Annual Report for DMS-0931642
Year 2014-2015
And
No-Cost Extension Year 2015-2016

INTRODUCTION

The Mathematical Biosciences Institute (MBI) is a multi-disciplinary initiative that facilitates interaction between the mathematical sciences (which includes mathematics, statistics, and computational science) and the biosciences (which includes the biological sciences, medical sciences, and environmental sciences that relate to the living world). The Institute is devoted to the mathematical biosciences, which includes all areas of research in bioscience where participation of the mathematical sciences will lead to important progress. MBI offers a vigorous program of research and education, and fosters the growth of an international community of researchers in mathematical biology.

The mission of MBI is:

- To foster innovation in the application of mathematical, statistical, and computational methods in the resolution of significant problems in the biosciences
- To foster the development of new areas in the mathematical sciences motivated by important questions in the biosciences
- To engage mathematical and biological scientists in these pursuits
- To expand the community of scholars in mathematical biosciences through education, training, and support of students and researchers.

To support this mission, MBI programs are designed to reinforce and build upon existing research efforts in the mathematical biosciences, and to inspire and accelerate the expansion of the community and its intellectual growth. These include emphasis year programs, current topic workshops, education programs, and research projects. The administrative and governance structure of MBI are designed to support the mission of the Institute. MBI addressed the following scientific challenges in its programming during 2014-2015:

Need to learn the scientist's language: In order to contribute to the solution of problems in the biosciences, mathematicians and statisticians must first learn some science. In particular, they must learn the bio-scientist's language before they can understand the problems clearly enough to bring the power of the mathematical sciences to bear. The continuing rapid pace of research in the biosciences precludes most active biomedical researchers from devoting substantial effort to learning additional mathematics. MBI actively encourages mathematical scientists to learn the bio-scientists' language, and to work with them in highly interdisciplinary teams working the boundaries of mathematics and science.

Need to develop new mathematical/statistical models and techniques: While we can expect that established methods in mathematical science will be of immediate use, the quantitative analysis of fundamental problems in bioscience will require new ideas and new techniques. Similar observations apply to diverse research areas across the biosciences ranging from the study of basic structures in the brain to the expression, regulation, and control of genes. MBI is providing a forum for scientists to begin

modeling these systems in ways which are scientifically relevant yet amenable to analysis that requires skillful approximations and new techniques.

Need to increase the community's size: The current size of the mathematical bioscience community is relatively small when compared to the demands of life sciences. MBI encourages the participation of established mathematicians and statisticians in mathematical bioscience and continues to nurture new generations of researchers.

MBI activities fall under five principal categories (scientific programs, postdoctoral fellows, national impact, education, and diversity) and MBI is developing new programs in each of these categories: workshops, institute partners and mentoring, early career awards and long-term visitors, education programs, and diversity and outreach.

The MBI directorate for 2014-2015 included: Martin Golubitsky, Ph.D. (Principal Investigator and Institute Director); Tony Nance, Ph.D. (Deputy Director responsible for administering the postdoctoral program); Greg Rempala, Ph.D. (Deputy Director responsible for providing scientific advice and liaison to the workshop organizing committees); Helen Chamberlin, Ph. D. (Associate Director responsible for diversity issues); Laura Kubatko, Ph.D. (Co-Principal Investigator and Associate Director responsible for the summer education programs); Janet Best, Ph.D. (Associate Director responsible for the summer graduate program); and Andrej Rotter, Ph.D. (Associate Director responsible for providing leadership for relations between MBI and the Ohio State University Medical Center and chair of the MBI Colloquium Committee).

MBI had seven full-time administrative staff members plus three student employees for 2014-2015. The specific positions included: one Financial and Human Resources Manager (Nikki Betts); one Program Coordinator (Matthew Thompson); two Program Assistants (Will Gehring and Casey Jacobs); one Office Administrative Associate (Rebecca Martin); one Systems Manager (Michael Siroskey); one Web Applications Developer (Alex Kasler); and one Systems Specialist (Jason Bray).

MBI had 20 postdoctoral fellows continuing or starting their program during 2013-2014. They were Marcio Albasini Mourao, Noelle Beckman, Richard Buckalew, Josh Chang, Ruchira Datta, Kimberly Fessel, Jeff Gaither, Wenrui Hao, Karly Jacobsen, Jae Kyoung Kim, Kang-Ling Liao, Leopold Matamba Messi, Jay Newby, Matt Oremland, Michael Schwemmer, Michal Seweryn, Leili Shahriyari, Lucy Spardy, Marc Sturrock, and Ying (Joy) Zhou.

A. INFORMATION ON MBI PROGRAMS

1. MBI Emphasis Program: *Cancer and Its Environment*

Cancer is one of the world's biggest killers. Cancer is initiated from cells with specific genetic mutations that cause them to lose control of proliferation. This loss of proliferative control, whilst necessary, is not sufficient to cause cancer; subsequent mutations and selection need to occur. Cancer is an evolutionary disease, where rounds of mutation and selection will drive the emergence of a tumor. The selection

pressures that a growing tumor encounters are manifold but can largely be classified as microenvironmental. The tumor microenvironment consists of the extracellular matrix, growth promoting and inhibiting factors, nutrients (including oxygen and glucose), chemokines, and importantly, other cell types including (but not limited to) fibroblasts, immune cells, endothelial cells and normal epithelial cells. In order for selection to operate properly there needs to be variation in the tumor population - tumors are known to be genetically extremely heterogeneous. This genetic heterogeneity produces phenotypic heterogeneity in which individual tumor cells can have distinct phenotypic behaviors within the same tumor.

As the tumor mass grows, so does the heterogeneity; eventually the mass becomes too large to be supported by nutrient diffusion alone, so some subset of the tumor population then becomes hypoxic. This hypoxia will eventually give way to cell death if nutrient levels continue to fall but the tumor has two ways to combat this problem. First it can begin to utilize a different nutrient source (e.g. glucose) by altering its metabolism and second it can initiate the process of angiogenesis from nearby vessels. The process of recruiting and growing a new vasculature, once fully realized, gives the tumor an almost limitless nutrient source and also a highway to other parts of the human body. Metastases are cells that successfully break away from the primary tumor and initiate new tumors at secondary sites. There can be many of these metastatic cancers at many different sites in the body and ultimately, for most patients, it is these cancers that cause death.

There are hundreds of types of cancer, classified by the tissue from which they arise and by the type of cells involved. For example, leukemia is a cancer of white blood cells, carcinoma is a cancer originating from epithelial cells and glioma is cancer of the brain. There are also many ways to treat cancer, most of which start with surgery and end with chemotherapy and/or radiotherapy. In recent years we have seen the emergence of immunotherapies and molecularly targeted therapies. Immunotherapies exploit the immune system by either enriching or aiding its ability to attack the cancer. Molecularly targeted therapies exploit the fact that specific mutations are present in a large proportion of the cancer cells and block the activity of these mutations. Both of these new therapies have had differing degrees of success but, as in most treatments, failure is ultimately caused by the emergence of a resistant tumor population that tends to be more aggressive and less easy to treat.

This brief overview illustrates the complex interactions at the molecular, cellular and tissue levels involved in the emergence and development of cancer, and emphasizes the need for mathematical models that synthesize a framework for understanding the existing phenomena and that make testable predictions as to how interventions will influence the outcome.

Emphasis Program Organizing Committee

MBI Emphasis Year on *Cancer and Its Environment* 2014-2015 Organizing Committee

- Alexander Anderson (Integrated Mathematical Oncology, H. Lee Moffitt Cancer Center & Research Institute)
- Rick Durrett (Department of Mathematics, Duke University)
- Mariam Eljanne (Physical Sciences-Oncology, National Institutes of Health (NIH))
- Avner Friedman (Department of Mathematics, The Ohio State University)
- Kirk Jordan (Data Centric Systems, IBM Corporation)
- John Lowengrub (Mathematics, University of California, Irvine)
- Guido Marcucci (Comprehensive Cancer Center, The Ohio State University)

- Hans Othmer (School of Mathematics, University of Minnesota)
- Vito Quaranta (Vanderbilt Ingram Cancer Biology Center, Vanderbilt University)

Emphasis Program Workshops
MBI hosted seven emphasis program topic workshops in 2014-2015:

1. *Workshop 1: Ecology and Evolution of Cancer*
   September 15-19, 2014
   Organizers: David Basanta (Moffitt Cancer Center), Jasmine Foo (University of Minnesota), Rick Durrett (Duke University), Carlo Maley (University of California, San Francisco)
2. *Workshop 2: Metastasis and Angiogenesis*
   October 13-17, 2014
   Organizers: Mark Chaplain, Trachette Jackson, Lance Munn, Hans Othmer
3. *Workshop 3: Cancer and the Immune System*
   November 17- 21, 2014
   Organizers: Avner Friedman, Gregory Lesinski, Ami Radunskaya
4. *Workshop 4: Tumor Heterogeneity and the Microenvironment*
   February 02- 06, 2015
   Organizers: Alexander Anderson (H. Lee Moffitt Cancer Center & Research Institute), Trevor Graham (Barts Cancer Institute), Michael Ostrowski (The Ohio State University), and Charlie Swanton (London Research Institute)
5. *Workshop 5: Treatment, Clinical Trials, Resistance*
   February 16- 20, 2015
   Organizers: Mariam Eljanne (National Institutes of Health), Peter Shields (The Ohio State University), Jack Tuszynski (University of Alberta), Larry Nagahara (National Cancer Institute), and Kristin Swanson (Northwestern University)
6. *Workshop 6: Targeting Cancer Cell Proliferation and Metabolism Networks*
   March 23- 27, 2015
   Organizers: Baltazar Aguda (Disease Pathways, LLC), Vito Quaranta (Vanderbilt University), Robert Gatenby (H. Lee Moffitt Cancer Center & Research Institute) and Santiago Schnell (University of Michigan Medical School)
7. *Workshop 7: Stem Cells, Development, and Cancer*
   April 13- 17, 2015
   Organizers: Heiko Enderling (Moffitt Cancer Center), Thomas Hillen (University of Alberta), and John Lowengrub (University of California, Irvine)

2. <u>Additional MBI Programs and Initiatives</u>

1. *Boot Camp: How to Simulate and Analyze Your Cancer Models with COPASI*
   September 29 – October 1, 2014
   Organizers: Stefan Hoops (Virginia Polytechnic Institute and State University), Pedro Mendes (University of Connecticut Health Center), and Kathy O'Hara (Virginia Polytechnic Institute and State University
2. *Current Topic Workshop: Axonal Transport and Neuronal Mechanics*
   November 3 -7, 2014
   Organizers: Paul Bresloff, Kristian Franze, Kyle Miller, Jay Newby, Daniel Suter
3. *Current Topic Workshop: Evolutionary Game Theory*
   April 27 – May 1, 2015

Organized by: Andrew Belmonte (Pennsylvania State University), Vlastimil Krivan (University of South Bohemia), John Nagy (Scottsdale Community College), Zhijun Wu (Iowa State University)

4. *Workshop on Topics in Applied Dynamical Systems: Equivariance and Beyond*
   May 24-27, 2015
   Organizers: Peitro-Luciano Buono (University of Ontario Institute of Technology), Marie Leite (University of South Florida), Yunjiao Wang (Texas Southern University), Martin Krupa (INRIA) and Yuan Lou (The Ohio State University)
5. *Spatially-varying stochastic differential equations, with application to the biological sciences*
   July 7-10, 2015
   Organizers: Peter Craigmile (The Ohio State University), Radu Herbei (The Ohio State University)

Education

MBI hosted two education programs in 2014-2015:

1. 2015 Summer Undergraduate Program
   June 8 - August 14, 2015
   The program consisted of three parts:
   a. *Two-Week Program* (June 2-13, 2015): Tutorials, computer labs, and short-term team efforts designed to introduce students to a variety of topics in mathematical biology.
   b. *REU Program* (June 15 – August 9, 2015): An 8 week individualized research experience as part of a research team at one of the participating host institutions. Host institutions were: Arizona State University, Indiana University – Purdue University Indianapolis, The Ohio State University, The Pennsylvania State University, University of Pittsburgh, and the Virginia Bioinformatics.
   c. *Capstone Conference* (August 10-14, 2015): A student centered conference featuring talks and posters by students doing research in mathematical biology, keynotes by prominent mathematical biologists, a graduate studies recruitment fair, and other special features.

2. Joint 2015 MBI-CAMBAM-NIMBioS Summer Graduate Program: Nonlinear Dynamics in Biological Systems
   June 1-12, 2015
   Organizers: Anmar Khadra (McGill University) and Santiago Schnell (University of Michigan Medical School)
   This summer school focused on the theory, mathematical modelling and experimental study of biological rhythms. The workshop included a boot camp to introduce the basic mathematical tools and techniques used in studying biological rhythms. In depth explorations of specific problems were presented and students worked in small groups on projects, which they presented at the end of the two week workshop.

Visiting Lecture Program

MBI developed the Visiting Lecturer Program (VLP) in 2009. The program sponsors visits of mathematical biologists to institutions that have large numbers of undergraduate students who are members of groups that are underrepresented in the mathematical sciences community. The purpose is to encourage members of these groups to go to graduate school and to develop careers in the

mathematical biosciences. In addition to delivering a lecture on mathematical biology that is accessible to an undergraduate audience, the lecturers met with individual students and with groups of interested faculty and students to further this purpose.

Janet Best (Mathematics, Ohio State University) April 7, 2015 lecture at Morehouse College
The Dynamics of Sleep
To sleep "like a baby" means to sleep peacefully and soundly. Yet parents often observe that their infant's sleep has frequent interruptions and perhaps a short sleep-wake cycle; statistical analysis confirms that infant sleep and adult sleep have different dynamical structures. Perhaps it is the prevalence of chronic sleep disorders that makes adults look back wistfully at sleeping babies. Compounding the difficulty of managing a sleep disorder is the news that disruptions in normal sleep-wake activity have been associated with many long-term health consequences. I will discuss what is known about the biological basis of sleep including controversies in the field. I will then show how mathematical models, both deterministic and random, help us to understand sleep-wake rhythms from newborns to adults while also yielding insights into some sleep disorders. The results are sure to change the way you think about sleep and will reveal opportunities to participate in uncovering the mathematical structures that arise in sleep and other state transitions.

Public Lecture Series
MBI continued to be instrumental in the Science Sundays Public Lecture Series sponsored by the College of Arts and Sciences at OSU. Science Sundays lectures are held monthly during the academic year and provide a forum to interest, engage, and inform the public about a wide range of current and emerging issues in science that touch our everyday lives.

In 2014-2015, eight public lectures were given:

1. *Mathematical tools bring hidden beauty to light*
   Margot Gerritsen (Associate Professor, Energy Resources Engineering)
   September 14, 2014
2. *Neutrino Hunters: Chasing a Ghostly Particle to Unlock Cosmic Secrets*
   Ray Jayawardhana (Dean, York University in Toronto)
   October 12, 2014
3. *Mathematics and Music: the Beauties in Pattern*
   James Sneyd (Professor, University of Auckland, Royal Society of New Zealand)
   November 2, 2014
4. *Genetically Modified Organisms: Debunking the Myths*
   Martina Newell-McGloughlin (Director, University of California System-wide Biotechnology Research and Education Program)
   December 7, 2014
5. *Black Holes, Waves of Gravity & other Warped Ideas of Dr. Einstein*
   Clifford Will (Distinguished Professor, University of Florida)
   January 11, 2015
6. *The Human Population: Its Past and Its Prospects*
   Joel Cohen (Professor,) Columbia University
   February 8, 2015
7. *Digital Tailoring, Grooming and Simulation in Pixar Films*
   Fran Kalal (Cloth and Simulation Technical Director at Pixar Animation Studios)
   March 8, 2015
8. *A Worm's Tale: Secrets of Evolution and Immortality*

Craig Mello (Investigator, Howard Hughes Medical Institute)
April 12, 2015

MBI Colloquium Program

The MBI Colloquium brings in prestigious researchers from around the world to give high-level talks to non-expert scientists as well as spend time with MBI post-docs. The talks are live video streamed.

2014-2015 Colloquia:

1. *Strength of Evidence* for Clinical Trials and Biomarkers** in Tailored Therapeutics****
   Stephen Ruberg (Distinguished Senior Research Fellow, Eli Lilly and Company)
   September 22, 2014 3:00 - 3:50PM
2. *Similarity and homology in proteins.*
   Nick Grishin (Southwestern Medical Center, University of Texas)
   October 06, 2014 3:00 - 3:50PM
3. *Stable Discretizations and Robust Preconditioners for Multi-physical Systems*
   Jinchao Xu (Department of Mathematics, Pennsylvania State University)
   October 20, 2014 3:00 - 3:50PM
4. *Mechanical and Chemical Signaling Between Plant Stem Cells: Computational Models and Experiments*
   Elliot Meyerowitz (Biology and Biological Engineering, California Institute of Technology)
   October 27, 2014 3:00 - 3:50PM
5. *Stochastic Models of Stem Cell Renewal and Dedifferentiation in Cancer*
   Alexandra Jilkine (ACMS, University of Notre Dame)
   November 10, 2014 3:00 - 3:50PM
6. *The Role of Mathematical Models in Understanding Pattern Formation in Developmental Biology*
   Hans Othmer (School of Mathematics, University of Minnesota)
   November 24, 2014 3:00 - 3:50PM
7. *Swarm Cognition in Honey Bees*
   Kevin Passino (EEOB, The Ohio State University)
   December 01, 2014 3:00 - 3:50PM
8. *A multistate model for time to cancer recurrence and death incorporating a cured fraction*
   Jeremy Taylor (Biostatistics - School of Public Health, University of Michigan)
   January 26, 2015 3:00 - 3:50PM
9. *Modelling Stripe Formation in Zebrafish*
   Bjorn Sandstede (Mathematics, Brown University)
   February 23, 2015 3:00 - 3:50PM
10. *Collective action and the collaborative brain*
    Sergey Gavrilets (Mathematics, University of Tennessee)
    March 02, 2015 3:00 - 3:50PM
11. *All the way with Gaston Floquet: A theory for flicker hallucinations*
    Bard Ermentrout (Department of Mathematics, University of Pittsburgh)
    March 09, 2015 3:00 - 3:50PM
12. *3D Genome Reconstruction: How and Why*
    Mark Segal (Department of Biostatistics, University of California, San Francisco)
    April 06, 2015 3:00 - 3:50PM
13. *New methods to improve modeling and prediction of protein structure, dynamics and function*
    Andrzej Kloczkowski
    April 20, 2015 3:00 - 3:50PM

Early Career Awards
Early Career Awards are aimed at non-tenured scientists who currently have continuing employment and who hold a doctorate in any of the mathematical, statistical and computational sciences, or in any of the biological, medical and related sciences. Awardees engage in an integrated program of tutorials and workshops tied to the scientific theme and are expected to interact with local and visiting researchers.

2014-2015 Early Career Awardees:

1 Harsh Jain
Department of Mathematics, Florida State University
January 2015 - April 2015

2. Min Tang
Institute of Natural Sciences, Shanghai Jiaotong University
January 2015 - March 2015

3. Alexandra Jilkine
University of Notre Dame
August 2014 - December 2014

4. Kun Zhao
Department of Mathematics, Tulane University
January 2015 - May 2015

Long Term Visitors Seminar
With the number and scientific breadth of MBI's Long Term Visitors and Early Career Awardees, MBI features seminar talks by Long Term Visitors. These talks are held during non-workshop weeks at MBI.

2014-2015 Long Term Visitor Seminar Speakers:

1. *Evolutionary Games*
Rick Durrett (Department of Mathematics, Duke University)
September 24, 2014 10:20 - 11:15AM
2. *Stochastic dynamics of cancer recurrence*
Jasmine Foo (Department of Mathematics, University of Minnesota)
October 07, 2014 10:20 - 11:15AM
3. *A Hybrid Model for Tumor Growth*
Hans Othmer (School of Mathematics, University of Minnesota)
October 21, 2014 10:20 - 11:15AM
4. *From Microscopic to Coarse-Grained PDE Models of Pedestrian Traffic*
Ilya Timofeyev (Mathematics, University of Houston)
October 28, 2014 10:20 - 11:15AM
5. *A stochastic model for the normal tissue complication probability (NTCP) in radiation treatment*
Thomas Hillen (Mathematical and Statistical Sciences, University of Alberta)
November 12, 2014 10:20 - 11:15AM
6. *Solving polynomial systems, with applications in biology*
Dan Bates (Department of Mathematics, Colorado State University)
December 02, 2014 10:20 - 11:15AM
7. *Experimental and Mathematical Modeling in Vascular Bioengineering*
B. Rita Alevriadou (BME and Cardiovascular Medicine, The Ohio State University)

January 27, 2015 10:20 - 11:15AM

8. *Tumor Hele-Shaw type model at the stiff pressure limit*
   Min Tang (Institute of Natural Sciences, Shanghai Jiaotong University)
   February 24, 2015 10:20 - 11:10AM
9. *Computer Simulations of Yeast Mating Reveal Robustness Strategies for Cell-Cell Interactions*
   Ching-Shan Chou (Department of Mathematics, The Ohio State University)
   March 03, 2015 10:20 - 11:10AM
10. *Topological pressure and the detection of structure in long finite sequences*
    Daniel Thompson (Mathematics, The Ohio State University)
    March 10, 2015 10:20 - 11:10AM
11. *Plasticity and the management of conflict in animal societies*
    Ian Hamilton (MBI - Long Term Visitor, The Ohio State University)
    March 17, 2015 10:20 - 11:10AM
12. *Periodic solutions to compartmental epidemiological models and the effect of an asymptomatic class*
    Ernest Barany (Department of Mathematics, New Mexico State University)
    March 31, 2015 10:20 - 11:10AM
13. *Solving Gene Networks through the Unique Lens of microRNA-regulated Genes from Cancer Genomes*
    Preethi Gunaratne (Biology and Biochemistry Department, University of Houston)
    April 07, 2015 10:20 - 11:10AM
14. *Differential equation models of solid tumor treatment with taxanes and platinum compounds*
    Harsh Jain
    April 21, 2015 10:20 - 11:10AM
15. *Uniform Distribution in Negative Chemotaxis*
    Kun Zhao (Department of Mathematics, Tulane University)
    May 05, 2015 10:20 - 11:10AM
16. *Functional Implications of An Altered Collagen Fiber Ultrastructure*
    Gunjan Agarwal (Davis Heart and Lung Research Institute)
    May 12, 2015 10:20 - 11:10AM

Conference Awards

The MBI Conference Award is a program that started as a diversity initiative in which untenured junior faculty, postdocs, and graduate students are awarded a fully funded trip to attend a MBI workshop of the winner's choice. MBI works with event organizers to set up an evaluation procedure to identify winners at national meetings, including the AWM, NAM, and Infinite Possibilities Conference. MBI intends to expand this program by working in conjunction with AWM, Blackwell-Tapia organizers, and others.

In 2014-2015, MBI awarded four Conference Awards:

1. Arezou Ghesmati
   Department of Mathematics, Texas A & M University
   A Residual Based Aposteriori Error Estimation in a Fully Automatic hp--FEM for the 2 and 3-D Stokes Model Problem
   AWM Workshop Poster Presentations and Reception at the
   2015 Joint Math Meeting (January 2015)
2. Pamela E. Harris

Department of Mathematical Sciences, United States Military Academy
Adjoint Representation of a Classical Lie Algebra and the Support of Kostant's Weight Multiplicity Formula
NAM Presentations by Recent Doctoral Recipients (January 2015)

3. Asya Spears
   Department of Biostatistics, UCLA
   A Method for Sample Size Estimation Making Use of Data from Pilot Studies
   2015 Infinite Possibilities Conference in Corvallis Oregon (March 2015) at the 2015 Joint Math Meeting
4. Sousada Chidthachack
   College of Education & Human Development, University of Minnesota
   Not Just Math Because I Can Get That in School: High School Students Evaluate the Impact of an Urban Mathematics Program
   2015 Infinite Possibilities Conference in Corvallis Oregon (March 2015)

MBI Initiatives for 2015-2016

MBI Emphasis Semester on Mathematical Molecular Biosciences Fall 2015
This one-semester program brought together researchers from mathematics, chemistry, physics, biology, computer science, and engineering to explore new ways to bridge these diverse disciplines, and to facilitate the use of mathematics to solve open problems at the forefront of the molecular biosciences.

An important trend in contemporary life sciences is that with the availability of modern biotechnologies, traditional disciplines, such as physiology, plant biology, neuroscience etc, are undergoing a fundamental transition from macroscopic phenomenological ones into molecular based biosciences. In parallel with this development, a major feature of life sciences in the 21st century is their transformation from phenomenological and descriptive disciplines to quantitative and predictive ones. Revolutionary opportunities have emerged for mathematically driven advances in biological research. Experimental exploration of self-organizing molecular biological systems, such as HIV viruses, molecular motors and proteins in Alzheimer's disease, are examples of dominating driving forces in scientific discovery and innovation in the past few decades. However, the emergence of excessive complexity in self-organizing biological systems poses fundamental challenges to their quantitative description, because of the excessively high dimensionality and the complexity of the processes involved. Mathematical approaches that are able to efficiently reduce the number of degrees of freedom, and model complex biological systems, are becoming increasingly popular in molecular biosciences. Multiscale modeling, manifold extraction, dimensionality reduction and machine learning techniques are introduced to reduce the complexity of biomolecular systems while maintaining an essential and adequate description of the biomolecules of interest.

Currently, a major barrier for mathematical scientists to work in this field is the lack of knowledge in molecular biology, while a major barrier for biologists is the lack of knowledge about modern mathematical tools and techniques that have been developed in the past 20 years. This semester workshop program is designed to help bridge gaps between molecular biologists and mathematical scientists and to facilitate their collaborations. There is enormous potential in this area for integrative interdisciplinary research in which theoreticians and experimentalists develop solutions to challenging

problems in tandem. This program acted as a catalyst to fully exploit these synergies, and created a network of collaborations that sustains future activities in this area beyond the duration of this program.

Organizing Committee for Fall 2015

- Emil Alexov
  Computational Biophysics and Bioinformatics, Clemson University
- Ridgway Scott
  Computer Science and Mathematics, University of Chicago
- Reidun Twarock
  Mathematics and Biology, University of York
- Guowei Wei
  Department of Mathematics, Michigan State University

Events Planned for Fall 2015

1. *Workshop on Omics Data Analysis*
   September 16- 18, 2015
2. *Workshop 1: Geometric and Topological Modeling of Biomolecules*
   September 28 - October 02, 2015
3. *Workshop 2: Multiple Faces of Biomolecular Electrostatics*
   October 12-16, 2015
4. *Workshop 3: Modeling and Computation of Transmembrane Transport*
   November 16- 20, 2015
5. *Workshop 4: Mathematical Challenges in Drug and Protein Design*
   December 07- 11, 2015

MBI Emphasis Semester on Dynamics of Biologically Inspired Networks: Spring 2016

Networks and deterministic and stochastic dynamical systems on networks are used as models in many areas of biology. This underscores the importance of developing tools to understand the interplay between network structures and dynamical processes, as well as how network dynamics can be controlled. The dynamics associated with such models are often different from what one might traditionally expect from a large system of equations, and these differences present the opportunity to develop exciting new theories and methods that should facilitate the analysis of specific models. Moreover, a nascent area of research is the dynamics of networks in which the networks themselves change in time, which occurs, for example, in plasticity in neuroscience and in up regulation and down regulation of enzymes in biochemical systems.

There are many areas in biology (including neuroscience, gene networks, and epidemiology) in which network analysis is now standard. Techniques from network science have yielded many biological insights in these fields and their study has yielded many theorems. Moreover, these areas continue to be exciting areas that contain both concrete and general mathematical problems. Workshop 1 explored the mathematics behind the applications in which restrictions on general coupled systems are important. Examples of such restrictions include symmetry, Boolean dynamics, and mass-action kinetics; and each of these special properties permits the proof of theorems about dynamics on these special networks.

Workshop 2 focused on the interplay between stochastic and deterministic behavior in biological networks. An important related problem is to understand how stochasticity affects parameter

estimation. Analyzing the relationship between stochastic changes, network structure, and network dynamics poses mathematical questions that are new, difficult, and fascinating.

In recent years, an increasing number of biological systems have been modeled using networks whose structure changes in time or which use multiple kinds of couplings between the same nodes or couplings that are not just pairwise. General theories such as groupoids and hypergraphs have been developed to handle the structure in some of these more general coupled systems, and specific application models have been studied by simulation. Workshop 3 brought together theorists, modelers, and experimentalists to address the modeling of biological systems using new network structures and the analysis of such structures.

