Day 5

Philip Maini (University of Oxford) started off the last day by presenting the work of Helen Byrne University of Nottingham) and her colleagues on the role of angiogenesis and vasculogenesis in solid tumor growth, presenting various mathematical modeling approaches. Tumors can be consid-



ered as non-healing wounds since processes like angiogenesis and vasculogenesis, both of which are found in normal wound healing, are not well regulated in tumors. He gave an overview of angiogenesis and vasculogenesis, the primary processes involved in the formation of new blood vessels. Angiogenesis includes the proliferation of endothelial cells and their migration, while vasculogenesis directs the mobilization of bone-marrow derived endothelial progenitor cells into the bloodstream. A tumor produces tumor angiogenic factors (TAFs) that promote and increase tumor mass due to the influx of nutrients and this promotes angiogenesis and vasculogenesis. He explained that finding proper parameter values for the model (noting that experimental results play an important role) and choosing the proper functional forms in equations (relating to the robustness of the model) are important modeling issues to be carefully considered. He presented a compartmental model (tumor, blood, and bone marrow) made up of six ODEs. First, subsystems were analyzed in which either angiogenesis or vasculogenesis is the dominant process. The outcomes represent vascularized wounds and non-vascularized wounds depending on the tumor's initial size. Its initial size governs the strength of the angiogenic response. Several steady states and bifurcations regarding the tumor are present and are similar in both the sub-models. In the full model with both angiogenesis and vasculogenesis occurring, similar bifurcation structures are seen as well. The main goal of this exploration was to determine how vasculogenesis impacts the growth rate of tumors and the degree of vasculogenesis in the tumor. One result of the study showed that a strong enough vasculogenic response that increases tumor growth rate may not be further impacted by adding angiogenesis. The opposite is true as well. However, each process acting simultaneously causes the tumor to grow to a larger end size compared to the situation when each process acts at a moderate level in isolation.

In summary, the model shows wholly angiogenic and wholly vasculogenic tumors/tissues exhibit similar growth dynamics and that tumor/tissue growth rate enhances when both vasculogenesis and angiogenesis are active. Furthermore, the model suggested that targeting the TAF production may or may not help patients, depending on where in parameter space they are. Antivascular therapies may need to target both endothelial cells (ECs) (i.e., inhibit angiogenesis) and endothelial progenitor cells (EPCs) (i.e., inhibit vasculogenesis).

Next he presented multiscale modeling of angiogenesis which considers a spatial component. Continuum models provide useful insight but cannot reproduce the details of vascular morphology nor can they couple factors that act on different scales. The model includes a vascular layer (modeled by an agent-based model), diffusible species (modeled with a PDE), a cellular layer (modeled with ODEs), and a sub-cellular layer comprised of agent-based modeling, PDEs, and ODEs. In modeling the vascular layer, a hexagonal network is assumed, where pressure drops across the network and Kirchoff's laws determine flow in each vessel. The vessel radii adapt to blood flow rate, shear stress, and VEGF (vascular endothelial growth factor). Vessels get wider in response to these angiogenic growth factors. He showed a simulation of this model, displaying that as the normal cells use up oxygen, the oxygen deprived cells produce VEGF which cause the vessels to widen and also promote angiogenesis, leading to a vascularized state. Another result showed that starting with differing vessel densities leads to similar final vessel density. He showed another simulation that represented impaired wound healing and finally a statistical summary that could be extracted from the model. The research in this area implies that existing models of vascular tumor growth can be adapted to study wound healing, where tissue growth and angiogenesis occur simultaneously. He concluded that mathematical modeling has an important role to play in gaining insight into mechanisms that regulate normal and aberrant wound healing. Picking the type of modeling technique depends on the issues and questions at hand.

Kevin Kesseler (University of North Carolina, Chapel

Hill) presented the last talk of the workshop which elaborated on why the G2 checkpoint (in the cell cycle) is relevant to wound healing. Wounds may contain contaminants that can damage cellular DNA which, in turn, negatively affects cell proliferation, an important aspect of healing. These particular processes occur during the G2 cell cycle phase. He gave an overview of the cell cycle and specifically the transition from the G2 phase to the M phase, which is the mitotic phase where the cell divides. They were interested in what the G2 DNA damage checkpoint is. If there is DNA damage then a damage signal pathway is initiated to stall the G2 phase and allow time for DNA repair before the cell cycle continues so that it can divide successfully. He explained that the goal of modeling the G2 DNA damage checkpoint was to be able to determine if known protein-protein interactions are sufficient to explain observed behavior of the G2 checkpoint. In addition, they hope to increase their understanding of the biology of how the G2 checkpoint functions and to make predictions that may be verified by experiments or to simulate conditions which are difficult or impossible to produce experimentally. He elaborated on specific strategies for modeling the G2 DNA damage checkpoint, such as modeling the G2 to M transition, via the protein active nuclear MPF which is activated by a bistable switch. In addition, modeling the mechanism by which the G2 phase is stalled is also important, by adding proteins involved in MPF regulation and their respective interactions. Finally, understanding how the DNA damage response pathway is initiated and how the repair actually happens is another important modeling goal. Simulations of the model output were then presented from a simple model of three proteins (including MPF) where there are two positive feedback loops and two inhibitory mechanisms. The output displayed a bistable switch of the G2 to M transition. The next model included two compartments: the nucleus and the cytoplasm of the cell, incorporating the role of other proteins in the cytoplasm that affect MPF to inhibit its activation and also help reactivate it to stop and start the G2 to M transition. In addition, the model includes subsystems of the proteins CDFb and CDFc and things that relate to their activation, deactivation, and sequestering as well as the MPF subsystem. The model is rule-based and created using software written at Los Alamos National Laboratory called BioNetGen. Results of this larger, more detailed model were then discussed. For instance, if MPF and the Plk1 gene are over-expressed, then mitosis is prevented. However, a constitutively active Plk1 causes the cell to go into mitosis even if there is a damage signal, which is consistent with experimental results. Experimental results also suggest that Plk1 depleted cells delay and even prevent mitotic entry and also are delayed in recovering from a damage arrest. The simulations of the model agree with these experimental results, although they believe that the model does not yet have the complexity needed to capture the phenomenon of preventing mitosis. He then looked at mitotic recovery in Wee1 depleted cells, which will go into mitosis faster than normal cells. The model simulations are consistent with this outcome as well. Lastly, he showed a simulation that predicted that depletion of the pkMyt1 gene causes a cell that has DNA damage to have a buildup of MPF in the nucleus, a hypothesis that is to be tested experimentally in the near future.

Conclusion

One of the main reasons this workshop was so successful was because of the diversity of the audience. The participants were experimentalists, physicians, mathematical modelers, and physicists. Instead of each group remaining separate from the other groups there was a lot of communication across groups. The experimentalists and physicians had good questions and ideas for the modelers and vice versa. The organizers seemed to have a good vision for making the meeting productive so that new ideas would be generated and pursued. New cross-disciplinary collaborations have already been established as a result of this workshop.

WORKSHOP 6: NEUROSCIENCE ISSUES IN EARLY DEVELOPMENT (APRIL 27 - MAY 1, 2009)

Organizers

- **Ken Miller** (Ctr. for Theoretical Neurosciences, Columbia University, NY)
- **Fred Wolf** (MPI for Dynamics and Self-Organization, Dept. of Nonlinear dynamics, FRG)

Overall Summary

This workshop brought together experimentalists and theoreticians working on, among other things, the development of specific connection patterns in the brain, the development of cortical maps, and experience-driven plasticity. One of the main thrusts of the research presentations given at the workshop was the development of patterned structures called "maps" in the nervous system. Sensory information, say from a region of the skin or the retina, is mapped onto a particular region of the brain, maintaining certain topographic relationships.

Much research has been done in recent years to not only determine the molecules underlying these effects, but also to develop theoretical frameworks for understanding the mechanisms involved.

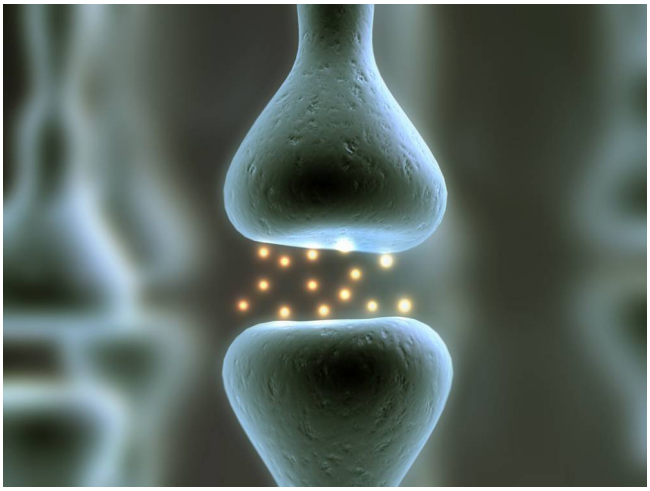
Some of these maps exhibit "critical periods": specific windows of time during which feature maps are very sensitive to abnormal sensory input, and after which the maps are essentially unaffected by the same abnormal sensory input. One of the goals of this research area, and a major challenge for theoreticians, is to understand mechanisms underlying critical periods. The workshop clarified these challenges and encouraged fresh energy and approaches for tackling them.

In addition to the study of the formation of feature maps, the workshop also presented research on the development of particular spatiotemporal response features, such as the selective activation of a retinal cell by a light stimulus moving in a preferred direction.

Summary of Presentations

Day 1

The workshop organizers opened the conference by welcoming the participants and emphasizing the good timing of the workshop to re-conceive what is happening in neurodevelopment due to the dramatic increase of technology during the



past year. They further pointed out that this is also a good time for experimentalists and theoreticians to come together to articulate new challenges in this area.

Greg Lemke (The Salk Institute, La Jolla, CA) began by posing a problem that has preoccupied scientists for centuries "How are eyes connected to the brain?" He explained the use of molecular genetic methods in mice to get insight on how neurons interact during the formation of topographic neural maps. These maps are comprised of axonal connections in which the positional coordinates of a set of input neurons are mapped onto the corresponding coordinates of their targets. They are a feature of nearly all sensory modalities and are seen throughout the nervous system. He described a quantitative model for the development of one arm of the retinocollicular map: the wiring of the nasal-temporal axis of the retina to the caudal-rostral axis of the SC. The model was based on retinal ganglion cell (RGC) competition with other retinal ganglion cells. This competition is governed by comparisons of the signaling intensity experienced by RGCs expressing differing levels of EphA receptor protein-tyrosine kinases, whose expression is exponentially graded across the nasal-temporal axis of the retina.

Jianhua Cang (Northwestern University) presented the second talk on the same topic entitled "Functional Development of Retinotopic Maps." He started by posing to fundamental questions: "How does a neuron know its position and where to go during development?" and "What is the functional significance of topographic maps?" After an overview of the visual pathway in mammals he described his functional approach to measure neural activity by using imaging and comparing the experimental data with a computational mod-

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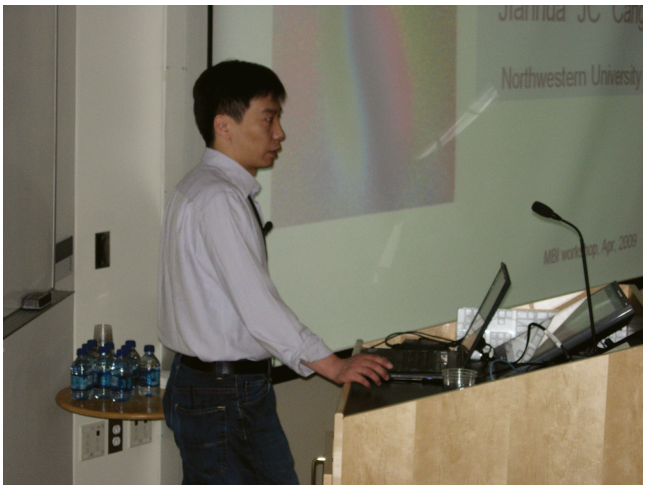
el. Using this methodology the results revealed the contributions of ephrin-As and activity-dependent mechanisms in retinocollicular map formation.

The third talk was given by David Willshaw (University of Edinburgh). The work he presented questions the importance of each of the molecular based mechanisms that act together to form the ordered retinotopic maps found in the vertebrate retinotectal or retinocollicular systems. Then he described the model he published Development, 2006, which was designed with experimental evidence in mind and involves genetic manipulation of a putative molecular mechanism, disturbing the retinocollicular projection in a mouse. According to this model, retinal axons form such maps by effectively self-sorting according to the labels that they carry. This model leads to specific predictions about the state of the molecular labels on the colliculus. Then he highlighted the importance of a quantitative measure of the local and global order of the map and described his current work on developing this measure based on the fact that in an ordered map neighborhood relations are preserved. He applied his measure to some of the map examples presented in the previous talk.

Alexei Koulakov (Cold Spring Harbor Laboratory) gave the fourth and final talk of the day. Under the title "Toward the standard model of neural development," he focused on the challenge of combining various factors that contribute to the development of connectivity matrix in the brain in a single model approach. He proposed that the problem of network formation can be thought of as an optimization principle of an affinity potential that depends on the network graph and includes many diverse factors. The model combines Hebbian learning rules and the Sperry chemoaffinity principle and is similar to formulating the Standard Model in particle physics that combines disparate forms of fundamental interactions.

Day 2

To begin the second day, Andrew Huberman



(Stanford University School of Medicine) continued the discussion of the formation of the topographic maps, in particular tiled retinal mosaic maps. He described the processes that take place in the retina and the different types and subtypes of Retinal ganglion cells (RGC). These cells are the bottleneck of visual information leaving the eye. There are at least two dozen RGC subtypes, and each responds to a unique aspect of the visual scene (motion, direction, color, etc.) and sends that information to the brain where it is processed into perceptions and behavior. To delineate the complete map of brain connections made by individual RGC subtypes, his lab carried out a genetic screen to identify mice with i) RGC mosaics selectively labeled with green fluorescent protein (GFP) and ii) no GFP+ cells in retinorecipient areas. The experimental results showed that central projections or 'maps' of each RGC mosaic exhibit remarkable specificity: different RGC subtypes project their axons to different combinations of target nuclei and those axons occupy distinct depths, or layers across the full extent of their targets. Moreover, within each mosaic-specific layer, RGC axons form regularly tiled arrays.

In the second talk of the day Jenny Rodger (University of Western Australia) showed experimental results on mice behavior to address the role of

visual enrichment in the development of topography in ephrin-A-/- mice. Ephrin-A-/- mice have deficits in visuomotor behavior due to disordered visual system circuitry. These mice have already been used to demonstrate the role of spontaneous retinal activity in refining topography during development. She showed that an enriched visual environment in early postnatal life significantly improves the accuracy of retinocollicular topography in ephrin-A-/- mice. Thus the ability to measure the specific behavioral consequences of these cellular changes provides a direct assessment of structure-function relationships in the brain.

In the next presentation Daniel A. Butts (University of Maryland, College Park) started with an overview on retinal waves. This spontaneous neuronal activity is present in the mammalian retina prior to light-driven activity, and is known to be required for synaptic refinement in the lateral geniculate nucleus (LGN) and the cortex. Then he explained how by studying the complex spatiotemporal patterning of retinal waves, they have designed experiments that focus on the informative aspects of these waves that can drive development. He finished by posing other questions that should be incorporated in the same framework.

The third talk continued on the topic of spontaneous neural activity and was presented by Matthias Hennig, (University of Edinburgh). His work addresses the question "Is neural activity specifically regulated during development?" In order to investigate in detail the properties of retinal waves, he compared a computational model with multielectrode array recordings. In the model the synchronizing effect of synaptic transmission is balanced by the desynchronizing effect of the refractory mechanism. The model predicts the experimentally observed randomness of initiation sites, trajectories and sizes of retinal waves. The findings indicate that early-stage retinal waves are regulated according to a very specific principle, which maximizes randomness and variability in the resulting activity patterns. Moreover, the resulting activity contains events on all length scales, and is therefore unbiased with respect to scale or sequence of events, which may be an important prerequisite for the normal visual system development. Finally, the scale-free character of retinal waves might present the visual system with an early opportunity to adapt to input statistics later encountered during natural vision.