Biological systems use control to achieve desired dynamics and prevent undesirable behaviors. Consequently, the study of network control is important both to reveal naturally evolved control mechanisms that underlie the functioning of biological systems and to develop human-designed control interventions to recover lost function, mitigate failures, or repurpose biological networks. Workshop 4 addressed the challenging subjects of control and observability of network dynamics.

Organizing Committee for Spring 2016

- Pete Ashwin
  College of Engineering, Mathematics and Physical Sciences, University of Exeter
- Nina Fefferman
  Ecology and Evolutionary Biology, University of Tennessee
- Martin Feinberg
  Chemical Engineering & Mathematics, The Ohio State University
- Leon Glass
  Department of Physiology, McGill University, Macdonald Campus
- Adilson Motter
  Physics, Northwestern University
- Mason Porter
  Mathematical Institute, University of Oxford
- Ruth Williams
  Mathematics, University of California, San Diego

Events Planned for Spring 2016

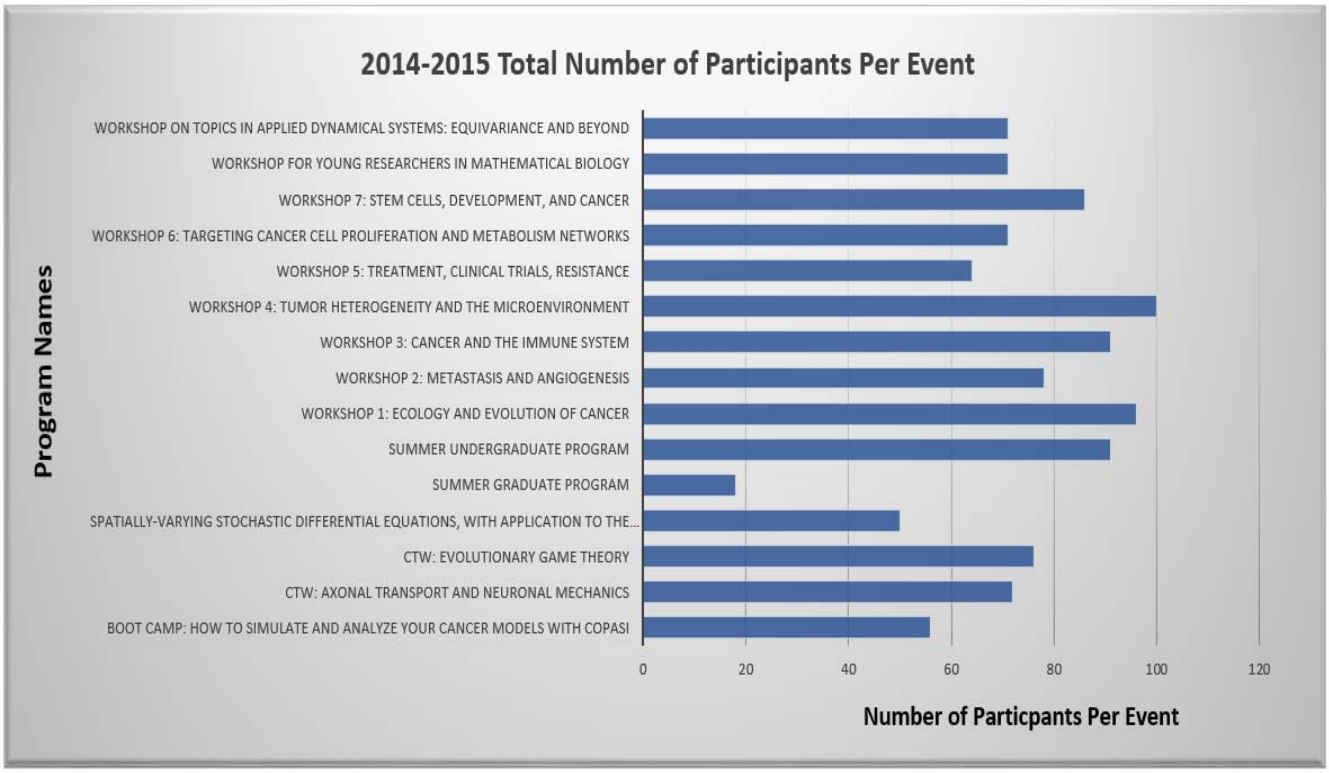
1. *Workshop 1: Dynamics in Networks with Special Properties*
   January 25- 29, 2016
2. *Workshop 2: The Interplay of Stochastic and Deterministic Dynamics in Networks*
   February 22- 26, 2016
3. *Workshop 3: Generalized Network Structures and Dynamics*
   March 21- 25, 2016
4. *Workshop 4: Control and Observability of Network Dynamics*
   April 11- 15, 2016

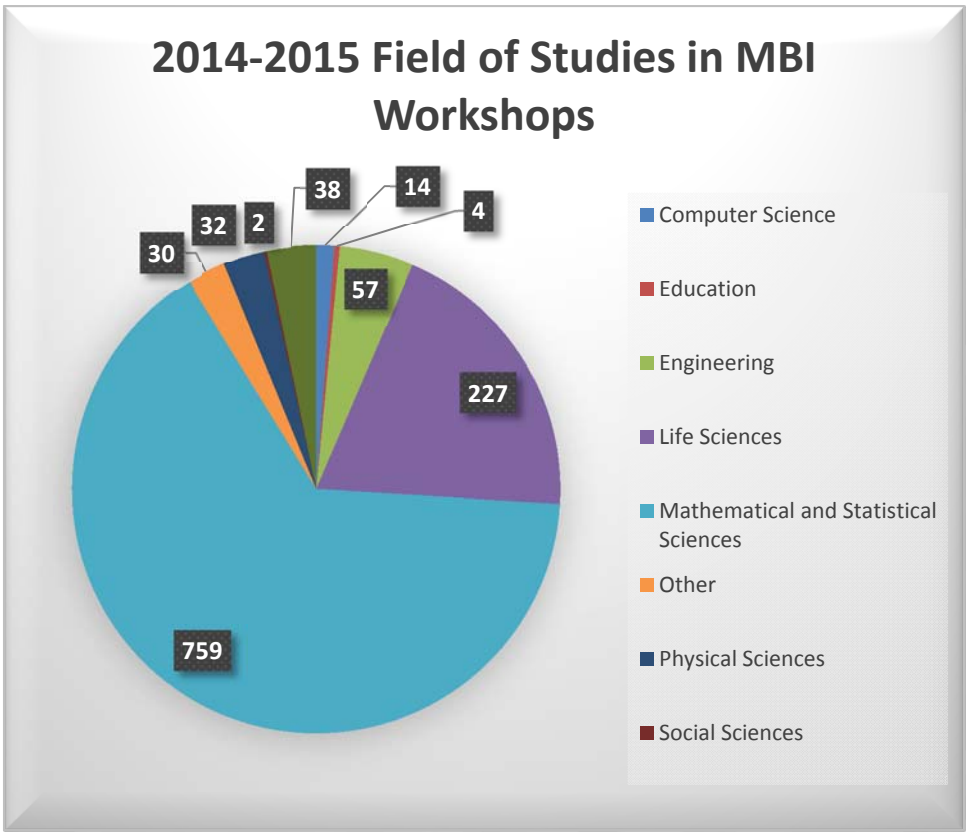
Web Initiatives

- Redesigned, updated, and migration of MBI visitor registration system
- Redesign of MBI Postdoc Wiki
- Expanded video streaming capabilities

3. <u>Participant Data</u>

1091 participants took part in MBI's 2014-2015 current topic workshops and emphasis semester programs.





Diversity Data
MBI's diversity data is self-reported, with nearly 40% of participants either declining to supply this information or not answering the question. With our database MBI is able to keep track of reported data. Of the 1091 participants who responded 277 are African American, Hispanic, or Native American; thus 25% of those reporting are from underrepresented groups.

Geographic Data
MBI attracts researchers from around the country and indeed around the world to its workshops. In the 2014-2015 year researchers from at least 40 of the 50 states have attended MBI programs.

Internationally, MBI has attracted participants from at least 32 countries. By far the largest numbers are from the United Kingdom and Canada. The percentage of international participants during this grant year was 16.9%.

4. <u>Visitors</u>

Attracting long-term visitors (LTV) to MBI is one of the main purposes in hosting emphasis programs. The LTV, along with postdoctoral fellows, create a stimulating research atmosphere that continues between workshops. During the past few years, MBI has attempted to add to the numbers of LTV in several ways. First, from the beginning of discussions with emphasis program organizers, MBI makes it clear that part of their responsibility is to arrange for long-term visits for themselves and for others. Second, MBI experimented with a math (rather than a bio) centered emphasis program for 2011-2012 (Stochastics in Biological Systems); indeed this program did enlarge the number of LTV. Third, MBI

created the Early Career Awards program (ECA), which enables young tenure-track researchers to spend three to nine months at MBI in coordination with emphasis programs. This program began in earnest in 2010 with the beginning of an early NSF grant (DMS-0931642).

2014-2015 Early Career Awardees

1. Harsh Jain
   Department of Mathematics, Florida State University
   January 2015 - April 2015
2. Alexandra Jilkine
   University of Notre Dame
   August 2014 - December 2014
3. Min Tang
   Institute of Natural Sciences, Shanghai Jiaotong University
   January 2015 - March 2015
4. Kun Zhao
   Department of Mathematics, Tulane University
   January 2015 - May 2015

2014-2015 Long-Term Visitors

1. Ernest Barany
   Department of Mathematics, New Mexico State University
   January 2015 - May 2015
2. Dan Bates
   Department of Mathematics, Colorado State University
   August 2014 - December 2014
3. Boseung Choi
   Computer Science and Statistics, Daegu University
   July 2015
4. Rick Durrett
   Department of Mathematics, Duke University
   September 2014 - October 2014
5. Jasmine Foo
   Department of Mathematics, University of Minnesota
   September 2014 - October 2014
6. Gemunu Gunaratne
   Physics Department, University of Houston
   March 2015 - April 2015
7. Preethi Gunaratne
   Biology and Biochemistry Department, University of Houston
   March 2015 - April 2015
8. Thomas Hillen
   Mathematical and Statistical Sciences, University of Alberta
   September 2014 - November 2014
9. Mohammed Ibrahim
   Mathematics, University of Ilorin
   April 2015 - May 2015
10. Kevin Leder
    Industrial and Systems Engineering, University of Minnesota

September 2014 - November 2014

11. Hans Othmer
    School of Mathematics, University of Minnesota
    October 2014 - December 2014
12. Maciej Pietrza
    Biostatistics, Ohio State University College of Public Health
    August 2015 - August 2016
13. Deena Schmidt
    Department of Biology & Department of Mathematics, Case Western Reserve University
    May 2012 - February 2015
14. Ilya Timofeyev
    Mathematics, University of Houston
    September 2014 - November 2014
15. Kenny Salau
    Mathematics, Arizona State University
    August 2014
16. Ian Stewart
    Dept. of Mathematics, University of Warwick
    September 2014

B. MBI POSTDOCTORAL EDUCATION

The MBI had 20 postdoctoral fellows and researchers continuing or starting their program during 2014-2015. They were Noelle Beckman, Richard Buckalew, Josh Chang, Ruchira Datta, Kimberly Fessel, Jeff Gaither, Wenrei Hao, Karly Jacobsen, Jae Kyoung Kim, Kang Ling Liao, Leopold Matamba Messi, Marcio Mourao, Jay Newby, Matt Oremland, Michael Schwemmer, Michael Seweryn, Leili Shahriyari, Lucy Spardy, Marc Sturrock, Joy (Ying) Zhou.

Postdoctoral candidates apply to MBI through mathjobs.org or by direct application (now rare). MBI received 232 applicants in 2014-15 and made five hires.

Postdoctoral Fellows Duties and Opportunities

- Postdoc Seminar: Each post-doc is asked to give one 50-minute colloquium level talk each year. They usually receive feedback from these talks from the Directors. The MBI postdoctoral fellows organize the weekly series (during weeks when no other MBI event is planned).
- Postdoc Mentoring: Each MBI postdoc is asked to choose two designated scientific mentors: one from the mathematical sciences and one from the life sciences. Designated mentors can be researchers at Ohio State or at other MBI Institute Partners. When the designated mentor resides outside of Columbus, MBI provides travel funds for the postdoc to visit with the mentor as often as is needed. Usually these trips are for one-week and occur 3-4 times annually.
- Employment after Leaving MBI: Postdoc job searches are usually mentored by the postdoc's scientific mentors and by the Directors and Senior Scientific Advisor. Their searches have been successful at a wide variety of institutions.
- MBI Courses for Postdoctoral Fellows: This is a new program aimed at increasing the skill sets of MBI postdocs while they are in residence at MBI. These courses are video- streamed.

- Professional Development Seminar: MBI Senior Scientific Advisor, Mike Reed, organizes seminars for the MBI Postdoctoral Fellows on professional issues, such as how to prepare a two-minute elevator talk, how to prepare a job talk, how to prepare a grant proposal, pointers on teaching, the need for a professional website, etc. The fellows critique each other's performances in a friendly atmosphere.
- Postdoc Teaching: MBI has a cooperative program with the Mathematics Department that permits the MBI postdoctoral fellows to gain this teaching experience. Post-docs who wish to teach in a department other than Mathematics are handled on a case-by-case basis.
- Postdocs and Workshop Final Reports: Each MBI post-doc is asked to participate in the writing of final reports for two MBI workshops.
- Grant Applications and MBI Postdoctoral Fellows: MBI postdoctoral fellows are encouraged to submit at least one grant proposal to either NSF or NIH during their stay at MBI.
- Postdoc Annual Reviews: Each postdoc is formally evaluated annually. The postdocs are asked to submit a form that details their work during the past year and asks them to describe their research directions for the next year. The Directorate reads these forms and two directors meet with each postdoc to discuss his or her progress and their goals for the next year.

1. <u>Research Interests for MBI Postdoctoral Fellows</u>

Noelle G. Beckman
Ecology, Evolution, Behavior, University of Minnesota
Noelle investigated the roles of plant-animal, plant-microbe, and plant-plant interactions in limiting populations and maintaining diversity in temperate and tropical ecosystems. Using statistical models to analyze experimental and observational data, she can quantify the relationship between plant attributes and plant interactions with their environment to enable prediction for unstudied species, gain insight into the mechanisms for species coexistence, and understand ecosystem responses to change. Using mathematical and computational approaches, Noelle investigated processes occurring over multiple spatial and temporal scales in order to address questions of species coexistence. She worked to develop stochastic spatial models and analytical approximations to examine the interacting effects of seed dispersal and natural enemy attack on plant spatial patterns and the influence of these local interactions on plant diversity.

Richard Buckalew
Mathematical Biology, Ohio University
Mathematical Biology: Ordinary and Partial Differential Equations models of the cell cycle in Saccharhomyces and Drosophila. Dynamics of the pulmonary immune response to infection. Richard's main interest was in the behavior of large ensembles of cells and the patterns that can emerge from simple interactions between them.

Josh Chang
Biomathematics, University of California, Los Angeles
Josh was excited about a variety of fields in the mathematical and physical sciences including but not limited to inverse problems, PDEs, homogenization theory, statistical physics, computer vision, and stochastic processes. His prior research has focused on regularization techniques applicable to inverse problems and computer vision. He has also worked on modeling of neurophysiology using reaction-diffusion equations. Aside from mathematical neuroscience, he was particularly curious about cancer growth, quorum sensing, pattern formation, scar formation, and models of nutrient delivery in vascular

networks. Somewhat tangentially, he also liked to explore methods for transit modeling and other practical problems related to civil engineering.

Ruchira Datta
Mathematics, UC Berkeley
Ecology of the human organism, mathematical and computational biology, game theory, machine learning. She modeled the human organism as an evolving ecological community. In particular, she modeled the development and progression of cancer, its resistance to therapy, and metastasis.

Kimberly Fessel
Mathematics, Rensselaer Polytechnic Institute
Kimberly's research focused on developing a comprehensive nonlinear wave model for the governing physics of the transduction mechanism in the inner ear. This work required a detailed analysis of the fluid-solid interaction dynamics of the cochlea, as well as the utilization of various perturbation methods and numerical techniques.

Jeff Gaither
Mathematics, Purdue University
Jeff's research focused on the realm of genetics. He had ongoing projects in phylogenetics, genetical physics, and the statistical theory which underlies large-scale genomic sampling. Protein-RNA interactions and their influence on RNA secondary structure.

Wenrui Hao
Applied and Computational Mathematics and Statistics, University of Notre Dame
Wenrui applied numerical algebraic geometry methods and numerical partial differential equation methods to mathematical problems arising in biology, such as tumor growth, blood coagulation, and deriving efficient numerical methods for large scale computing. The mathematical tools that he used included PDEs, numerical algebraic geometry, bifurcation analysis, and computational methods.

Karly Jacobsen
Mathematics, University of Florida
Karly's research is focused on the spread and control of disease at a range of scales, from cells within a tumor to individuals and communities at the population level. She worked in oncolytic virotherapy, the use of cancer-targeting viruses in the treatment of solid tumors, where she modeled the spatial spread of viruses by cell-to-cell fusion as well as interactions of the tumor, virus, and immune response. Using analytical and numerical techniques, she analyzed the corresponding partial differential equation systems to investigate mathematical questions such as well-posedness and dynamical behavior as well as to gain clinical insights into tumor control. At the population level, Karly was interested in how the structure and seasonality of community and environmental networks affected the spread of infectious diseases such as cholera. Ordinary differential equations, dynamical systems, and graph theory are used to investigate disease dynamics.

Jae Kyoung Kim
Mathematics, University of Michigan, Ann Arbor
Jae's research has focused on developing theories and models to understand biological rhythms. Basic questions are: Is there an easier way to find hidden or unknown biochemical interactions? How do complex biochemical networks generate rhythms and control period? He has worked closely with several experimental groups in biology to develop new protocols to test model predictions.

Kang-Ling Liao
Applied Mathematics, National Chiao Tung University, Taiwan
Kang-Ling was interested in ordinary differential equations and dynamical systems. She focused on the dynamics for gene expressions of somitogenesis in zebrafish. During the development of embryo, the clock gene expression exhibits synchronous oscillation in the tail bud and a traveling wave pattern arises from the posterior to the anterior of the presomitic mesoderm. The oscillation slows to a stop and cells form into somites. In order to investigate these phenomena, we considered the mathematical models which depict the kinetics of the zebrafish segmentation clock genes subject to direct autorepression by their own products under time delay, and cell-to-cell interaction through Delta-Notch signaling. The theoretical and numerical results not only provide some criteria and parameter regimes observed in somitogenesis, but also present how delays affect the dynamics of these models. Kang-Ling planned to perform similar methodologies to patch model in ecology to explore how delay affects the dynamics of the model and investigate the global dynamics of the model. She also planed to study the cancer immunoediting and attempt to construct a pertinent model which fits experimental data to investigate the mechanism of how tumor cells escape from the immune system.

Leopold Matamba Messi
Applied Mathematics, University of Georgia
Leopold's interests were in mathematical image analysis, numerical analysis of partial differential equations, applied mathematics, and statistics. In his Ph. D. dissertation, he used finite difference and Galerkin methods to construct continuous piecewise polynomial approximations of the continuum TV-L2 image decomposition model. He plans to expand on this work to other total variation based image decomposition models. This includes the application of the stochastic Gillespie Algorithm to simulate ecosystems indicators within the Ecological Network Analysis framework. Leopold was collaborating with Julie Rushmore (Odum School of Ecology, University of Georgia) to study dynamics of the social network of the community of chimpanzees of the Kibale National Forest (Uganda, East Africa), and its impact on disease transmission in the community.

Marcio Albasini Mourao
Indiana University
Márcio was interested in understanding how macroscopic behavior arises from simpler multiple interactions over time and space. He's currently investigating biological phenomena, but his long-term goal is to expand his research to biological, social, economic or even political systems. Márcio's work involved a combination of both theoretical and computational models.

Jay Newby
Mathematics, University of Utah
Jay's interests lied in stochastic processes and their application to biological problems. Although his primary area of focus was cellular neurobiology, he has also done work in intracellular transport, gene regulation, and population dynamics. During his time at MBI, Jay intended to investigate the link between the collective network behavior and cellular processes within an individual neuron, understand better how cellular processes (such as gene regulation) contribute to synaptic plasticity, and develop new perturbation methods to analyze rare events in jump Markov processes.

Matt Oremland
Mathematics, Virginia Tech

Matt's research was in the area of mathematical analysis of agent-based models (ABMs), particularly in terms of solving optimization problems. He has primarily worked on ABMs of biological systems. He has also developed a framework for analysis of ABMs that involves data fitting, statistical validation, optimal control theory for discrete dynamical systems, and a variety of heuristic methods.

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

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

Leili Shahriyari
Mathematics, University of California Irvine
Computational Biology: Mathematical modelling of biological process, Alignments, DNA Computing. Computer Science: Algorithms, Machine learning. Mathematics: Differential geometry, Partial differential equations, Graph theory. Statistics: Stochastic Processes

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

Marc Sturrock
Applied Mathematics, University of Dundee
Marc has studied a variety of areas including: spatio-temporal modeling, gene regulatory networks, negative feedback loops, intracellular signaling pathways, systems biology, and cancer modeling.

Ying (Joy) Zhou
Mathematics, University of Washington
Joy's research has focused on mathematical models for geographic range shifts of plants and animals under climate change. Math tools include deterministic and stochastic dynamical systems, integral operators, and PDEs.

C. MBI PUBLICATIONS

The following publications were produced at the MBI during 2014-2015:

Publications
MBI POSTDOCTORAL FELLOW RESEARCH PUBLISHED IN 2014 and 2015

1. R Azencott, **A Beri**, Y Gadhyan, N Joseph, C-A Lehalle and M Rowley. Real-time market microstructure analysis: online transaction cost Analysis, *Quant Fin* 14 (7) 1167-1185, [2014]
2. D Chan, M McCombs, S Boegner, HJ Ban, and **SL Robertson**. Extinction in discrete, competitive multi-species patch models, Discrete and Cont Dynam Sys Series B, 20 (6) (2015) 1583-1590
3. **J Chang**, V Savage and T Chou. A path-integral approach to Bayesian inference for inverse problems using the semiclassical approximation J Stat Phys Vol. 157 No. 3 (2014) pp. 582–602
4. **J Chang** and T Chou. Iterative graph cuts for image segmentation with a nonlinear statistical shape prior, J Mathematical Imaging and Vision Vol. 49 No. 1 (2014) pp. 87-97
5. **D Chen**, A Bobko, A Gross, R Evans, C Marsh, V Khramtsov, T Eubank, and A Friedman. Involvement of tumor macrophage HIFs in chemotherapy effectiveness: Mathematical modeling of oxygen, pH, and glutathione. *PLOS ONE*, 2014
6. **D Chen**, Modeling and computation of heterogeneous implicit solvent and its applications for biomolecules, Molecular Based Math Biology 2014
7. Y Chen, **J Kim**, A Hirning, K Josic and M Bennett. Emergent genetic oscillations in a synthetic microbial consortium, Science Vol. 349 No. 6251 (2015) pp. 986-989
8. **J Chifman** and L Kubatko. Quartet Inference from SNP Data Under the Coalescent Model, Bioinformatics, 2014.
9. OC Collins, **SL Robertson**, and K Govinder. Analysis of a waterborne disease model with socioeconomic classes, Math Biosci, 269 (2015) 86-93
10. **CO Diekman**, K. Dasgupta, V. Nair and K. Unnikrishnan. Detecting neuronal connectivity from serial patterns in spike train data. *Neural Computation* Vol. 26 No. 7 (2014) 1263-1297
11. **CO Diekman** and M. Golubitsky. Network symmetry and binocular rivalry experiments. J Math Neuroscience Vol. 4 (2014) pp. 12
12. **MC Eisenberg** and MAL Hayashi. Determining identifiable parameter combinations using subset profiling, Mathematical biosciences 256, 116-126 2014
13. M Flourakis, E Kula-Eversole, A Hutchison, T Han, K Aranda, D Moose, K White, A Dinner, B Lear, D Ren, **CO Diekman**, I Raman, and R Allada (2015). A conserved bicycle model for circadian clock control of membrane excitability. Cell, 162:836-848.

14. DA Forero-Pena, P Chaparro, A Vallejo, Y Benavides, **JB Gutierrez**, M Arevalo-Herrera, and S Herrera. *Knowledge attitudes and practices on malaria in Colombia*. Malar J. 2014 May 1;13:165. doi:10.1186/1475-2875-13-165.
15. B Franz, **C Xue**, K Painter, and R Erban. Travelling waves in hybrid chemotaxis models, Bull. Math. Biol., 76(2): 377-400, 2014.
16. A Friedman, B Hu, and **C Xue**. On a multiphase multicomponent model of biofilm growth, Arch. Rational Mech. Anal., 211(1): 257-300, 2014.
17. ME Halloran, A Vespignani, N Bharti, LR Feldstein, KA Alexander, M Ferrari, J Shaman, JM Drake, T Porco, JNS Eisenberg, SY Del Valle, E Lofgren, SV Scarpino, **MC Eisenberg**, D Gao, JM Hyman, S Eubank, and IM Longini. Ebola: mobility data, Science 346 (6208) 2014
18. **W Hao** and A Friedman. The LDL-HDL Profile Determines the Risk of Atherosclerosis: A Mathematical Model. PloS ONE Vol. 9 No. 3 (2014) pp. e90497
19. L Hu, **D Chen**, and GW Wei. Impact of geometric, thermal and tunneling effects on nano-transistors, J Computational Physics 290, 169-187 2015
20. J Hu, **H Kang** and H Othmer. Stochastic analysis of reaction-diffusion processes *Bull Mathematical Biology* 2014, Vol. 76(4) pp. 864-894
21. **HV Jain**, A Richardson, M Meyer-Hermann, and HM Byrne. Exploiting the synergy between carboplatin and ABT-737 in the treatment of ovarian carcinomas *PLoS One* (2014)
22. **H Kang**, T Kurtz, and L Popovic. Central limit theorems and diffusion approximations for multiscale Markov chain models *Annals Applied Probability*, 2014, Vol. 24(2) pp. 721-759
23. **D Koslicki** and DJ Thompson. Coding sequence density estimation via topological pressure. *J Mathematical Biology*, 1-25, 2014.
24. NA Krishna, HM Pennington, CD Coppola, **MC Eisenberg,** and RC Schugart. Connecting Local and Global Sensitivities in a Mathematical Model for Wound Healing, Bull. Math. Biol 77 (12) 2015
25. JSH Kwan, Y-H Hsu, C-L Cheung, J Dupuis, A Saint-Pierre, JEriksson, **SK Handelman**, A Aragaki, D Karasik, PP Pramstaller, C Kooperberg, AZ Lacroix, MG Larson, K-SLau, M Lorentzon, I Pichler, PC Sham, D Taliun, L Vandenput, P Kiel, AA Hicks, RD Jackson, C Ohlsson, EJ Benjamin, and AWC Kung. Meta-analysis of genome-wide association studies identifies two loci associated with circulating osteoprotegerin levels *Human Molecular Genetics* (July 2014)
26. **K Liao**, X Bai, and A Friedman. Mathematical modeling of interleukin-27 induction of anti-tumor T cells response. PloS ONE Vol. 9 No. 3 (2014) pp. e91844
27. Y Louzoun, **C Xue**, G Lesinski, and A Friedman. A mathematical model for pancreatic cancer growth and treatments, J Theoretical Biology, 351(21): 74-82, 2014.
28. A Matzavinos, **B Shtylla**, Z Voller, S Liu and M Chaplain. Stochastic modeling of chromosomal segregation: Errors can introduce correction *Bull Math Biology* (2014)
29. N Meshkat, S Sullivant, and **MC Eisenberg**. Identifiability results for several classes of linear compartment models, Bull. Math. Biology 77 (8) 2015
30. V Naumov, W Nicholson, I Price, **SK Handelman**, JF Hunti. Engineering surface epitopes to improve protein crystallization US Patent WO 2014063098 A3:
31. **D Schmidt** and PJ Thomas. Measuring edge importance: a quantitative analysis of the stochastic shielding approximation for random processes on graphs *J Mathematical Neuroscience* 4:6 (2014)
32. W Sadee, K Hartmann, **M Seweryn**, M Pietrzak, **SK Handelman**, and GA Rempala. Missing heritability of common diseases and treatments outside the protein-coding exome *Human Genetics* (Aug 2014)
33. X Tao, N Hoenich, **SK Handelman SK**, Levin NW, P Kotanko P, Handelman GJ. Transfer of low-molecular weight single-stranded DNA through the membrane of a high-flux dialyzer. *The International Journal of Artificial Organs* 2014, 37(7):529-538

34. D Terman, J Rubin, and **CO Diekman**. Irregular activity arises as a natural consequence of synaptic inhibition. *Chaos* Vol. 23 No. 4 (2014) 046110.
35. JH Tien, Z Shuai, **MC Eisenberg**, and P van den Driessche. Disease invasion on community networks with environmental pathogen movement J Math Biology 70 (5) 2015
36. A Veliz-Cuba, B Aguilar, **F Hinkelmann**, and R Laubenbacher. Steady state analysis of Boolean molecular network models via model reduction and computational algebra *BMC Bioinformatics (2014)*
37. BA Yan, A Moreno, M Galinski, J Kissinger, and **JB Gutierrez**. *Mathematical model of susceptibility, resistance, and resilience in the within-host dynamics between a Plasmodium parasite and the immune system*. Mathematical Biosciences. Volume 270, Part B, December 2015, 213–223. doi:10.1016/j.mbs.2015.10.003
38. S Chatterjee, **D Koslicki**, S Dong, N Innocenti, L Cheng, Y Lan, M Vehkapera, M Skoglund, LK Rasmussen, E Aurell, and J Corander, SEK: sparsity exploiting k-mer-based estimation of bacterial community composition. *Bioinformatics*, 30(17), 2423-2431, 2014.
39. **D Koslicki**, S Foucart, and G Rosen, WGSQuikr: fast whole-genome shotgun metagenomic classification. *PLoS ONE*, 9(3), e91784, 2014.
40. S Foucart and **D Koslicki**, Sparse recovery by means of nonnegative least squares. *IEEE Signal Processing Letters*, 21(4), 498--502, 2014.
41. A Friedman, CY Kao, and **R Leander**. On the dynamics of granuloma. *J Mathematical Analysis and Applications* Volume 412 (2014), 776–791
42. **R Leander**, EJ Allen, SP Garbett, and DR Tyson. Derivation And Experimental Comparison Of Cell-Division Probability Densities, *J Theoretical Biology* Volume 359 (2014),129-135.
43. **R Leander** and A Friedman. Modulation of the cAMP response by G alpha i and G beta gamma: a computational study of G protein signaling in immune cells. *Bull Mathematical Biology* Volume 76, Issue 6 (2014), 1352-1375
44. **R Leander**, S Lenhart, and V Protopopescu. Optimal control of continuous systems with impulse controls. *Optimal Control Applications and Methods*, (2014)
45. DE Frankhouser, M Murphy, JS Blachly, **J Park**, MW Zoller, J-O Ganbat, J Curfman, JC Byrd, S Lin, G Marcucci, P Yan and R Bundschuh. PrEMeR-CG: Inferring Nucleotide Level DNA Methylation Values from MethylCap-Seq Data *Bioinformatics* Sept 1, 2014
46. **P Hurtado**, S Hall and S Ellner. Infectious Disease in Consumer Populations: Dynamic Consequences of Resource-Mediated Transmission and Infectiousness *Theoretical Ecology* Vol. 7 (2014) 163-179
47. **K-Y Lam** and Y Lou. Evolutionarily stable and convergent stable strategies in reaction-diffusion models for conditional dispersal. *Bulletin of mathematical biology*Vol. 76 No. 2 (2014) pp. 261-91
48. **K-Y Lam** and Y Lou. Evolution of conditional dispersal: evolutionarily stable strategies in spatial models. *J Math Biology* Vol. 68 No. 4 (2014) pp. 851-77
49. **K-Y Lam** and D Munther. Invading the ideal free distribution, *Special Issue in Honor of Chris Cosner's 60th Birthday, Discrete Contin. Dyn. Syst. Ser. B, accepted*.
50. A Friedman and **K-Y Lam**. On the stability of steady states in a granuloma model, *J. Differential Equations*, *256 (2014) 3743-3769.*
51. **K-Y Lam** and W-M Ni. Advection-mediated competition in general environments, *J. Differential Equations*, *in press.*
52. **W-C Lo**, H-O Park and C-S Chou. Mathematical Analysis of Spontaneous Emergence of Cell Polarity. *Bulletin of Mathematical Biology*, 2014, DOI 10.1007/s11538-014-9982-2
53. **W-C Lo**. Morphogen Gradient with Expansion-Repression Mechanism: Steady-State and Robustness Studies. *Discrete and Continuous Dynamical Systems-B*, 2014, 19(3):775-787.

54. **W-C Lo**, R Arsenescu, and A Friedman. Mathematical model of the roles of T cells in inflammatory bowel disease. *Bulletin of mathematical biology* Vol. 75 No. 9 (2013) pp. 1417-33
55. L Comita, S Queenborough, S Murphy, J Eck, K Xu, M Krishnadas, **N Beckman**, and Y Zhu. Testing predictions of the Janzen–Connell hypothesis: a meta-analysis of experimental evidence for distance- and density-dependent seed and seedling survival *J Ecology* Vol. 102 No. 4 (2014) pp. 845-856
56. NL Stephenson, AJ Das, R Condit, SE Russo, P Baker, **NG Beckman**. 2014. Rate of tree carbon accumulation increases continuously with tree size. *Nature.* DOI: 10.1038/nature12914
57. **NG Beckman**, R Dybzinski, and D Tilman. 2014. Neighborhoods have little effect on fungal attack or insect predation of developing seeds in a grassland biodiversity experiment. *Oecologia* 174 (2): 521-532.
58. **J Chang** and T Chou. Iterative graph cuts for image segmentation with a nonlinear statistical shape prior. *Journal of mathematical imaging and vision* Vol. 49 No. 1 (2014) pp. 87-97
59. **JC Chang**, VM Savage, and T Chou. A path-integral approach to Bayesian inference for inverse problems using the semiclassical approximation. *J Statistical Physics*. DOI: 10.1007/s10955-014-1059-y
60. **K Liao** and Y Lou. The effect of time delay in a two-patch model with random dispersal. *Bull Math Biology* Vol. 76 No. 2 (2014) pp. 335-76
61. **K Liao**, X Bai and A Friedman. Mathematical modeling of interleukin-27 induction of anti-tumor T cells response. *PloS one* Vol. 9 (3) (2014) e91844
62. **K-L Liao**, X-F Bai, and A. Friedman. 2014, Mathematical modeling of Interleukin 35 promoting tumor growth and angiogenesis, *PLoS ONE*, No. 9(10), e110126.
63. A Friedman and **K-L Liao**, 2015, The role of the cytokines IL-27 and IL-35 in cancer, *Math Biosciences and Engineering*, accepted
64. M-J Lai and **L Matamba Messi**. *Hierarchical multiscale decomposition: modes and rates of convergence*. Submitted to SIAM Multiscale Modeling and Simulation (03/2014).
65. **L Matamba Messi**, G Huguet, and D Terman. *Blocking spreading depolarization in a neuron-astrocyte network model.* Submitted to PLOS Computational Biology (02/2015)
66. **J Newby** and **M Schwemmer**. Effects of moderate noise on a limit cycle oscillator: counterrotation and bistability. *Physical review letters* Vol. 112 No. 11 (2014) pp. 114101
67. P Bressloff and **J Newby**. Path integrals and large deviations in stochastic hybrid systems. *Physical review. E, Statistical, Nonlinear, and soft matter physics* Vol. 89 No. 4 (2014) pp. 042701
68. TJ Lewis and **MA Schwemmer**. Weak Coupling Theory. *Encyclopedia of Computational Neuroscience* (D. Jaeger and R. Jung eds.), Springer. 2014
69. SF Feng, **M Schwemmer**, SJ Gershman, and JD Cohen. Multitasking versus multiplexing: Toward a normative account of limitations in the simultaneous execution of control-demanding behaviors. Cognitive, Affective, & Behavioral Neuroscience 14 (1) 2014
70. **MA Schwemmer**, AL Fairhall, S Denéve, and ET Shea-Brown. Constructing precisely computing networks with biophysical spiking neurons, J Neuroscience 35 (28), 2015
71. **MA Schwemmer** and TJ Lewis. The robustness of phase-locking in neurons with dendro-dendritic electrical coupling, J Math Biology 68 (1-2), 2014
72. P Davison, NE Leonard, A Olshevsky, and **M Schwemmer**. Nonuniform line coverage from noisy scalar measurements, IEEE Transactions on Automatic Control 60 (7) 2015.
73. G Rempala, L Ignatowicz, P Kisielow, **M Seweryn**, and L Wojciech. The same self-peptide selects conventional and regulatory T cells with identical antigen receptors. *Nature Communications* 2014

74. P Matula and **M Seweryn**. On Etemadis subsequences and the strong law of large numbers for random fields *Rocky Mountain J Mathematics* 2015
75. M Pietrzak, GA Rempała, **M Seweryn,** and J Wesołowski. Limit Theorems for Empirical R\'enyi Entropy and Divergence with Applications to Molecular Diversity Analysis, *Test*, May 2015
76. P Matuła and **M Seweryn**. Acknowledgement of Priority "Weighted Averages of Random Variables and Exact Weights" *Demonstratio Mathematica* 2014
77. R Mascarenhas, M Pietrzak ,RM Smith, A Webb, D Wang, AC Papp, JK Pinsonneault, **M Seweryn**, G Rempala, and W Sadee. Allele-Selective Transcriptome Recruitment to Polysomes Primed for Translation: Protein-Coding and Noncoding RNAs, and RNA Isoforms, *PLoS One* 2015
78. A Webb, AC Papp, A Curtis, LC Newman, M Pietrzak, **M Seweryn**, **SK Handelman**, GA Rempala, D Wang, E Graziosa, RF Tyndale, C Lerman, JR Kelsoe, DC Mash and W Sadee. RNA sequencing of transcriptomes in human brain regions: protein-coding and non-coding RNAs, isoforms and alleles *BMC Genomics* 2015
79. **SK Handelman**, **M Seweryn**, RM Smith, K Hartmann, D Wang, M Pietrzak, AD Johnson, A Kloczkowski, and W Sadee. Conditional entropy in variation-adjusted windows detects selection signatures associated with expression quantitative trait loci (eQTLs) *BMC Genomics* 2015
80. J Schwartzbaum , **M Seweryn**, C Holloman, R Harris, **SK Handelman**, GA Rempala, R-P Huang, B Burkholder, A Brandemihl, H Kallberg, T Borge Johannesen, A Ahlbom, M Feychting, TK Grimsrud, Association between Prediagnostic Allergy-Related Serum Cytokines and Glioma *PLoS One* 2015
81. **SK Handelman**, JM Aaronson, **M Seweryn**, I Voronkin, JJ Kwiek, W Sadee, JS Verducci, and DA Janies. Cladograms with Path to Event (ClaPTE): A novel algorithm to detect associations between genotypes or phenotypes using phylogenies *Computers in Biology and Medicine*, Vol 58, March 2015
82. R Lu, RM Smith, **M Seweryn**, D Wang, C Hartmann, A Webb, W Sadee, and GA Rempala. Analyzing allele specific RNA expression using mixture models, *BMC Genomics* 2015
83. **K Fessel**. A model for the nonlinear mechanism responsible for cochlear amplification *Math Biosciences and Engineering* 2014
84. **W Hao** and A Friedman. The LDL-HDL Profile Determines the Risk of Atherosclerosis: A Mathematical Model. *PloS one* Vol. 9 (3) (2014) e90497
85. **W Hao**, RI Nepomechie, and AJ Sommese. Singular solutions, repeated roots and com-pleteness for higher-spin chains, *Journal of Statistical Mechanics: Theory and Experiments*, P03024, (2014).
86. A Friedman and **W Hao**. A mathematical model of atherosclerosis with reverse cholesterol transport and associated risk factors, *Bull Math Biology,* accepted, (2014).
87. A Friedman, **W Hao**, and B Hu. A Free Boundary Problem for Steady Small Plaques in the Arteryand their Stability, Journal of Differential Equations , accepted, (2014).
88. **W Hao**, Z Xu, C Liu, and G Lin. A Fictitious Domain Method with a Hybrid Cell Model for Simulating Motion of Cells in Fluid Flow, Journal of Computational Physics, Volume 280, pp. 345–362, (2015).
89. **W Hao**, ED Crouser and A Friedman, Mathematical model of sarcoidosis , PNAS , Vol. 111 No. 45, pp. 16065–16070, (2014).
90. **W Hao**, BH Rovin and A Friedman. Mathematical model of renal interstitial fibrosis, PNAS ,Vol. 111 No. 39, pp. 14193–14198, (2014). (Reported at Nature Reviews Nephrology)
91. A Friedman and **W Hao**. A mathematical model of atherosclerosis with reverse cholesterol transport and associated risk factors, Bulletin of Mathematical Biology , accepted, (2014)
92. **W Hao** and A Friedman. The LDL-HDL profile determines the risk of atherosclerosis: A mathematical model, PLOS ONE, 9(3): e90497, (2014).

93. **M Sturrock**, **W Hao**, J Schwartzbaum, DD Kinnamon, and GA Rempala. A mathematical model of pre-diagnostic glioma growth*, J Theoretical Biology*, accepted.
94. M Burch, **K Jacobsen**, J Tien, and G Rempala. Network-based analysis of a small Ebola outbreak. *Mathematical Biosciences*, in press.
95. **K Jacobsen** and SS Pilyugin. Analysis of a mathematical model for tumor therapy with a fusogenic oncolytic virus. *Mathematical Biosciences*, Vol. 270, Part B: 169-182 (2015).
96. **K Jacobsen**, L Russell, B Kaur and A Friedman. Effects of CCN1 and macrophage content on glioma virotherapy: A mathematical model. *Bull Mathematical Biology*, (77): 984-1012 (2015).
97. **JK Kim**, Z Kilpatrick, M Bennett and K Josic. Molecular mechanisms that regulate the coupled period of the mammalian circadian clock *Biophysical Journal* Vol. 106 No. 9 (2014) 2071–2081
98. **JK Kim**, K Josic, and MR Bennett. The validity of quasi steady-state approximations in discrete stochastic simulations, *Biophysical Journal* (2014)
99. A Goriki, F Hatanaka, J Myung, **JK** Kim, T Yoritaka, S Tanoue, T Abe, H Kiyonari, K Fujimoto, Y Kato, A Matsubara, DB Forger, and T Takumi. A novel protein, CHRONO, functions as a core component of the mammalian circadian clock, *PLoS Biology* 12 (2014)
100. M Zhou, **JK Kim**, D Forger, and D Virshup. Phosphoswitch regulates and compensate circadian period (*In revision* for Mol Cell).
101. **MA Mourão**, L Satin, and S Schnell. Optimal experimental design to estimate statistically significant oscillatory periods in time course data. *PLOS ONE* 9, e93826 (2014)
102. **MA Mourão**, J Hakim, and S Schnell. Connecting the dots: the effects of macromolecular crowding on cell physiology. Biophysical journal 107 (12), 2761-2766.
103. **MA Mourão**, D Kreitman, and S. Schnell. Unravelling the impact of obstacles in diffusion and kinetics of an enzyme catalysed reaction. Phys. Chem. Chem. Phys., 2014, 16, 4492-4503, DOI: 10.1039/C3CP52417E.
104. **M Sturrock**, A Hellander, S Aldakheel, L Petzold, and MAJ Chaplain. The role of dimerisation and nuclear transport in the Hes1 gene regulatory network. Bull Mathematical Biology 76 (4) 2014
105. M Chaplain, M Ptashnyk, and **M Sturrock**. Hopf bifurcation in a gene regulatory network model: Molecular movement causes oscillations, Mathematical Models and Methods in Applied Sciences 25 (06) 2015
106. **M Sturrock**, PJ Murray, A Matzavinos, and MAJ Chaplain. Mean field analysis of a spatial stochastic model of a gene regulatory network, J mathematical biology 71 (4) 2015
107. **M Sturrock** and AT Dawes, Protein abundance may regulate sensitivity to external cues in polarized cells, J The Royal Society Interface 12 (106) 2015
108. **M Oremland** and R Laubenbacher. (2015). Optimal harvesting of a predator-prey agent-based model using difference equations, *Bull Math Biology*, DOI:10.1007/s11538-014-0060-6.
109. **M Oremland**, K Michels, A Bettina, C Lawrence, B Mehrad, and R Laubenbacher. A computational model of invasive aspergillosis in the lung, *BMC Systems Biology.* DATE?
110. S Christley, R Neilan, **M Oremland**, R Salinas, and S Lenhart. Optimal control of the SugarScape agent-based model via an approximation model, *Optimal Control, Applications and Methods*
111. **L Shahriyari** and N Komarova. The role of the bi-compartmental stem cell niche in delaying cancer, Physical Biology, 2015.

D. 2014-2015 TOPIC SELECTION

To support the MBI mission, MBI programs were designed to reinforce and build upon existing research efforts in the mathematical biosciences, and to inspire and accelerate the expansion of the community

and its intellectual growth. These include emphasis year programs, current topic workshops, education programs, and research projects. The administrative and governance structure of the MBI are designed to support the mission of the Institute.

MBI programs are aimed at bringing mathematical scientists and bioscientists together to discuss ways in which the mathematical sciences are being used to solve significant problems in the bio and biomedical sciences and how problems from the biosciences are opening new areas of research for mathematicians, statisticians, and computational scientists. The Director consults widely in the mathematical bioscience community for appropriate subjects for emphasis years. MBI encourages the wider mathematical and scientific communities to propose ideas for programs.

MBI activities involve input from the Board of Trustees, Scientific Advisory Committee, Local Scientific Advisory Committee, Emphasis Year External Advisory Committee and Workshop Organizers. Detailed information about each committee follows:

1. <u>Board of Trustees (BOT)</u>

Governance in program planning is provided by a Board of Trustees. The Board consists of individuals with leadership experience in the public and private sectors, and of recognized scientists in fields related to the MBI activities. The Board meets annually to advise the directors and The Ohio State University regarding management of the institute, to review its scientific programs, and to suggest new programs and give advice regarding programmatic goals.

For 2014-2015, Board Members and their terms:

1. Anna Barker
   School of Life Sciences, Arizona State University
   January 2012 - December 2017
2. Carolyn Cho
   Quantitative Pharmacology & Pharmacometrics, Merck, Sharp & Dohme
   January 2015 - December 2017
3. Rebecca Doerge
   Statistics, Purdue University
   January 2014 - December 2016
4. Irving Epstein
   Howard Hughes Medical Institute, Brandeis University
   January 2012 - December 2017
5. James Keener (Chair)
   Mathematics, University of Utah
   January 2012 - December 2017
6. Kirk Jordan
   Data Centric Systems, IBM Corporation
   January 2007 - December 2015
7. Nancy Kopell
   Department of Mathematics and Statistics, Boston University
   January 2013 - December 2015
8. Thomas Kurtz
   Mathematics and Statistics, University of Wisconsin

January 2015 - December 2017

9. Claudia Neuhauser
   Biomedical Informatics and Computational Biology, University of Minnesota Rochester
   May 2012 - December 2015
10. Alan Perelson
    Theoretical Biology and Biophysics Group, Los Alamos National Laboratory
    January 2012 - December 2017
11. John Reinitz
    Departments of Statistics, Institute of Genomics & Systems Biology, University of Chicago
    January 2012 - December 2017
12. Blake Thompson
    Institutional Affairs, Battelle Memorial Institute
    January 2010 - December 2014
13. Michael Waterman
    Biological Sciences, Mathematics, and Computer Science, University of Southern California
    January 2010 - December 2015

Past Board Members:

1. Rita Colwell
   Center for Bioinformatics and Computational Biology, University of Maryland
   January 2009 - December 2013
2. John Guckenheimer
   Mathematics Department, Cornell University
   January 2009 - December 2011
3. Robb Krumlauf
   Scientific Director, Stowers Institute for Medical Research
   January 2007 - December 2010
4. Barbara Kunz
   Health and Life Sciences Global Business (HLSGB), Battelle Memorial Institute
   January 2007 - December 2009
5. Mark Lewis
   Department of Mathematical Sciences & Department of Biological Sciences, University of Alberta
   January 2007 - December 2011
6. Robert Miura
   Department of Mathematical Sciences, New Jersey Institute of Technology
   January 2007 - December 2012
7. Stephen Ruberg
   Distinguished Senior Research Fellow, Eli Lilly and Company
   January 2007 - December 2009

2. <u>Scientific Advisory Committee (SAC)</u>

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.

For 2014-2015 committee members and their terms:

1. Fred Adler
   Mathematics and Biology, University of Utah
   2014 - 2016
2. Dan Coombs
   Department of Mathematics, University of British Columbia
   2014 – 2016
3. Thomas Chou
   Biomathematics, University of California, Los Angeles
   2012 - 2015
4. Abba Gumel
   School of Mathematical and Statistical Sciences, Arizona State University
   2013 - 2016
5. Alan Hastings
   Department of Environmental Science and Policy, University of California, Davis
   2014 – 2016
6. Shandelle Henson
   Department of Mathematics, Andrews University
   2012 – 2014
7. Trachette Jackson
   Department of Mathematics, University of Michigan
   2012 – 2014
8. Nan Laird
   Biostatistics, Harvard University
   2012 – 2014
9. Michael Mackey (Chair 2014)
   Applied Mathematics in Bioscience and Medicine, Physiology, McGill University
   2011 – 2015
10. Qing Nie
    Biomedical Engineering & Mathematics, University of California, Irvine
    2013 - 2015
11. Mette Olufsen
    Department of Mathematics, North Carolina State University
    2014 - 2016
12. Javier Rojo
    Department of Mathematics and Statistitcs, University of Nevada
    2014 – 2016
13. Jonathan Rubin (Chair)
    Department of Mathematics, University of Pittsburgh
    2013 - 2015

14. Santiago Schnell
    Department of Molecular & Integrative Biology, Department of Computational Medicine & Bioinformatics, Brehm Center for Diabetes Research, University of Michigan
    2014 - 2016
15. Hal Smith
    Department of Mathematics & Statistics, Arizona State University
    2014 – 2016
16. Jack Tuszynski
    Oncology, University of Alberta
    2012 – 2014

Past Committee Members:

1. Reka Albert
   Department of Physics, Pennsylvania State University
   2006 – 2008
2. Linda Allen
   Department of Mathematics and Statistics, Texas Tech University
   2009 – 2011
3. Alexander Anderson
   Integrated Mathematical Oncology, H. Lee Moffitt Cancer Center & Research Institute
   2011 – 2013
4. Adam Arkin
   Department of Bioengineering, University of California, Berkeley
   2007 – 2009
5. Herb Bresler
   Health and Life Sciences, Battelle Memorial Institute
   2006 – 2008
6. Paul Bressloff
   Department of Mathematics, University of Utah
   2011 – 2013
7. Mark Chaplain
   Division of Mathematics, University of Dundee
   2008 – 2010
8. Chris Cosner
   Department of Mathematics, University of Miami
   2011 – 2013
9. Gerda de Vries
   Mathematical and Statistical Sciences, University of Alberta
   2011 – 2013
10. Mark Denny
    Biology, Stanford University
    2008 – 2010
11. Leah Edelstein-Keshet
    Mathematics, University of British Columbia
    2006 – 2008
12. Tim Elston
    Applied Mathematics, University of North Carolina, Chapel Hill
    2011 – 2013

13. Bard Ermentrout
    Department of Mathematics, University of Pittsburgh
    2009 – 2011
14. Lisa Fauci
    Department of Mathematics, Tulane University
    2006 – 2008
15. Greg Forest
    Mathematics, University of North Carolina, Chapel Hill
    2011 – 2013
16. Louis Gross
    Depts. of Ecology & Evolutionary Biology & Math, University of Tennessee
    2006 – 2008
17. Sorin Istrail
    Computer Science, Brown University
    2006 – 2008
18. Nicholas Jewell
    Biostatistics and Statistics, University of California, Berkeley
    2007 – 2009
19. Reinhard Laubenbacher
    Center for Quantitative Medicine, University of Connecticut Health Center
    2011 – 2013
20. Douglas Lauffenburger
    Biological Engineering, Massachusetts Institute of Technology
    2006 – 2008
21. Suzanne Lenhart
    2008 - 2010
22. Naomi Leonard (Chair 2011-2012)
    Mechanical and Aerospace Engineering, Princeton University
    2009 - 2012
23. Mark Lewis (Chair 2009-2010)
    Department of Mathematical Sciences and Department of Biological Sciences, University of Alberta
    2007 - 2010
24. Andre Longtin
    Physics and Center for Neural Dynamics, University of Ottawa
    2010 - 2012
25. Sharon Lubkin
    Mathematics, North Carolina State University
    2011 - 2013
26. Gregory Mack
    Environmental Monitoring and Assessment, Battelle Memorial Institute
    2006 - 2008
27. Paul Magwene
    Biology, Duke University
    2009 - 2011
28. L. Mahadevan
    School of Engineering and Applied Sciences, Harvard University
    2010 - 2012

29. Philip Maini
    Centre for Mathematical Biology, University of Oxford
30. Claudia Neuhauser
    Ecology, Evolution, and Behavior, University of Minnesota
    2006 - 2008
31. Karl Niklas
    Plant Biology, Cornell University
    2008 - 2010
32. Lior Pachter
    Department of Mathematics, University of California, Berkeley
    2008 - 2010
33. Alan Perelson
    Theoretical Biology and Biophysics Group, Los Alamos National Laboratory
    2006 - 2008
34. Linda Petzold
    Mechanical Engineering, University of California, Santa Barbara
    2007 - 2009
35. Michael Reed
    Mathematics, Duke University
36. John Rinzel
    Center for Neural Science, New York University
    2006 - 2008
37. Stephen Ruberg
    Statistics, Purdue University
38. Steven Rust
    Battelle Memorial Institute
    2009 - 2011
39. Stanislav Shvartsman
    Lewis-Sigler Institute for Integrative Genomics, Princeton University
    2008 - 2010
40. James Sneyd
    Mathematics, The University of Auckland
    2008 - 2010
41. Terence Speed
    Bioinformatics, Walter & Eliza Hall Institute of Medical Research
    2008 - 2009
42. John Taulbee
    Procter & Gamble
    2008
43. Terry Therneau
    Division of Biostatistics, Mayo Clinic
    2008
44. Frank Tobin
    Tobin Consulting LLC, Tobin Consulting LLC
    2006 - 2008
45. John Tyson
    Computational Cell Biology, Virginia Polytechnic Institute and State University
    2006 - 2008

46. Steven Vogel
    Biology, Duke University
    2007 - 2009
47. Michael Waterman
    Biological Sciences, Mathematics, and Computer Science, University of Southern California
    2006 - 2008
48. Raimond Winslow
    Department of Biomedical Engineering, Johns Hopkins University
    2006 – 2008

3. <u>Local Scientific Advisory Committee (LSAC)</u>

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.