The last talk of the day was presented by Ilana Witten (Stanford University). The work she presented addressed the questions "How does the brain align spatial representations across modalities?" In particular, she focused on auditory and visual stimuli and used barn owls as the system of study. The optic tectum of these night predators is involved in orienting behavior across both modalities, auditory and visual, in which synaptic plasticity play an important role. This motivated a computational model to study the shift of one modality in the plasticity. She detailed the model formulation which includes a firing rate model and Hebbian rule. Then the possible plasticity regimes were described in relation with the parameter space (correlation strength and visual displacement angle). Dr. Witten concluded that (1) asymmetric plasticity emerges directly by Hebbian learning, and small differences in the receptive field properties cause a large asymmetry in the division of plasticity between modalities.

At the end of the second day the organizers proposed to have a discussion section on the topics presented during the first two days of the workshop before continuing with talks in a different area on Wednesday. The speakers formed a panel to lead the discussions. During this time participants had the opportunity to further discuss issues raised during the day's talks.

Day 3

The third day of the workshop marked a transition in the focus of the research presentations. The talks on this day focused on the cortex rather than the retina. The first talk of the day was given by Richard Nowakowski (UMDNJ-Robert Wood Johnson Medical School) about positional information from cell cycle timing. Dr. Nowakowski first described the development of the mouse neocortex in general terms: the brain grows quickly, producing the cells that will constitute the neocortex during a six-day period starting on embryonic day 10 and continuing until day 17. As the cells are progressing through the cell cycle stages they are also migrating from the ventrolateral portion of the neocortex to the dorsomedial portion. This migration sets up a gradient in the cell cycle lengths across the surface of ventricular zone. There are also spatial gradients of transcription factors across the surface of the ventricular zone. These two gradients, since they specify the timing and location of cells in the cell cycle, can be viewed as the basis for a coding scheme for the localization of neocortical cells. Dr. Nowakowski presented this idea as an analogy with navigation on the high seas: to determine the position of a ship one needs both an accurate clock and a sextant. The cell cycle

length is the analogue of the clock, and the transcription factor is analogous to the sextant. This forms a so-called "Navigation Hypothesis" in cell cycle timing.

The second talk of the morning was given by Siegrid Loewel (Friedrich-Schiller University of Jena) who presented research on the dynamic architecture of the cortex during development and after lesions. The first part of her talk focused on experiments carried out in cat visual cortex. The first set of experiments she described used moving bars within the receptive fields of directionally-selective cells and "flank" bars, which are outside the receptive fields of those cells. They found that the addition of a flank bar that moves in the same direction as the moving bar enhances the directional effect of the cell, and one that moves orthogonally suppresses the effect. She concluded from these experiments and others that horizontal connections between cells with non-overlapping receptive fields make a major contribution to these contextual effects. The next set of cat experiments she described were designed to investigate strabismic amblyopia. She found a clear anatomical correlate of strabismic amblyopia in the primary visual cortex and the network modifications they observed are consistent with the perceptual deficits of strabismic amblyopia.

Dr. Loewel next changed gears to discuss experience-dependent changes in the visual cortex of mice. She described her lab's experimental technique to optically image cortical plasticity in mice. She and her lab asked the question of whether or not ocular dominance plasticity is age-dependent. They concluded that it is: they found no OD plasticity and reduced learning in mice over 110 days old. Finally, Dr. Loewel presented results of experiments where she induced local cortical strokes and found that no OD plasticity is possible after a local stroke. Her conclusions can be summarized as follows: there is a clear anatomical correlate of strabismic amblyopia already in the visual cortex; OD plasticity and visual learning after MD in mice are age-dependent; and a cortical stroke, even one outside the visual cortex, prevents OD plasticity.

The final speaker of the morning session was Dmitry Tsigankov (Max Planck Institute for Dynamics and Self-Organization) who presented research about chemical labels in the development of ocular dominance patterns. Specifically, Dr. Tsigankov looked at gradients of these chemical labels since gradients of chemical labels play a strong role in the formation of the cortical map. One of the central questions that Dr. Tsigankov started out with was: how do cortical maps (of ocular dominance, orientation preference, etc.) form? There is an old idea that the formation of these maps is activity-dependent, but another idea is that these connections have been determined in the genome. He showed, among other things, that the ocular dominance structure can be produced by a single chemical gradient and purely excitatory lateral interactions.

The first speaker of the afternoon session was Josh Trachtenberg (UCLA) who presented an alternative view of binocular plasticity. Dr. Trachtenberg's lab does experiments on the mouse visual cortex to understand how experience determines plasticity. It has been known since the 1960s that suturing shut the lid of one eye during a critical window of time early in development causes functional blindness in that eye. The Trachtenberg lab uses various experimental techniques like suturing the contralateral or ipsilateral eye prior to the classically defined "critical period" and studying the effect on the other eye. They found that ipsilateral and contralateral eye projections do not compete for cortical territory. They also found that the ipsilateral eye projection is uniquely sensitive to binocular vision. As a way of summing up, Dr. Trachtenberg stressed that in his view so-called "binocular competition" is neither binocular nor competitive, at least not in the sense that it had been thought to be previously. This presentation sparked a lot of discussion as several participants

weighed in with their thoughts on the "binocular competition" concept.

The final speaker of the day was Megumi Kaneko (UCSF) who talked about experience-dependent plasticity in the developing visual cortex. Dr. Kaneko uses monocular deprivation (MD) and studies the changes that are induced in the visual cortex. This competitive, experience-dependent plasticity is called ocular dominance plasticity (ODP). It has been suggested that inputs from two eyes compete for a postsynaptic reward that induces plasticity by selectively affecting synapses serving the two eyes. Numerous observations have led to the hypothesis that brain-derived neurotrophic factor (BDNF) is such a retrograde "reward" signal. Dr. Kaneko's research group tested this hypothesis by inhibiting TrkB kinase activity during the induction of cortical plasticity in vivo. Since TrkB is bound and activated by BDNF they expected this to significantly alter the changes in the cortex due to MD. Instead they found that TrkB inactivation during MD had no detectable effect on changes in cortical responses to the deprived eye or the open eye. This result, along with others, suggested that TrkB signaling plays a role in enhancement of responses or growth of new connections, instead of a role in competition. In fact, they hypothesized that binocular cooperation, rather than competition, is the mechanism at work in the recovery process since they observed that deprived-eye responses were restored more rapidly when both eyes were left open than when the occlusion was switched to the other eye.

Furthermore, Dr. Kaneko and colleagues determined that what had been thought of as experience-driven competition is really the outcome of two distinct processes, the second of which depends on tumor necrosis factor-alpha (TNF-a) which mediates homeostatic synaptic scaling.

To summarize, Dr. Kaneko's lab has demonstrated important mechanisms in three stages of the course of MD and recovery: first, an initial loss of deprived-eye responses, independent of TrkB and TNF-a; second, a homeostatic increase of open-eye response that is dependent on TNF-a; and third, a recovery of deprived-eye response that depends on TrkB kinase.

Day 4

The Thursday session began with back to back talks given by Ken Miller and Taro Yoizumi (both from Columbia University). These two talks were a composite large talk on the modeling of ocular

dominance plasticity, which are sculpted by correlated spontaneous activity early in development. The work of T.K. Hensch suggests that the shape of the lateral circuitry, in particular the inhibition component, dynamically changes during development. In order to obtain a non-uniform, stripe-like OD pattern, the inhibition neural circuits play an essential role and differences in the maturity of the inhibitory circuits are crucial in understanding two important developmental stages of visual plasticity in a unified manner: pre-CP and CP plasticity. The reduction of spontaneous activity level caused by maturation of inhibition increased the sensitivity of the cortex to the visual stimulus and opened the CP.

In the second part of their talks, biological elements with different time constants were considered in their model of OD plasticity. In that model, there were three separable plasticity processes. The model not only captured the eventual mature OD pattern of the cortex, but also captured transient behaviors, which many traditional models do not. In their numerical studies of their learning rule they deduced that: 1) the learning rule must depend on past as well as present synaptic strengths in order to reproduce the MD result in the monocular cortex, 2) the fast Hebbian component requires a built-in stabilization mechanism, e.g., maximal and minimal weight limits. Slow homeostatic plasticity cannot stabilize an unstable Hebbian component, and 3) in order to robustly avoid an overshoot of synaptic strength under MD, homeostasis and LTP/LTD should control independent factors.

After a short break, the next talk was a shift from

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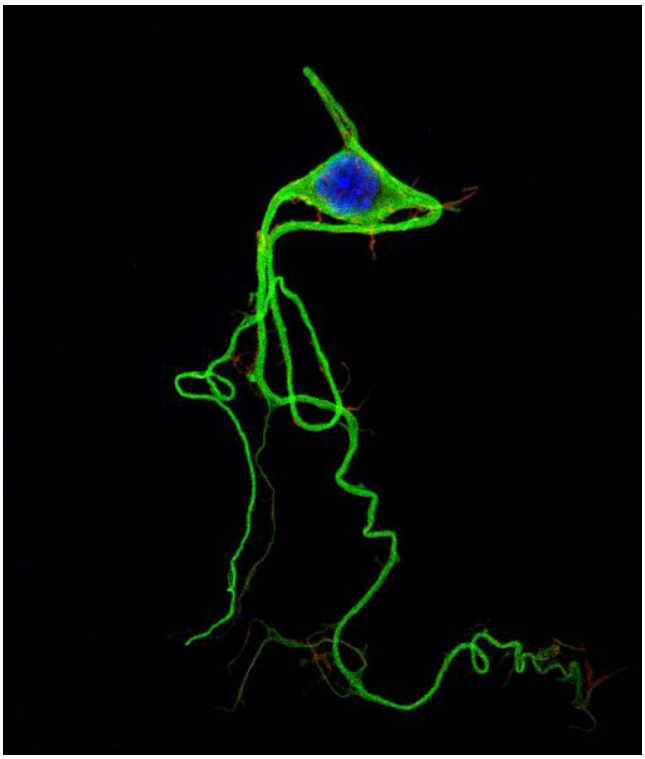
modeling to experimental results on "Early circuits that regulate cortical development and plasticity" presented by Patrick Kanold (University of Maryland, College Park). This talk contrasted the others of the previous days in that instead of focusing on Hebbian driven spontaneous activity driving the formation of cortical circuitry, Dr. Kanold focused on the role of the subplate neurons (SPNs). These neurons are among the earliest born cortical neurons; they reside in the white matter (beneath the cortex) and disappear during development. SPNs act like a "teacher" helping thalamic neurons to make strong and precise connections to their cortical target neurons. By relaying thalamic input and controlling the balance of excitation and inhibition, SPNs can influence the correlations between thalamic and cortical activity and thereby synaptic plasticity. Together, understanding the role of the SPN provides a framework demonstrating that plasticity during the critical period is the product of a complex and dynamically changing circuit in which SPNs play a key role.

After the lunch break, the next section continued with Justin Crowley (Carnegie Mellon University). His lab is interested in understanding the mechanisms of neural circuit formation in the visual system and employs a three pronged approach combining anatomical imaging, physiological imaging, and proteomics studies. He addressed the question of how are cortical columns formed and what roles do patterned activity and molecular cues in their formation. During his talk he outlined his lab's strategies of (1) phenomenology (fixed tissue and time lapse study of circuit formation), (2) manipulation of activity patterns, and (3) exploration of molecular organization (proteomics). They found that (1) despite disruptions to the retinal input, axons terminated periodically in V1, (2) LGN layer location determines axon pattern in cortex, and (3) retinothalamic anatomy does not affect thalamocortical anatomy.

The next talk on the development of cortical maps in the visual cortex was given by Leonard White



Neuron from a chicken embryo.

(Duke University Medical Center). He outlined the functional maps which arise in developing visual cortex as response to selectivities becoming organized into columnar patterns of population activity. In particular, Dr. White showcased results from recent studies of developing orientation and direction maps indicate that both maps are sensitive to visual experience, but not to the same degree or duration. Direction maps have a greater dependence on early vision while orientation maps remain sensitive to experience over a longer period of cortical maturation. There is also a darker side to experience: abnormal vision through closed lids produces severe impairments in neuronal selectivity rendering these maps nearly undetectable. Thus, the rules that govern their formation and the construction of the underlying neural circuits are modulated - for better or worse - by early vision. Direction maps, and possibly maps of other properties that are dependent upon pre-

cise conjunctions of spatial and temporal signals, are most susceptible to the potential benefits and mal-adaptive consequences of early sensory experience.

The final talk of the day was given by David Fitzpatrick (Duke University Medical Center) on how "Experience with moving visual stimuli drives the early development of cortical direction selectivity." The onset of vision occurs when neural circuits in the visual cortex are immature, lacking the full complement of connections and the response selectivity that defines functional maturity. Direction selective responses, as outlined in the previous talk by Leonard White, are particularly vulnerable to the effects of early visual deprivation, but how stimulus-driven neural activity guides the emergence of cortical direction selectivity remains unclear. To explore this issue, the Fitzpatrick lab developed a novel motion training paradigm in order to monitor the impact of experience on the development of direction selective responses in visually naive ferrets. Training with a moving stimulus, but not with a flashed stimulus, strengthened the direction-selective responses of individual neurons and preferentially reversed the direction biases of neurons that deviated from their neighbors. Both effects contributed to an increase in local coherence, suggesting that early experience with moving visual stimuli drives the rapid emergence of direction selective responses in visual cortex.

Day 5

The day began with Mark Huebener (Max Planck Institute of Neurobiology) talking on the "Early development of orientation maps in ferret visual cortex." Sparse electrical recordings from individual neurons in ferret revealed orientation selective single units about 10 days before the earliest orientation maps have been reported with intrinsic signal imaging, but whether these neurons are organized into an orientation map remains unknown. In the youngest ferrets exhibiting visual responses, almost all neurons responded strongly and nearly exclusively to horizontal stimuli. This unexpected regime of "all-horizontal" tuning lasted for about a week, P21-27. Subsequently, around the time of eye-opening, cells lost their all-horizontal tuning and responded largely unselectively to all orientations. Despite such broad tuning during this period, cells were already organized into a smooth map of orientation preference with occasional pinwheels. Later still, orientation selectivity improved further, but map structure remained largely similar. Thus, during the initial development of visual response properties, neurons in the visual cortex undergo dramatic and exquisitely orchestrated changes in orientation tuning as one regime of functional organization gives way to another.

The next talk of the morning was given by Fred Wolf (Max Planck Institute for Dynamics and Self-Organization) where he presented joint work done with M. Kaschube, S. Lowell, and L. White (and others) on the evolution of orientation preference over 65 million years. They dealt with quantifying orientation pinwheel abundance (pinwheel density considered as number of pinwheels per mm2 multiplied by column spacing2). The pinwheel density for all of these species turns out to be approximately π. Beyond this, Wolf et al. considered if orientation columns are placed strategically. They found that the orientation maps (with the visual cortex's shift-twist symmetry) are matched to natural scenes and that the rotation symmetry largely constrains the expected structure of correlation functions. It is surprising that species separated by over 65 million years of evolution exhibit quantitative universality of orientation column design.

Matthias Kaschube (Princeton University) presented joint work with Fred Wolf and others on the formation of ocular dominance columns (ODCs) on a growing cortical domain. In studies of cat visual cortex, the spacing of the ODCs is roughly the same in immature and mature animals even though the size of the cortex more than doubles, suggesting a rearrangement of the initial OD pattern. Previous studies of Oster and Bressloff on a one-dimensional representation of cortex concluded that new ODCs must necessarily be inserted with cortical growth. Kaschube et al. studies were performed on two-dimensional domains, and their findings suggest that the OD pattern could instead exhibit a sheering so that a pattern of vertical stripes would become a zig-zag distorted pattern with the same number of ODCs. This distortion would still approximately preserve the ODC spacing.