2014-2015 committee members and their terms:

1. Ralf Bundschuh (- 2016)
   Departments of Physics and Biochemistry, The Ohio State University
2. James Cogdell (- 2016)
   Mathematics, The Ohio State University
3. Kevin Coombes (2014-2016)
   Biomedical Informatics, The Ohio State University
4. Meg Daly (- 2015)
   Evolution, Ecology, and Organismal Biology, The Ohio State University
5. Andrea Doseff (- 2016)
   Internal Medicine, The Ohio State University
6. Martin Feinberg (- 2016)
   Chemical Engineering & Mathematics, The Ohio State University
7. Avner Friedman (- 2015)
   Department of Mathematics, The Ohio State University
8. Rebecca Garabed (2014 - 2016)
   Veterinary Preventive Medicine, The Ohio State University
9. Matthew Kahle (2014 - 2016)
   Mathematics, The Ohio State University
10. Douglas Kniss (- 2016)
    OB&GYN, The Ohio State University
11. Laura Kubatko
    Statistics/EEOB, The Ohio State University
12. Sebastian Kurtek (2014 - 2016)
    Statistics, The Ohio State University
13. Gustavo Leone (- 2015)
    Molecular Virology, Immunology, and Medical Genetics, The Ohio State University
14. Shili Lin (- 2016)
    Statistics, The Ohio State University
15. Thomas Magliery (- 2016)

Chemistry, The Ohio State University
16. Stuart Mangel (- 2016)
    Department of Neuroscience, The Ohio State University
17. Elizabeth Marschall (- 2016)
    Evolution, Ecology,and Organismal Biology, The Ohio State University
18. William Martin (- 2016)
    College of Public Health, The Ohio State University
19. Roger Ratcliff (- 2016)
    Psychology, The Ohio State University
20. Wolfgang Sadee (- 2015)
    Internal Medicine, College of Medicine (OSUMC), The Ohio State University
21. Larry Schlesinger (- 2015)
    Center for Microbial Interface Biology, The Ohio State University
22. Chandan Sen (- 2015)
    Depts of Surgery & Molecular & Cellular Biochemistry, The Ohio State University
23. Amanda Simcox (- 2015)
    Molecular Genetics, The Ohio State University
24. R. Keith Slotkin (2014-2016)
    Molecular Genetics, The Ohio State University
25. Parthasarathy Srinivasan (- 2016)
    Computer Science and Engineering and Department of Biomedical Informatics, The Ohio State University
26. Don Stredney (- 2015)
    Research Dept., The Ohio State University

Ex Officios:

1. Janet Best
   Mathematics, The Ohio State University
2. Catherine Calder
   Department of Statistics, The Ohio State University
3. Helen Chamberlin
   Molecular Genetics, The Ohio State University
4. Marty Golubitsky
   Mathematical Biosciences Institute, The Ohio State University
5. Tony Nance
   Mathematical Biosciences Institute, The Ohio State University
6. Grzegorz Rempala
   Mathematical Biosciences Institute, The Ohio State University
7. Andrej Rotter
   Department of Pharmacology, The Ohio State University

Former Committee Members:

1. Irina Artsimovitch
   Microbiology, The Ohio State University
2. Samir Ghadiali
   Biomedical Engineering, The Ohio State University
3. Erich Grotewold
   Dept. of Plant Cellular and Molecular Biology, The Ohio State University

4. Richard Hart
   Biomedical Engineering, The Ohio State University
5. Tim Huang
   Human Cancer Genetics Program, The Ohio State University
6. Kay Huebner
   Molecular Virology, Immunology and Medical Genetics, The Ohio State University
7. Dan Janies
   Dept. of Biomedical Informatics, The Ohio State University
8. Stanley Lemeshow
   Biostatistics, The Ohio State University
9. Yuan Lou
   Department of Mathematics, The Ohio State University
10. Deborah Parris
    Molecular Virology, Immunology, and Medical Genetics, The Ohio State University
11. Dennis Pearl
    Department of Statistics, The Ohio State University
12. David Terman
    Mathemathics Department, The Ohio State University
13. Joe Travers
    Neuroscience, The Ohio State University

4. Workshop Organizers

The 2014-2015 year was the MBI Emphasis Year on Cancer and Its Environment. The organizing committee members were:

1. Emil Alexov (Computational Biophysics and Bioinformatics, Clemson University)
   Alexander Anderson (Integrated Mathematical Oncology, H. Lee Moffitt Cancer Center & Research Institute)
2. Rick Durrett (Department of Mathematics, Duke University)
3. Mariam Eljanne (Physical Sciences-Oncology, National Institutes of Health (NIH))
4. Avner Friedman (Department of Mathematics, The Ohio State University)
5. Kirk Jordan (Data Centric Systems, IBM Corporation)
6. John Lowengrub (Mathematics, University of California, Irvine)
7. Guido Marcucci (Comprehensive Cancer Center, The Ohio State University)
8. Hans Othmer (School of Mathematics, University of Minnesota)
9. Vito Quaranta (Vanderbilt Ingram Cancer Biology Center, Vanderbilt University)

E. MBI WORKSHOP REPORTS

Reports for Events in 2014-2015:

Workshop 1: Ecology & Evolution of Cancer
(September 15-19, 2014)
Organizers: David Basanta (Moffitt Cancer Center), Jasmine Foo (University of Minnesota), Rick Durrett (Duke University), Carlo Maley (University of California, San Francisco)
Report by: Michael Schwemmer, Leili Shahriyari, and Joy Zhou

MONDAY, SEPTEMBER 15, 2014

Patterns of clonal evolution in human cancers
Trevor Graham (Barts Cancer Institute, QMUL)
The process of clonal evolution underpins the maintenance of a normal healthy colon, and the unwanted evolution of mutant cells leads to the development of colon cancer. However, despite the central importance, a quantification of the parameters that define the clonal evolutionary process in human colon (and indeed all human tissues) has remained lacking. The current understanding is derived from studies performed in model organisms, and it is uncertain if and how these insights apply to humans. In this talk, Dr. Graham described how he has combined a novel lineage tracing strategy in human colon (that allows the fate of different clonal lineages to be visualised) with a simple mathematical model that allows him to infer the parameters governing clonal evolution in the human gut. This parameterisation allows the age of colon tumours to be determined. Using this model, Dr. Graham showed that human intestinal cells evolve through a process of neutral drift, and that the neutrality of this process is disrupted by mutation to a certain gene that functions as a key tumour-suppressor in the colon. Lastly, Dr. Graham discussed how he has coupled multi-region sampling of established colorectal cancers with whole-genome sequencing and other genomic analysis to infer how colorectal cancers evolve. His results imply that clonal evolution is not a process of stepwise clonal sweeps as the standard textbook model implies.

Reconstructing human cancer progression from private and public mutations
Darryl Shibata (USC Keck School of Medicine)
In this talk, Dr. Shibata discussed a method to study the early cell division that occurs in tumor initiation. The start of human tumorigenesis is difficult to study because most human tumors are undetectable until they reach about 1 cm in size (~1 billion cells). However, Dr. Shibata showed that it is possible to reconstruct even the first few divisions after tumor initiation through the analysis of somatic mutations in large present day tumors. Using coalescent theory, “public” mutations in the initiating cell will be present in all present day tumor cells. Assuming a simple exponential clonal expansion, “private” mutations that arise during the first few cell divisions will be present in most but not all present day tumor cells. The earlier a private mutation occurs, the greater its frequency in the final tumor. By sampling multiple regions from the same large human tumor, it is possible to identify public and private mutations, and then infer the early events after human tumor initiation. Studying the initial cell divisions that occur in a tumor could lead to early cancer prevention therapies as well as earlier diagnoses of whether a tumor is benign or malignant.

Nutrition and cancer: Choosing the right model
John Potter (Fred Hutchinson Cancer Research Center)
In this talk, Dr. Potter discussed how the dominant theory of carcinogenesis does not do a very good job of underpinning known associations between cancer and specifically: alcohol; dietary fat; obesity; vegetables, fruit, and single nutrients; hormones; and inflammation. Dr. Potter went on to describe the dominant theory of carcinogenesis in detail. He then showed that the theory does not account for certain empirical findings, and then pointed out that there are other theories that can help one think more clearly about diet and cancer, in particular. Noting that an important universal (but often ignored) characteristic

of cancer is disrupted tissue microarchitecture, Dr. Potter utilized insights from development and morphogenesis to suggest that cancer can be considered as something like disordered development. Dr. Potter then showed that there is evidence that developing cells can sense their systemic and nutritional environment and that exogenous nutrients and endogenous hormones can directly regulate at least one key morphogenetic/morphostatic signaling system and determine cell fate. Dr. Potter then argued that environmental influences rather than just a genetic program might drive the development of cancer cells.

Modeling metastasis using zebrafish
Richard White (Memorial Sloan-Kettering Cancer Center)
Metastatic disease is the defining feature of advanced malignancy, yet the mechanisms by which it occurs and affects host physiology are poorly understood. Comprehensive genomic studies of human metastatic cancers have revealed striking heterogeneity within primary tumors, and also between different metastases from the same patient. For these reasons, models that capture this heterogeneity will be necessary to design effective strategies to abrogate the metastatic phenotype. In this talk, Dr. White discussed how his laboratory is using the zebrafish to aid in understanding metastasis. The zebrafish is a recent addition to animal models of human cancer, and studies using this model are rapidly contributing major insights. Zebrafish develop cancer spontaneously, after mutagen exposure and through transgenesis. The tumours resemble human cancers at the histological, gene expression and genomic levels. The ability to carry out in vivo imaging, chemical and genetic screens, and high-throughput transgenesis offers a unique opportunity to functionally characterize the cancer genome. Moreover, increasingly sophisticated modelling of combinations of genetic and epigenetic alterations will allow the zebrafish to complement what can be achieved in other models, such as mouse and human cell culture systems. Dr. White then went on to discuss an application of using the zebrafish to study melanoma, or skin cancer.

The cancer ecosystem: Niche construction without homeostatic controls
Kenneth Pienta (Johns Hopkins University)
In this talk, Dr. Pienta discussed how insights from ecology may aide in the development of new cancer treatments. In particular, Dr. Pienta argues that cancer creates its own ecosystem through niche construction. Niche construction is the process whereby organisms modify their own and/or each other's niches through their metabolism, activities, and/or choices. This can result in changes in one or more natural selection pressures in the external environment of populations. Niche-constructing species may either alter the natural selection pressures of their own population, of other populations, or of both. In ecology, foundation species are species that have a strong role in structuring a community. Cancer cells act as a foundation species and also act as ecosystem engineers to construct new system niches. Dr. Pienta then pointed out that, unlike most constructed ecosystems that eventually reach a point of homeostasis (equilibrium) that creates an environment that allows the foundation species to thrive, cancer exhibits no homeostasis. Dr. Pienta then discussed how niche disruption therapy could be used in treating prostate cancer patients.

The promise of comparative oncology: What dogs and elephants can teach us about cancer in humans
Joshua Schiffman (Huntsman Cancer Institute/University of Utah)

Dr. Schiffman discussed how the growing field of comparative oncology offers an excellent opportunity to understand the evolutionary origins of cancer. Understanding the evolutionary origins of cancer is vital for treating cancers that stem from genetic causes. Studying how cancers evolve in other animals can provide vital insights into the evolutionary process. For instance, some species (like elephants) are resistant to cancer while other species (like dogs) are very prone to develop cancer. Dr. Schiffman then went on to discuss how using the approach of comparative oncology, understanding the increased cancer risk in purebred dogs and designing complementary clinical and genomic trials can aid in the development of novel cancer prevention strategies for humans. Similarly, studying both the evolutionary and possible functional mechanisms for the low cancer rate in both Asian and African elephants could also lead to the development of new and powerful treatments for cancer in humans.

TUESDAY, SEPTEMBER 16, 2014

Evolutionary game theory and cancer
David Basanta (Moffitt Cancer Center)
Cancer is an evolving disease. Tumor cells are highly heterogeneous and live in an ecosystem where interactions shape the fitness of the cells. Seeing as how game theory studies how the interactions between players in a given game shape their payoffs, Dr. Basanta discussed how game theory can be a powerful tool to aid in understanding how interactions shape tumor dynamics. He then gave an overview of classical game theory, focusing on a few canonical games. Evolutionary game theory can be applied to cancer, where the players are the cell types, the strategies are the phenotype, and the payoff is measured in fitness. Dr. Basanta argued that using game theory to study cancer is quite useful because one does not need to understand a lot of the problem to apply game theory and obtain useful results. Furthermore, game theory allows one to focus on interactions, leads to relatively simple models, and is mathematically tractable. Lastly, Dr. Basanta applied a simple game theoretical model to a form of prostate cancer and showed how even this simple model can be used to guide hormonal treatment for certain cell types which can help to prevent cancer.

Tumor heterogeneity and therapy as a rock-scissors-paper game
Joel Brown (University of Illinois at Chicago)
In this talk, Dr. Brown discussed ways to predict whether or not advanced prostate cancer patients would respond favourably to a certain drug treatment. Once cancerous, prostate tumor cells still rely on testosterone for successful cell division and proliferation. Anti-androgens and testosterone suppression can halt cell proliferation and provide an attractive therapy. Distance from vasculature may promote tumor heterogeneity and at least two “cytotypes” --- testosterone requiring cells near vessels, testosterone independent ones far from vasculature. Furthermore, therapy may select for a third, testosterone producing cytotype. As such, Dr. Brown presented a game theoretical model for the dynamics of each of these cytotpyes in response to: 1) the frequency of the different cytotypes, 2) the scale and degree of angiogenesis, and 3) different therapeutic strategies. Using this model, Dr. Brown showed that the nature of the tumor microenvironments strongly influences the pre- and post-therapy outcomes. In particular, by combining patient data with model behaviour following anti-androgen treatment, Dr. Brown showed that one might be able to infer whether or not the patient will respond

favourable to second line therapies specifically targeting testosterone requiring and testosterone producing cytotypes.

Modeling mimicry in the microenvironment
Ruchira Datta (MBI)
Dr. Datta's talk dealt with the application of mimicry to modelling cancer. In nature, many animals mimic one another for the purposes of either preying on other species or evading predators. Dr. Datta proposes that cancerous cells mimic phenotypes of wounded tissue duping the immune system into executing wound healing programs and leading the immune system to cooperate in carcinogenesis. The evidence for this hypothesis comes from imaging studies of metastasis that found that tumors grow towards blood vessels and effectively create a door into the blood stream to allow tumor cells to spread. Dr. Datta then went on to suggest that the ways that animals cope with mimicry might lead to new therapeutic approaches for cancer. She then ended with an outline for how she will go about modelling wound mimicry.

Multitype branching processes: from bacteria to cancer
Tibor Antal (Edinburgh University)
The speaker began with a review of recent developments in the theory of two type birth-death branching processes. The simplest model for bacterial growth is a backward Komogorov equation, which leads to a differential equation for birth-death process. Then the speaker walked us through a series of models for cell division with mutations, from those for bacterial growth and those for cancer cell division. The difference in cancer cells is that you need to include death. The models mentioned here include the Wright-Fisher model that's revisited in 2007, Bozic's 2010 branching process model. In terms of applications of these models, the speaker showed an example of fighting drug resistance with combination of therapies. One important extension for these types of models will be to include space.

Shaping Tumor Heterogeneity: Phenotypic selection versus Clonal targeting
Jill Gallaher (Moffitt Cancer Center)
This talk is based on the fact that tumor cells are a heterogeneous mix of cells. There are different phenotypes and genotypes. The speaker only talked about phenotypes but she will also touched on genotypes as well. The speaker showed an agent-based model to explore genotypic and phenotypic progression and selection as a result of different sequences of treatment environments. This approach allows researchers to investigate interactions of single cells and evolution of the collective heterogeneous population in an environment with spatial competition. The eventual goal is personalized cancer medicine, which is to design targeted drug combinations that facilitate optimal outcomes and crucially are patient specific.

WENDSDAY, SEPTEMBER 17, 2014

An integrated approach to understanding tumor-stromal interactions in cancer progression and treatment
Alexander Anderson (Moffitt Cancer Center)

Cancer is complex, multi-scale and heterogeneous. The speaker makes an analogy between organs and an ecosystem, so that we can look at cancer from an ecological perspective. To be more specific, an evolving tumour interacts with and manipulates its surrounding microenvironment in a complex dynamic spatiotemporal manner. The complex dialogue between these heterogeneous populations ultimately drives tumor progression, and highlights the fact that purely experimental approaches are unpractical given the multitude of interactions and time scales involved. The talk highlights the potential of using an integrated theoretical and experimental approach to tackle this complexity through two distinct examples. The first considers melanoma and focuses on the role of senescent fibroblasts. The speaker and his team developed a hybrid multiscale mathematical model of normal skin (vSkin) and use it to understand how the key cellular (keratinocytes, melanocytes and fibroblasts) and microenvironmental variables regulate skin homeostasis and how their transformation can lead to cancer. Based on the experimental and theoretical results it is conclude that, senescent fibroblasts create a pro-oncogenic environment that synergizes with mutations to drive melanoma initiation and progression and should therefore be considered as a potential future therapeutic target. They use the vSkin model to test such a therapeutic strategy, aimed at restoring homeostasis via manipulation of the tumor microenvironment. This study also suggests a potential link between aging in the skin microenvironment and the development of melanocytic neoplasms. The second considers the role of reactive stroma in prostate cancer evolution using a hybrid multiscale mathematical model that incorporates a histologically accurate representation of the peripheral zone. The model specifically considers how stormal dependent and stromal independent prostate cancers evolve and how interactions between tumor and stroma facilitate or inhibit tumor evolution.

Calculus of stem cells

Natalia Komarova (Department of Mathematics, University of California, Irvine)

Identifying the exact regulatory circuits that can stably maintain tissue homeostasis is critical for our basic understanding of multicellular organisms, and equally critical for figuring out how tumors circumvent this regulation, thus providing targets for treatment. Despite great strides in the understanding of the molecular components of stem-cell regulation, the overall mechanisms orchestrating tissue homeostasis are still far from being understood. Typically, tissue contains the stem cells, transit amplifying cells, and terminally differentiated cells. Each of these cell types can potentially secrete regulatory factors and/or respond to factors secreted by other types. The feedback can be positive or negative in nature. This gives rise to a bewildering array of possible mechanisms that drive tissue regulation. In this talk, the speaker described a novel stochastic method of studying stem cell lineage regulation, which allows to identify possible numbers, types, and directions of control loops that are compatible with stability, keep the variance low, and possess a certain degree of robustness.

Quantitative experimental platforms to measure the evolutionary dynamics of drug resistance in vitro

Shannon Mumenthaler (Medicine, University of Southern California)

The microenvironment for tumor growth is heterogeneous. Spatial and temporal gradients of nutrients, oxygen, and drug can create physical niches that drive cellular adaptation and force tumor cells to adopt various strategies to survive. This talk really highlights how the tumor microenvironment affects the fitness of cancer cells and influences the overall composition of the tumor. The speaker introduced an

HCS imaging platform that is really powerful because 1) it can assay many different conditions simultaneously (it can take multiple measurements of the same cell at the same time); 2) it handles both 2D and 3D results; 3) researchers can manipulate the physical conditions of the microenvironment. The ability to experimentally capture the heterogeneity of the microenvironment and resulting cellular behavior is imperative for achieving a full understanding of the evolutionary dynamics of a tumor. For example, apply image analysis, the speaker presented estimates of birth and death rates (by fitting it to exponential models) of cells.

As a second part of the talk, the speaker presented an evolutionary model for cell resistance. Populations of sensitive and resistant cells are mixed mathematically. The imaging approach has been applied to inform this stochastic compartment-based tumor model of pre-existing drug resistance in non-small cell lung cancer. Each compartment represents a specific tumor environmental niche and this integrative modeling framework is then used to predict rebound growth kinetics and tumor composition (i.e. % resistance). In particular, we provide insight into the magnitude by which the microenvironment influences these results and how one might utilize drugs that target the interface between the microenvironment and tumor cells (e.g. TH-302, a hypoxia activated pro-drug) to achieve a better clinical outcome. Identifying, measuring, and targeting tumor heterogeneity is important for the successful treatment of cancer.

Edge effects in evolutionary dynamics of spatially structured tumors

Artem Kaznatcheev (Computer Science, McGill University)

It is typically assumed in analytic evolutionary game theory models of cancer that the population is inviscid: the probability of a cell with a given phenotypic strategy interacting with another depends exclusively on the respective abundance of those strategies in the population. To overcome this limitation, the speaker showed how to use the Ohtsuki-Nowak transform to approximate spatial structure and study the effect of interaction neighborhood size. In particular, the focus was on the change in neighborhood size at a static boundary -- such as a blood-vessel, organ capsule, or basement membrane. In the case of the go vs. grow game, this edge effect allows a tumor with no invasive phenotypes expressed internally to have a polyclonal boundary with both invasive and non-invasive cells. This approach may serves as a useful analytic compliment to the more common simulation based methods of modeling the effects of spatial structure on cancer dynamics.

HPV Clearance and the Neglected Role of Stochasticity

Marc Ryser (Duke University)

The potential role of stochastic cell dynamics in the time it takes to clear an HPV infection has received little attention has been paid to. In this talk, the speaker showed how to combine mechanistic mathematical models at the cellular level with epidemiological data at the population level to disentangle the respective roles of immune capacity and cell dynamics in the clearing mechanism. The results suggest that chance - in form of the stochastic dynamics of basal stem cells - plays a critical role in the elimination of HPV-infected cell clones. In particular, we find that in immunocompetent adolescents with cervical HPV infections, the immune response may contribute less than 20% to virus clearance -- the rest is taken care of by the stochastic proliferation dynamics in the basal layer. In HIV-negative individuals, the contribution of the immune response may be negligible.

Evolutionary Dynamics of Tumour Heterogeneity and Plasticity

Kamran Kaveh (Applied Mathematics, University of Waterloo)

Stem cell proliferation accounts for not only their own growth but also the growth of non-stem tumor cells in a hierarchal form and create strong epigenetic heterogeneity in tumors. Cancer stem cells are believed to have strong plastic phenotypic property tuned by microenvironment, which can affect their selection dynamics. The speaker presented a general Moran type model to include differentiation and plasticity for cancer stem cell selection. Analytical and simulation results were presented for fixation probability and time to fixation in such a model. The model was applied to niche succession and clonal conversion in colorectal cancer both in the presence and absence of primary plasticity between stem cells in the niche and their early progenitors. We also address the effect of microenvironment by introducing a spatial model which incorporates variations in fitness parameters as well as geometry of the organ. The findings showed that the fixation probability is a strong function of plasticity rate and differentiation probabilities inside stem cell niche. We compare our findings with observations of Vermeulen et al (Science 2013) on stem cell dynamics of intestinal tumor initiation.

Stem Cell Dynamics in the Microenvironment of Normal Colon Crypts, and the Initiation, Progression and Therapy of Colon Cancer

David Axelrod (Rutgers University)

The speaker presented an agent-based model of stochastic cell dynamics in human colon crypts. In the model, it was assumed that each cell's probability of proliferation and probability of death is determined by its position in two microenvironment gradients along the crypt axis, a divide gradient and in a die gradient. A cell's type is not intrinsic, but rather is determined by its position in the divide gradient. Cell types are dynamic, plastic, and inter-convertible. Parameter values were determined for the shape of each of the gradients, and for a cell's response to the gradients. The behavior of the model was verified by its ability to reproduce the experimentally observed monoclonal conversion by neutral drift, the formation of adenomas resulting from mutations either at the top or bottom of the crypt, and by the robust ability of crypts to recover from perturbation by cytotoxic agents. An example of the use of the virtual crypt will be given, viz., the evaluation of different cancer chemotherapy protocols.

Thursday, SEPTEMBER 18, 2014

Stochastic and deterministic evolutionary dynamics in hierarchically organized tissues

Arne Traulsen (Max-Planck Institute for Evolutionary Biology)

Dr. Traulsen addressed the somatic evolution in Chronic Myeloid Leukemia, Paroxysmal Nocturnal Hemoglobinuria, or Acute Promyelocytic Leukemia. He investigated the dynamic of acute promyelocytic leukemia before and during therapy with regard to disease initiation, progression and therapeutic response. So he developed a non-spatial generic model with considering various steps of differentiation. The model was based on the fact that the tissues are typically organized hierarchically and the dynamics of cancer progression can be strongly affected by this population structure. He assumed that mutations arising in primitive cells can lead to long lived or even persistent clones, but mutations arising in further differentiated cells are short lived and do not affect the organism.

Evolutionary dynamics of resistance to cancer therapy

Ivana Božić (Harvard University)
Metastatic dissemination to surgically inaccessible sites is the major cause of death in cancer patients. Targeted treatments are often initially effective against metastatic disease and invariably fail due to resistance. The major strategy proposed for overcoming resistance is combination therapy. Dr. Božić developed a mathematical model to illuminate the evolutionary dynamics of resistance to anti-cancer treatment and provide important information for the design of treatments that aim to control resistance. She discussed recent approaches, which combine mathematical modeling of resistance together with clinical data, and pointed to the reasons behind treatment failure in patients with metastatic disease. The conclusion was the dual therapy results in long-term disease control for most patients, if there are no single mutations that cause cross-resistance to both drugs; in the patients with large disease burden, triple therapy is needed.

Tumor growth and clonal heterogeneity during expansion and treatment
Philipp Altrock (Harvard University)
Dr. Altrock used a mouse xenograft model to investigate the impact of sub-clonal heterogeneity on tumor phenotypes and the competitive expansion of individual clones. The result was that tumor growth can be driven by a minor cell subpopulation which enhances the proliferation of all cells within a tumor by overcoming environmental constraints and can be outcompeted by faster proliferating competitors. This can result in tumor collapse. He also using a mathematical model described how that non-cell autonomous driving of tumor growth supports clonal interference, stabilizes clonal heterogeneity and enables inter-clonal interactions, which can lead to new phenotypic tumor traits. When treatment is administered, heterogeneity can be reduced, also reducing evolutionary and metastatic potential. He adjusted and informed his mathematical framework to model different treatment strategies and optimize treatment processes, in particular in HER2+ breast cancer tumors.

Reevaluating causation in cancer
Katherine Liu (University of Minnesota)
Knowing when, where, and how to intervene requires understanding the complex causal structures involved in cancer progression. The most dominant model for investigating cancer – the identification of biomarkers – is grounded in simplistic assumptions of the underlying causality. Alternatively, there are evolutionary and ecological models, but these are largely dependent on theoretical work and computer simulations, with few available empirical models. The speaker introduced a novel approach that embraces the evolutionary, ecological, and developmental dimensions of cancer. Then she discussed the use of microbial experimental evolution as an approach to understand evolutionary and ecological causality associated with the mechanisms important to cancer. She pointed that not modeling cancer proper, microbial experimental evolution systems placed in a proper conceptual framework can give tractable ways to study the underlying evolutionary, ecological, and developmental mechanisms involved in cancer progression.

The Creative Roles of Selection and Drift in the Angiogenic Switch in Cancer
John Nagy (Arizona State University)

At first, Dr. Nagy explained the angiogenic switch and he defined the angiogenesis signal as the sum of individual cell contributions. While neoangiogenesis clearly benefits tumor cells, the signal creating it is a public good and therefore susceptible to free-riders. Previous modeling studies predicted that these free-riders can invade, damage and perhaps destroy developing tumors, growing as a tumor-on-a-tumor, or hypertumor. The open question becomes, why are hypertumors apparently rare? Dr. Nagy showed, using more realistic extensions of the original models, that selection favoring free-riding is expected to be overwhelmed by genetic drift in most cases. Adaptive dynamics analysis of a deterministic model of the energetic costs and benefits of angiogenesis and proliferation predicts the existence of an evolutionary stable (ESS) angiogenesis commitment, but this ESS is always a repeller. The expectation, then, is runaway selection for extreme vascular hypo- or hyperplasia. However, the selection gradient is very shallow compared to that for other traits, specifically proliferation. Therefore, evolutionarily unfavorable angiogenesis phenotypes may still invade if they are coupled to even marginally more favorable proliferation strategies through a mechanism logically identical to linkage disequilibrium. A simulation of this evolutionary theater predicts that this disequilibrium mechanism dominates the evolution of the angiogenic switch. At the end, he predicted that angiogenic switch is evolutionary transient in all tumors so deterministic ESS for angiogenesis is clinically irrelevant.

TGFBeta inhibition in Prostate to Bone Metastasis

Arturo Araujo (H. Lee Moffitt Cancer Center and Research Institute)

Dr. Araujo started his talk by explaining the bone metastasis in the prostate cancer and the reason of needing a better therapy. He also talked about how he became interested in the subject and how he approached it. Prostate cancer frequently metastasizes to bone with approximately 90% of the men displaying evidence of skeletal lesions upon autopsy. Despite medical advances, prostate to bone metastases remain incurable with treatments being mainly palliative. Dr. Araujo integrated biologic and computational approaches to generate a hybrid cellular automata model of normal bone matrix homeostasis and the prostate cancer-bone microenvironment. Understanding the normal basic multicellular unit (BMU) bone remodeling process is critical for the generation of a robust computational model. He introduced a model which accurately reproduces the basic multicellular unit bone coupling process, such that introduction of a single prostate cancer cell yields a vicious cycle similar in cellular composition and pathophysiology to models of prostate-to-bone metastasis. Notably, the model revealed distinct phases of osteolytic and osteogenic activity, a critical role for mesenchymal stromal cells in osteogenesis, and temporal changes in cellular composition. To evaluate the robustness of the model, he assessed the effect of established bisphosphonate and anti-RANKL therapies on bone metastases. At approximately 100% efficacy, bisphosphonates inhibited cancer progression while, in contrast with clinical observations in humans, anti- RANKL therapy fully eradicated metastases. Reducing anti-RANKL yielded clinically similar results, suggesting that better targeting or dosing could improve patient survival. He established a computational model that can be tailored for rapid assessment of experimental therapies and delivery of precision medicine to patients with prostate cancer with bone metastases.