The next talk was given by Nicholas Swindale (University of British Columbia) on "Cortical maps as content-addressable memories." An extraordinary amount of information is processed by the visual cortex and multiple cortical feature maps overlay each other in a polymap over V1. The cortex then has afferents which connect up to the higher areas, which in turn send back feedback signals. Incorporating these biological substrates into a computational model, Swindale found (1) broad, sometimes patchy, tangential distributions of the feedback axons, (2) multiplicative scaling

of tuning curves modulated by attention, (3) multiplicative interactions between apical and basal dendritic inputs, and that (4) the cortical network could decode (that is, distinguish) xN activity patterns with Nx feedback projections. This latter finding suggests a functional efficiency of having cortical feedback instead of a purely feedforward cortical architecture.

The concluding talk of the workshop was by Mitya Chklovskii (Howard Hughes Medical Institute) on the "Maximization of the connectivity repertoire: a statistical principle behind the shapes of dendritic arbors." The shapes of dendritic arbors are fascinating and important, yet the principles underlying their complexity and diversity remain unclear. By analyzing basal dendritic arbors of 2171 pyramidal neurons sampled from mammalian brains, Mitya's lab discovered three statistical properties: the dendritic arbor size scales with the total dendritic length, the spatial correlation of dendritic branches within an arbor has a universal functional form, and small parts of an arbor are self-similar. In order to explain their findings, they propose that the properties result from maximizing the repertoire of possible connectivity patterns between dendrites and surrounding axons while keeping the cost of dendrites low. The uncovered solution is consistent with their observations and predicts scaling relations that can be tested experimentally. These results represent the first step towards a unifying view of the relationship between neuronal morphology and function.

WORKSHOP 7: DROSOPHILA DEVELOPMENT (JUNE 8-12, 2009)

Organizers

- **Michael Levine** (Dept. of Molecular & Cell Biology, UC, Berkeley)
- **Hans Othmer** (School of Mathematics, U. Minnesota)

Overall Summary

This workshop covered four broad topics that are particularly well suited for quantitative analysis: whole-genome analysis, basic mechanisms of pattern formation, computational modeling, and gene regulatory networks in development. The genomes of 12 different Drosophila species have recently been completely sequenced and assembled, providing a plethora of data to analyze. Whole-genome methods provide the comprehensive identification of genes and associated regulatory DNA responsible for complex developmental processes, including segmentation, gastrulation, neurogenesis, and wing morphogenesis. The program discussed current progress in these areas with an eye towards future modeling efforts. Gene regulatory networks can be used to create predictive changes in patterning processes, and to determine the mechanistic basis for the genesis of embryonic diversity and novelty during insect evolution. Workshop participants discussed the logic and topology of these networks, and also considered future goals such as the development of better visualization methods.

Summary of Presentations

Day 1

The theme of the first day was Whole-Genome Analysis, which consisted of six talks by experimentalists, computational biologists and an applied mathematician. Julia Zeitlinger (Stowers Institute for Medical Research) gave the first talk which looked at the evolution of the dorsal-ventral (DV) transcriptional regulatory network in closely re-

The next speaker was Norbert Perrimon (Howard Hughes Medical Institute, Harvard Medical School) who talked about large scale analyses of signaling networks. His discussion focused on the insulin receptor-signaling pathway in Drosophila. Recent studies using cell-based RNA interference (RNAi) screens infer that large numbers of genes regulate signaling pathways but they cannot provide network structure directly. Perrimon illustrated that understanding a particular cell signaling pathway requires identification of all pathway components, the pathway dynamics (feedback loops, time course gene expression, etc.), and the directional flow of information through the network. He showed how to describe the insulin receptor-signaling pathway in this manner by combining parallel genomewide RNAi screens and mass spectrometry.

In the last talk before lunch, Eileen Furlong (EMBL Heidelberg, Germany) spoke about dissecting the logic in developmental regulatory networks. One main challenge in biology is to understand how the genome is used to direct the development of complex tissues and organisms. Genetic studies have uncovered various transcription factors necessary for cell fate specification, but little is know about how these regulators function at the molecular level. Few of their target genes are known, let alone the architecture of the underlying transcriptional network in which they operate. Furlong described her work to bridge this gap, which involves integrating genetic, genomic, and computational approaches to understand the transcriptional network that drives the selection of cell fates within the mesoderm. She brought up the point that people are currently building gene regulatory networks when they should be focusing on building cis-regulatory networks, and this generated a lively discussion. By combining ChIP-chip through a time-course of Drosophila development, her group systematically identifed cis-regulatory module occupancy during developmental progression. The topology of the network was unexpected, showing extensive combinatorial regulation and temporal enhancer occupancy. She also briefly mentioned CAD, a database of enhancers with characterized spatio-temporal expression within the mesoderm that her lab has developed.

After lunch, Thomas Kornberg (University of California at San Francisco) delivered a somewhat

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lated Drosophila species. It is well accepted that changes in cis-regulatory elements that regulate transcription are an important driving force for the evolution of species. Zeitlinger investigated how such changes affect a transcriptional regulatory network during development by looking at the DV patterning network in D. melanogaster, D. simulans, D. erecta, and D. yakuba. The approach used was chromatin immunoprecipitation combined with high throughput-sequencing (ChIP-seq) to compare the genome-wide distribution of two transcription factors: transcriptional activator Twist and repressor Snail. The data uncover a much larger than expected regulatory network, which integrates diverse patterning processes during development.

Lior Pachter (University of California at Berkeley) gave the second talk, which focused on various mathematical questions and issues involved with genome alignments of Drosophila at the nucleotide level, and how the alignments can be used to study the functional drivers of genome evolution. With a view towards large-scale alignment of thousands of Drosophila genomes, Pachter presented two main challenges: the statistical challenge of how the choice of statistical model of genome evolution affects biological inferences and the combinatorial challenge of how data from a large number of genomes can be analyzed effectively. He also discussed how to quantify alignment uncertainty using a method called Fast Statistical Alignment, a new multiple sequence alignment program that is more accurate and much faster than previous methods.

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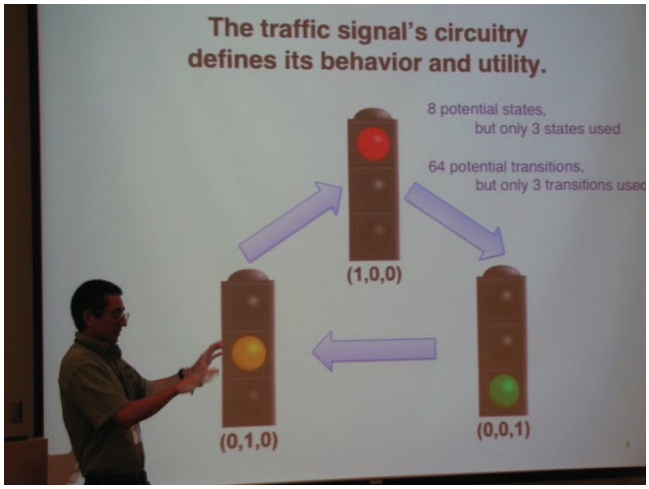
After lunch, Thomas Kornberg (University of California at San Francisco) delivered a somewhat controversial talk about the mechanisms of morphogen dispersion and action. Morphogens are signaling proteins that move across a field of cells to form a concentration gradient across a developing tissue. Signaling protein gradients elicit concentration-dependent responses from target cells. On one of his introductory slides, Kornberg hypothesized that signaling specificity is incompatible with passive diffusion, which sparked a discussion. He then introduced cytonemes, which are specialized filopodia that ferry signaling proteins. The remainder of the talk focused on evidence that morphogen signaling proteins disperse by moving along cytonemes after transfer to target cells at points of direct contact. Specifically, his evidence was for movement along cytonemes of Dpp from



Dpp-expressing cells in the Drosophila wing disc). Several people in the audience were skeptical of his evidence and a lively discussion ensued. Kornberg concluded that the contours of morphogen distribution seem to depend both on the stability of cytoneme contacts and the efficiencies of movement.

Alexander Stark (IMP, Vienna; and Broad Institute and CSAIL, MIT) gave the next talk on the comparative genomics of gene regulation in Drosophila. A systematic understanding of gene regulation relies on the global knowledge of the different classes of regulatory motifs and their targets. Stark and his collaborators used comparative information from whole genome alignments of the 12 Drosophila species to identify instances of regulatory motifs and to discover novel types of regulatory motifs. He also described work in predicting and validating microRNA (miRNA) genes in Drosophila. Stark concluded by emphasizing that comparative analysis of miRNAs and regulatory motifs in Drosophila uncovers fundamental principles of gene regulation and provides a framework for future approaches toward understanding tissue formation and development.

The last speaker of the first day was Manolis Kellis (Computer Science, MIT). He talked about regulatory genomics and epigenomics in Drosophila. His group is developing computational methods to address various questions about gene regulation and does so in collaboration with large-scale experimental efforts. The ultimate goal is to define a coherent map between genome sequence and gene expression patterns in Drosophila development. Kellis described the use of comparative genomics of the 12 Drosophila genomes to look for evolutionary signatures associated with genes and regulatory elements. He also spoke about methods for the de novo discovery of chromatin marks (or states), which are a way to annotate functional sites in the genome, associated with roles such as enhancer, promoter, etc. The introduction of these chromatin states generated a lively discussion with lots of questions from the audience. By combining evolutionary signatures and chromatin signatures together, his group has put together a global map of regulatory important regions in the Drosophila genome, and a complete map of high-confidence instances of conserved regulatory motifs and motif combinations within them. Kellis presented much more data than results, with the intention of getting people interested in discussing this problem, and he succeeded in doing so.

Day 2

The topic for the second day presentations was Basic Mechanisms. Edwin Ferguson (University of Chicago) presented the first talk. He focused on the mechanisms underlying Dpp-receptor dorsal-ventral patterning in the Drosophila embryo. The Bone Morphogenetic Protein (BMP) family member decapentaplegic (dpp) is transcribed

uniformly over the dorsal 40\% of the blastoderm embryo. In contrast, BMP signaling, which mirrors Dpp-receptor interactions, is present in only a subset of the dpp expression domain. He hypothesized that the pattern of BMP signaling arises from the spatial restriction of Dpp-receptor interaction. In order to test this hypothesis his lab developed a technique using PVI to detect receptor-bound BMPs. They are currently analyzing the mechanisms underlying positive feedback. They propose that an increase in receptor availability in regions of previous signaling both increases capacity for future signaling and acts as a sink for BMP ligands, thereby narrowing the signaling domain. The BMP target gene eiger is a component of feedback. Eiger, a Tumor Necrosis alpha homolog, signals through the Jun N-terminal kinase pathway to promote Dpp - receptor interactions. While the effects of eiger mutations on BMP signaling can be visualized in multiple sensitized genetic backgrounds, loss of eiger in an otherwise wild-type embryo has no phenotype. These data indicate that feedback is genetically redundant, and they are currently investigating other possible feedback components.

Haini Cai (University of Georgia) presented her work on Chromatin boundary elements (CBEs). She started with a brief background on CBEs, or insulators, which can block enhancer-promoter interactions and/or limit the spread of silent chromatin. She presented several models for the mechanisms of action of CBEs but the mechanisms are still unknown. She posed the question: ''Do CBEs play an important role in endogenous gene regulation?'' and provide some examples but points out the lack of information. Then she focused on the SF1, a chromatin boundary in the Drosophila Antennapedia Hox cluster. It is located between the divergently transcribed Hox gene Scr and a non-Hox gene ftz. SF1 exhibits strong enhancer-blocking activity in embryos and protects the miniwhite reporter from the influences of surrounding chromatin. She presented recent studies showing that SF1 interacts with neighboring genomic elements

to form DNA/chromatin loop domains. As a consequence she proposes that SF1 facilitates the formation of independent gene regulatory domains to modulate stage- and tissue- specific enhancer-promoter interactions.

Claude Desplan (New York University) presented the third morning talk, focused on patterning or better said "absence" of patterning in the Drosophila eye. The eye looks homogeneous from the outside but presents variation in proportion and spatial distribution of different photoreceptors. He showed how a very organized pattern occurs in fish and poses the question: Why stochastic distribution of photoreceptors in Drosophila? The use of the word ''stochastic'' instead of ''random'' generated some controversy in the audience that was later pursued during lunch. He explained that though the distribution of these ommatidial subtypes is spatially randomized throughout the eye, subtype fate determination is robust such that each R7 and R8 expresses a particular rhodopsin in a stable manner and conserved ratio. Hence a second questions arises: How does the eye ensure robustness? He described two distinct roles for the K50 homeodomain transcription factor, Defective proventriculus (Dve) and suggested that the fly eye utilizes transcriptional repression to mask inherently noisy gene expression and ensure

robustness.

During the first afternoon talk Seth Blair (University of Wisconsin) continued the topic of developmental patterning by using the wing of the fruit fly as a model system. His talk Crossveins and the extracellular regulation of BMP signaling briefly introduced the audience to wing formation and explained the differences between longitudinal veins and crossveins. Crossveins are especially sensitive to reduction in BMP signaling and Gbb is also required for their development. The system is interesting when mutations are added and different crossvein patterns result. He showed the effects of varying crossveinless 2 (cv-2), which is expressed and acts locally. Then he introduced Davids Umilis' exchange model for a single cell to explain the cv-2 biphasic response. This simple model predicts a cv-2 biphasic response in only 17 percent of parameter space. The response is biphasic for Gbb but not for Dpp. He then explored alternative mechanisms to obtain a biphasic response and associated models.

David Arnosti (Michigan State University) continued with the use of mathematical approaches to decode the ''grammar'' of cis regulatory elements. A popular model for transcriptional enhancers is the ''enhanceosome'' that features a highly constrained cis element design. Their analysis of short-range repressors on defined regulatory elements indicates that a second, more flexible form of design ("billboard" enhancer) better describes the activity of many developmental regulatory elements. He provided detail on the fractional occupancy model. This work will lead to the development of powerful bioinformatics approaches to interpret cis regulatory genomic sequences.

Arthur Lander (University of California, Irvine) presented the third talk in the afternoon. He started explaining how a more engineering oriented view in biology has recently started. Much research on morphogen gradients has shifted from purely mechanistic questions "how gradients form and how morphogens signal?" to strategic ones "how gradients perform well in the face of various kinds of constraints and perturbations?" For example, quite a few cellular and molecular processes have been described as contributing to robustness and precision. Do these processes constitute true strategies of control? Why are there so many of them? Why are some used in certain gradients but not others? He presented examples from Drosophila development to address these questions.

The day ended with a presentation on Drosophila organism-scale modeling by David Umulis (Purdue University). The main question he addressed is: How is the dorsal surface of Drosophila patterned? He pointed out that in earlier models there were not positive feedback terms and results did not correspond well with observations. Ways to improve these models are to include positive feedback, pre-patterns information, and/or geometry. His group developed a data-driven, 3D, organism-scale model of bone morphogenetic protein (BMP)-mediated embryonic patterning in Drosophila. The model tested 7 different receptor/feedback mechanisms and 8 different geometry/gene expression scenarios for their ability to reproduce the mean distributions of pMad signaling in both wild-type and more than twenty different mutant embryos. He showed that positive feedback of a secreted BMP binding protein, coupled with the measured embryo geometry, provides the best agreement between model and experiment. The inclusion of all-important factors in a 3D model represents a significant step forward in the systems biology of development.

Day 3

The central topic of the third day was Modeling and began with a talk by John Reinitz (SUNY at Stony Brook). He presented a model for the non-modular enhancer behavior of eve stripe 7 regulation in Drosophila. The goal is to predict gene expression from sequence and transcription factor concentrations, which is an important unsolved problem in molecular genetics. His hypothesis is "the independence of CRMs (cis-regulatory modules or enhancers) is ensured by short range (150bp) repression; repressors bound to binding sites in a given CRM are far away to affect activator in a separate CRM." He provided details on the use of the eve gene of Drosophila as a testbed for

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finding the general rules by which sequence controls gene expression in metazoa and points out that the complexity of the experimental phenomena require precise quantitative models for their interpretation. He demonstrated how two types of nonadditive behavior can be understood using a quantitative model in conjunction with quantitative expression data from promoter-reporter constructs.

Ben Shilo (Weizmann Institute of Science) gave the second talk. As in some of the previous talks, his research relates to the question: How is a morphogen gradient generated within the broad domain of uniform BMP expression? He defined developmental robustness as the ability of embryos to develop reproducibly, despite environmental and genetic variations and applied this general principle as a guide to find the patterning mechanisms. The mechanistic basis for the model relies on shuttling of BMP ligands towards the region containing the lowest level of inhibitor, to generate a sharp and robust morphogen gradient. He then extrapolated the findings from flies to Xenopus taking into account the presence of an additional ligand in Xenopus (termed ADMP), which behaves in the opposite manner to BMPs. In Xenopus, ADMP is expressed on the opposite side of the embryo, at the dorsal side, and its expression is repressed by BMP signaling.

The last morning talk was presented by Maria Samsonova (St.Petersburg State Polytechnical University, Russia). Her talk focused on the mechanisms of canalization and embryonic regulation in the morphogenetic field, which controls the segment determination in Drosophila. The data for this characterization are quantitative gene expression at cellular resolution in space and about six minutes in time. She provided details on the data processing, model formulation, and parameterizations. She then concluded: a) the segmentation morphogenetic field of Drosophila shows classic canalization behavior in the sense of Waddington, b) canalization of the hb border requires the activity of zygotic gap genes, c) the same is true of at least five other borders, and d) in general, canalization of the gap gene system happens because of gap gene cross-regulation.

Starting the afternoon session, Reka Albert (Pennsylvania State University) talked about modeling the Drosophila segment polarity network and lessons learned about the robustness of gene regulatory networks. Most genes that influence the segmentation of the Drosophila embryo act only transiently, yet the segment polarity genes have a stable expression pattern that defines and maintains the borders between different parasegments. These genes refine and maintain their expression through a network of intra- and intercellular regulatory interactions between gene products. Albert presented three related models of these interactions and how they lead to stable gene expression patterns. The modeling framework consisted of synchronous Boolean, asynchronous Boolean and a continuous-Boolean hybrid model (which is a piecewise linear ODE-based model). Together, these models span the range between discrete and continuous modeling. The results of the synchronous, asynchronous Boolean and hybrid models convincingly demonstrate the Boolean models' capability for effectively describing the basic structure and functioning of gene control

networks when detailed kinetic information is unavailable. Her take home message was that the topology of regulatory networks has a major role in determining their dynamical behaviors. She also referenced BooleanNet as an easy way to simulate Boolean models.

The last talk of day 3 was given by Hamid Bolouri (Division of Biology, Caltech). His title was: Reconstructing condition-specific gene regulatory interactions in the absence of perturbation data. Development is ultimately encoded in gene regulatory interactions and transcription factor (TF) perturbations have been used widely to predict candidate TF targets. However, identification of regulatory interactions between TFs and their target genes has been difficult, time-consuming, expensive and unreliable without TF-specific perturbation data. Bolouri talked about identifying the network of gene regulatory interactions that underlie the development of T-cells in mice, and the computational approaches his group is developing to address the challenges listed above. He used BioTapestry software (www.BioTapestry.org) for the explicit visualization of the network of regulatory relationships that appear to operate during T-cell specification.

Day 4

The first talk of the fourth day, entitled Bicoid-dependent embryonic patterning in Drosophila, was given by Stephen Small (New York University). He discussed an integrated approach to understanding the cis-regulatory logic responsible for controlling the expression of Bicoid transcription factor target genes in a manner dependent on position along the anterior-posterior axis. Bicoid plays an important role in establishing the Drosophila body plan; among the known Bicoid targets (approximately 20) are genes involved in the proper development of head and thoracic structures. To identify Bicoid-dependent elements in the Drosophila genome, Dr. Small described the use of a combination of bioinformatics methods and published ChIP-Chip data to identify clusters of Bicoid-binding sites that are then tested for in vivo activity by in situ hybridization experiments. He also discussed data mining techniques for the identification of sequence motifs or binding site arrangements that correlate with target gene positioning.

Angela Stathopoulos (Division of Biology, Caltech) then spoke on Patterning a field of cells: a comparison of dorso-ventral patterning of the embryo and anterior-posterior patterning of the wing disc. The talk included unpublished data about Dorsal, a NF-kB related transcription factor. Dorsal forms a nuclear concentration gradient in the early Drosophila embryo, patterning the dorsal-ventral axis to specify mesoderm, neurogenic ectoderm and dorsal ectoderm cell fates. These patterning events are thought to be determined by the concentration of nuclear Dorsal; however, the actual levels of nuclear Dorsal have not been quantified. Dr. Stathopoulos described a quantitative imaging method to characterize the dynamics of Dorsal nuclear gradient formation while simultaneously examining Dorsal target gene expression in nuclei along the dorsal-ventral axis. Results suggest that the multiple gene expression outputs observed along the dorsal-ventral axis do not reflect simple steady-state levels of the Dorsal nuclear gradient.

The title of the third talk, given by Stephen T. Crews (UNC Chapel Hill), was The Regulation of Drosophila CNS Midline Neuronal and Glial Development and Transcription. The regulatory circuitry of the midline cells (motorneurons, local interneurons, projection neurons, and glia) controls not only the generation of the distinct cell types, but also their migration, axon guidance, and glial-axonal interactions. Dr. Crews employed in situ hybridization to investigate the spatial and temporal expression of 278 midline-expressed genes and assembled the data into searchable, web-based database. Among the specific genes discussed were single-minded (sim), Notch, and lethal of scute (l(1)sc). Midline precursor and mature cell types at each stage of CNS development were also imaged using confocal microscopy, and Dr. Crews showed that midline glial migration, ensheathment, and subdivision of axon commissures are mediated by the Wrapper (midline glial-expressed) and Neurexin IV (neuronal and axonal-expressed) heterophilic adhesion proteins.

The last talk before lunch, titled The gene hierarchy that controls Drosophila mesoderm invagination, was given by Maria Leptin (Institute of Genetics, University of Cologne). Dr. Leptin spent a great deal of time establishing the genetic hierarchy downstream of the transcriptional activator Twist, which is required for all aspects of mesoderm development. The first steps in the establishment of the mesoderm, the formation of the ventral furrow, presents a tractable system in which one can easily trace the steps from Twist to the target genes responsible for morphogenetic activity. Dr. Leptin showed that six zygotically active Twist target genes are necessary to direct furrow formation, five of which directly affect cell shape changes and the sixth being the transcription factor Snail.

In the last part of the talk, Dr. Leptin suggested that a full characterization of the network downstream of Snail will be required for a complete understanding of how the dorso-ventral patterning cascade controls morphogenesis via Twist.

The afternoon began with a talk by Hans Othmer (University of Minnesota) on Robustness of Pattern Formation in Development. The talk focused on two questions: 1) how the correct genes turn on at the correct point in space at the correct time in development to produce the numerous cell types present in an adult, and 2) how the outcome is buffered against variations in enzymes, precursors, environmental changes, size of the system, etc. These questions were discussed in the specific context of scale-invariance: how different size embryos lead to normally-proportioned adults, both in Drosophila and in Xenopus. Dr. Othmer showed that scale invariance in early anterior-posterior patterning can be explained using experimentally-known facts about the dynamics of Bicoid, a protein involved in anterior development. Scale invariance in dorsal-ventral patterning comes about by a similar mechanism. He further showed that dorsal-ventral patterning in Drosophila can be understood in terms of three modules, and that positive feedback at the level of a surface binding protein explains the experimentally observed shape contraction.

Stanislav Shvartsman (Lewis-Sigler Institute for Integrative Genomics, Princeton University) gave the final talk of the day on MAPK substrate competition in the Drosophila embryo. Dr. Shvartsman explained that signal integration necessary for proper developmental patterning can be mediated by a simple enzymatic network and two inductive signals. The signals are provided by the Bicoid protein, which establishes the antero-posterior morphogen gradient, and the localized activation of the MAPK pathway at both anterior and posterior poles. Dr. Shvartsman's model also includes phosphorylation by MAPK of three proteins: the uniformly distributed transcriptional repressors Capicua and Groucho (relieving their repression of the terminal gap genes), and Bicoid (potentiating its transcriptional effects). Interestingly, modification of Bicoid by MAPK has an additional, reverse effect on MAPK phosphorylation and signaling. The end result is a MAPK-substrate competition network that integrates the anterior and terminal signals.

Day 5

Christine Rushlow (New York University) began the final day of the workshop with a talk titled Zelda, a key activator of the early Drosophila genome. Zelda (for Zinc-finger early Drosophila activator) is a zinc-finger protein first identified in the Rushlow Lab that binds specifically to cis-regulatory motifs, which are overrepresented in the upstream regions of many precellular blastoderm (pre-CB) genes. Mutant embryos lacking Zelda are defective in cellular blastoderm formation, and fail to activate many genes essential for cellularization, sex determination, and pattern formation. Dr. Rushlow further proposed that the biological role of Zelda in the preblastoderm embryo is to ensure the coordinated accumulation of batteries of gene products during the maternal-zygotic transition. This early preparedness is to allow sufficient time for the formation of molecular machines involved in cellular blastoderm formation and gastrulation, counting of X chromosomes for dosage compensation and sex determination, and pattern formation.

Manfred Frasch (University of Erlangen-Nuremberg) followed with his talk on Transcriptional and signaling networks during mesodermal tissue development in Drosophila. Dr. Frasch described the transcription and inductive signaling networks that lead to the progressive delineation of cell fates of the developing heart and other mesodermal tissues. Transcription factors of note are the NK homeodomain factor Tinman (Tin) and the T-box factors Dorsocross (Doc). Both Tin and Doc function within the dorsal vessel in myocardial cell diversification and differentiation. Tin acts in the early

Drosophila residua. Photo by Karl Magnacca.

mesoderm in combination with Dpp signals to promote the development of all dorsal mesodermal tissue derivatives, and Doc genes are essential for proper cardiomyocyte formation. A model of the regulatory interactions involving these important cardiogenesis factors in the Drosophila embryonic mesoderm was presented.

The third talk of the day, by Alistair Boettiger (Levine Lab, UC Berkeley), was titled Transcriptional Precision in the Drosophila Embryo. The talk began with a series of detailed images of nascent RNA transcripts within embryos. This imaging allows for a sensitive read out of the stochastic effects in gene regulation. Mr. Boettiger showed that elongation regulated genes are expressed more synchronously than initiation regulated genes, and that genes with multiple enhancers (shadow enhancers) are more robust to fluctuations in activator concentrations. In the second half of the talk, Mr. Boettiger discussed an approach to modeling the embyronic transcriptional network topology.

The final talk of the workshop was Gene Regulatory Evolution in a Class of Equivalent Developmental Enhancers by Albert Erives (Dartmouth College). The subject of the talk was the set of regulatory DNA sequences that are critical for specifying the number of different gene expression states available to a cell and the situations in which a cell transitions between these states. These regulatory DNAs are vastly more numerous and complex than the easily identifiable protein-coding DNAs that they regulate. Dr. Erives began with a discussion of why regulatory DNA is so important, first using a traffic signal as a simple example of how circuitry defines behavior, and then showing the combinatorial complexity present in Drosophila. He then surveyed the current obstacles to identifying regulatory "grammar" and "syntax", using a set of neurogenic ectoderm enhancers (NEEs) as an example. There has been significant sequence evolution in orthologous NEEs of different Drosophila species, making them an interesting system for the study of how natural selection acts on binding site organization. Dr. Erives concluded his talk with a discussion of how regulatory genomics could be used to move from Drosophila to address the larger questions of Metazoan origins.

Conclusion

This was a very successful workshop. It had a large number of participants and speakers, and the participants were a mix of theoreticians and experimentalists from a variety of disciplines: math, physics, bioengineering, genetics, cellular biology, biochemistry, entomology, zoology, computational biology, computer science, medical research, and more. The audience was engaged and asked many questions during each talk, with some talks turning into a lively group discussion that continued outside the lecture hall. This workshop provided a great networking opportunity and a number of new collaborations started as a result.

CURRENT TOPIC WORKSHOPS

MATHEMATICAL AND COMPUTATIONAL MODELS IN BIOLOGICAL NETWORKS (OCTOBER 20-24, 2008)

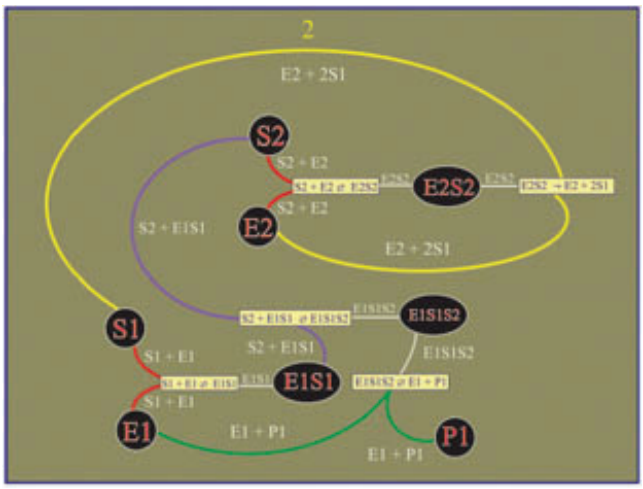
Organizers:

- **Marty Feinberg** (Chemical Engineering and Mathematics, OSU)
- **Eduardo Sontag** (Mathematics, Rutgers)
- **Gheorghe Craciun** (Mathematics, U. Wisconsin-Madison)

Overall Summary

The amount of experimental data describing biological network structure has increased dramatically in recent years. However, our understanding of how the interactions between network components determine function in complex biological networks is still relatively superficial. The problem is complicated by the fact that every network can be represented mathematically by its own system of (often nonlinear) differential equations. Fortunately, there is important information that can be gleaned from the network structure alone, such as the system's capacity for multistability, i.e., the capacity for a biological network to switch between distinct steady states. A focus of this meeting was this very question of the relationship between reaction network structure and the capacity for multistability. Are there criteria that would allow one to determine if a given network can exhibit multistable behavior for at least some system parameter values? Similarly, are there networks which cannot admit multistability regardless of the parameter values?

This Focus Group Meeting contained scheduled talks over three days, followed by two additional days of unscheduled sessions. All talks were characterized by spirited discussion of the important issues. This report is a summary of those scheduled talks only.



Summary of Presentations

Day 1

Morris Hirsch (Department of Mathematics, University of California at Berkeley) presented an overview of research in Monotone Dynamics. He began by surveying some of the historical developments in the area. Beginning with the notion of a flow, he discussed the development of the idea of an attractor starting with Alan Turing's computer generated results in 1952. He then introduced the idea of a monotone system and discussed various convergence criteria, including convergence in the cooperative Lotka Volterra system. Monotone systems respond in predictable ways to perturbations and have robust dynamical properties. This makes them reliable candidates for components of larger networks, and can be analyzed using control theoretic methods. In addition, if a system is strongly monotone the ordering on the initial conditions can be extended to their limit sets. The talk was followed by some lively discussions on recent work in the area including an extension of Smale's result on embedding arbitrary systems in strongly monotone systems.

The next presentation by German Enciso (Harvard Medical School) was titled "Studying switches and oscillations using I/O monotone dynamical sys-

tems." The talk discussed the analysis of long term behavior of large biochemical models through their decomposition into monotone systems, which in this context turns out to be systems with exclusively positive feedback. Information about the dynamical properties of the system such as global attractivity to equilibrium, or the presence of switches and oscillations can be obtained from computing, or in some cases experimentally measuring steady state response curves. The monotone decomposition of a large gene regulatory network was discussed. The second half of the talk focused on the analysis of certain non monotone systems, such as systems with negative feedback where the steady state response function has a globally attracting fixed point when viewed as a discrete map. Once again, the convergence results were based strictly on the network topology, and could naturally be extended to reaction diffusion systems and delay equations. As an illustration, Enciso ended his talk with a discussion on the existence of asymptotically stable equilibria and periodic solutions in a cyclic delay system with negative feedback and Hill function type nonlinearities.