Cancer as somatic cheating: Resource acquisition and monopolization in cancer evolution

Athena Aktipis (University of California San Francisco)

Dr. Aktipis started her talk by explaining the observed abnormal proliferation cases in plants. Then she provided a review of somatic cheating in cancer like phenomena across the tree of life including the six independent branches of complex multicellularity; multicelluarity and cooperation, cancer across the tree of life, types of somatic cheating, resources use and metastasis, and resource transfer. The speaker

divided the multicelluarity cheating in two types of the demographic cheating and the economic cheating. Then she focused on forms of economic cheating that involve resource acquisition and monopolization, including upregulated metabolism and disregulated signaling for limiting resources. At the end, she described model results showing that resource cheating may be central to cancer evolution and progression to malignant disease.

Optimization of radiation schedules for proneural gliomas via mathematical modeling
Kevin Leder (University of Minnesota)
Dr. Leder started his talk by explaining the background of the Giloma and radiation. Gliomas are the most common and malignant primary tumors of the brain and are commonly treated with radiation therapy. Despite modest advances in chemotherapy and radiation, survival has changed very little over the last 50 years. Radiation therapy is one of the pillars of adjuvant therapy for GBM but despite treatment, recurrence inevitably occurs. In this talk, Dr. Leder explained his mathematical model for the tumor response to radiation that takes into account the plasticity of the hierarchical structure of the tumor population. Then he compared the results of the model with the results of the experiments. At the end, using the mathematical model he could develop an optimized radiation delivery schedule.

Modeling cancer evolution from genomic data
Niko Beerenwinkel (*Eidgenössische Technische Hochschule Zürich*)
Dr. Beerenwinkel divided his talk in two parts; intra-tumor genetic diversity and metastasis formation. Cancer evolution is a stochastic evolutionary process characterized by the accumulation of mutations and responsible for tumor growth, clinical progression, immune escape, and drug resistance development. Evolutionary theory can be used to describe the dynamics of tumor cell populations and to make inference about the evolutionary history of a tumor from molecular profiling data. Dr. Beerenwinkel presented recent approaches to modeling the evolution of cancer, including population genetics models of tumorigenesis, phylogenetic methods of intra-tumor subclonal diversity, and probabilistic graphical models of tumor progression. Then he discussed methods for distinguishing driver from passenger mutations.

BOOT CAMP: How to Simulate your Cancer Models with COPASI
(September 29 – October 1, 2014)

Organizers: Stefan Hoops (Virginia Polytechnic Institute and State University), Pedro Mendes (University of Connecticut Health Center), and Kathy O'Hara (Virginia Polytechnic Institute and State University
Report by: Márcio Duarte Albasini Mourão, Ruchira Datta, and Kimberly Fessel

MONDAY, SEPTEMBER 29, 2014

Introduction to COPASI (lecture)
Pedro Mendes
Dr. Pedro Mendes began his lecture with an explanation of what COPASI is and what COPASI does. He proceeded by providing a brief description of published articles about COPASI and indicating which one

should be used when citing the tool. He also provided relevant info on documentation and support about the tool.

Dr. Mendes then provided a basic description of models in COPASI as well as the ordinary differential equations (ODEs) based kinetic models included in the tool. These do not only include the law of mass action but also a number of reaction rates based on the law of mass action that are used to model different types of reaction kinetics. The speaker introduced us to the structural properties of models, which include mass conservation and elementary flux modes. He also introduced the concept of stochastic kinetics, which is included in COPASI by the use of the Gillespie's algorithm.

Dr. Mendes then described a number of different analyses that can be performed using COPASI. These included parameter scanning, sampling, sensitivity analysis and regression. He finished with a description of different outputs that can be produced by the tool.

Defining Models (tutorial)
Stefan Hoops
Dr. Stefan Hoops provided a brief description of the COPASI interface and guided us through the introduction of simple models in COPASI. Participants were guided in the introduction of species, reactions and reaction rates. The later can be selected from a variety of possibilities provided by the tool. This choice really depends on the model that is being created as well as the question that is being addressed. Participants were also guided in the introduction of general properties of the model such as the time, quantity and volume units.

Dr. Hoops then explained how COPASI translates reaction into differential equations, which can be visualized in COPASI. Participants were also introduced to a number of different characteristics that can be extracted from the introduction of the model, such as the stoichiometry matrix. Depending on their expertise, COPASI provides a lot of information that can be useful to different users.

Time course simulation (hands-on)
Pedro Mendes
Dr. Mendes started by providing a description of the structure and function of MAPK cascades. He proceeded to guide us in the introduction of a previously developed model of the MAPK cascade into COPASI: the Huang & Ferrel model published in 1996. For the purpose, Dr. Mendes provided a description of the SBML language and its usefulness. He also provided us with a description of the BioModels database, from where participants downloaded the model.

In COPASI, participants were guided to set up the units of the model as well as introduce/change initial conditions and parameter values. Dr. Mendes then explained to participants how to produce plots, with an emphasis on the production and visualization of time course data derived from the imported model.

Steady state and ultrasensitivity analysis (hands-on)
Pedro Mendes
Dr. Pedro Mendes guided participants in the process of finding and analyzing the steady states of the Huang & Ferrel model. He explained the question and interpreted the conclusions that had been reported in the Huang & Ferrel model. Dr. Mendes then set the goal for the section: reproduce the results that had been published in the paper. For the purpose, he guided participants on 1) setting up the plot that participants were interested in visualizing; 2) running the model to re-produce one of the

key-plots of the Huang & Ferrel model. To accomplish this goal, participants were introduced to general sensitivity analysis concepts and how to produce these analyses using COPASI.

Oscillations in MAPK (hands-on)
Pedro Mendes
Dr. Mendes guided participants in downloading the Kholodenko model (2000) from the BioModels database and then analyzing it using COPASI. Participants were able to generate time course behavior from COPASI and look at the oscillations produced by the model, so to compare it with the outcome reported in the published paper. He then guided participants to manipulate a relevant parameter of the model and evaluate how this parameter influenced the oscillations: both frequency and amplitude. Participants were also guided to produce different plots with COPASI, so to facilitate the analysis of different oscillatory behavior.

TUESDAY, SEPTEMBER 30, 2014

Sensitivity Analysis (lecture)
Pedro Mendes
Dr. Mendes began his lecture by providing a definition of sensitivity analysis (SA), a way to measure how outcomes depend on input parameters, and by describing the basics of this field. By assuming a linear relationship, one can induce parameter perturbations about a given point of interest and measure the resulting variable response. He then explained that researchers are often interested in changes to steady state or transient quantities with the former often being easier to investigate than the later. He also illustrated the differences between scaled and unscaled sensitivities. He mentioned that considering scaled quantities offers a major benefit in that these values are easily comparable with each other; whereas, unscaled sensitivities are not. Dr. Mendes then highlighted applications of SA to metabolic control analysis. When studying flux and enzyme activity, SA results for all rates involved sum to one, but for mass conservation scenarios, the sensitivities of the reaction rates sum to zero. He emphasized that because of these observations, one finds that the so-called "rate-limiting step" really depends on experimental conditions. Dr. Mendes also addressed ideas about robustness and fragility. Depending on the case at hand, robustness to parameter changes (low sensitivity to perturbations) or fragility (high sensitivity) may be desired. For example in drug design, he commented that one should look for system fragility to produce the most system change possible; modification of robust parameters does not alter the system much, and drug design for such quantities should be avoided. Dr. Mendes concluded his talk by mentioning how COPASI performs SA, namely, with finite differences.

Sensitivity Analysis for MAPK Models (hands-on)
Pedro Mendes
In this portion of the boot camp, participants were encouraged to follow along with Dr. Mendes by obtaining the Schoeberl et al. (2002) model from the BioModels Database (http://www.ebi.ac.uk/biomodels-main/BIOMD0000000019). The authors of this work examine a particular mitogen-activated protein kinase (MAPK) cascade involved in epidermal growth factor receptor signal pathways. Once participants had loaded this model into COPASI, they were asked to run the dynamic time course and check the model's steady state. Dr. Mendes then demonstrated how sensitivity analysis can be applied to study the model's steady state. COPASI offers the user choices for selecting the SA effect (single variables, all variables, etc.) as well as the cause (single variable, etc.). Both the scaled and unscaled sensitivities are calculated. Dr. Mendes also noted that COPASI's parameter scan function can check sensitivities for many different initial concentrations of a particular chemical in succession. The participants performed sensitivity analysis on both a single and all

parameters to determine the effects on the steady state of a single output. By comparing the scaled sensitivities of all parameters, one can quickly get a feel for which values affect the solution the most; nonetheless, Dr. Mendes commented that multisite effects are often more efficient than any single site because as one rate parameter is changed, other parameters become more important. After the demonstration, participants were allotted approximately 40 minutes of free time to explore other MAPK models including work by Bianconi et al. (2012), Kim et al. (2007), Huang and Ferrel (1996), and Kholodenko (2000).

Optimization (lecture)
Pedro Mendes
Optimization problems arise in many biochemical networks applications including metabolic engineering, evolutionary studies, drug design, and parameter estimation. In general, numerical optimization algorithms involve the initial parameter guess, objective function evaluations, parameter updates, and the stopping criterion dictating satisfaction in the objective. Dr. Mendes explained that there are many ways to minimize (or maximize) an objective function and that the main difference among various algorithms is the way the parameter values are updated between function evaluations. Optimization algorithms fall into several broad categories including those based on derivatives, direct search (geometric), evolutionary ideas that mimic reproduction, or stochastic methods that mimic chemical or animal movements. Dr. Mendes went on to explain the details of various optimization techniques including steepest decent, Newton method, Levenberg-Marquardt, simplex, Nelder-Mead, random search, evolutionary, genetic, simulated annealing, and particle swarm. Each method possesses advantages and disadvantages, and Dr. Mendes highlighted some of the considerations to take into account when selecting an optimization method (e.g. the dimension of the model).

Optimization applied to MAPK models (hands-on)
Pedro Mendes
Participants were directed to reexamine the Schoeberl et al. (2002) model now in the context of optimization. Overexpression of ERKpp has been indicated in patients with cancer, and thus one may wish to minimize ERKpp production in this MAPK model. Under the tasks header, COPASI has a tab labeled "Optimization." Within this program one selects the objective function, the parameters over which to optimize, and the desired optimization method. Dr. Mendes led the hands-on portion of the optimization module by selecting minimization of the ERKpp steady state as the objective function and six rates of reaction as the optimization parameters in COPASI. The participants then explored the results of the steepest decent method as well as the particle swarm method. The remainder of the session was spent comparing the two methods and discussing how the computation time may be reduced for the particle swarm method.

WEDNESDAY, OCTOBER 1, 2014

Dr. Mendes noted that to fit more complex models, one needs to do *different experiments*, not the same experiment over and over again. One needs to do more perturbations and different perturbations.

Parameter Identification (lecture)
Pedro Mendes
Certain sets of parameters are *not identifiable*, if multiple sets of parameter values give the same behavior. Dr. Mendes explained that if even in principle, some parameters can never be identified, then one needs to simplify one's model. One way to detect this situation is to plot values for pairs of parameters. For instance, in the Michaelis-Menten equation, $K_{cat}E$ appears only as a product, so these

two parameters are never individually identifiable. This is *structural unidentifiability*. Instead, one might give a name such as V_{max} to the product $K_{cat}E$ and try to identify that. COPASI can do a Monte Carlo search around the solution, to find parameter values neighboring the previously found points. If, say, V_{max} is 10, then K_{cat} and E will have high mutual information as their product will always be 10. This gives a hint that the parameters are not identifiable. In COPASI, this procedure requires discretizing the data.

Model Validation (lecture)
Pedro Mendes
Dr. Mendes noted that while fitting a model to data shows that it *can* explain those data, it doesn't show that the model is generally valid. Validation is an important step, where one uses the model to explain a *different set of data* than the one already used to fit the model. If the model does not validate, one needs to go through another iteration of the experiment/modeling cycle.

Fitting and Validating a Model (hands-on)
Pedro Mendes
Dr. Mendes used an example to demonstrate how to fit a model and estimate parameters, and to input validation data into COPASI to measure the distance between the fit and these data. COPASI can use various methods to rescale the columns: it can make the mean squared residuals similar, or the means, or the standard deviations. If an estimated parameter hits a boundary value, this suggests the boundary needs to be moved. If the parameter boundaries span less than two orders of magnitude, COPASI uses the uniform distribution to check parameter values within the boundaries; otherwise it uses the log-uniform distribution. The residuals should have no trend, should be random, and should be close to zero relative to the values. COPASI can display the correlation matrix among the fit parameters, or the Fisher information matrix, to help identify a manifold of parameter sets that fit the data (due to structural unidentifiability). One can use random restarts to guard against a local optimum which is not a global optimum. Dr. Mendes noted that Newton's method should *never* be used if the steady state is already given. COPASI allows a combination of genetic algorithms, which are good for getting close to a solution, and gradient-based methods, which are good at refining a solution from nearby.

Events in COPASI (hands-on)
Pedro Mendes
Dr. Mendes used a model of cell division to demonstrate the use of events in COPASI. In this model, cells grow continually; when the level of cyclins reaches a certain threshold, the cell divides, and all concentrations go down because the molecules are partitioned among the daughter cells. Events are described by Triggers, Targets, and Expressions. Each trigger is a logical expression transitioning from a false value to a true value. Dr. Mendes noted that it's preferable to use inequalities rather than equalities in these expressions, since the equality may fail to hold simply due to fixed precision numerics. Each target is a model object to which to apply changes. Each expression gives a new value of the target. (Alternatively, the expression can be a probe, which reports the state of the system without side effects on the model values.) Dr. Mendes described how to use events to find the period of an oscillation, and then can define a function using that period as an objective for optimization. In a model with events, COPASI cannot do Steady State Analysis, since the repeated evaluations as in, e.g., Newton's method might trigger events.

Parameter Scan and Replication (hands-on)
Pedro Mendes
Dr. Mendes explained how to do repeated simulations of a stochastic model, and also how one can randomly sample parameters, from a uniform, log-uniform, normal, or log-normal distribution. One can

run the model for some time before producing any output, to remove the burn-in from the report. COPASI can be run on supercomputers; it uses the BLAS and LAPACK libraries, which are already parallelized. Certain tasks which are embarrassingly parallel, such as parameter scan, parameter sampling, repeating stochastic simulations, or repeating optimization or parameter estimation runs, can be distributed on a Condor pool, though this takes some effort to set up.

Future Work (lecture)
Pedro Mendes
Dr. Mendes would like in the future to enable COPASI to use delay differential equations and stochastic differential equations. He also would like COPASI to be able to find *all* steady states rather than just a single steady state—perhaps using Gröbner bases, as suggested by Dr. Reinhard Laubenbacher.

Workshop 2: Metastasis and Angiogenesis
(October 13-17, 2014)
Organizers: Mark Chaplain, Trachette Jackson, Lance Munn, Hans Othmer
Report by: Kang-Ling Liao, Marc Sturrock, Wenrui Hao

Monday October 13, 2014

Tumors, wounds and retinae: modelling angiogenesis in development and disease
Mike Watson (Heriot-Watt University)
Dr. Watson introduced several mathematical models to describe how vascular growth and adapt in physiological processes. The main goal of these models is to develop a model for application to different physiological conditions characterized by angiogenesis, such as capillary formation, tumor-induced angiogenesis, and wound healing angiogenesis. He then provided a hybrid discrete-continuum modeling approach which includes discrete tip cells migration, matrix metalloproteinases, gradient in VEGFF, and extracellular protein. This model simulates vessel growth with blood flow through the vasculature. Their simulations predict the formation of strongly dilated capillary loops around the optic nerve. Moreover, this model also can be extended to describe solid tumor growth, wound healing, and retinal development. The results show that the experimentally-informed, hybrid modeling approach describes the angiogenesis in various physiological scenarios. Angiogenesis is generally characterized by heterogeneities in capillary bed architecture and blood flow and hence has strong potential for shunt formation. Moreover, models of tumor-induced angiogenesis are rather difficult to test robustly due to the wide variety of histological data available and wound healing angiogenesis is a more rigorous challenge. Hence, we still need to modify this model to overcome these challenges.

Modelling squamous cell carcinoma invasion in vitro, in vivo and in silico
Andy South (Thomas Jefferson University)
The squamous cell carcinoma (SCC) is in the top 10 Scottish cancer registrations and cause more than 300,000 deaths per year. It is observed in skin, esophagus, lung, and cervix. The normal squamous epithelia let daughter cells differentiate into keratinized cells, but abnormal squamous epithelia disrupt differentiation to variable degrees with thickening. Moreover, recently experiments showed that the Notch genes or Notch pathway genes are mutated in a significant proportion of SCC. SCCs trigger the process of local invasion away from the surface and into the surrounding tissue. Dr South introduced a model for SCCs in vitro by including tumor and normal cells derived from the skin. They used this model to describe the normal cell differentiation and tumor cell invasion in a laboratory setting. By considering different complex cultures, 2D and 3D, of the immune compromised mice, this model successfully displays the SCC invasion in vivo such that it captures several aspects of cancer cell invasions. This model

also provides methods to test intervention strategies and interrogate parameters inaccessible to biological experimentation.

Multiscale Modelling of Cancer Cell Motility

Paul Bates (Biomolecular Modelling Laboratory, London Research Institute)

Dr. Bates first pointed out phylogenic relationships between heterogeneous tumor regions, which has been done by Charles Swanton's lab. Then he showed a movie about the key program of heterogeneity, and a question about cancer heterogeneity: how to search system state space. This is mainly based on amoeboid type cell motility of metastasizing tumor cells in the extracellular matrix (ECM), which is based on typical network model: simulate MAPX pathway through differential equations. This model includes cell motility, which is essential in many biological processes including cancer metastasis. After extensive benchmarking of the computational model, using in vitro data, he predicted cancer cell motility in vivo. Moreover, their model was successfully challenged to predict the effect of different cancer metastasis.

Modelling cell-extracellular matrix interaction

Luigi Preziosi (Politecnico di Torino)

The cell-extracellular matrix (cell-ECM) interaction and the mechanical properties of cell nucleus are two basic factors in cell movement across fiber networks and micro-channels. Dr. Preziosi introduced several mathematical models to solve cell-ECM problem. First, the speaker provided a basic multiphase PDE model for cell-ECM. Next, in order to let the model more practical, this model includes the cell adhesion mechanics and the influence of nucleus stiffness in the motion of cells. Moreover, they assumed that the nucleus of the cells is as an elastic membrane surrounding a liquid droplet or as an incompressible elastic material with Neo-Hookean constitutive equation. Under these settings, this model can be used to obtain a necessary condition for which cells enter cylindrical structures. Their simulation results showed that the interplay between mechanical deformability of the nucleus and the capability of the cell plays an important role in adhesive bonds establishment.

Tuesday October 14, 2014

Computational and experimental studies of breast cancer metastasis

Aleksander Popel (Department of Biomedical Engineering, Johns Hopkins University)

Dr. Popel presented some recent experimental results on breast cancer metastasis, which is related to the tumor microenvironment. These results reveal the roles of blood and lymphatic vasculatures in metastatic organs. Then he presented some analysis of these results, such as the roles of the stromal cells, and some interactions between the stromal cells and cancer cells. After this, he introduced a mathematical model of tumor vasculature. The 3D computational results show metastatic sites, modeling of blood flow, interactions and transport between molecules. Finally he gave an agent-based model of tumor growth, which takes into account cancer stem cells. Some results are shown to demonstrate the framework.

Numerical challenges in models of tissue-scale tumour cell invasion

Alf Gerisch (Fachbereich Mathematik, Technische Universitat Darmstadt)

Dr. Gerisch introduced the process of tumor cell invasion by giving several biological examples, and pointed out the feasibility of math modeling to study this problem. While the difficulty of the math modeling is the efficient simulation of nonlocal partial differential equation models. The numerical simulation can answer the effects of cell-cell and cell-matrix adhesion. He then proposed his computation method, FFT-based approach, to solve the major computational bottleneck. His second topic is numerical method for uncertainty quantification in order to estimate parameters appearing in

the model, which cannot be obtained by experiments. Thus the uncertainty and sensitivity of these parameters are very important to judge the value of the model and possibly for proposing required dedicated experiments. Finally he outlined a framework for uncertainty quantification based on fast adaptive stochastic collocation on sparse grids.

How quantitative modelling can inform on disease pathogenesis: lessons from liver
Dirk Drasdo (Institut National de Recherche en Informatique Automatique)
Dr. Drasdo began by explaining how mathematical models can open up promising new approaches towards a quantitative understanding of pathologies and of disease processes, including processes that occur at the multicellular tissue level. To illustrate this, he considered three different examples of interdisciplinary approaches integrating biological models and mechanisms of processes contributing to disease progression at various scales within mathematical modelling frameworks. In his first example a multi-cellular spatial temporal model predicts a previously not recognized and subsequently validated order principle underlying liver regeneration after drug-induced damage, as it occurs for example after overdosing acetaminophen. In his next example, a mathematical model integrating information from the spatial temporal model of the first example with the chemical reactions known to detoxify liver from ammonia in health liver is presented. This model succeeded to indicate the lack of an important reaction. Experiments triggered by this model prediction led to finding of a so far unrecognized good candidate reaction that might be clinically utilized in case of hyperammonemia. Dr. Drasdo's finished his talk with a third example that addressed the spatial-temporal molecular control of the regeneration process within a mechanistic multi-scale model spanning the molecular, cellular, tissue and body scale.

Crawlers can also swim: new modes of movement in the ECM
Hans Othmer (University of Minnesota)
Dr. Othmer started his talk by describing how cells that can crawl can also swim. He spoke about in general how locomotion involves the detection and transduction of extracellular chemical and mechanical signals, integration of the signals into an intracellular signal, and the spatio-temporal control of the intracellular biochemical and mechanical responses that lead to force generation, morphological changes and directed movement. Punctuating his talk with various videos, he showed that while many single-celled organisms use flagella or cilia to swim, there are two basic modes of movement used by eukaryotic cells that lack such structures -- mesenchymal and amoeboid. The former, which can be characterized as `crawling' in fibroblasts or `gliding' in keratocytes, involves the extension of finger-like filopodia or pseudopodia and/or broad flat lamellipodia, whose protrusion is driven by actin polymerization at the leading edge. This mode dominates in cells such as fibroblasts when moving on a 2D substrate. In the amoeboid mode, which does not rely on strong adhesion, cells are more rounded and employ shape changes to move -- in effect 'jostling through the crowd' or `swimming'. He showed that pure crawling and pure swimming are the extremes on a continuum of locomotion strategies, but many cells can sense their environment and use the most efficient strategy in a given context. He discussed some of the mathematical and computational challenges that this diversity poses.

Transport, metabolic & shear stress effects in vascular remodeling
J. Alexander Tyrrell (Thomson Reuters)
Dr. Tyrrell started his talk by providing a brief background about vascularization, with particular focus on "normalization" of tumor blood vessels. He spoke about how this normalization has shown promise to improve the efficacy of subsequently-administered chemotherapeutics. He went on to describe how the anti-angiogenic drugs targeting VEGF signaling have been shown to improve the vessel network structure and function, enhancing the transport of systemically-injected drugs. Dr. Tyrrell also spoke about how during normalization, a wide range of effects are observed on vessel diameters, tortuosity,

permeability, and blood flow, eventually producing a more efficient network but he noted that there still remain many unknowns regarding this type of adaptive remodelling. In an effort to better analyze how blood vessels adapt and remodel, Dr. Tyrell and his colleagues have developed a physics model that simulates vascular structure and function from meso to macro scales, thereby capturing important dynamics that can be observed and measured using two-photon imaging and other experimental techniques. Though challenges remain (such as incorporating more realistic rheology and sprouting), their model has helped better understand the complex, nonlinear processes involved in the normalization of tumor vasculature.

Wednesday October 15, 2014

Mathematical Modelling with Fully Anisotropic Diffusion and Applications to Glioma Growth
Thomas Hillen (University of Alberta)
Dr. Hillen introduced the notion of fully anisotropic diffusion to begin his talk. He stated that it describes a random walk with different diffusion rates in different directions. He mentioned that this fully anisotropic diffusion model does not obey a maximum principle and can even lead to singularity formation in infinite time. He went on to apply this anisotropic diffusion to model glioma growth. The glioma cells movement depend on fibers and he illustrated this using various videos. Dr Hillen derived his partial differential equation model from a transport equation using hyperbolic scaling, parabolic scaling and moment closure techniques. The diffusion tensor in his model was informed by diffusion tensor imaging of real brain data. He then showed various simulations and attempts to validate his model with data from the cross cancer institute. He ended his talk by showing how his model could also be applied to wolf movement in Alberta.

Role of tumor-associated endothelial cells in tumor metastasis
Pawan Kumar (The Ohio State University)
Metastatic process involves several steps, such as release of tumor cells from the primary tumor, survival in circulation, interaction with vascular endothelium, and invasion of target organs. In this talk, Dr. Kumar introduced their current experimental results about the metastasis of head and neck cancers. They found that patients who have cancer metastasis usually have significantly higher Bcl-2 positive blood vessels. This result provides a hypothesis that tumor cell metastasis maybe triggered by the Bcl-2 expression in tumor-associated endothelial cells. They used a SCID mouse model to demonstrate this hypothesis. This mouse model not only demonstrated their hypothesis, but also showed that Bcl-2 increases the secretion of IL-6 to enhance epithelial-mesenchymal transition. Moreover, since most of the cancer cells have rapid cell death in harsh circulatory conditions such that the early steps in metastasis are completed more efficiently than the later steps. Their experiments also demonstrated that the population of circulating tumor cells is increased in Bcl-2 positive circulating endothelial cells in the blood samples. Hence, they conjecture that tumor cells can be protected from cell death and chaperoned to distal sites by binding with the circulating endothelial cells.

Mathematical analysis of PDE models of chemotaxis
Tong Li (University of Iowa)
Chemotaxis is the directed movement of cells toward the chemical concentration gradient. It happens in wound healing, immune response, and cancer metastasis. In this talk, the speaker introduced the Keller-Segel (KS) model of chemotaxis. They derived a quasilinear system of hyperbolic-parabolic equations from the KS model by taking zero diffusion rate of the chemical substance. For this modified model, they analyzed the Cauchy problem, global well-posedness, blow-up criterion, and the long time behavior of classical solutions. Moreover, the traveling wave behavior driven by chemotaxis was observed

experimentally and KS model also display this pattern. Hence, they also investigated the existence and the nonlinear stability of large-amplitude traveling wave solution to the system by energy estimate, L2-estimates, and H1-estimates.

Dynamic changes in cellular mechanics regulates cancer cell migration/invasion
Samir Ghadiali (The Ohio State University)
Tumor cells obtain a highly motile ability in a process that epithelial to mesenchymal transition (EMT). These cells invade into surrounding tissues in the primary tumor. How changes in cell mechanics during EMT influence the initial tumor-detachment and invasion phases of metastasis is still unclear. In this talk, the speaker introduced their work that they used a combination of computational techniques to study this question in tumor cells and stromal cells. Their results showed that tumor cells become significantly stiffer during EMT and ECM with stromal fibroblasts enhance invasion. Hence, they used gene mutation experiments to either reduce tumor cell stiffness or prevent ECM remodeling to reduce the tumor load and invasion. In conclusion, changes in cell stiffness may be a novel biomechanical marker of oncogenic EMT that can be quantitatively correlated with the degree of metastasis. Dynamic change in cell stiffness facilitates increased detachment from primary tumor and invasion into the ECM. Altering the biomechanical properties of tumor cells can prevent metastatic behavior. Altering the biomechanical properties of stromal fibroblasts and ECM remodeling can be sued to mitigate tumor cell invasion.

Uncertainty quantification for image driven modeling and simulation
Petros Koumoutsakos (ETHZ)
In this talk, Dr. Koumoutsakos introduced imaging, modeling, and simulation tools for the investigation of angiogenesis. He then explained the differences and the relations between models in vitro, in vivo, and in silico. He also showed the large difference in scalars in cancer (or in tissue level) and angiogenesis (or in cell level). Dr. Koumoutsakos used the subcellular element model which includes actin fibers, polarization, cell density, polymerization, and depolumerization to describe the angiogenesis. He also mentioned some challenge of predictive simulations for these methods and also introduced a Bayesian uncertainty quantification and propagation framework to connect experiments and simulations.