Patrick De Leenheer (University of Florida) spoke about persistence in biochemical reaction networks (BRNs) in his aptly-titled talk "Persistence in biochemical reaction networks." The presentation began with a brief introduction of BRNs and some necessary notation. A BRN is said to be persistent if any initially present chemical species does not disappear. Necessary conditions for persistence were given algebraically. Moreover, De Leenheer et al. obtained sufficient conditions for persistence, which combine graphical and algebraic conditions. The RKIP network was investigated in detail to illustrate his approach, and the persistent behavior of this complicated system was verified by applying simple graphical and algebraic tools.

The afternoon session began with a talk by Martin Feinberg entitled "A Partial Roadmap to Chemical Reaction Network Theory." The talk was divided into four sections: 1) a quick chemistry primer, 2) a discussion of some "toy" problems, 3) an exposition on two relevant theorems, and 4) some additional theory. In the first part of the talk, Feinberg described how differential equations arise from underlying chemical reactions, and how to think of these systems of equations as geometric constructs. He then used a number of "toy" examples to motivate the remainder of his talk, followed by a detailed description of the deficiency zero theorem and the deficiency one theorem. With these theorems in hand Feinberg showed how one might determine if a set equations admit one or more positive equilibria, unstable positive equilibrium, nontrivial periodic solutions, and how the answers to these questions depend on the equation parameters for a number of model systems.

Gheorghe Craciun spoke on "Multiple equilibria in biochemical reaction networks." To begin, Craciun presented the case of enzyme catalysis with unordered binding of two substrates and asked simply if it can be determined that the network has the capacity for multiple equilibria for some choice of parameters. This question can be answered by looking at the associated polynomial function of the reaction network $p(c, k)$; if $p(c, k)$ is injective for all k, which is true if and only if the determinant of the Jacobian of $p(c, k)$ does not vanish for any k, then the reaction network cannot admit multiple equilibria. However, calculating the determinants can be difficult for even simple networks. Craciun then described a method for determining if a network admits multiple equilibria using the Species-Reaction Graph, and applied this technique to a number of example networks.

The title of the presentation by David Anderson (University of Wisconsin-Madison) was "The deficiency zero theorem, global stability, and stationary distributions." A chemical reaction network (CRN) consists of the chemical species, complexes, and reactors, and can be modeled stochastically (when the number of molecules is small), or deterministically (when molecules are abundant). For a deterministic CRN, Feinberg's deficiency zero theorem states that for a weakly reversible CRN with deficiency of zero, there is a unique equilibrium for any choice of rate constants in each positive stoichiometric compatibility class, and this equilibrium is locally asymptotically stable. Anderson and colleagues generalized the theorem for to address the question of global stability in deterministic CRNs. An alternate version of the deficiency zero theorem was also presented to deal with stochastic models of CRNs.

Day 2

In his second presentation, Morris Hirsch discussed the extensions of some of the results from the previous presentation to systems that are not monotonic. Competitive systems are systems where every interaction is negative, and many results from co-operative systems extend naturally to these systems. In particular, the quasi-cooperative Lotka Volterra system, which is a feedforward cascade

of monotone units, has globally attracting fixed point in each orthant. Furthermore, these results extend to coherent systems, which are systems where every loop is positive, i.e., every chain of interactions has an even number of negative interactions. The talk ended with a discussion of joint work in the area among some of the speakers present, and a brief summary of recent results.

Anne Shiu (University of California, Berkeley) spoke on "The smallest multi-stationary mass-preserving chemical reaction network." Shiu described how Chemical Reaction Network Theory (CRNT) was developed to study how many steady states exist in a given small network. Some connections were drawn between mass-action kinetics and computational algebra for the purpose of exploring the steady states of CRNs. Toric dynamical systems (TDSs) were then presented as nice examples of CRNs. TDSs are mass-action kinetics systems with a complex balancing state. It was shown that a mass-action kinetics system is a TDS if and only if simple binomial conditions are satisfied and the algebraic conditions can be calculated by applying matrix tree theorem. Furthermore, deficiency theory tells us how many binomials needed to know a system is a TDS. Finally, the multistationarity property of square networks was examined algebraically. It was shown that the square is a smallest multistationary, mass-preserving, reversible CRN under certain conditions. The example of ligand-reactor-antagonist-trap (LRAT) demonstrated how the theories and computations can be applied.

Carsten Conradi (Max Planck Institute for Dynamics of Complex Technical Systems) presented a talk titled "Multistationarity in biochemical reaction networks with mass action kinetics." He began with a mathematical description of BRNs and a precise definition of multistationarity. Motivated by Feinberg's CRNT, Conradi's method of finding the existence of two different positive steady state solutions that satisfy the same algebraic constraints involves first transforming the system equations and obtaining a new solution set. He based this work on the idea of generators for pointed polyhedral cones, and the results were formalized in two lemmas. The conditions for multistationarity, both necessary and sufficient, were presented. Conradi concluded his talk with an example of his technique being used to find solutions of a double phosphorylation mechanism.

The talk *Phenotypes in mathematics: bistability, long transients, or "fuzzy math"?* was given by Adam Halasz (West Virginia University). Noisy dynamical systems, as models of gene regulatory networks, were studied to reveal the correlation between biological phenotype and dynamical steady states. The *lac* operon was shown as an example of a bistable system with transitions between the two equilibria due to stochastic effects. Phenomenologically, the corresponding two metabolic states coexist and transit because of fluctuations. An example of a biological response that is not bistable and yet leads to two distinct phenotypes is competence in *B. subtilis*. Entry into a competent state is stochastic, but exit from that state is deterministic.

Another similar example is that of persistence in *E. coli*. The talk concluded with a discussion of the properties of persisters and possible mechanisms for persistence.

Biological clocks are among the most studied phenomena in mathematical biology. Daniel Forger (Michigan State University) discussed the application of techniques from mathematical analysis to the generalized Goodwin equations, which are an extension of the basic feedback network describing protein transcription. The equations contain a single nonlinear term describing the effect of the activated protein on the mRNA. Assuming that the system was oscillating, he used Fourier Analysis to derive exact formulae for time periods and average value of the nonlinear function along the solution, which in turn led to a bound for the smallest possible time period for the system. Important biological factors such as the transcription or

translation rates do not affect this minimum. The speaker also evaluated an index for the sensitivity of the nonlinear function to the concentration of activated protein using Fourier coefficients. The Generalised Goodwin equations were found to have large magnitude sensitivity, which is uncommon in genetic feedback networks, leading one to expect the presence of special biochemical mechanisms with high sensitivity in order for genetic clocks to oscillate.

Day 3

Maya Mincheva (Northern Illinois University) began the third day of the meeting with her talk "Oscillations of biochemical reaction networks." As oscillations are common phenomena in BRNs, it is important to search for and formalize generally-applicable graph-theoretic conditions for oscillations. To this end Mincheva first showed how BRNs can be described as bipartite graphs, then described how one could determine if a system has a simple Hopf bifurcation or Turing instability.

Due to scheduling conflicts, none of the authors of this report were present for the talk by Eduardo Sontag (Rutgers University).

MULTISCALE METHODS IN BIOLOGY (NOVEMBER 2-4, 2008)

Organizer

- **Mark Alber** (Mathematics, Notre Dame)

Overall Summary

The goal of the Workshop was to bring together researchers in mathematical biology, applied mathematics, biological physics, and bioengineering in order to determine important open problems in the field of multiscale modeling in biology and determine overlap between interests of the participants. The hope is this would create an activity group affiliated with the MBI to encourage efforts in this field in future, including development of new mathematical methods and adaptation of methods from applied mathematics developed for other applications such as physics and material science.

Brief description of some questions raised by individual participants:

Philip Maini suggested testing different cell-based models using a standard problem similar to that which was done for networks (NW). In DREAM, competition data is given to different groups: NW -> ODE -> solution -> time series -> reconstruct the NW. This will also help in determining the role of artifacts in specific models and help set a standard in the field of biological modeling. This can also be done by comparison with biological data with many cells traced. Dr. Maini also emphasized the importance of feedback in biological problems.

Bjorn Birnir, Herbert Levine, and Marcos Katsoulakis discussed scaling problems for simulations involving "super cells." Dr. Birnir mentioned importance of control theory methods for problems with feedback. Marcos Katsoulakis also talked about coarsening in Monte Carlo simulations.

Herbert Levine emphasized importance of having focused efforts in modeling (special years) similar to the activities of the international *Dictyostelium* discoideum group in biology, including a large conference every year.

Mark Alber spoke about the importance of the derivation of continuous limits for cell-based models (both lattice and off lattice) which would take into account cell-cell adhesion, cell volume and cell membrane fluctuations. He also emphasized the importance of coupling CPM and off lattice modeling approaches in order to take elastic properties of cells into account. He mentioned previous results from the theory of colloids as a helpful

starting point. He emphasized the importance of introducing sophisticated mathematical models based on stochastic systems. Also, better biological justification should be provided for terms used in many PDE models used in mathematical biology including nonlinear diffusion equations.

Timothy Newman spoke about off lattice models and emphasized the importance of connecting macroscale models with gene manipulation ex-

periments. He also mentioned that going from discrete to continuous models might leave out some important nonlinear correlations and lead to oversimplification especially when modeling development.

One suggestion for the focus of a future related workshop was to connect models of multicellular structures more closely with experimental data, in particular, gene networks. This connection is most clear in the area of development, where the vast majority of experiments involves the manipulation of gene expression, either in the entire embryo or in subsets of cells, and then observes changes to the embryonic phenotype. The experimental probe (gene manipulation) and the experimental observable (embryo) are separated by several orders of magnitude, spanning signal transduction, cell biology, and cell-cell interactions. It appears that modeling could play a key role in connecting these scales, thereby aiding the interpretation of experiments. Similar considerations apply to other multicellular systems, such as tumor growth, wound healing, and various tissue pathologies.

Summary of Presentations

Day 1

The first day was focused on discussing hybrid systems and connections between discrete and continuous models. The focus group organizer, Mark Alber (University of Notre Dame), gave a brief introduction to various types of multiscale modeling (MSM) that connects applied math, physics, and biology. He mentioned several conferences that have a focus on MSM as well as diverse research groups that have been working on similar problems with respect to MSM. It was noted that more collaboration among groups would be beneficial to furthering the field. A review of the relevant literature was also given.

Philip Maini (Oxford University) gave the first talk which focused on multiscale modeling of tumor growth in colorectal cancer. The colon consists of

a large number of structures called colon crypts, where each crypt can be thought of as a population consisting of three main cell types: stem cells, transitional cells, and differentiated cells. Initially, he discussed a continuous, nonspatial model which modeled intestinal tissue renewal, based on related previous discrete models in the literature which ignored feedback in the system. However, he pointed out that feedback is a necessary part of biological systems and went on to discuss the addition of feedback in the model; first as a linear term and then with more sophistication, such as a bounded feedback. The next iteration of model development included spatial effects (cell movement, position), cell-cell interactions (adhesion, signaling), as well as individual cell processes, such as the cell cycle governing cell fate (differentiation, proliferation). He mentioned the difficulty in determining what portion of the results might be due to artifacts of the model. This topic and the role of feedback in biological systems became important issues of discussion during the meeting. Lastly, he briefly discussed a hybrid cellular automaton model of metabolic changes during carcinogenesis and the role of glucose and oxygen

supplies on regulating the energy of a cell.

The next talk was given by Mark Alber (University of Notre Dame) on multiscale modeling of thrombus (clot) formation. He provided the biological motivation by showing experimental images of injuries undergoing blood clotting and wound healing. Various cell types are involved in the clotting process: plasma/quiescent platelets, red blood cells, platelets with high fibrin (which are the main clot formers), and activated platelets. At the macro scale, blood flow field was described by the incompressible Navier-Stokes equations and was numerically solved using the projection method. At the micro scale, cell movement, cell-cell adhesion, cell-flow and cell-vessel wall interactions were described through an extended stochastic discrete Cellular Potts Model (CPM). Some of the challenges that arose from these modeling efforts are (1) the coupling of continuous deterministic and discrete stochastic models, (2) the derivation and study of continuous limits of discrete models, (3) three dimensional extension and parallelization of algorithms, (4) reconstruction and analysis of three dimensional confocal microscopy images of clots, and (5) experimental design and setup to study the elastic properties of clots. He presented the results from simulations that demonstrated the development of an inhomogeneous internal structure of the thrombus, a feature confirmed by preliminary experimental data. In addition, predictions about different stages in thrombus development were given. These can be tested experimentally and he suggested specific experiments to do so. He also demonstrated that the dependence seen in the simulations of thrombus size on the blood flow rate was close to that seen in experiments. He ended his talk by discussing the possibility of making the CPM more complicated, by adding more levels of detail (e.g., cell-cell adhesion). This led to more discussion with audience members asking if CPM was the best choice and, in general, asking which cell-based models are good to use:

- Which cell-based models are good for multiscale modeling?
- How can one carry out sensitivity analysis of multiscale models? Can we use oversimplified models for a few parameters? How to get multiscale data?

Timothy Newman (Arizona State University) gave the next talk about connecting scales in models of embryogenesis. He began by giving an overview of key stages in embryonic development in metazoa, noting that embryogenesis spans multiple scales from gene expression due to intracellular signaling, up to cell-cell interactions, and finally morphogenesis at the embryonic scale. As an alternative/improvement to the Cellular Potts Model (CPM), he introduced a novel grid-free cell-based model called the Subcellular Element Model (SEM) which includes both cell mechanics and signaling effects. This was applied to chick embryogenesis and in terms of biomechanics, the SEM results agreed well with experimental rheology data. In addition, the model raised questions about the role of vortices in primitive streak formation (which defines the vertebrate axis). In this application, the SEM effectively connected the macro and micro scales, showing that such grid-free models may be promising tools in multiscale modeling. It was noted that cell-based models allow for large system simulation, but do not have the precision of subcellular models when looking at smaller scales. The following were questions that arose from this talk:

- How should macroscale models be connected to gene manipulation experiments
- How should discrete be connected to continuous models: is this an oversimplification (i.e., developmental systems)?

The final talk of the first day was given by Markos Katsoulakis (University of Massachusetts, Amherst). He discussed mathematical strategies for obtaining coarse-grained (CG) approximations of many-body stochastic systems. He emphasized the following three themes in his talk: the role of stochasticity in many-body systems, the potential for systematic model reduction via CG to bridge scale disparities, and how to build the correct stochastic CG model. Starting with simple examples, he discussed temporal coarse-graining approaches such stochastic differential equation (SDE) approximations of the master equations in chemical kinetics and stochastic averaging methods in systems with temporal scale separation. He then presented hierarchiacal coarse-graining methods and related challenges arising in many-particle systems both in equilibrium and out-of-equilibrium settings. He noted that, at different resolutions, CG models may consist of macroscopic PDEs, stochastic PDEs, or CG kinetic Monte Carlo algorithms. He also discussed the feasibility of spatio-temporal adaptivity methods for the coarse-graining of microscopic simulations, having the ability to adjust during the simulation if substantial deviations are detected from a suitable error indicator. Finally, motivated by related problems in the simulation of macromolecular systems, he presented math-

CURRENT TOPIC WORKSHOPS

Dictyostelium Aggregation.

ematical strategies for reversing the coarse-graining procedure.

The first day ended with a discussion session which addressed some of the major questions brought up during the day's talks. Most of the discussion was centered on the importance of feedback in biological systems. Two examples where feedback was noted to be important were in (1) developmental biology, where feedback exists between cells and their environment, affecting the internal state of the cell; (2) in *Dictyostelium*, where the various models have actually somewhat converged on results as far as aggregation is concerned. Other questions about feedback were also raised:

- How do errors propagate forward when there is feedback? Knowing the error at each level might be possible, but this information alone may not be enough to accurately quantify total error.
- How does one ensure due to feedback that the approximations are valid? For example, if feedback caused substrate to be used up significantly, then the mean field approximation might break down.
- Can other degrees of freedom (besides on the genetic level) play a role?
- What is the role of feedback with the environment?
- Can control theory/methods be used to understand feedback? As in the work of John Doyle and others.