Quantifying vascular architecture: relating form to function
Jim Baish (Bucknell University)
In this talk, Dr. Baish introduced recent results that improve traditional measures of vascular geometry which are included vessel density and diameter. The goal of this study is to display the geometry of the blood vessels to clinical outcomes. The speaker also introduced the main ideas of transport fundamentals, network science, percolation theory, reliability theory, system dynamics, and fractal geometry. They tried to use all these ideas to explain how the arrangement of blood vessels influences their ability to deliver nutrients and therapeutic agents in tumors. Moreover, the speaker also mentioned and compared the similarities and differences between normal and tumor vasculature.

Thursday October 16, 2014

Mathematical modeling of tumor-driven angiogenesis. A mean field model
Vincenzo Capasso (Università degli Studi di Milano)
First Dr. Capasso gave an introduction about vasculogensis and angiogenesis, and some motivation, which is based on the growth of blood vessel. Tumor –induced angiogenesis is an interesting problem for both biology and mathematics. He then explored some established angiogenesis treatment, and gave his biological problem, diagnosis and therapy by using mathematical modeling. The outline of his

talk is: 1) math model; 2) relevant empirical measures; 3) multiple scale; 4) statistical estimations. The math model is a stochastic fibre system based on hausdroff function. He gave some analytical results for this math model for the underlying fields. Finally he showed some numerical results based on this model to explain the validation of model comparing the experimental data.

Perfusion heterogeneity in tumors as a challenge for optimal nanotherapeutics delivery
Hermann Frieboes (Bionegineering, University of Louisville)
Dr. Frieboes used a mail box example to demonstrate the tumor is targeted by drug and particles. Tumor vascular perfusion is abnormal leading to impaired transport. Then he used a paper to show the tumor regions, which is based on heterogeneity distribution of drug for breast cancer. He pointed out the importance of perfusion flow, what's going on between tumor and blood. By introducing animal model and particle fabrication, heterogeneity is typically tailored to design systems that exhibit optimal tumor tissue uptake. The method he proposed is following: model development, determine parameter values, and hypothesize effects of parameters, and simulation /comparing with experimental data. The numerical results are shown to demonstrate some clinical implications.

Dimension of cancer invasion
Peter Friedl (Cell Biology, Radboud University Nijmegen)
Single-cell or collective invasion results from coordination of cell shape, deformability and actin dynamics relative to the tissue environment. Both, in vitro and in vivo models provide complementary insights into modes and mechanisms of cell movement. In monomorphic 3D invasion models in vitro, an obligate step of collective invasion is the degradation of extracellular matrix (ECM). Thereby, the density of the ECM determines the invasion mode of mesenchymal tumor cells. In 3D in vitro models, fibrillar, high porosity ECM enables single-cell dissemination, whereas dense matrix induces cell-cell interaction, leader-follower cell behavior and collective migration as an obligate protease-dependent process. Conversely, in vivo monitored by intravital multiphoton second and third harmonic generation microscopy, abundant tissue microniches provide invasion-promoting tracks that enable collective migration along tracks of least resistance. As main routes, non-destructive contact-guidance is mediated by preformed multi-interface perimuscular, vascular and –neural tracks of 1D, 2D and 3D topography. Whereas in vitro models predict a major role for beta1/beta3 integrins in sustaining invasion, in vivo targeting of intergrins induces unexpected plasticity of invasion, including collective and amoeboid single-cell dissemination, followed by enhanced micrometastasis, implicating integrin-independent dissemination as effective route to metastasis and challenging in vitro approaches. In conclusion, in vitro and in vivo models deliver diverse, often dedicated environments which impact the type, efficacy and mechanism of invasion. Computational modeling thus needs to take the physical and molecular organization of tissues into account.

Feedback, lineages and vascular tumor growth
John Lowengrub (University of California at Irvine)
Dr. Lowengrub started his talk by talking about various forms of growth control in normal cells and stem cells, such as negative feedback and positive feedback. He went on to discuss how most tissues are hierarchically organized into lineages. He noted that tumors arise when the carefully regulated balance of cell proliferation and programmed cell death (apoptosis) that ordinarily exists in normal homeostatic tissues breaks down. Dr. Lowengrub went on to present new mathematical models to simulate the spatiotemporal dynamics of cell lineages in vascularized solid tumors. His models aimed to uncover the reasons why tumor cells progress through lineage stages regulated by feedback. His models accounted for protein signaling factors produced by tumor cells, and vascular endothelial cells in the microenvironment that direct self-renewal, differentiation and proliferation pathways. Dr. Lowengrub's

models show how the development of heterogeneous cell distributions and the formation of vascular niche-like environments for stem cells can be created. Prof Lowengrub punctuated his talk with various detailed simulation movies and experimental movies/images. He ended his talk by demonstrating how feedback processes play a critical role in tumor progression, heterogeneity, vascularity and the development of morphological instability.

Generation of microvascular networks in normal and tumor tissues: A biological patterning problem
Timothy W. Secomb (University of Arizona)
Dr. Secomb introduced the audience to structural control of the vascular system at the beginning of his talk. He spoke about the need of a tree-like hierarchical structure for the efficient transport of blood in the vascular system (describing this as a biological patterning problem). Without predetermined spatial patterns, networks must develop these hierarchical tree-like structures for efficient convective transport over large distances, combined with dense space-filling meshes for short diffusion distances to every point in the tissue. Moreover, he spoke about how networks must be capable of restructuring in response to changing functional demands without interruption of blood flow. Through the use of theoretical simulations based on experimental data, Dr. Secomb demonstrated that this patterning problem can be solved through over-abundant stochastic generation of vessels in response to a growth factor generated in hypoxic tissue regions, in parallel with refinement by structural adaptation and pruning. Dr. Secomb went on to present essential biological mechanisms for the generation of adequate and efficient vascular patterns and he also presented predictions concerning impairments in vascular properties resulting from defects in these mechanisms. His results provide a framework for understanding vascular network formation in normal or pathological conditions. With regard to tumor microcirculation, the simulations presented by Dr. Secomb suggested possible factors leading to characteristic features including poor tissue oxygenation in the presence of adequate overall perfusion, and persistent instability of vessel structure and flow patterns.

Friday October 17, 2014

Biomechanics of cancer invasion and vessel function
Lance Munn (Massachusetts General Hospital & Harvard Medical School)
Dr. Munn showed some mechanical forces control examples arising from tumors: cell membrane transition, anchoring protein transport and fluid component movement. Both of these examples involve solid mechanical forces, which is very important when the cell and ECM grows uncontrolled (such as proliferation and apoptosis dysfunctions). Then a mechanical model based on fluid force is presented to explain the cell migration and invasion, which is potentially contributing to metastasis. Some computational results are shown the effects of shear stresses to drive blood vessel contractions to optimize flow and plasma. Then the speaker shows lymphatic pumping process, which is central to immune function and homeostasis by shear shear stress-activated nitric oxide production. Some results are shown the interface between mechanics and biology. Although it is not well-explored, it gave another perspective for modulating tumor progression.

Impedance Spectroscopy for Imaging and Quantifying Tissue Properties
Shaurya Prakash (The Ohio State University)
In this talk, Dr. Prakash presented the development of electrochemical impedance spectroscopy (EIS) as a new tool for imaging and quantifying tissue properties. EIS measures a current or voltage response of a system to an alternating voltage or current signal and records the response as complex impedance. The key idea is that the input is a small amplitude signal and therefore permits use of small-signal theory and linearization to analyze system response through data containing both magnitude and phase

information. Dr. Prakash's group used EIS to generate images of morphologically distinct regions in excised human liver tissue to differentiate, based on differences in electrical conductivity and permittivity, the tumor and non-tumor regions. The impedance data was then reduced to equivalent tissue structure images showing the ability to use EIS as an imaging technique, with direct comparisons to visual representation by digital photography and clinical validation by histopathology images.

Towards patient-specific modeling of angiogenesis-driven tumor-associated edema in gliomas
Kristin Swanson (Northwestern University)
Dr. Swanson presented some of her work in the area of glioblastoma modeling. Glioblastoma is the most aggressive form of primary brain tumor, is predominantly assessed with gadolinium-enhanced T1-weighted (T1Gd) and T2-weighted magnetic resonance imaging (MRI). Pixel intensity enhancement on the T1Gd image is understood to correspond to the gadolinium contrast agent leaking from the tumor-induced neovasculature, while hyperintensity on theT2/FLAIR images corresponds with edema and infiltrated tumor cells. None of these modalities directly show tumor cells; rather, they capture abnormalities in the microenvironment caused by the presence of tumor cells. Dr. Swanson presented an extension of a previously developed mathematical model of glioma growth to explicitly incorporate edema formation allowing us to directly characterize and potentially predict the effects of anti-angiogenics on imageable tumor growth. She presented a comparison of simulated glioma growth and imaging enhancement with and without bevacizumab which supported the current understanding that anti-angiogenic treatment can serve as a surrogate for steroids and the clinically driven hypothesis that anti-angiogenic treatment may not have any significant effect on the growth dynamics of the overall tumor cell populations. However, the simulations do illustrate a potentially large impact on the level of edematous extracellular fluid, and thus on what would be imageable on T2/FLAIR MR. Additionally, by evaluating virtual tumors with varying growth kinetics, Dr. Swanson was able to show that tumors with lower proliferation rates will have the most reduction in swelling from such treatments.

CTW: Axonal Transport and Neuronal Mechanics
November 3 -7, 2014
Organizers: Paul Bresloff, Kristian Franze, Kyle Miller, Jay Newby, Daniel Suter
Report by: Jeff Gaither, Michal Seweryn, Lucy Spardy

MONDAY, NOVEMBER 3, 2014

Axonal transport of neurofilaments
Anthony Brown (The Ohio State University)
Dr. Brown began the workshop by introducing neurofilaments, which are space-filling protein polymers in axons that function to maximize axonal cross-sectional area. In addition to their structural role, these polymers are also cargoes of axonal transport, moving anterogradely and retrogradely along microtubule tracks in rapid bursts of movement interrupted by prolonged pauses. This stop-and-go behavior results in a slow average rate of movement, termed slow axonal transport. The hypothesis in Dr. Brown's laboratory is that neurofilament transport is a principal determinant of the neurofilament content and distribution along axons, and thus a principal determinant of axonal morphology. Therefore, it is important to understand the mechanisms that regulate neurofilament transport. In previous work, they have shown that axonal neurofilaments can lengthen by joining end-to-end, called end-to-end annealing, and that they can also be shortened by a severing mechanism, which is a novel phenomenon for intermediate filaments. These mechanisms give rise to a broad range of neurofilament lengths in axons, which raises intriguing questions about the mechanism of movement. Dr. Brown

showed that short neurofilaments move rapidly and continuously in one direction, rarely reversing, whereas long filaments exhibit long pauses and frequent reversals, resulting in much less net movement. Long-term imaging of neurofilaments using a multi-field tracking technique has revealed that severing and annealing are robust phenomena and that short filaments anneal more frequently than long filaments, whereas long filaments sever more frequently than short filaments. These observations suggest that there is a dynamic cycle of neurofilament severing and annealing in axons that regulates the length and axonal transport of these cytoskeletal polymers.

Slow Axonal Transport and Axon Morphology: How Nerves get into Shape
Peter Jung (Ohio University)
In Dr. Jung's laboratory, the fundamental hypothesis is that the overall flux of neurofilaments determines the overall caliber of the axon while local changes in caliber are determined by local modulation of neurofilament transport velocity. This hypothesized relationship between axon caliber and neurofilament velocity can be studied using the nodes of Ranvier, which separate two myelinated sections of myelinated axons. At the nodes of Ranvier, axons exhibit constrictions, which reduce the local caliber of the axon to a fraction of what it is at the internodes. Using their hypothesis, this suggests that a local reduction of caliber should go along with a proportionate increase in neurofilament transport rate. In his talk, Dr. Jung described their working model for neurofilament transport and how the associated rate constants are extracted from fluorescent imaging experiments at the myelinated segments and the nodes of Ranvier. He then showed how the predicted change of caliber matches up with experimentally determined abundances of neurofilaments at the nodes and internodes. Furthermore, since the nodes of Ranvier are also where the vast majority of ion channels are located, Dr. Jung asks whether nodal constrictions play a role in conduction velocity. To address this, he introduced a computational model of a myelinated axon, which incorporates detailed morphology of the axon including nodal constrictions. Dr. Jung's findings indicate that nodal constrictions modulate conduction velocities and allow for a significant reduction of the fiber diameters for targeted conduction speeds in comparison to an unconstricted axon.

A stochastic multiscale model that explains the segregation of axonal cyctoskeleton in diseases
Chuan Xue (The Ohio State University)
In many neurodegenerative diseases, the normal organization of the axonal cytoskeleton is disrupted. In her talk, Dr. Xue introduced a mathematical model used to study how the normal organization of the axonal cytoskeleton is developed and maintained in health, and how it is perturbed in diseases. Under normal conditions, the axonal microtubules and neurofilaments form a mixture in cross-section and the caliber of an axon is roughly constant over long distances. However, if treated with IDPN, a compound that causes similar symptoms as amyotrophic lateral sclerosis (ALS), microtubules and neurofilaments segregate into different regions on a time scale of hours, and the axon swells locally on a time scale of days. Although these phenomena have been reported for over 40 years, the underlying mechanisms are still poorly understood. In this talk, Dr. Xue presented results that suggest that IDPN blocks NF transport which leads to MT-NF segregation.

Axonal Transport and Long-Term Memory Storage
Sathya Puthanveettil (The Scripps Research Institute)
Little is known regarding the identity of the population of proteins and RNAs that are transported to and localized to synapses and how this transport is regulated in neurons. Dr. Puthanveettil addressed this by studying the molecular composition of transport complexes and how the transport is regulated during long-term memory storage in the sea slug *Aplysia californica* and in mice. He showed that several hundreds of proteins and RNAs are transported by kinesins, the molecular motor that mediates

anterograde transport to synapses from the cell body. Further, the axonal transport is regulated in specific neurons for long-term memory storage. Dr. Puthanveettil's research brings important insights into the function of axonal transport in synapse formation and memory storage.

Bidirectional Transport: Moving Beyond Tug-of-War (except for the cool neurofilament stuff from this morning)

Scott McKinley (University of Florida)

Transport in neurons is intrinsically bidirectional, with each movement modality carried out by molecular motors in either the kinesin (anterograde) or the dynein (retrograde) families. In his talk, Dr. McKinley introduced a fundamental challenge that his work addresses -- because all motors are present at a given time, there must be competition and/or cooperation among motors that simultaneously bind a single vesicle to nearby microtubules. It has been assumed for much of the last decade that the competition must resolve itself through some kind of tug-of-war; but recent evidence shows conclusively that this is often not the case in vivo. Dr. McKinley introduced multiple biological mechanisms, along with associated mathematical models, that may lead to resolving theory with experimental observations.

Microtubule transport of mRNA in dendrites

Jay Newby (MBI)

A key component in the cellular mechanisms underlying learning and memory involves the distribution and delivery of mRNA to synaptic sites in dendrites. Dr. Newby introduced a minimal three-state random intermittent search model of motor-driven mRNA transport to explore the question of why motor-driven mRNA are observed moving bidirectionally. He analyzed this model by computing the probability an mRNA is delivered to a synaptic target and the average delivery time (MFPT). His findings indicate that if the branched geometry of the dendrite is ignored, a purely unidirectional transport strategy will result in the smallest MFPT at any given delivery probability. Incorportating the branched geometry of the dendrite into the model, he shows that a phase transition exists for a critical delivery probability where bidirectional strategies improve the corresponding MFPT. Finally, he introduced a modelextension that includes a detailed, biophysical model of a multimotor complex coordinated through a tug-of-war. He concluded by exploring how various measurable, physical quantities, such as adenosine triphosphate, can be tuned to optimize cargo delivery.

TUESDAY, NOVEMBER 4, 2014

The kinesin adaptor Calsyntenin-1 regulates axon branching, axonal transport and microtubule dynamics

Mary Halloran (University of Wisconsin)

Dr. Halloran showed how the kinesin adaptor, Calsyntenin-1 (Clstn-1) is an essential regulator of axon branching and neuronal compartmentalization. Precise regulation of axon growth and branching is crucial for neuronal circuit formation. Moreover, the highly complex morphology of neurons makes them highly dependent on protein/membrane trafficking and transport systems. Her results indicate that Clstn-1 is required for formation of peripheral but not central sensory axons, and for peripheral axon branching in zebrafish. Live imaging of endosomal trafficking in vivo illustrate that Clstn-1 regulates transport of Rab5 containing endosomes from the cell body to specific locations of developing axons. Her results suggest a model in which Clstn-1 patterns separate axonal compartments and defines their ability to branch by directing trafficking of specific endosomes. In her work, Dr. Halloran used live imaging with EB3-GFP to characterize MT dynamics during axon development in vivo and found that Clstn-1 knockdown causes aberrant retrograde EB3 comets in axons, indicating defects in MT polarity.

Furthermore, loss of Clstn-1 slows anterograde MT comets. This suggests that in addition to regulating trafficking of cargo along MTs, Clst

Workshop 3: Cancer and the Immune System
November 17-21, 2014
Organizers: Avner Friedman, Gregory Lesinski, Ami Radunskaya
Report by: Wenrui Hao, Jeff Gaither, Matt Oremland

MONDAY, NOVEMBER 17, 2014

An Overview of Cancer and the Immune System
Avner Friedman (The Ohio State University)
In this opening talk, Dr. Friedman gave basic information about the interactions between cancer and the immune system and introduced themes which would be explored in later talks. He identified the different phenotypes of macrophages and listed the four types of CD4 + T-cells. He also described the roles these different cells play in combating a tumor: the macrophages and dendritics identify it while the T-cells actually fight it. One of the talk's high points was Dr. Friendman's description of a tumor's ability to `re-educate' the immune system to work for its own benefit, by corrupting macrophages so that they increase VEGF production.

An overview of cancer immunotherapies: a modeling perspective.
Ami Radunskaya (Pomona College)
Dr. Radunskaya spoke of the challenges involved in modeling the immune system's response to cancer. She first surveyed the common approaches to cancer immunotherapy, among them cancer vaccines, checkpoint blockading, and adaptive cell transfer. Each of these strategies entailed difficulties which made it, if not wholly impracticable, then at least somewhat limited in its applicability. The chief goal for designers of cancer immunotherapies at large is how to get the immune system to participate more in fighting cancer. An interesting difficulty on this front is that if the immune system is encouraged too much, it might resist and actually decrease its exertions, out of an evolved "suspicion" which is an impressive (though in this case inconvenient) testament to its complexity and efficiency.

Regulatory T cell networks in human cancer and immune therapies
Theresa Whiteside (University of Pittsburgh)
Dr. Whiteside's talk focused on regulatory T cells and the different ways, good and bad, in which they interact with cancer. She emphasized that there are a multitude of Treg types, and identified natural or thymical-delivered Tregs, which conduct the responses to self-antigens, as well as inducible or peripheral Tregs, which expand in the microenvironment and govern the response to a rather broader class of antigens. A theme of her talk was that there is no simple answer to the question "Are Tregs good or bad for cancer patients?" The truth is that some Tregs are helpful, some are harmful, some are equivocal, and many have effects that are not at all understood at present. There are indeed Tregs which unequivocally suppress the body's anti-tumor responses, and whose population it therefore seems reasonable to attempt to reduce: techniques for the ridding of harmful Tregs include Treg depletion and selective blocking.

High-throughput Sequencing and Single Cell Analysis of the Immune Repertoire
Ben Wendel (The University of Texas at Austin)

Mr. Wendel discussed the difficulties of sampling and sequencing the immune repertoire that is generated through V (D)J recombination, and introduced a new technique, the Molecular Identifier clustering-based IR-Seq or MIDCIRS, to perform this task. The MIDCIRS achieves the unprecedentedly low error rate of around 1 in 30,000 nucleotides for high throughput IR sequences. Mr. Wendel also presented methodological advances in single cell analysis; one of the great problems in this realm is identifying extremely rare T-cells, whose proportion in a population may be less than one part in a million. These pioneered techniques, the basis of which is the enrichment of pMHC tetramers, has new applications to the analysis of tumor-penetrating lymphocytes. It is possible that in the near future these advanced might lead to improved screening and treatment regimens for cancer patients.

Immune elements reshape cancer stemness and invasiveness
Ilona Kryczek (University of Michigan)
Dr. Kryczek's talk focused on the interactions between tumor cells and immune-system cells on the microscopic scale. She first gave some background and related some conspicuous findings from her past studies, one of which was that a tumor is capable of "reprogramming" immune cells in their vicinity, severely curtailing the body's natural immune response. She then described some new findings, among which were the conclusions that immune cells can actually alter cancer stem cells on a genetic level. Dr. Kryczek also presented an oncogenesis model grounded upon the Knudsen hypothesis, which is that cancer is the result of an accumulation of mutations in the DNA of a cell. She closed with the admission that the local behavior of cancer is very complicated, but emphasized that further study is necessary and could be immensely profitable.

Innate Immune Responses to Mitochondrial Nuclear Mismatch-The Smoking Gun?
Michael Lotze (University of Pittsburgh)
Dr. Lotze's talk concerned the nuclear protein HMGB1 which is part of the makeup of every metazoan, and its relation to cancer. He began with some interesting layman's facts about genetics, such as that human beings have 99.98% of their DNA in common and are distinguished principally by their mitochondrial diversity, which is derived entirely from the female parent. One pervasive ingredient in our genetic repertoire is the protein HMGB1, and Dr. Lotze also discussed the role of this protein in pancreatic cancer. His chief experimental finding was that HMGB1 enhances autophagy, which the natural process of self-degradation of a cell. Autophagy has been linked to both the development of cancer and to its suppression; however, autophagy is an enormous subject and Dr. Lotze's linking it to such a universal protein as HMGB1 is important, even if no immediate new cancer-treatment strategy is directly suggested.

Interactions between pancreatic stroma and immune suppression.
Gregory Lesinski (The Ohio State University)
Dr. Lesinski discussed the role of activated fibroblasts, also called pancreatic stellate cells or PSC, in producing inflammation in the pancreatic region. His results are of a definite character and have interesting and useful implications. Specifically, Dr. Lesinski found that when PSC cells were removed from patients of advanced pancreatic cancer or chronic pancreatic and allowed to exist independently, they generated large amounts of cytokines such as interleukin-6. Collectively these data suggest that PHC are intermediaries between local and global inflammation changes in pancreatic conditions. The obvious conclusion is that by attacking or inhibiting PHC, the spread of pancreatic cancer might be halted or modulated.

Tuesday November 18, 2014

Adoptive cell therapy using tumor-infiltrating lymphocytes (TIL)
Shari Pilon-Thomas (Moffitt Cancer Center)
Dr. Pilon-Thomas began the talk by explaining that TILs are associated with improved prognosis results, with at least 56% of patients partially responding. She then outlined the experimental process: tumors are removed, separated into fragments, cultured with IL-12 to expand the T cell count. These T cells were then reintroduced into the patient and responses were observed. It was noted that this treatment is expensive, at a cost near $66,000 per patient. Scans from partial responders in lung and leg tumors were presented along with a non-response in a liver tumor. This was followed by results from clinical trials, wherein there was a 38% overall response rate. Questions on how to improve therapy were then posed. In the pre-surgery phase, various pathways in murine colon cancer were investigated. Results indicated that ipilimumab treatment resulted in increased IFN-gamma production. In the TIL expansion phase, targets for enhancement of TIL proliferation were identified, and results showed that 4-1BB could modulate resident dendritic cells.

Gene-engineered T cells for the adoptive immunotherapy of cancer
Daniel Powell (University of Pennsylvania)
This talk began with the statement that tumor-infiltrating lymphocyte (TIL) accumulation predicts survival in melanoma patients. The process was similar to that described by Dr. Pilon-Thomas; Dr. Powell's results showed approximately 50% response. Dr. Powell then noted several important characteristics for response: the process must begin with a reactive T cell population, the cells must be persistent after culturing, and successful cells tended to be less differentiated. Survival in ovarian cancer was shown to be similar. Dr. Powell then presented results showing that IL-7 and IL-15 increase T cell frequency in solid tumors; the next step is to investigate checkpoint inhibitions. He then suggested the benefits of mathematical modeling for design of optimal personalized combination therapy. He then outlined the chimeric antigen receptor (CAR) approach, and outlined of how CAR therapy works in practice. In vitro results showed high anti-tumor reactivity after CD27 co-stimulation, indicating that CD27 plays an important role in the formation of T cell memory. In a 3-patient study, it was found that each CAR cell killed approximately 1000 tumor cells. In an expanded study of 22 patients, 19 showed complete response to CAR treatment. This was followed by a discussion of ways to improve CAR T cell accumulation specifically in tumors as opposed to normal tissue. Dr. Powell concluded his talk by showing how a dual-signaling CAR could distinguish between normal and tumor tissue.

Regulation of angiogenesis by TIE2-expressing monocytes/macrophages in breast cancer
Tim Eubank (The Ohio State University)
Dr. Eubank began with an overview of macrophage phenotypes including M1, M2abc, and M2d (tumor-associated macrophages, TAM). He then explained the role of macrophages in breast cancer, including mention of drugs that have been developed to target TAMs. This was followed by the introduction of TIE2-expressing monocytes (TEMs) and discussed their identification. This was followed by the explanation that TEMs migrate to areas where tumor angiogenesis is happening. The significance of TEMs is that they support tumor vasculature. Dr. Eubank then presented the hypothesis of the study: that CSF1 is important in the presence of macrophages. This was supported by results indicating that CSF1 regulates TIE2, even in human cells cultured in vitro. TEM migration was then discussed, and it was shown that TEMs support angiogenesis. CSF1 augments TEMs in vivo, but not M1s. Results from TEM flow cytometry showed that CSF1 upregulates TIE2+. Experiments were conducted on macrophage TIE2 knockout mice in which TIE2 receptor expression was tabulated. Dr. Eubank concluded by introducing a potential interaction network for an associated mathematical model.

Getting the right therapies to the right place at the right time

Sarah Hook (University of Otago)

Dr. Hook began by asking if the issue of the title could be addressed by mathematical modeling, emphasizing that it was necessary to achieve local effects in the tumors. She cited the lack of success with vaccines, noting that the tumor microenvironment is immune-suppressive. She then discussed means to reduce immunosuppression: combination therapies involving vaccines, cytokines, antibodies, and small molecules. This led to the question of getting therapies to the right place; this led to the introduction of nanoparticles, which are similar in structure to many pathogens, causing them to be more easily taken up by immune cells. Nanoparticles are also passively accumulated by tumors, allowing them to take advantage of environmental response systems. Results were presented that indicated that smaller particles had a higher uptake rate. This section was concluded by posing the question of whether or not it would be feasible to model nanoparticle delivery. Dr. Hook then focused on therapy timing; in particular, it is necessary for the antigen and adjuvant to arrive at the same time. She noted that this arrival could be coordinated with nanoparticles, and gave an example of how this might work in a sustained delivery scheme. She then posited that this process might be optimized via math modeling. Current experiments are measuring release rates in vivo, and results are currently obtained through trial and error. Dr. Hook then discussed several options for combination therapy, including pro-drug treatment with an activating enzyme and chemotherapy plus immunotherapy. She concluded by suggesting that mathematical modeling could be used to determine optimal timing for drug delivery.

IL-27 as a potential therapeutic for cancer

Xue-Feng Bai (The Ohio State University)

Dr. Bai began by introducing the differences between passive and active immunotherapy, and then focused on a discussion of IL-27, a member of the IL-12 family. It was noted that IL-27 has an impact on lymphocyte signaling pathways and that it has both pro- and anti-tumor properties. In fact, results in the literature have been contradictory in regards to the role of IL-27 in tumor growth. Dr. Bai presented results that IL-27 increases Treg production as well as the production of IL-10, and that IL27EB13-deficient mice show very poor anti-tumor response. The question of the mechanism by which IL-27 enhances anti-tumor response was raised. On the one hand, IL-27 is known to encourage T cell production, but the role of IL-10 in tumor immunity is still not clear. The remainder of the talk focused on whether IL-27 could be used an effective cancer therapeutic. In particular, adeno-associated viral IL-27 (AAV-IL-27) depletes Treg and induces TILs to produce IFN-gamma; while these results are promising, the effect is ultimately limited. Furthermore, AAV-IL-27 inhibits organ-specific autoimmunity. Finally, Dr. Bai discussed combination therapy for anti-PD-1, which is necessary because single therapy treatments produce low response rates. Some ideas for combination therapy were introduced, and promising results for B16 melanoma were presented.

Wednesday November 19, 2014

STAT3 Signaling Dysregulates Myelopoeisis in Cancer

Matthew Farren (The Ohio State University)

Dr. Farren presented some new findings about STAT3 signaling and its relationship to tumor cells, particularly in the study of breast cancer. In one specific study, it was found that breast tumor cells increased their STAT3 signaling and thereby decreased the quantity of PKC in myeloid progenitor cells. Conversely, if the STAT3 in a cancer cell was suppressed, the cell died. Taken all together, Dr. Farren;s data strongly argue for a previously unknown relationship between STAT3 and PKC signaling conduits, which might well provide insight into the molecular foundation for a tumor's blockade in the

differentiation of myeloid cells. A final and intriguing conclusion is that by encouraging PKC activity, one might be able to inhibit cancer's attempts to suppress the immune system's attempts to fight it.

Bistability induced by tumor-immune system interactions.
Yoram Louzoun (Bar -Ilan University)
Dr. Louzan examined "feedback loops" which arise when a tumor succeeds in misleading and exploiting the immune system. This can take either of two forms: either immune cells are attracted to the tumor and increase its growth, or they are inhibited from killing existing tumor cells. Either scenario results in a net increase in tumor cells, and these new or preserved cells exploit the immune system in the same way, producing a sort of self-stoking cycle. The equilibrium towards which such a system might tend is commonly called (in the context of mathematics) "bistability." Dr. Yoram Louzan concocted models for the feedback-scenarios described above, and then derived necessary conditions for bistability to be achieved. The talk's take-home message was that the immune system cannot typically decree a tumor's ultimate fate in a feedback-type environment.

The Immune System and Cancer: Friends or Foe?
Helen Byrne (University of Oxford)
In this talk, Dr. Byrne introduced some ongoing projects: Antibody derived cellular cytotoxicity, targeting hypoxic tumor regions with genetically-engineered macrophages. Then she showed a system of ordinary differential equation including normal cells, tumor cells, macrophages, and chemoattractant. An oscillatory dynamics network and bifurcation analysis are presented for this simple model. Then she explained this mathematical phenomenon by using biology: the type of solutions depends on the rate of tumor cell lysis and the macrophage density in the circulation. A summary for this model is drawn: Simple model to investigate interactions between tumor, normal tissue and macrophages. Then she moved to another topic: antibody dependent cell mediated cytotoxicity for targeting cancer cells. Then she gave an ODE model of ADCC including antibody, unbound/bound tumor receptors, NK cells and tumor cells. Then she showed biological insight and biological predictions.

Modeling Cancer-Immune System Dynamics
Lisette de Pillis (Harvey Mudd College)
Dr. Pillis' talk comprised an overview of some advances and particular modes of cancer immunotherapy that have been made since 2000. One problem she emphasized is that of tumor dormancy, in which a tumor might remain benignly in a body for months or years and then abruptly become malignant (this phenomenon is known as "re-emergence.") One promising immunotherapeutical avenue that has received considerable attention in recent years is that of vaccinations prior to a tumor's appearance, or injections either directly into a tumor or just of the more familiar intravenous character. Dr. Pillis presented the DC Melanoma model, whose results agree with a collection of published data. She also presented another model, more mathematical in character, which was founded on a system of differential equations. All these experiments and models are aimed at harnessing the immune system's power to impede or altogether halt the spread of cancer.

Macrophage-Cancer Cell Interactions drive Tumor Invasion Types
Andreas Buttenscion and Thomas Hillen (University of Alberta)
Buttenscion first introduced the primary tumor formtion and local invasion, and gave brief outline about model: short range invasion, cellular potts model, which focuses on macrophage t tumor boundary to answer one question: what makes tumor cells invade? Then an interaction between macrophage and tumor cell are presented. The hamiltonian/effective energy is introduced to this model. Initial condition for this model is about macrophage density which is high at boundary and drops sharply with increasing

tumor depth. Then a PDE model the diffusion of the chemicals is introduced to CSF and EGF.Then he moved to the question: what drives this invasion? results similar when cells consume paracrine loop signals. Finally he summarized his talk as: difference in chemotactic strengths drive invasion initial conditions, cellular adhesion and mitosis required for invasion types.

The effect of T-cell homeostasis on solid and liquid tumors
Mark Robertson Tessi (Moffitt Cancer Center)
First, the speaker showed the similarity among mathematicians, experimentalists and clinicians. Biologists understand novel mathematics for its own sake, give insight to a particular issue in oncology. Then he proposed decision-support modeling: needs to be parameterized by available clinical data. Then an example about LDL leukemia is presented. The reason is clinical need for basic decision support, experimental evidence of homeostatic dysfunction. Homeostatic nature of T cells is presented in an ODE system including naive cells and follows exponential growth.Then a overview of normal T-cell model is presented: ODE is associated with clinical simulation. Finally he introduced some multiple possible routes to the diseased state.

Thursday November 20, 2014

Use of HSV-1 for oncolytic viral therapy
Balveen Kaur (The Ohio State University)
First, Dr. Kaur gave a brief description of function of HSV-1 gene attenuated to make OV, providing a virus with ability to kill. Then she introduced herpes simplex virus which has characteristics important for tumor oncolysis. They include infecting human cells with high efficiency and a rapid lytic cycle that amplifies to a burst size. She also mentioned oncoVex which deletes both copies of ICP34.5 and expresses GM-CSF. She noted that the spatial relationship between Ve and "Halo" can be indicative of necrosis. While clinical testing is ongoing, understanding challenges to treatment are key, such as vasculostatin, suppressed tumor growth and angiogenesis.

Oncolytic viral therapies and the balance between the memory and effector immune responses
Raluca Eftimie (University of Dundee)
Over the past years, oncolytic viruses have generated much interest for cancer therapies, mainly due to the fact that once a virus is injected into the patient it can actively search for cancer cells and destroy them, without significant side effects. However, the anti-tumor effect of oncolytic viruses is greatly diminished by the anti-viral immune response. Experimental studies have shown that the sequential administration of two viruses that carry the same tumor antigen can overcome the anti-viral immune response by generating both anti-tumor effector and memory responses. However, the importance of memory versus effector immune responses in eliminating and controlling the tumors is still an open question.

Here, Dr. Eftimie introduces a mathematical model for cancer-immune-virus interactions, and uses it to investigate the delicate balance between the anti-viral and anti-cancer immune responses. She also investigates the interplay between the effector and memory immune responses in improving the outcome of cancer therapies.

A mathematical model for the immunotherapy of advanced prostate cancer
Yang Kuang (Arizona State University)
A mathematical model of advanced prostate cancer treatment is developed to examine the combined effects of androgen deprivation therapy and immunotherapy. Androgen deprivation therapy has been

the primary form of treatment for advanced prostate cancer for the past 50 years. While initially successful, this therapy eventually results in a relapse after two to three years in the form of androgen-independent prostate cancer. Intermittent androgen deprivation therapy attempts to prevent relapse by cycling the patient on and off treatment. Over the past decade, dendritic cell vaccines have been used in clinical studies for the immunotherapy of prostate cancer with some success. Dr. Kuang's model examines the efficacy of dendritic cell vaccines when used with continuous or intermittent androgen deprivation therapy schedules. Numerical simulations of the model suggest that immunotherapy can successfully stabilize the disease using both continuous and intermittent androgen deprivation.

Involvement of tumor macrophage HIFs in chemotherapy effectiveness: Mathematical modeling of oxygen, pH, and glutathione.

Duan Chen (University of North Carolina, Charlotte)

Dr. Chen introduced a mathematical model of tumor macrophage which involves four variables: hypoxia, acidity, high glutathione (GSH) concentration and fast reducing rate (redox). He then talked about the roles of macrophages in tumor angiogenesis, distinct characteristics of tumor microenvironment: acidic environment, fast reducing rate, high intracellular glutathione concentration and hypoxia. Then he gave some experimental observations about the extracellular PH value and oxygen tension. After this, he asked the question "how to alter the tumor microenvironment?" He then gave a mathematical model based on a system of partial differential equations with a free boundary that shows how macrophages play a significant role in tumor growth and angiogenesis.

Dynamics and optimal control of tumor-immune interactions under metronomic chemotherapy

Urszula Ledzewicz (Southern Illinois University)

Dr. Ledewicz introduced a question for cancer treatments: how can you optimize the antitumor, anti angiogenic and pro immune effects of therapy by modulating dose and administration schedule? Then she talked about metronomic chemotherapy, an alternative to MTD (maximum tolerated dose), and discussed its benefits from the biomedical point of view, including not just cytotoxic effect on the tumor, but also anti-angiogenic and pro-immuno effects. Then she gave a mathematical modeling for metronomic chemotherapy where three main compartments are taken into account: tumor, vasculature and the immune system. The model comes from combining a model for anti-angiogenic signaling (Hahnfeldt et al) with a classical model for tumor-immune system interactions (Stepanova et al) and incorporating a single input control function that represents cytotoxic, anti-angiogenic and pro-immune action of low dose chemotherapy. The analysis of the model as a dynamical system indicates that it inherits the geometrical characteristics of the tumor-immune system interactions model like multi-stability with benign and malignant region of attractions. This gives a useful insight into the proper construction of the objective which would have as a goal to provide a maintenance program rather than to eradicate the tumor. She then noted an interesting relation between saddle-node bifurcations and immune-surveillance. Finally, she discussed some partial results about the form of the optimal protocols which relate to the metronomic chemotherapy as a biologically optimal dose BOD.

The Role of the Immune Response in CML

Doron Levy (University of Maryland)

Chronic Myeloid Leukemia (CML) is a myeloproliferative disorder caused by the formation of the Philadelphia Chromosome, which produces the BCR-ABL gene that codes for a constitutively active tyrosine kinase. In this talk Dr. Levy thanked his collaborators and gave an overview of their recent results on mathematically modeling the role of the immune response in the progression of CML.
This model accounts for the immune response. Then he draw some biological conclusions from the math model. After studying some examples of CML they incorporated drug resistance into the model, which

allowed them to address the question: What is the probability of developing resistance by the time of detection? He validated his model by fitting patient's data.

Mechanisms of glioma formation: computational and experimental studies on the role of pre-existing vessels vs. neoangionesis

Pedro Lowenstein (University of Michigan)

As glioma cells infiltrate the brain they become associated with various microanatomical brain structures such as blood vessels, white matter tracts, and brain parenchyma. How these distinct invasion patterns coordinate tumor growth and influence clinical outcomes remain poorly understood. Dr. Lowenstein and his collaborators have investigated how perivascular growth affects glioma growth patterning and response to anti-angiogenic therapy within the highly vascularized brain. Orthotopically implanted rodent and human glioma cells are shown to commonly invade and proliferate within brain perivascular space. This form of brain tumor growth and invasion is also shown to characterize de-novo generated endogenous mouse brain tumors, biopsies of primary human glioblastoma, and peripheral cancer metastasis to the human brain. Perivascularly invading brain tumors become vascularized by normal brain microvessels as individual gliomas cells use perivascular space as a conduit for tumor invasion. Agent-based computational modeling recapitulated biological perivascular glioma growth without the need for neoangiogenesis. They tested the requirement for neoangiogenesis in perivascular glioma by treating animals with angiogenesis inhibitors bevacizumab and DC101. These inhibitors induced the expected vesselnormalization, yet failed to reduce tumor growth or improve survival of mice bearing orthotopic or endogenous gliomas while exacerbating brain tumor invasion. Our results provide compelling experimental evidence in support of the recently described failure of clinically used antiangiogenics to extend the survival of human glioma patients.

Friday November 21, 2014

Mathematical modeling of Interleukin-35 promoting tumor growth and angiogenesis

Kang-Ling Liao (Mathematical Biosciences Institute)

Dr. Liao began her talk by summarizing and outlining the IL-12 cytokine family, of which IL-35 is a member. She noted that while IL-23 and IL-12 are pro-inflammatory, IL-27 and IL-35 are inhibitory. She then discussed the role of each of these as well as the subunit structure of IL-35. In particular, the role of IL-35 is to suppress T cell proliferation and promote angiogenesis, though the mechanism of tumor promotion is still unclear. Dr. Liao then explained the goal of the mathematical model: to obtain a qualitative fit with experimental data and to use the model to compare efficacy of various therapeutic protocols. Experimental results from transgenic mouse experiments show that IL-35 expression promotes tumor growth, suppresses CTL response, increases tumor angiogenesis, and increases MDSC response. In the mathematical model, IL-35 is mainly produced by Tregs. Two cases were simulated in the model: the behavior of J558-IL-35 tumor cells and J558-ctrl tumor cells. Results were summarized in the form of total cell and cytokine counts. Simulation results showed a qualitative fit with experimental data in all cases, and even a quantitative fit with melanoma data. Next the question of whether blocking IL-35 is effective as therapy was posed. Changes were made in the model to investigate this question, and the model predicted that a continuous injection scheme would be more effective than intermittent injections. Dr. Liao concluded by presenting results from experimental data of pancreatic cancer, which agreed with the predictions of the mathematical model.

A mathematical model for pancreatic cancer growth and treatments

Chuan Xue (The Ohio State University)

This talk was motivated by the importance of understanding pancreatic cancer. The structure of the pancreas was outlined, and followed by the presentation of results from treatment data. The goal of the study was to determine how pancreatic cancer grows and to understand how treatments work. To this end, the interaction network for an ODE model was shown, followed by the equations for the model plus six cytokines. Due to the complexity of the model and the high number of parameters, Dr. Xue explained how QSSA and change of variables were used to reduce the system to a resultant four-equation ODE model, making the number of parameters feasibly manageable. Simulation results were compared with data in the form of survival curves for TGF-beta silencing and for EGFR silencing and TGF-beta sequestration. These data showed a qualitative fit. To investigate drug efficacy and the immune response, several parameters were varied and bistability analysis was conducted. The implications of these simulation results are that treatments can be effective if parameters are correctly perturbed. In future work, Dr. Xue noted an interest in expanding the model to account for issues such as spatial structure, hypoxia, Treg function, and metastasis.

Modeling the effects of macrophage content and CCN1 on glioma virotherapy
Karly Jacobsen (Mathematical Biosciences Institute)
Dr. Jacobsen began her talk by introducing oncolytic viruses, noting that they work by selectively killing cancer cells. The talk was focused on glioma therapy with oncolytic herpes simplex virus. CCN1 limits oncolytic efficacy in glioma, increases macrophage migration towards infected glioma cells, and increases macrophage-mediated viral clearance by binding macrophage integrin alpha-m-beta-2. The interaction network for the mathematical model was introduced, followed by in vivo results. These experimental results showed that blocking CCN1 increases oncolytic virus (OV) replication and improves the time to disease progression. It was also noted that OV treatment yields a wide range of responses, even in genetically identical mice. The PDE model corresponding to the interaction network was introduced along with an explanation of variables and assumptions. Equations and boundary conditions were explained. This was followed by results for the spatio-temporal evolution of the variables. One of the key conclusions was that macrophage content is a key parameter. This conclusion was compared with experimental data, showing that smaller macrophage activation corresponds to more effective therapy. Dr. Jacobsen then discussed the simulation of combination therapy of OV and antibodies; results indicate that in the case of intermediate macrophage content, the combination of treatments is more effective than either treatment alone. Simulation results for various density profiles were presented. The talk was concluded by noting that results from these simulations may be used in the future to design more effective oncolytic vectors.

Workshop 4: Tumor Heterogeneity and the Microenvironment
(February 2-6, 2015)
Organizers: Alexander Anderson (H. Lee Moffitt Cancer Center & Research Institute), Trevor Graham (Barts Cancer Institute), Michael Ostrowski (The Ohio State University), and Charlie Swanton (London Research Institute)
Report by: Ruchira Datta, Karly Jacobsen, Matthew Oremland

MONDAY, FEBRUARY 2, 2015

Carcinogenesis in Context: Tumor Heterogeneity as a Function of Host Biology
Mary Helen Barcellos-Hoff (NYU School of Medicine)
Dr. Barcellos-Hoff began her talk by discussing the importance of understanding causes for tumor diversity. She then reviewed the role of cell biology and epidemiology in tumor diversity. Results were presented from several recent publications, including a study on diversity of tumors in mice. The benefit of studying breast cancer in mice is that it gives rise to diverse tumors; the difficulty is that the mice

often die of lymphoma before developing breast cancer. Some methods for avoiding this situation were presented. Results from Trp53 null transplantation were presented, and resultant carcinomas were classified according to their differing histology. An experiment was conducted in which the Trp53 null donor fragments were transplanted into hosts and tracked for 13 months. There was a marked difference in tumor development in juveniles and adults; it was hypothesized that this is due to differences in gene expression. Results were used with a human host profile. The talk then switched focus to the role of radiation in tumor development. The mammary gland was exposed to a small dose of radiation and the gene ontology was discussed; there were a number of persistent changes in this tissue as compared to the wildtype. The effects of intergalactic radiation in space were the focus of the remainder of the talk; it was shown that some tumors grow faster after exposure to this type of radiation while others do not. It was also shown that the age of exposure was a significant factor in terms of tumor growth. Dr. Barcellos-Hoff concluded by discussing the evolution of cancer; in particular, how complexity in the microenvironment increases at each step of cancer development.

A Big Bang model of human colorectal tumor growth
Christina Curtis (Stanford University)
Dr. Curtis began with an overview on cancer as an evolutionary process, noting that she was most interested in how clonal lineages develop over time. To date, there seem to be few driver mutations in individual tumors, and intra-tumor heterogeneity (ITH) is pervasive at the genomic, phenotypic, and cellular levels; these findings challenge the sequential model of clonal lineage. There is a lack of information on ITH. The colon was presented as a model system due to its well-defined stages and the available knowledge of the stem cell organization. Molecular data was used in order to build a computational spatial model that could be used to infer parameters from those data. This model was used to understand the sequential model; however, sampling from the sequential model did not entire support an evolutionary view of colorectal cancer. A Big Bang model has been proposed that would correlate reasonably with the sampling obtained from the cancer development at various stages. ITH was found at every scale of sampling and was uniformly high at multiple scales. An unexpected spatial structure was observed in adenomas as opposed to carcinomas, suggesting that the evolution is not the same in both cases. In the big bang model, most mutations occur very early on, and this is confirmed by mutational observations over time. The computational model was used to model tumor growth; in particular, it was able to incorporate spatial structure. It was found that adjacent glands showed variable survival advantages, and that most private alterations happen before they are measurable. The computational model can be tweaked to perform patient-specific simulations.

Environmental Control of Cellular States Associated with Plasticity and Cell Fate Decisions
Thea Tisty (University of California, San Francisco)
The product of the p16INK4a/CDKN2A locus encodes a cyclin-dependent kinase (CDK) inhibitor that functions as a negative regulator of cyclin/CDK complexes. In addition to governing regulation through the cell cycle, this protein also regulates the production of chromatin remodeling proteins downstream of E2F. Dr. Tisty and collaborators identified cell surface markers associated with repression of p16INK4a/CDKN2A and found that they allowed direct isolation of rare cells from healthy human breast tissue that exhibit extensive lineage plasticity. This subpopulation of cells has the ability to enter a state that can transcribe pluripotency markers, Oct3/4, Sox2 and Nanog at levels similar to those measured in human embryonic stem cells and to acquire an epigenetically plastic state sensitive to environmental programming. *In vitro*, *in vivo* and teratoma assays demonstrated that either a directly-sorted (uncultured) or a single cell-derived (clonogenic) cell population from primary human tissue can differentiate into functional derivatives of each germ layer, ectodermal, endodermal and mesodermal. In contrast to other cells that express Oct3/4, Sox2 and Nanog, these human endogenous Plastic

Somatic cells (ePS cells) are mortal, express low telomerase activity, expand for an extensive but finite number of population doublings, and maintain a diploid karyotype before arresting in G1. These types of cellular states, exhibiting elevated plasticity, can be directed towards multiple cell fates dictated by the microenvironment.

Tumor Progression: Non-Genetic Cancer Cell Population Heterogeneity and Plasticity Drive Non-Darwinian Somatic Evolution

Sui Huang (Institute for Systems Biology)

The progression towards increasingly sophisticated aggressiveness of cancer cells during the course of treatment, including therapy resistance, is typically explained by a somatic Darwinian evolution: selection of cancer cell clones that carry random genomic mutations that (by chance) confer the new more malignant phenotype. However, the immense non-genetic heterogeneity and the plasticity of cell phenotype offer a new level for evolutionary mechanism that transcends (but does not exclude) the Neo-Darwinian scheme. By relaxing the rigid genotype-phenotype relationship that is tacitly assumed to explain the Darwinian expansion of the fittest mutant clone, cell phenotype plasticity accelerates evolution. The plasticity of cell phenotype is not random: it is constrained and channeled by the principles of stochastic, nonlinear dynamics through which the gene regulatory network (GRN) coordinates gene expression to produce complex, coherent phenotypic states of the cell.

In this framework, Dr. Huang and collaborators postulate that cancer cells are "stuck" in "cancer attractors": latent, normally unused stable states in the vast theoretical space of all possible gene expression patterns of the genome. Cancer attractors are the inevitable by-products of the trial/error scheme of rewiring the GRN during evolution. They can be imagined as the normally unoccupied side-valleys in Waddington's epigenetic landscape that must be avoided during the developmental descent of immature (stem) cells to the mature states of differentiation, the lowest point in the main valleys. Near-lethal therapeutic intervention on cells stuck in such abnormal attractor states opens –via symmetry-breaking bifurcations that epitomize the desired destabilization of the cancerous cell states– access to yet more aberrant attractors in the unused regions of the landscape further away from the normal developmental trajectories. They encode even less mature, "degenerate" states, and following such bifurcations are inevitably occupied by some cancerous cells for simple entropy reasons.

In this Dr. Huang explained the basic principles of non-Darwinian dynamics on the quasi-potential (=epigenetic) landscape of the GRN. Further, he explained why therapy, or any attempt to destabilize the cancerous state, will, (in addition to intended apoptosis) also cause "rebellious cells" to spill over into attractors of increased stemness and hence, promote malignancy and produce therapy resistance. Experimental data that document this phenomenon will be presented as well as results of first attempts to curb such evasive behavior.

Under Pressure: Tumor evolution after therapy

Joseph Costello (University of California, San Francisco)

Dr. Costello discussed how adjuvant chemotherapies affect tumor evolution in low grade glioma, stressing the importance of understanding residual disease and its genetic drivers by studying the clonal dynamics between surgery and recurrence. His talk focused on the genetic approach of the study and addressed two main questions: how different are tumors at diagnosis compared to recurrence and how chemotherapy impact evolution of the tumors does. Using exome sequencing, Dr. Costello and his collaborators studied pieces of the original and recurrent tumors from which they created the phylogenetic tree. They concluded that there is a wide spectrum of relatedness between original and recurrent tumors. Temozolomide (TMZ) treatment was correlated with hypermutation and progression

to glioblastoma multiforme (GBM). Further, it was shown that TMZ induces hypermutation and that the TMZ associated hypermutations were functional, activating the P13K pathway and inactivating the G1/S checkpoint regulator. Potential explanations for the range in susceptibility of patients to hypermutations were given as areas of future study. The speaker finished by discussing evidence that epigenetic heterogeneity defines similar clonal relationships as genetic heterogeneity.

Genetic intra-tumor heterogeneity sheds light on lung cancer evolution
Elza de Bruin (University College London Cancer Institute)
Dr. de Bruin discussed the genetic evolution of non-small cell lung cancer (NSCLC) and the various levels of intratumoral heterogeneity in fourteen patient samples. They performed multi-region exome sequencing on the adenocarcinoma and adenosquamous samples and analyzed the resulting phylogenetic trees. Location of the potential lung cancer driver genes, such as EGFR and p53, on the phylogenetic trees was determined; results indicated that driver mutations are predominantly clonal (occurring on the trunk) and only about 24% spatially separated and heterogeneous. In contrast, driver mutations in renal cancer were predominantly subclonal with 71% spatially separated and heterogeneous. Dr. de Bruin and her collaborators investigated genetic heterogeneity across tumor types in The Cancer Genome Atlas (TCGA) and found that almost all driver genes are clonal but can also occur subclonally. The NSCLC samples also revealed spatial heterogeneity in copy number and translocations. A temporal dissection of mutational signatures across cancers showed a greater contribution of APOBEC mutations in later stages indicating that APOBEC-mediated mutagenesis fosters subclonal diversity. Clinical implications were discussed included sampling bias, illusion of clonality, subclonal driver mutations, and subclonal actionable mutations.

Tumor heterogeneity and microenvironment: Intratumoral Darwinian dynamics
Robert Gatenby (H. Lee Moffitt Cancer Center & Research Institute)
Discussing evolutionary triage and landscape ecology as they relate to heterogeneity in cancers, Dr. Gatenby sought to link molecular changes with Darwinian forces of environmental selection and phenotypic adaptation. Results were presented from a mathematical model which incorporated a fecundity/survivorship trade-off. It was shown that evolutionary triage permits a wide range of genetic paths to the same cancer fitness maximum and that heterogeneity can be maintained only by variations in environmental selection forces. Virtual biopsies were performed which indicated that most genes can be a “driver” or “passenger” depending on environmental conditions, prior genetic arc of the cell, and extant populations. Simulations demonstrated a new concept which they call “never” mutations, i.e. mutations that are never observed because up or down regulation unconditionally reduces fitness. The speaker proposed targeting these mutations as a new direction for therapy and mentioned that *in vivo* studies are in progress. Incorporating a lesson from landscape ecology, he related the selection pressures on gray and fox squirrel populations in North Carolina to intratumoral regional environmental selection forces. A procedure was presented for habitat identification in MRI images of glioblastoma multiforme (GBM) and the change in GBM habitats after radiation or chemotherapy was analyzed. Dr. Gatenby concluded by emphasizing the overarching goal of developing techniques in order to use imaging as a surrogate marker for molecular heterogeneities.

TUESDAY, FEBRUARY 3, 2015
Plasticity in cancer stem cells

On the edge of chaos - morphogenic and microenvironmental control of intestinal stem cells
Simon Leedham (University of Oxford)

The speaker began with an overview of the intestinal stem cell fate in the crypt as well as niche succession including neutral and biased drift in murine and human. He gave several examples of intestinal stem cell studies which showed that genetic mutation burden is not the whole story and, as in the theme of the workshop, the microenvironment plays an important role. In particular, inflammation can disrupt morphogenic balance and promote non-stem and even post-mitotic tuft cell de-differentiation. Dr. Leedham focused on hereditary mixed polyposis syndrome (HMPS), a rare familial syndrome causing cancer in the colon which is accompanied by a change from mesenchymal to epithelial compartment expression which disrupts the morphogenic balance. Mouse and *in vitro* models were developed which capture the Gremlin/Wnt interaction and show that progenitor cells form ectopic crypts, proliferate, acquire somatic mutations and lead to dysplasia. He concluded by discussing the implications for colorectal cancer heterogeneity and therapeutic possibilities that take into account tumor resilience promoted by plasticity and the importance of restoring signalling balance by drug targeting.

Connective tissue stem cells in cancer
Daniel Worthley (University of Adelaide)
Dr. Worthley spoke on heterogeneity in the stroma, focusing on the hypothesis that if cancer-associated fibroblasts (CAF) are a new mesenchymal lineage then they must arise from existing or reprogrammed connective tissue stem or progenitor cells. His work aimed to test the origin and hierarchy of CAF *in vivo*, determine if normal connective tissue stem cells exist in bone and bowel and consider the application to cancer. A specific transgenic marker, Grem1-creERT, was developed in order to perform lineage tracing for mesenchymal stem cells which resulted in the identification of osteochondroreticular stem cells (OSR). In addition, the speaker presented related work on lineage tracing of the pericryptal fibroblast sheath in the mouse small intestine which resulted in the identification of compartment-specific intestinal reticular stem cells. Dr. Worthley concluded by discussing co-evolution in cancer and the translation of this work to stromal therapies.