There was also a side discussion about where the biological communities' interest lies in terms of cell-based entities. Many focus solely on genes rather than cell level factors. This led into a short discussion on another of the questions raised earlier in the day: Which cell-based models are good for multi-scale modeling? A suggestion was made to calibrate all available models on one biological problem to compare them. In addition, the issue regarding model artifacts was also discussed as a sub-problem of this, something that could be studied under the above suggestion. This was noted to be related to the issue of wanting to connect macroscale models to gene manipulation experiments. Further, the idea of creating a competition of some sort to foster work on these and other questions was also posed. Bjorn Birnir offered a suggestion regarding coarsening techniques, such as the classification of "super cells" and the methods of scaling theory.

The discussion period also addressed the issue of sensitivity analysis of multi-scale models, where it was noted that only using a few parameters might oversimplify things too much. In addition, if models have too few parameters, there might not be enough detail; whereas too many parameters leads to difficulties in model validation and complications in analysis, making it hard to extract meaning and/or mechanisms behind the observed behaviors.

Briefly, the need to acquire multiscale data was brought up. Lastly, a question was addressed about whether the processes/methods used to go from discrete systems to continuous systems were oversimplified. For example, many cells move based on factors of one cell; nonlinear interac-

tions between degrees of freedom and transitioning from discrete to coarse graining. One can use a PDF assuming there is statistical independence. If in reality there is no statistical independence, how close is the approximation? It is better for large densities, but not so good for small cell density.

Day 2

The second day of the focus group meeting started off with a talk by Jianzhong Su (University of Texas at Arlington) on multiscale issues from molecular and cellular level modeling. Jianzhong began by introducing the problems associated with implants, including the usual stages of wound healing and foreign body reactions in implants. He also reviewed previous mathematical models of these processes and the series of events that are modeled, using a diagram to illustrate. He presented results for a new model that captured the attraction of macrophages to the implant, which increased the collagen fiber growth. The fiber growth occurred in a traveling wave-like fashion. Secondly, he presented work done on modeling synaptic transmission via the release of neurotransmitters. He talked about random release events that typically activate receptors within a single postsynaptic site, giving rise to miniature postsynaptic currents or "mini's." Both spontaneous and activation induced release occurs and the goal is to understand the fundamental difference between these release types. He discussed other relevant biological background, including the NMDM receptors that receive the glutamate particles. A diffusion PDE model of glutamate diffusion was presented as the base (simple) model. The basic hypothesis was that evoked releases were released on top of one of the receptors in the center (denoted R6), and the spontaneous release was released on a receptor (denoted R16) at the edge of the receptor "grid." Another model was then used, where the receptor mode (i.e., probability that the receptor is open, Popen) was taken into account, starting with three closed channels and two open. There was no difference in Popen with respect to spontaneous vs. evoked release if glutamate was released on top of the receptors, i.e. when each receptor was directly below the release site. However, if released from the center versus released from the edge, then there was a twenty-fold difference in the peak of Popen between the two postsynaptic receptors, R6 and R16. Looking at release from the center, with respect to different receptor modes, there was as little as a two-fold difference in the peak value of Popen. This corresponded well to experiments that showed that blocking the evoked release resulted in a reduction in spontaneous receptor activity. He mentioned that the rate at which the releases rise was too fast, due to the fact that calcium signaling was not considered, an important part in the release mechanisms (Herbert Levine would address this in his talk). He noted that multiscale modeling would be helpful, since the vesicles containing the neurotransmitters do not release all their contents at once, which would be a different release mechanism. It was noted by Herbert Levine that the type of MSM needed would be on a different scale than many of the problems brought up thus far in the workshop. This is a multiscale problem going from proteins upward to the cell scale phenomena versus going from cells upward. In other words, it is a multiscale model, just one scale lower than those being discussed at the workshop.

The second talk, by Herbert Levine (University of California, San Diego), complemented the material presented by Jianzhong Su. He discussed the immense complexity of neurons and how this complexity is typically not captured in neural networks. In terms of the synapse, this also is true, where neural models make many "nice" assumptions about behavior which are simply not true of real synapses. He went over the pre-synaptic processes and the role of calcium in causing a morphological change of endosomes containing neurotransmitters to release its contents once docked at an active zone. This release process is inherently stochastic. He emphasized that calcium dynamics are an inherently spatially-extended nonlinear dynamical process. He reviewed intracellular calcium handling, specifically, positive feedback via calcium induced calcium release (CICR), which give rise to excitable dynamics. He then went over a model by Tsodyks and Markram, regarding neurotransmitter depletion, i.e. synaptic depression. However, the model did not take into account calcium dynamics (i.e. calcium facilitation) and there is no stochasticity considered with respect to vesicle release. Thus, he noted the need to either (1) consider a full biophysical model of the pre-synaptic zone and/or (2) make phenomenological modifications to the model. With respect to (1), the details regarding the calcium sensor were considered in a new microphysical model of pre-synaptic Ca dynamics. The program M-Cell (a Monte Carlo simulation tool) was used to perform simulations of the calcium diffusion process, where individual calcium ions were tracked. With the model, the interplay between geometry and synaptic facilitation was explored and it predicted that synapses with greater than 2-fold facilitation must contain the calcium amplification

provided by the endoplasmic reticulum. He discussed comparing these results to those of a PDE model of the same, a work still in progress, as a test case to explore limitations of PDE models versus an individual particle based model, to determine, for instance, whether or not stochasticity in the individuals is important overall. He noted some of the difficulties of developing such a PDE. He also discussed the addition of other cell types (i.e., astrocytes) that are present at the synapse and can signal and sense glutamate which, in turn, can raise the release probability of calcium. This can increase the noise as well, which implies that there must be a balance and, in fact, experimentally measured astrocytic coupling makes the transmission optimal when the neuron is active. Lastly, he brought up various issues beyond the biophysical attributes of the synapse. These included possible important functions of neurons or neural networks that depend on a more sophisticated synapse (i.e. when a simple model is sufficient and when more complexity is needed) and how things might change when a more complex stochastic process is considered. He ended with a figure showing the various scales one might think about with respect to the neural system with the currently discussed work at the level of neurons and synapses:

1 m	CNS
10 cm	Systems
1 cm	Maps
1 mm	Networks
100 µm	Neurons
1 µm	Synapses
1 Å	Molecules

He then explained that the challenge will be to figure out which degrees of freedom are essential for which types of information processing.

Leonard Sander (University of Michigan, Ann Arbor) talked about a generalized Cahn-Hilliard equation for biological applications. He was interested in the relationship between discrete and continuous treatments of growing biological systems, such as fronts of cells invading a wound or in a growing tumor. First he discussed a discrete stochastic model in which cells can move, proliferate, and experience cell-cell adhesion. He then compared this model with a coarse-grained, continuum description of this phenomenon by means of a generalized Cahn-Hilliard equation (GCH) with an added term to account for proliferation. He talked about two interesting regimes with different kinds of front propagation, depending on the amount of cell-cell adhesion. In the case of subcritical adhesion, he showed that there were propagating "pulled" fronts, similar to those of the Fisher-Kolmogorov equation. He discussed the problem of finding the appropriate front velocity and noted that his theoretical predictions were in good agreement with a numerical solution of the GCH equation. In the case of supercritical adhesion, he found a nontrivial transient behavior. He concluded by showing that the results of continuum and discrete models agreed with each other for the regimes he analyzed. An interesting question was raised by an audience member about the role of cell shape/density and its connection to proliferation rate, noting that squished cells and sparsely placed cells have very different proliferation rates, at least experimentally. Sander said that in tumor cell lines (which was what he specifically looked at), this was not such an issue because tumor cells do not have large contact inhibition rates.

For the final talk on day two, Andre Levchenko (Johns Hopkins University) presented iterative computational/experimental analysis of the NF-κB signaling pathway and focused on the tools and paradigms involved. He began by showing a simple model of negative feedback, where damped oscillations occur. However, with respect to control engineering, damped oscillations are not a robust feature. Parameter values can be chosen such that either oscillations or normal time courses occur. This was compared to experimental data in an IKB (inhibitor of NF-κB) "double-double" knock-out experiment. He discussed the

time scales of different chemokine genes that are dependent on IKB. Some knockout experiments will cause other elements to be upregulated to compensate for the reduced amount being produced. To understand how this compensation mechanism works, he looked at the constitutive IKB degradation process. In fact, the model suggested a new way to look at this process, suggesting the initial interpretation of the data may have been incorrect. He presented results on the effects of IKB on gene transcription and discussed experiments in which the addition of NFκB to individual cells caused an over expression of NFκB. This artificially increased the positive feedback of the system. Taking this into account allowed the model to capture the data that, at first, seemed to be contradictory to the original model results. In fact, cells behaved relatively the same with respect to NFκB expression. He stressed that understanding the way experiments are conducted is a very important part of calibrating/validating one's model. He also discussed the various iterations of model development and refinement due to the experimental data that became available, noting that adding complexity is sometimes necessary in order to match new data with which it may have conflicted. A second topic that he presented was with respect to gram negative bacteria which move and aggregate via quorum sensing as seen via luminescence. He briefly discussed the signal transduction pathway regulating quorum sensing toward luminescence. Dr. Levchencko suggested that decoupling positive feedback loops in an attempt to understand them via synthetic biology was a helpful strategy. He presented a simple model of signal transduction on quorum sensing with one type of feedback present, which exhibits bistability and the existence of hysteresis at various glucose concentrations. A second type of feedback was then included in the model and showed that having both types of feedback is actually quite important.

Day 3

The final day began with a presentation by Bjorn Birnir (University of California, Santa Barbara) on a dynamical systems simulation of myxobacteria, regulated by Dynamic Energy Budget (DEB) theory. An interacting particle system was used to model myxobacteria in a petri dish. He discussed a lattice versus an off-lattice model. The off-lattice model included cell characteristics (like social behavior) and motility (slime secretion and pili). Three myxobacteria strains were considered which differ in their type of motility. After discussing the myxobacteria life cycle and the fruiting body formation, he presented the model, which incorporated Dynamic Energy Budget (DEB). DEB describes how cells acquire and utilize energy for maintenance, growth, and division. The use of DEB in the model successfully linked the internal dynamics of the individual cell with the dynamics of the population. A Dynamic Energy Budget (DEB) model controled the reproduction (splitting) of the bacteria and triggered the transition from swarming into the starvation phase. In the starvation phase DEB, with the addition of C-signaling (which occurs when two cells are in end-to-end contact), controlled the different stages of the fruiting body formations culminating in sporulation. He also discussed finding the appropriate scaling parameter needed to go from the super individual to the individual.

Melissa Knothe Tate (Case Western Reserve University) then gave a talk focused on understanding mechanical adaptation of self-assembling cellular constructs, emphasizing the need for mathematical models. She first described the properties of bone as a dynamic, self-annealing material and then listed the multiple scales involved in this research field:

- Systems Level (skeleton)
- Organ Level (joints; bones)
- Tissue Level
- Cell Level
- Subcellular Level
- Molecular Level

She then presented how bone heals via a tight network of cells in response to mechanical signals as well as the flow of fluids and discussed an analytical approach that determined how efficient diffusion would need to be to distribute fluid effectively to "feed the cells." Loading of the bones is necessary in order to push the fluids out and enhance the transport. In addition, small molecular entities are important for cell metabolism and are needed in mechanical loading as well and convective transport. She then explained the different levels of predictive computational modeling needed to reverse engineer the system. At the tissue level, the use of finite element methods and heat transfer were considered; computational fluid dynamics was used at the sub-cellular level; and at the organ and tissue levels, which are poroelastic, they used the Navier Stokes equation. Finally, established experimental models were used in developing the computational models. She illustrated how the modeling was accomplished, explained which tools were used to model each part, and shared the predictions that were made. Results

led to the need for refinements on the model. Specifically, they changed the way they modeled the bone (tissue -> cell scales), by including site specific definition of material properties. This showed a counterintuitive flow in the bone. At cell -> sub-cell scales, she discussed the effect of model geometry on outcome and showed that the geometry was very important to capturing the proper flow of nutrients to the cells. So, including the microporosity characteristics proved important, bringing the system together from bone level to cell level. The counterintuitive flow came about due to the mechanoactive materials: porosity controls flow direction and permeability controls rate. This revealed that bone is more than just a sponge, resulting in the development of a new technology for helping wound healing, especially in immobile patients via a type of convective transport band aid (Convect-A-Med technology). She then discussed predictive mathematical modeling of cell adaptation, noting that, in development, there exists self assembly by stem cells. Questions arise such as, "What are the mechanics of the stem cells at an early state, before any pressure is exerted by blood flow via a heartbeat, for example?" and "What are the effects of mechanical stimuli on multipotent cell fate?" Very few studies examine stress ranges during the very early stages of development; yet, these stresses are very important to determining cell fate. In a mouse study, precise mechanical stresses were applied during early stages and genes relevant in determining cell type were assessed. A very low sheer stress was applied on the cells (1000 times smaller than that which a normal cell in the knee experiences at any given time). The cell shape was modulated, with the nucleus producing structural proteins, showing mechenosensitivity. In addition, the genes for collagen types 1 and 2 were upregulated. Even though fate had not yet been determined, the path the cells were on was a little more restricted than before. She discussed the goals and challenges of mathematical modeling with respect to self constructing cellular aggregates, noting new approaches are needed. The problem has great spatiotemporal variation in geometry/architecture as well as material properties. Thus, methods are needed to handle the non-continuum case, multiscale levels, nano-effects, and stochasticity. She ended by presenting the overall goal of ultimately being able to predict origin of life on earth (via understanding how single cells aggregate and form structures over time) and a more short term goal of guiding prioritization of mechanism elucidating experiments, to improve life on earth.

Andy Stein (University of Minnesota) gave the next talk which focused on the micromechanics of 3-dimensional collagen gel. He noted the importance of developing an accurate model for cell motility in order to understand such processes as tumor invasion, wound healing, vasculogenesis, and artificial tissue design. Given that cell motility is frequently studied in 3D collagen gels, it is desirable to have a mathematical model to describe cell-gel interactions. Various such models have been developed, treating the collagen as a linear, viscoelastic, material, but on the microscale, collagen is a network of fibrils, and it is not clear if such models are valid, especially at the large deformations cells impose on the gel. His goal was to accurately describe cell-gel interactions on the microscale level by treating the collagen as a discrete network of fibers. This first required the development of micromechanical models of the collagen gel itself. He presented a novel image processing algorithm for extracting the collagen network architecture from a stack of 3D images obtained from confocal microscopy. The two main components in the model were worm-like-chains and cross links which corresponded to different types of energy. He then discussed the behavior of different micromechanical models and compared his model to experimental data. In future work, he plans to include cells in the collagen network, which would require the addition of complex properties such as cell focal adhesion into his model.

The concluding talk of the workshop was given by

Alethea Barbaro on an interacting particle model of fish migration and associated scaling laws.

She discussed a model for spawning migration of capelin, whose presence is important for ecological stability. She modeled the migration process via an interacting particle model combined with some environmental information. It was a zonal model in which there were three different zones of interaction that determine where the particles travel. The model was two dimensional and took into account the *x* and *y* coordinates of the particles, the speed of fish (different from other similar models) and directional heading of the particle (determined by the sum of two terms representing interactions among particles and the reaction of particles to the temperature), and the current. The current field used was not based on actual data, but was an approximation of tidal currents. The temperatures used in the simulation were based on actual data. Each particle did not represent a fish, but instead represented multiple fish ("super-individual") i.e., a subschool. She explained that it was desirable to have the behavior and spatial patterns preserved when the number of particles changes, so she presented the notation and reasoning used for the scaling laws considered. Data from 1984-1985 was used to test the model and results were comparable with respect to the location into where the fish swam. In 1990, there was a different temperature map where there was only a small region where the particles were "comfortable" (i.e., temperature range was just right). Data showed capelin in different regions during a different time period, and the model also showed particles in the same areas. In February 2008, the model gave the following prediction: capelin would go farther off the coast and come into an unusual part of the coast where the fishing vessels would not normally go. In reality, the fishing industry shut down to prevent overfishing because they could not find any capelin where they usually looked. The timing and location of when and where the capelin actually did come in was predicted accurately by the model. She discussed strategies of how to carry out sensitivity analysis on the system, explaining that the parameter \beta (the weight that a particle places on temperature, rather than interaction) plays a significant role.

The final discussion session focused on the possibilities of organizing follow up workshops that would (1) include several experimentalists, (2) discuss "Multicellular Structures from Genetics Programs," and (3) be set up in such a way to devote more time to discussions. The goal of a follow up workshop may be to focus on setting up problems, but not necessarily solving them. Also, it was recommended to create a special issue of the Bulletin of Math Biology to focus on challenges and methods in multi-scale modeling. In addition, there was interest from postdocs on a possible summer school on multiscale modeling methods with research lectures (perhaps once a week), which could develop into MBI lecture notes.

Conclusions

This workshop brought together individuals from diverse fields, whose research, though varied in application, showed many similarities with respect to the challenges faced in modeling complex systems at various scales. The different perspectives proved to be an important component of the workshop, with individuals sharing their experiences and methods in hopes of elucidating answers to the difficult questions posed. The discussion sessions involved most participants and helped clarify the different issues that arise in multiscale modeling, leading to many important questions and specific challenges that call for new tools both experimentally and mathematically to aid in the process. Participants enjoyed the stimulating conversations that happened both inside and outside of the lecture hall, noting that the workshop succeeded in prompting individuals to collaborate on MSM problems with those outside their field. The organizers and participants considered the meeting very successful and helpful and are hopeful that this will serve as a stepping stone to future workshops and partnerships.

CURRENT TOPIC WORKSHOPS

CURRENT TOPIC WORKSHOP: SYSTEMS BIOLOGY OF BIOLOGICAL PROCESSES AND DISEASES: BIOLOGICAL PROBLEMS AND STATISTICAL SOLUTIONS (APRIL 16-17, 2009)

Organizers

- **Hongzhe Li** (Biostatistics and Epidemiology, University of Pennsylvania School of Medicine)
- **Shili Lin** (Statistics, OSU)
- **Tim Huang** (Molecular Virology, Immunology, and Medical Genetics, Human Cancer Genetics, OSU)

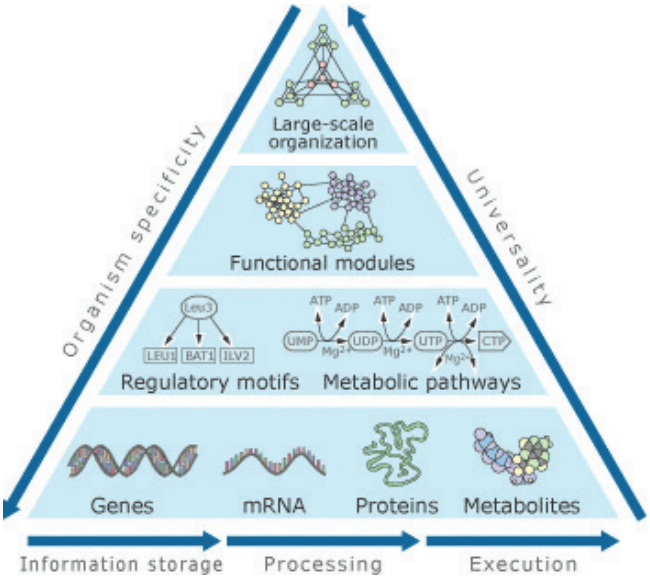
Summary of Presentations

Day 1

The first talk was given by Terry Speed (University of California at Berkeley). Dr. Speed presents how the recently developed microarray systems for gene-expression studies are already being superseded by new high-throughput next generation Illumina sequencing machines. The new methods are useful for evaluating differential expression of genes by estimating transcript abundance from reverse-transcribed mRNA from treated and untreated cells, and estimating copy number variation. The last part of his talk was a discussion on how to minimize the effects of artifacts and how to make results from different runs comparable to each other using new statistical methods.

The second talk was by Jun Zhu (Rosetta Inpharmatics, Merck Research Laboratories) on the topic "Integrating diverse data to elucidate multilevel regulations of biological systems: A systems approach for complex human diseases." Dr. Zhu described how Bayesian network analysis on a variety of data sources, including RNA microarray data, chip-chip data, protein array data, siRNA screening data, and DNA variation data to find the significant gene networks that can help identify new drug targets and biomarkers for diseases like obesity, diabetes, and heart disease.

The next talk was by Xianghong Jasmine Zhou (University of Southern California) who gave a presentation on "Integrated approaches to mapping genome to phenome." Genomic studies using microarray data with associated data are successfully used to reconstruct the biological basis for phenotypes. These types of associative studies have been less successful in finding the gene-gene interactions behind complex phenotypes. Dr. Zhou explained how her research group has developed graph-based multi-objective simulated annealing methods to indentify phenotype specific gene co-expression modules.



The first talk of the afternoon, "High-throughput assays in epigenomics research" was given by John Greally (Albert Einstein College of Medicine). Epigenomics is the area of gene regulation by other mechanisms than thorough features of the genome itself, such as cytosine methylation and transcription regulation. Microarrays and next generation sequencing are methods for finding methylated cytosine sites in the DNA, and associating methylation regulation with phenotype. Dr. Greally's research group is developing methods to work with the large amounts of data that are produced through epigenome wide assays at

the new Einstein's Center for Epigenomics. Areas of research include methylation regulation in cancer and neurological disease such as Huntington's disease.

The second talk of the afternoon was given by Kun Huang (OSUCCC BISR) on "A systems biology approach to model breast tumor microenvironment." Dr. Huang's project is on incorporating very different kinds of data into models for cancer developments. This includes cell-to-cell interaction data from microscopic imaging and molecular information from microarrays. The imaging data are collected as 2d-images and Dr. Huang's research group is developing algorithms for reconstructing the three dimensional environments and correcting for artifacts introduced by the preparation of the microscopic slides.

The last talk of the day was "Enhancing signal detection ability through information sharing," presented by Naisyin Wang (Texas A&M University). When studying dietary effects on the formation of colorectal cancers, identifying genes involved in the promotional stage is significant, as they play an important role in tumor formation. The difference in gene expression, as measured by microRNA and mRNA at the promotional stage is low compared to that of cancerous vs. normal cells. However, multivariate analysis from data collected from different experimental setups can be used to find the weak but significant differences that diet has on tumor formation.

Day 2

Dr. Gustavo Ayala gave a talk entitled "From Biomarkers to Modeling." At first, he emphasized the importance of studying biomarkers by pointing out that the number of publications related to biomarkers in Pubmed is huge (431,452), though only a few are clinically used, such as ER, PR, Her2, Proliferation rate, and C-kit. He then introduced the five phases of biomarker development for early detection and discussed some research conducted in his lab: prostatic adenocarcinoma, gene profiling using tissue microarray, and the convenience cohorts versus longitudinal cohorts. In the last part of this talk he discussed some new research projects about the relations between nerve cells and cancer cells. He also showed the effect of nerves on three-dimensional caners.

Dr. Forrest White gave his talk on "Biological insights from quantitative analysis of signaling networks." He started with the question: How does signaling regulate cellular response? He gave an answer using circuits as an analogy. His talk covers the following parts: 1) collect both phosphorylation data and phenotypic data and then do integrative data analysis (i.e., data-driven correlative analysis and quantitative mechanistic models) to study certain biological hypothesis, then come up with combinatorial inhibition strategies; 2) conduct quantitative signaling network analysis by mass spectrometry; 3) study ErbB receptor family signaling; that is, first, quantify the effect of HER2 expression and EGFR signaling, second, study the effect of HER2 over expression on EGFR signaling network and cell migration pathway, and third, compare Heregulin versus EGF simulation in Her2-expression cells; and 4) study EGFR receptor signaling pathway in the context of Glioblastoma.

In the afternoon, Simon W. Hayward (Vanderbilt University Medical Center) gave a talk on "Cellular interactions and prostate cancer progression." He mainly addressed the following two questions: 1) How does the stroma environment promote or facilitate tumor progression; and 2) Can interactions between stroma cells inform and influence interactions with adjacent epithelial cells. With some specific examples and data, he explained that: a) TGF-beta signaling elicits EMTs at the invading front of BPH1caftd1 tumors; and b) stroma-epithelia interactions cannot be considered as a simple two-way combination.

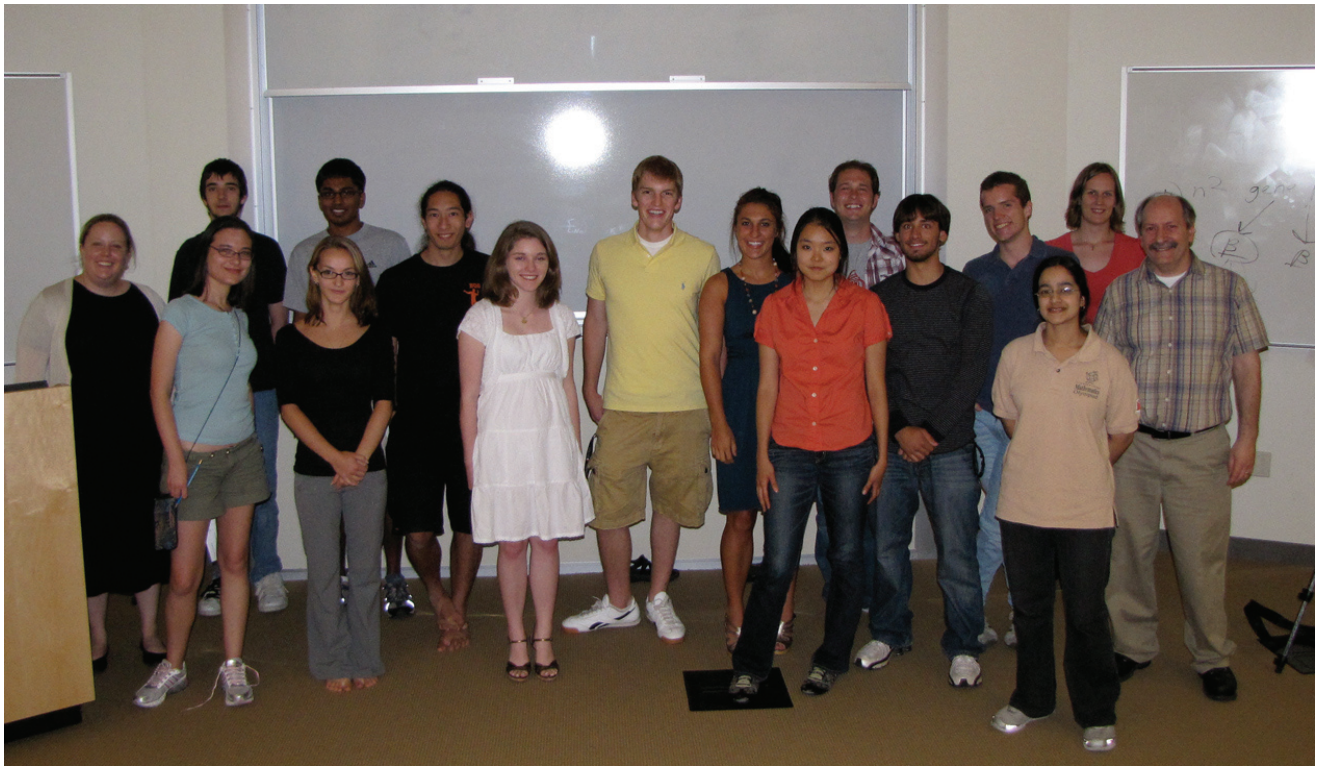
EDUCATION PROGRAMS

UNDERGRADUATE PROGRAM (JUNE 22-JULY 2, 2009)

The summer of 2009 marked the MBI's fourth annual Summer Program for Undergraduates that includes a two-week active survey of mathematical biology followed by a six-week Research Experience for Undergraduates (REU) program.

The first week of the program involved tutorials and hands-on computer labs in mathematical bioscience topics. The first day saw Dennis Pearl presenting key issues in statistical phylogenetics – aligning molecular sequences and inferring evolutionary trees. In the afternoon, Lori Hoffman led a computer lab, giving students a chance to try out the Clustal alignment program along with Phylip and MrBayes phylogenetics software. On Tuesday, MBI postdoctoral fellow Michael Rempe lead a morning tutorial on the principles of mathematical neuroscience, focusing on issues related to the Hodgkin-Huxley model and dynamical systems with application to modeling sleep rhythms and then gave participants experience with the XPP and MatLab programs in the afternoon computer lab. Wednesday saw Joe Verducci and Paul Blower presenting issues in the quantitative analysis of chemogenomic and pharmacogenomic data, while Li Yu supervised the afternoon computer lab using the R package and specialized "tau-path" programs. Kate Calder presented a lively tutorial on statistical analysis of environmental data the following day while Candace Berrete led the afternoon computer lab using R. The week concluded with Ken Huang covering selected topics in bioinformatics and Jie Zhang guided the students in trying out Matlab bioinformatics toolboxes and the DAVID online bioinformatics software in the computer lab that afternoon.

Dividing into teams, the students were given a chance to study a real problem in their chosen topic area during the second week. The two-week survey concluded with each of five teams participating in a mini-conference, making both poster and oral presentations on their projects. The mathematical neuroscience team (Barry Bohnet, and Christopher Mehfoud) presented their studies of the mechanisms underlying the circadian rhythm and what their model predicts about the phenomenon of jet lag. The phylogenetics project team (Olga Tkachenko and Nathaniel Chandler) presented an analysis of the evolution of the swine flu virus and testing its relation to geography, time, and host population. Next, the Environmental Statistics group (Erinne Kennedy, Hyebin Song, and Mathew Wildenborg) described their study of the association of deaths from cardiovascular related disease with the level of 10 micron sized particulates in selected U.S. Cities. The bioinformatics project, presented by Nathaniel Dynkiewicz, Meghan Ferrall, and Aubrey Leung, explored database techniques to discover gene co-expression networks in breast cancer and to identify biomarkers that predict prognosis in estrogen receptor negative patients. Finally, the chemogenomics team of Daphne Ezer, Sridevi Maharaj, and Kasun Waidyaratne examined the relationship between gene co-expression and cancer drug activity using the tau-path method. The collaborative nature of all of these efforts was illustrated as each student presented a substantial part of their group's work.



During this two-week program, the students also toured labs that use quantitative methods in the biological and medical sciences. This included a tour of the lab of neuroscientist Joe Travers who studies how neuronal circuitry processes sensory information. John Wenzel gave the group a tour of Ohio State's Museum of Biological Diversity with its major acarology and plant (more that a half million specimens each), insect (over 3.5 million specimens), fish (1.5 million specimens), and mollusk (150,000 specimens) collections that are available for both teaching and research. In the final tour, MBI Associate Director Libby Marschall and her team of graduate students showed off their work on the many projects in the Aquatic Ecology Laboratory.

At the conclusion of the two-week program, the REU component of the summer program then chose five students to spend six weeks going into much more depth in a research project in their chosen area. Sridevi Maharaja studied the problem of finding the distribution of orbits of concordance matrices under the group action of permuting the margins. This problem has application to identifying a subset of cancer cell-lines most likely to have a dependence relationship between gene expression and chemoresistance. Olga Tkachenko studied the evolution of penguins and was able to resolve a controversy in the literature regarding differences between the estimated phylogeny based on morphological data and the phylogeny based on mitochondrial molecular data. Erinne Kennedy followed up on the work of the environmental sciences team project by studying the health effects of 2.5 micron sized particulates in more depth. Barry Bohnet and Aubrey Leung were each involved in bioinformatics projects with Barry examining the correlation structure in gene expression arrays and Aubrey investigating genome-wide single nucleotide polymorphism data.

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

EDUCATION PROGRAMS

GRADUATE PROGRAM (JULY 27-AUGUST 14, 2009)

Organizers

- **Ian Hamilton** (Ecology, Evolution, and Organismal Biology and Mathematics, OSU)
- **Yuan Lou** (Mathematics, OSU).

A total of 22 graduate students and one undergraduate from departments of mathematics, statistics, and biological sciences participated in the MBI's Summer Graduate Education Program on *Mathematical Ecology and Evolution*. Of these participants, 20 came from U.S. Institutions, one from South Korea, one from Taiwan, and one from mainland China. Among these participants, eight are female and two are male African Americans.

The first week of the program included tutorial lectures in mathematics, statistics, biology, and computing. Ian Hamilton presented five lectures during the first week of the program. These tutorials were intended to be a general introduction on the evolutionary ecology of interacting phenotypes; including an introduction to evolutionary theory, evolutionary dynamics, the use of game theory in evolutionary ecology, and the evolution of cooperation, competition, and games between antagonists.

Yuan Lou also presented five lectures on the theory of Adaptive Dynamics with applications to the evolution of dispersal, consumer-resource models, and the evolution of virulence. The basic mathematical models are described by ordinary and partial differential equations.

In addition to these two lecture series, Paula Federico (MBI postdoctoral fellow) gave a lecture on "Introductions to Individual based models." Chuan Xue (MBI postdoctoral fellow) gave a lecture on "Introduction to MatLab."

Following these lectures, the project group leaders (Paula Federico, Rasmus Hovmoller, Deena Schmidt, and Chuan Xue; all current MBI postdocs) introduced their projects, after which the participants are divided into five groups according to their interests. There was an extra group since three participants decided to form one team to work on Adaptive Dynamics.

During the next two weeks of the program, the groups worked on their individual projects. On the final day of the program, each group presented their results to the entire group of participants and instructors.

All presentations and lectures are available online at http://www.mbi.osu.edu/eduprograms/graduate2009.html.

TEAM PROJECTS

Project 1: A phylogeographic distance metric for infectious disease
Project Leader: Dr. Rasmus Hovmoller
Participants: John Christensen, Shishi Luo, Jacob Porter, Tianjun Ye, Marina Yurieva, and Robert Zanstra

Project 2: Multiscale models of chemotaxis
Project Leader: Dr. Chuan Xue
Participants: Darius Wheeler, Jason Hammond, Jae Kyoung Kim, KangLing Liao, Jung Eun Kim, and Ran Yin

Project 3: Learn individual-based modeling basics by modeling fish movement behavior
Project Leader: Dr. Paula Federico
Participants: Isabel Averill, Vinodh Chellamuthu, Jason Graham, and Kamuela Yong

Project 4: Evolution of variance in mate choice
Project Leader: Dr. Deena Schmidt
Participants: Lisa Bono, Mauricio Gonzalez-Forero, Seongwon Lee, and Longla Martial

A numeric approach to Adaptive Dynamics
Project Leader: Yuan Lou
Participants: Justin Peyton, Richard Gejji, and Dan Munther

FUTURE PROGRAMS

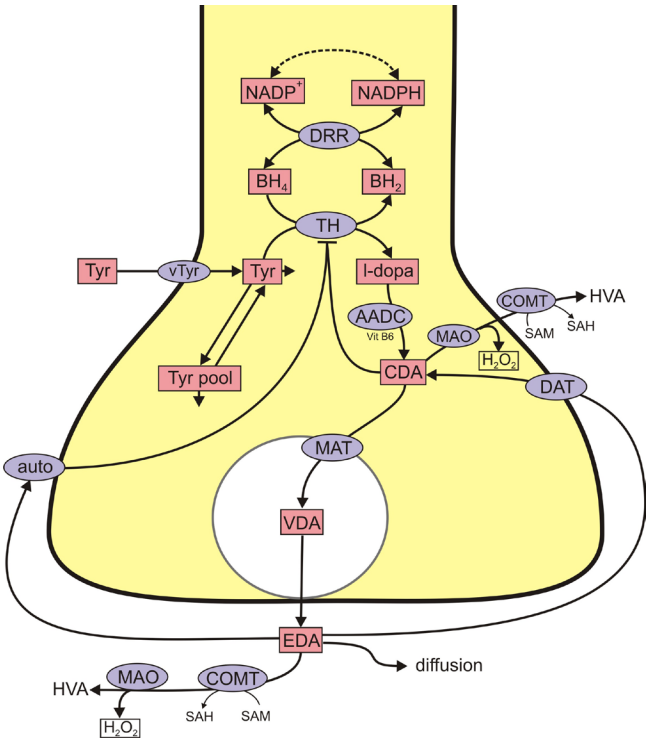
MOLECULAR INTERACTIONS WITHIN THE CELL: NETWORK, SCALE, AND COMPLEXITY
SEPTEMBER 2009 - AUGUST 2010

Organizing Committee

- **Reka Albert** (Physics & Biology, Pennsylvania State)
- **Eivind Almaas** (Physics, OSU)
- **Laszlo Barabasi** (Physics, Northeastern)
- **Jeff Hasty** (Bioengineering, UCSD)
- **Ian Holmes** (Bioengineering, UC, Berkeley)
- **Anatoly Kolomeisky** (Chemistry, Rice)
- **Jané Kondev** (Physics, Cornell)
- **Hao Li** (Biochemistry & Biophysics, UCSF)
- **Ron Weiss** (Electrical Engineering, MIT)

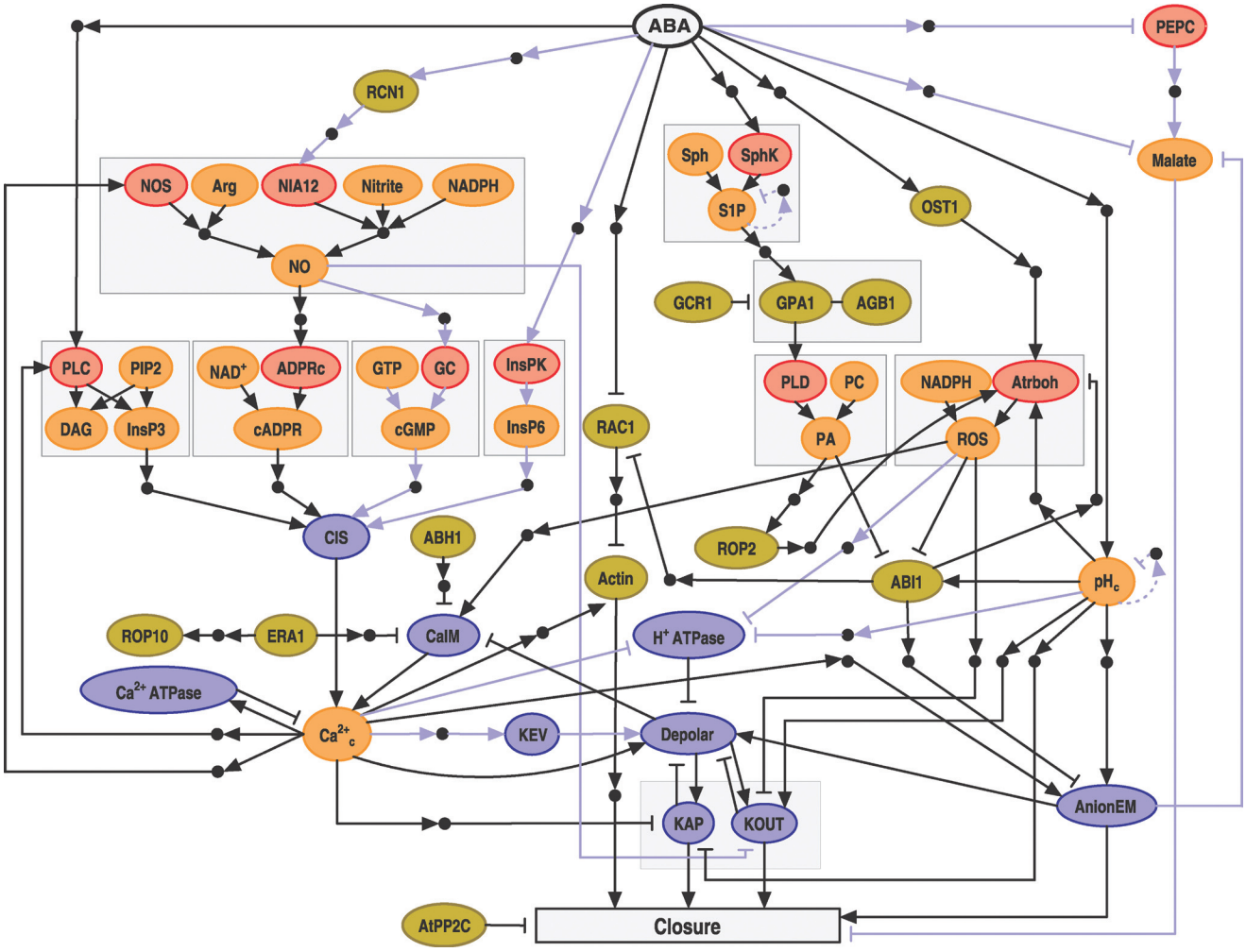
Biological processes can be characterized by different degrees of complexity at microscopic (genes, molecules), mesoscopic (protein-DNA complexes) and macroscopic (cells, organisms) levels. Historically, all biological systems have been studied at different levels. However, an increasing amount of experimental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

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



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

A unifying long-term goal of the proposed activities is to develop a unified approach to study the complexity of biological systems within cells.



Such a comprehensive view of biology will require an application and development of new mathematical methods. Current approaches include hidden Markov processes, stochastic dynamics, graph theory, partial differential equations, discrete mathematics and other tools of probabilistic modeling, machine learning and computational analysis. As in the past, it is expected that new frontiers in biology will both benefit from and stimulate the development of novel mathematical techniques.

Workshops

- *2009 Workshop for Young Researchers in Mathematical Biology* (August 24-26, 2009)
- *Workshop 1: Network Biology: Understanding metabolic and protein interactions* (September 14-18, 2009)
- *Workshop 2: Signal transduction and gene regulatory networks* (November 2-6, 2009)
- *Workshop 3: Synthetic biology* (January 25-29, 2010)
- *Workshop 4: Inference in Stochastic Models of Sequence Evolution* (February 22-26, 2010)
- *Workshop 5: Mathematical and experimental approaches to dynamics of protein-DNA interactions* (March 8-12, 2010)
- *Workshop 6: Transport in a cell* (April 12-16, 2010)

Current Topic Workshops

- *Current Topic Workshop: Computational challenges in integrative biological modeling* (October 5-9, 2009
- *Current Topic Workshop: Mathematical Developments Arising from Biology* (November 8-10, 2009)
- *Current Topic Workshop: Biofilms and Infectious Disease* (March 22-25, 2010)

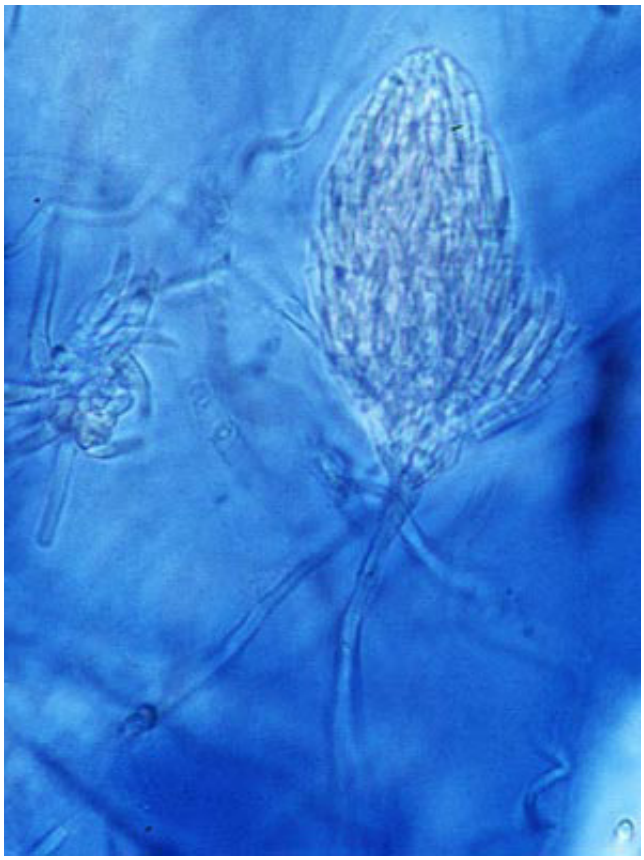
FUTURE PROGRAMS

EVOLUTION, SYNCHRONIZATION, AND ENVIRONMENTAL INTERACTIONS: INSIGHTS FROM PLANTS AND INSECTS
SEPTEMBER 2010 - AUGUST 2011

Organizing Committee

- **Vincent Gutschick** (Biology, New Mexico State)
- **Daniel Forger** (Mathematics, Michigan)
- **Mark Lewis** (Biological Sciences, Alberta)
- **Scott Nuismer** (Biological Sciences, Idaho)
- **David Rand** (Warwick Systems Biology Centre)
- **David Sumpter** (Mathematics, Uppsala)

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



Fungi sporulating. http://johnfriedmann.com/biogloss/Sporulation.htm

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

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

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

Nest of weaver ants. Pamalican Philippines. PHGCOM 03:03, 24 June 2008 (UTC).

behavioral mechanisms involved in coevolution of plant-insect communities will be understood in terms of fitness advantages incurred evolution and adaptation.

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

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

Workshops

- *Workshop 1: Mathematical Modeling of Plant Development* (September 27 - October 1, 2010)
- *Workshop 2: Circadian Clocks in Plants and Fungi* (October 25-29, 2010)
- *Workshop 3: Ecology and Control of Invasive Species, Including Insects* (February 21-25, 2011)
- *Workshop 4:* Insect Self-organization and Swarming (March 14-18, 2011)
- *Workshop 5: Coevolution and the Ecological Structure of Plant-insect Communities* (April 4-8, 2011)

PUBLICATIONS

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B. D. Aguda, Y. Kim, M. G. Piper-Hunter, A. Friedman, and C. B. Marsh (2008). MicroRNA Regulation of a Cancer Network: Consequences of the Feedback Loops Involving miR-17-92, E2F, and Myc, PNAS, 105(50), 19678-19683.

M. Clendenning, M.E. Baze, S. Sun, K. Walsh, S. Liyanarachchi, D. Fix, V. Schumemann, I. Comeras, M. Deacon, R.J. Wenstrup, S.T. Thibodeau, H.T. Lynch, H. Hampel, A. de la Chapelle (2008). New haplotype and genealogical data give important implications for the origins and prevalence of the American Founder Mutation of MSH2. Cancer Research; 68 (7):2145-2153.

M. Clendenning, L. Senter, H. Hampel, K.L. Robinson, S. Sun, D. Buchanan, M.D. Walsh, M. Nilbert, J.S. Green, J. Potter, A. Lindblom, and A. de la Chapelle (2008). A frame-shift mutation of PMS2 is a widespread cause of Lynch syndrome. Journal of Medical Genetics; 45: 340-345.

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H.L. Lin, T. Zuo, C. Lin, C.T. Kuo, S. Liyanarachchi, S. Sun, R. Shen, D.E. Deatherage, D. Potter, L. Asamoto, S. Lin, P. Yan, A. Cheng, M. Ostrowski, and T.H. Huang (2008). Breast cancer-associated fibroblasts confer AKT1-mediated epigenetic silencing of cystatin M in epithelial cells. Cancer Research; 68:10257-10266.

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D. Siegal-Gaskins, J.N. Ash, and S. Crosson (2009). Model-based Deconvolution of Cell Cycle Time-series Data Reveals Gene Expression Details at High Resolution. PLoS Computational Biology 5(8): e1000460.

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TECHNICAL REPORTS

A theory for the alignment of cortical feature maps during development
Paul C. Bressloff and Andrew M. Oster

Analysis of a biofilm model
Barbara Szomolay

The mitochondrial permeability transition pore confers excitability and CICR wave propagation
Andrew M. Oster, Balbir Thomas, David Terman, and Christopher P. Fall

Stability of Choice in the Honey Bee Nest-Site Selection Process
Andrew L. Nevai, Kevin M. Passino, and Parthasarathy Srinivasan

NEWSLETTERS

Autumn 2008, Volume 4, Issue 1
Winter 2009, Volume 4, Issue 2
Spring 2009, Volume 4, Issue 3