The Role of Heterogeneity in Cancer Progression and Treatment Failure
Alexander Anderson (H. Lee Moffitt Cancer Center & Research Institute)
Dr. Anderson began by stressing the importance of building biologically relevant models and mentioned key aspects of doing so. He then presented cancer progression as a complex system and made a comparison of organ systems to ecosystems. A breast cancer mathematical model was introduced as a hybrid cellular automata with continuous chemical fields. The model is multi-scale, with each cell running an internal metabolic network model. Simulations were used to highlight a homeostatic disruption scenario. Evolving statistics on glycolysis and acid resistance were shown as well. These were contrasted with laboratory experiment results. The effects of bicarb on tumor development were simulated, showing that the acid reduction was critical in inhibiting tumor growth. Chemotherapy was also simulated; results suggested that timing of therapy was critical as late treatment in some cases resulted in accelerated tumor growth. A variety of other treatments were discussed; combination therapy was simulated. Results showed that due to therapeutic intervention, there was no evolutionary advantage for the tumor to invade tissue space. Dr. Anderson then discussed the difficulty of genotype to phenotype mapping. A feed-forward neural network to produce varying phenotypes was presented. A two-dimensional cellular automata with embedded neural networks were used to investigate the evolution of glycolysis and the effect of oxygen switching. These simulations show how the system's evolution is affected by changes in the environment. Next a spheroid model was introduced in order to further study the mapping from genotype to phenotype. Treatment implications for three different

evolution schemes were presented. The effects of treatment were specific to which scheme was being implemented, further indicating the importance of environment.

Modeling resistance to endocrine therapies: molecular heterogeneity in breast cancer
Robert Clarke (Georgetown University Medical Center)
Dr. Clarke began by discussing the importance of estrogen receptors in the development of breast cancer and presenting clinical outcome data. The focus of the talk was to investigate some hypotheses on endocrine resistance. In particular, cell fate regulation was posed as the network module of highest interest. Computational and mathematical modeling tools are used to find topologies within high dimensional data and representing local topologies, respectively. Dr. Clarke emphasized the importance of estrogen receptors and reviewed some prior work on the topic. This work showed that breast cancer cells can switch reversibly and robustly between ER and GFR dependence. In modeling the early responses to antiestrogens, a differential dependency network was used to represent the local structure by probability distributions; this was used to identify motifs. Lab results showed the effects of the unfolded protein response and various gene responses to UPR; these were implicated in endocrine resistance by suggesting pro-survival autophagy. XBP1 was investigated in terms of its role as a central regulator of cellular metabolism. Experimentation shows that inhibition of autophagy resensitizes tumors to treatments such as Tamoxifen. The effect of cytokines and macrophages in the microenvironment was discussed next, followed by discussion of metabolism and energy deprivation mechanisms.

Mutations in the epithelium which shape the stroma
Owen Sansom (Beatson Institute / Glasgow Pancreatic Team)
Dr. Sansom began with a summary of pancreatic cancer, its lethality, and why it is so difficult to treat. The biology of the pancreas was then reviewed, emphasizing the amount of plasticity in the cell of origin. Dr. Sansom's research group have been focused on identifying novel therapeutic targets, implementing treatment in mice, and ultimately taking the treatments to human subjects. Results from mouse experiments were presented, investigating genes most likely to be responsible for tumor development. In particular, KRAS mutant cells were determined to be disadvantageous. Results from various tumors indicate large variation in pancreatic tumors, with different sensitivities. Next Dr. Sansom reviewed p53 mutations and how they were observed in vitro. He then noted that KPC tumors share many features of cancer in humans. Surgery for pancreatic cancer has low prognosis for quality of life, hence it is critical to develop a better understanding of the disease and improve treatments. Results show that the immune cell response corresponded highly in patients that survived, while hypoxia and a LOX signature were prevalent in patients that did not. Collagen crosslinking also predicts poor prognosis, as high collagen scores correlated with low survival rates. Manipulation of LOX had a direct effect on invasion. A LOX inhibitor combined with GEM treatment resulted in substantial improvements on survival and a visible effect on stroma collapse. However, this result did not hold when treatment was implemented late. Dr. Sansom then switched focus to CXCR2, presenting results indicating that CXCL2 and CXCR2 are associated with poor prognosis. Results on anti-CXCR2 inhibition showed significant reduction in metastasis. Pancreatic cancer experiments have not shown a very strong response to immunotherapy. A combination of CXCR2 treatment first, followed by immunotherapy next, showed improvement on prognosis.

The evolution of carrying capacity in constrained and expanding tumor cell populations
Philip Gerlee (Chalmers University of Technology)

Dr. Gerlee discussed changes in the microenvironment of a cancer cell via the ecological perspective of niche construction where individuals invest time and resources into either reproduction or niche construction. He presented results of an individual-based model where niche construction occurs as an increase in local carrying capacity. A specificity parameter controls the extent to which the niche is shared, allowing for modeling of both extrinsic and intrinsic adaptation. Evolutionary dynamics were investigated through a stability analysis on the mean-field model which showed that invasion fitness depends on specificity. In particular, as the niche becomes more localized there is a greater selection for carrying capacity. Adaptive dynamics was employed to investigate the long-term evolutionary trajectory of the system. When a trade-off between proliferation rate and carrying capacity is assumed, there is convergence to a singular strategy which is both evolutionary and convergence stable. Analysis of the spatial distribution of subclones showed that spatial segregation leads to monopolisation and, thus, spatial structure seems to resolve the niche construction paradox.

WEDNESDAY, FEBRUARY 4, 2015

Lessons learned from imaging heterogeneous responses to targeted therapy
Erik Sahai (London Research Institute)
Dr. Sahai addressed the question of what happens in the period between initial response and therapy failure in a melanoma model. ERK pathway activity was monitored by a biosensor and intravital imaging which indicated that the drug is active in the tumor after four hours but in the chronic phase there is a heterogeneous response with refractory regions of the tumor. They demonstrated that stromal fibroblasts are responsible for the reactivation of the ERK pathway in the melanoma cells and, in fact, the ERK inhibitor paradoxically activates ERK signaling in the stroma and further enhances matrix deposition and remodelling. Signals from the extracellular matrix then activate integrin/FAK/Src signalling in melanoma cells that leads to BRAF-independent ERK activation. The speaker hypothesized that the active stroma provides a safe haven for some cells to tolerate therapy and that these protected cells are ultimately the source of genetic resistance. Targeting the cells in the safe haven via combination therapy of BRAF inhibitors and FAK inhibitors was shown to reduce activity in residual disease and prevent therapy failure in a patient-derived xenograft model.

Heterogeneity in genetically engineered zebrafish cancer models
Richard White (Memorial Sloan Kettering Cancer Center)
Dr. White presented on the generation of phenotypic heterogeneity in zebrafish melanoma models. He began with an overview of the heterogeneity of human melanoma at the clinical, cellular and genomic levels as well as the advantages of using genetically engineered zebrafish models. Exome sequencing of zebrafish melanoma tumors and restriction-site associated DNA sequencing (RAD-seq) of sublineages within a tumor were performed. A mild correlation was found between the number of initiating events and later genetic events; the function of the additional mutations was explored. Evidence of kataegis, localized hypermutation over tight regions of genome, was also revealed. Analysis of copy number alterations showed a focal amplitude in a certain region of a relatively small number of genes in 10 out of 53 fish. Further study revealed that this region of syntenic activity is important but not in a single point like BRAF. Additionally, a subset of human patients in The Cancer Genome Atlas (TCGA) was identified that was characterized by the exact same copy number amplification. The speaker also discussed experimental techniques for investigating the cause of heterogeneity including a color switch for identifying homogeneous cell populations and RAD-seq for increasing genetic resolution. He concluded by commenting on the role of non-genetic plasticity in melanoma.

Cell intrinsic and extrinsic regulation of tumor invasion

Andrew Ewald (Johns Hopkins University)
Dr. Ewald discussed cell intrinsic and extrinsic dissemination in breast cancer for which metastasis is the major driver of mortality. He first addressed the question of how normal mammary tubes elongate through a 3D culture model which allows for branching morphogenesis to occur. Dr. Ewald and his collaborators found that, during development, normal epithelial cells have features characteristic of metastasis including loss of polarity, proliferation, and migration. Focusing on the issue of tissue invasion and dissemination, they investigated several breast cancer models including organoid assays. Normal and neoplastic tissues were explanted into identical microenvironments and, surprisingly, a lack of protrusions or dissemination was observed during growth of either cell population. However, when placed in a collagen rich microenvironment, single cell dissemination did occur in the neoplastic tissue. They further investigated how oncogenes and tumor suppressors regulate cell behavior by trying to induce cell migration while controlling the microenvironment. Expression of Twist1 was shown to be sufficient for inducing migration while deleting E-cadherin was not. They concluded from further study that epithelial cells can disseminate while maintaining their epithelial behavior, i.e. not undergoing a mesenchymal transition. In fact, 90% of invasion events *in vivo* were lead by cells with a basal type expression pattern. The leader cell population was shown to be an inducible molecular phenotype characterized by an increase in K14+ cells over time. Further, they showed that K14 is required for collective invasion and metastasis in 3D culture; that is, inhibition of the basal molecular program was shown to be sufficient to block cancer invasion.

The role of tumor heterogeneity in prostate cancer to bone metastases
David Basanta (H. Lee Moffitt Cancer Center & Research Institute)
Dr. Basanta presented three mathematical models relevant to the role of tumor heterogeneity in prostate cancer to bone metastases. A game-theoretic model with an invasion/proliferation payoff was used to study architecture driven selection. Tissue architecture was incorporated as a parameter controlling the number of cells with which a single cell can interact. Evolutionary phenotype composition was demonstrated to be very different on the edges of the tumor compared to the center. The second model was a hybrid continuous discrete cellular automaton model which investigated the dynamics of prostate cancer to bone metastases growth. Results of incorporating heterogeneity into the tumor cell populations indicated that the composition of seeding plays a critical role in determining tumor composition, tumor growth, and efficacy of standard therapies such as biphosponate and anti-RANKL. Finally, an ordinary differential equations model was presented for precision medicine of castrate resistant metastatic prostate cancer. Monoclonal population responses to single treatments were analyzed as well as the effect of multiple mutations on the order in which treatment should be applied. A genetic algorithm was also formulated in order to optimize treatment options and sequences. Dr. Basanta concluded by discussing experimental work driven by the results of the precision medicine model.

Genetic ablation of* smoothened *in stromal myofibroblasts promotes pancreatic cancer initiation
Michael Ostrowski (Ohio State University)
Dr. Ostrowski discussed joint work with Gustavo Leone, PhD, on pancreatic cancer. Virtually 100% of patients have Kras mutations, leading through a cascade via mutations in one of INK4A, TP53, PTEN, or BRCA2 through stages PanIN-1, PanIN-2, and PanIN-3 to pancreatic ductal adenocarcinoma. ADM (acinar-ductal metaplasia) is a key factor required for PanIN-1. Dr. Ostrowski's group was looking to resolve contradictory results on whether the presence of myofibroblasts improved or harmed survival. Tumor cells (mutant KRAS epithelial cells) make Hedgehog ligand; this activates *smoothened*, which downstream activates *Gli*, which eventually leads to epithelial transformation. The Hedgehog ligand could target fibroblasts via *smoothened*. Dr. Ostrowski's group made a mouse model in which they

could knock out *smoothened* with Cre. They found that ablation of *smoothened* led to fewer PanIN lesions, increased ADM, increased proliferation of fibroblasts and epithelial cells, and increased angiogenesis. In the *smoothened* deleted fibroblasts, Hedgehog signaling was enriched, and PI3-kinase signaling was altered. A proteasome-linked mechanism downregulated the PTEN tumor suppressor and led to increased expression and activation of AKT. They found in 3D culture that medium conditioned with fibroblasts with knocked out *smoothened* was able to drive the acinar to ductal transition, and enriched activated EGFR. Lowered *smoothened*, via UB2EK, reduced PTEN, leading to increased TGF-alpha. They found that in pancreatic ductal adenocarcinoma patient samples high *smoothened* was significantly correlated with low PTEN. This could explain an earlier failure of *smoothened* inhibitor to improve outcomes. They could knock PTEN out in the fibroblasts and the cells did not apoptose; they grew as well as the wild-type cells, perhaps even better. Loss of PTEN can lead to senescence in some cells, but they didn't see that in mesenchymal cells.

Neutral evolution and star-like phylogenies in next-generation sequencing data
Andrea Sottoriva (Centre for Evolution and Cancer, The Institute of Cancer Research)
Dr. Sottoriva began with a review of previous approaches to colorectal cancer research. He then presented results on ITH in tumor fragments, noting that there was high variegation and clone intermixing. He introduced the Big Bang model for tumor growth, hypothesizing that tumors begin with a single expansion in which new mutations occur continuously. The model posits that time, rather than selection, determines the predominance of a mutation. The implications of this model are that plasticity may be the solution to adaptation in the microenvironment, rather than clonal expansions. This implies that most cancer cells are well-adapted to a variety of environments. Dr. Sottoriva then explained how the Big Bang model predicts a star-like structure in the ancestry tree of the tumor. Rare mutations at the tips of the tree make it difficult for next-generation techniques to detect the mutations; thus next-generation sequencing is more effective at analyzing cells formed early in tumor development. Mutation distribution frequencies predicted by the model were compared with NGS data, showing qualitative similarity. A mathematical model was introduced for analysis of mutation evolution, describing the frequency of mutations. The model prediction lined up nicely with experimental data for several cancers; mutation rates were then derived from the mathematical model. This analysis was performed on a wide variety of cancers from the TCGA; several showed similar dynamics while other cancer types did not. This was explained as differences in microenvironment heterogeneity. Dr. Sottoriva concluded by noting that while not all cancers follow the Big Bang model, there appear to be a variety that do, and the formalization of the Big Bang model allows for analysis that was previously unavailable.

THURSDAY, FEBRUARY 5, 2015

Targeting immune-checkpoints in cancer
Sergio Quezada (University College London Cancer Institute)
Dr. Quezada began with a brief overview of CTLA-4 and its role in restricting immunity. He then posed the driving question for his own research: what happens in the tumor microenvironment? An experimental model was developed in order to study melanoma; results showed the ratio of CD8 and Foxp3 cells within tumor were very different than the ratio outside of the tumor microenvironment. The ratio was altered significantly when treatment was implemented. The mechanism of the treatment was brought up next; an in vivo model was used to investigate this. Results on effector and regulator cell counts were then presented and interpreted. Further studies investigated Treg depletion and the elimination of Trp1 Treg in the microenvironment. Dr. Quezada then posed the question: why are the regulator cells being killed in the tumor microenvironment but not outside of it? It was noted that there are far more macrophages in the tumor. The question of why Treg cells are preferentially targeted was

the focus of the next part of the presentation. Dr. Quezada then summarized the work presented thus far, and went on to show results from other studies on the importance of CTLA-4 in immune system modulation. Finally, Dr. Quezada posed the question of whether these mechanisms of immune-regulating antibodies are common in other types of cancer.

The evolving tumor microenvironment of high grade serous ovarian cancer (HGSC)
Fran Balkwill (Barts Cancer Institute, Queen Mary University of London)
Dr. Balkwill began by explaining the misnomer of ovarian cancer, and how it actually refers to a variety of cancers centered in a similar area. She noted that omental tissue is a magnet for tumor cells in HGSC. The CANBUILD project was then introduced; this project is aimed at engineering a 3D human tumor microenvironment that can grow in vitro. Analysis begins by characterizing the layers of the tumor microenvironment via genome, transcriptome, and proteome analysis. A set of 36 patient samples was used to obtain clinical annotations. Gene signatures were presented in adipocyte and tumor cells. Dr. Balkwill then presented some slides on extracellular matrix proteomic data; it was shown how protein levels change as the disease progresses through various stages. Two-photon microscopy was used as well, and leukocytes were observed in HGSC metastases. Tissue was then characterized mechanistically. The progress of CANBUILD was then summarized, and the datasets will begin to be integrated in March 2015. The workflow for tissue processing was outlined as well. Dr. Balkwill then switched gears to discuss completed work on cytokine networks in the tumor microenvironment. She discussed the issues with targeting inflammatory cytokines, noting the complexity of the cross talk between tumor and stroma. She posited that perhaps the advanced disease is being targeted too late. The focus of results was on IL-6 and the effects of anti-IL-6 antibodies on intracellular signaling. The effects of gefitinib were presented as well; *in vivo* effects were similar to those observed *in vitro*.

Ecological modeling of cancer
Yinyin Yuan (Centre for Evolution and Cancer, The Institute of Cancer Research)
Dr. Yuan began by stressing the importance of the microenvironment in cancer evolution and in the development and implementation of therapeutics. Her approach begins with histology analysis in order to characterize spatial distribution and infiltration. A software package in R entitled CRImage has been developed to perform this histology image analysis. Cell type and location information allows for creation of a density profile. Results are validated with tumor-based and cell-based comparisons. Lymphocyte infiltration is significant in breast cancer, but there is a lack of a standarized and objective scoring method for this type of data. In order to develop such a scoring method, a cancer density map is created and overlaid with lymphocyte data from histology. Mathematical techniques are used to classify the spatial distribution of various types of lymphocytes. Intra-tumor lymphocyte ratios (ITLR) is positively correlated with prognosis; in fact, ITLR predicts the outcome of chemotherapy and radiotherapy. To this end, Dr. Yuan is interested in using ITLR to identify treatment strategies. The expression of CTLA4 is associated both with ITLR and with prognosis. The Morisita measure is used to determine similarities in community structures of lymphocytes and cancer cells. A further quantification method, Getis-Ord hotspot analysis, was introduced to identify cancer niches in the microenvironment. Hotspots are identified for cancer cells and for lymphocytes; from these results co-localized hotspots are identified. These are correlated with good prognosis. Stromal cell counts were shown to be associated with poor prognosis. Local cancer ecosystems can be compared to diverse ecological systems; the Shannon diversity index is used to assess spatial heterogeneity.

Sequential monitoring of Follicular lymphoma uncovers rich and sparse patterns of evolution
Jude Fitzgibbon (Barts Cancer Institute, Queen Mary, University of London)

Dr. Fitzgibbon began by using a football stadium as metaphor for the genome. Each spectator corresponds to one gene; the environment is important. Perhaps most importantly, the genome can be regulated (e.g. the response to the performance in the event being watched). He then transitioned to discussion of Follicular lymphoma (FL), noting that it is widespread and that while the median survival is quite high (12 – 14 years), there is a lot of remission, and the disease is incurable. A sequential database from biopsies of patients in relapse have been collected over time, allowing for analysis of genotype and phenotype time course data. The origin of FL is now in question, as it is not the case of a t(14;18) translocation, as previously thought. Temporal profiling was performed on FL biopsy tissue, revealing several patterns in the evolution of FL, obtained from phylogenetic trees constructed from the data. Data show that 90% of cases had at least one mutation in an epigenetic regulator; mutations were less common in other gene categories. Analysis of FL tissue is complicated by the presence of non-tumor cells. Categorizing mutations as either clonal or subclonal allows for inference of mutation timing. EZH2 mutations were targeted for clonality assessment; this allows for preferential targeting of actionable mutations. Spatial profiling is important to ensuring that biopsies are taken from the same location at each time point, as there are likely spatial as well as temporal heterogeneities. After summarizing these results, Dr. Fitzgibbon presented several slides on cytogenetics in reference to talks given earlier in the conference.

Quantifying intratumour heterogeneity as a prognostic marker
Trevor Graham (Barts Cancer Institute, Queen Mary, University of London)
Dr. Graham began by describing the challenge of developing biomarkers, i.e., finding which of the myriad possible measurable variations among tumors are clinically relevant. He explained that carcinogenesis is an evolutionary process: DNA mutations comprise heritable variation in the population of tumor cells, and these can be selected, resulting in expansions of tumor subclones. Since cancer prognosis is determined by the future evolution of the tumor, evolutionary trajectories should be measured to assess prognosis. Some parameters characterizing evolvability are generation time, mutation rate, strength of clonal selection, heterogeneity in the microenvironment, and variability in the population. Here he focused on this last, namely within-tumor heterogeneity, as an easily measurable prognostic marker. A therapy constitutes a selective pressure; a diverse tumor would be more likely to be robust to this pressure, resulting in the outgrowth of a resistant subclone and worse outcome. Dr. Graham presented results in patients with lung adenocarcinomas showing that high diversity (more subclones) significantly predicted overall survival, independently of the overall mutation burden. In other results, high diversity within biopsies of patients with Barrett's esophagus predicted greater risk of progressing to esophageal cancer. On the other hand, phenotypic heterogeneity as measured on PET/CT scans by Moran's i, a spatial heterogeneity statistic, also appeared to predict prognosis. In sum, heterogeneity of structural genetic alterations appeared to be a universal prognostic indicator across various cancers and pre-cancerous conditions, and phenotypic diversity might be also. Finally, Dr. Graham described how he and collaborators were testing a large number of potential prognostic biomarkers *in silico* using a computational model of tumor evolution.

In vivo and in vitro modeling of epithelial and stromal heterogeneity of tumors
Simon Hayward (NorthShore University Health System)
Dr. Hayward began by explaining that paracrine interactions between mesenchymal cells and epithelial cells drive the differentiation of the epithelium, and then the loose connective mesenchymal tissue. For instance in the adult prostate, the epithelium and stroma are in continuous communication to maintain a differentiated epithelium and differentiated stroma. Dr. Hayward has been preparing tissue recombinants in cell culture using combinations of either normal or initiated epithelial cells from a human prostatic epithelial cell line, BPH-1, either normal fibroblasts or CAFs (cancer-associated

fibroblasts) extracted using collagenase/hyaluronidase, and rat tail collagen, then implanting the recombinants in nude mice. Implanting doing experiments extracting fibroblasts using collagenase / hyaluronidase. Both initiated epithelium and CAFs are required to drive carcinogenesis in this model: only with both do malignant tumors develop. So Dr. Hayward next asked, what mechanisms do CAFs use to elicit epithelial tumorigenesis? Truncating TGFbetaRII (TGF-beta receptor II), or blocking TGFbeta ligand, each reduced tumors relative to controls. But TGF-beta is a critical component in tumorigenesis elicited by CAFs. It is counterintuitive that deletion of a growth inhibitory pathway would directly suppress tumorigenesis. Dr. Hayward presented results showing that this could be explained by a mixture of different subpopulations of fibroblasts in the stroma, with differing TGFbeta activity and responses. Prostate cancer alters TGFbetaRII expression levels in adjacent stroma. Fibroblasts with differing TGFbetaRII status express different profiles of chemokines and cytokines. Interactions between fibroblasts with differing TGFbetaRII status can alter overall stromal to epithelial paracrine interaction. Stromal cells recruit myofibroblasts and correspondingly, become divergent. Separately, Dr. Hayward presented findings showing that grafts from a mixture of two different breast cancer cell lines, AT1 and CA1d, each derived from MCF10A, grew much better than grafts from either alone (the former didn't grow at all), verifying the suggestion of possible cooperation among cancer subclones made by Robert Axelrod, David Axelrod, and Ken Pienta in their 2006 paper. Dr. Hayward and collaborators found enhanced TGF-alpha and TGF-beta signaling in the mixture, suggesting blocking these pathways could reduce its proliferation.

FRIDAY, FEBRUARY 6, 2015

Laying the Roadmap for Stromal Signaling Pathways That Impact Epithelial Tumors
Gustavo Leone, Ohio State University

Dr. Leone explained that development of the worm *Caenorhabditis elegans* is stereotyped: cell divisions always occur in the same order and the lineage and fate of every cell has been completely mapped. Since its development is so well understood, Dr. Leone and collaborators wanted to use it to understand the influence of stromal cells on epithelial proliferation. Hyperproliferation would result in the development of two or more vulvae, rather than one, as normal. This required two hits, one from mutated gap1 (a RAS-related gene) and another due to RNAi knockdown of one of 39 genes. These genes, of which 31 had human orthologs, were regulatory hubs, some via chromatin remodeling, some via polyadenylation to regulate transcription, and some via regulation of translation. Of these genes, 19 were specific to the stroma. The 31 human orthologs mostly did not appear to differentially regulate human cancer cells themselves; however, the 31-gene signature could almost separate tumor stroma from normal stroma. Thus, these conserved tumor suppressive pathways in *stromal* cells suppress epithelial tumor growth. Dr. Leone and collaborators knocked down 25 of the 31 human orthologs in normal fibroblasts from human patients, then cocultured with them with human cancer cells (from each of 5 cell lines). This yielded differential proliferation in many cases. Separately, Dr. Leone and collaborators found 45 *C. elegans* genes whose knockdown induced the multi-vulva phenotype (of which 5 had been found in the earlier work with the gap1 mutation). 34 of these had human orthologs. These genes coded for histone-related proteins, lysosomal proteins, mitochondrial proteins, and transporters. In this way, Dr. Leone and collaborators are investigating how mesenchymal signals from developmental stromal pathways collaborate with specific oncogenic lesions to affect tumorigenesis.

The Breast Tumour Microenvironment: A Predictor of Clinical Outcome and Tumour Heterogeneity
Morag Park, McGill University

Dr. Park explained that whole tumor expression profiling had previously identified distinct molecular subtypes of breast cancer: luminal A, luminal B, HER2, and basal. Dr. Park and her lab wanted to know if stromal-specific expression profiles could also distinguish subtypes. They used LCMD (laser capture microdissection) to separate stromal cells from epithelial cells, then examined expression in the stroma. Tumor stroma did have quite distinct expression from normal stroma, and stromal gene expression also falls into distinct clusters--a different clustering from that based on epithelial gene expression. They identified six distinct subtypes I-VI of breast tumor stroma, with associated genes from distinct biological processes. These stromal subtypes were strongly associated with outcome. Stromal subtypes I, II and III, with enriched expression of genes involved in matrix remodelling, hypoxic/angiogenic, and activated fibroblasts respectively, were associated with poor outcomes. From each of the stromal subtypes they generated a gene signature with which they could rank any sample's expression levels. Tumor epithelial cells whose stroma was of subtype II (hypoxic) did match the gene signature, i.e., hypoxia induced similar changes in both stromal and epithelial cells. On the other hand, the activated fibroblast signature was stroma-specific. They found that 26 stromally derived genes (SDPP) were sufficient to predict patient outcome. These genes were involved in three clusters: immune cells, absence of *Wnt*/*Frizzled*, and angiogenesis. Combining stromal subtypes with epithelial subtypes yielded better predictions of outcome. Stromal gene expression reflected the relative abundance of specific cell types within the stroma, namely B cells, T cells, and fibroblasts. Normal stroma samples have many fewer T cells and many more fibroblasts than triple negative tumor stroma. Patients with low CD8+ T cells, or in which CD8+ T cells were excluded from the tumor bed, had the worst outcomes.

Tumor Heterogeneity in Breast Cancer Progression: A View From The Trenches
E. Shelley Hwang, Duke University

Dr. Hwang began by describing DCIS (ductal carcinoma in situ), a non-obligate precursor of invasive breast cancer diagnosed in 50,000 new cases annually, usually on mammograms of asymptomatic patients. What proportion of DCIS patients will progress to invasive carcinoma, and at what rate, are not known. Dr. Hwang described the increase in DCIS as an unintended consequence of the increase in mammograms. Overdiagnosis, the diagnosis of a "disease" which will never cause symptoms or death in a patient's lifetime, is a side effect of testing for early forms of disease which may turn people into patients unnecessarily and may lead to treatments that do no good and perhaps do harm. So, Dr. Hwang has worked on trying to distinguish which trajectories among DCIS patients would progress to IDC (invasive ductal carcinoma). Looking at chromosomal alterations had not yielded compelling distinct molecular factors. Looking at histone deacetylation, acetyl-H4 and acetyl-H4K12 markers were less seen in both DCIS and IDC than normal epithelium. So then she looked at breast density/stiffness, specifically comparing the ECM (extracellular matrix) in patients undergoing prophylactic mastectomy or reduction mammoplasty versus patients with tumors. Dr. Hwang and collaborators found that tumor progression correlates with significant ECM remodelling, including increased stromal density, enhanced mechanosignallling, stiffening, and infiltration by CD68+ macrophages. She also has been working with Dr. Graham and collaborators to compare genetic divergence, phenotypic divergence, and radiographic characteristics (as described in his earlier talk in this workshop) between DCIS patients and patients whose DCIS had gone on to metastasize. With other collaborators she will use immunohistochemistry and automated image analysis to investigate the expression of suspect genes in the tumor microenvironment.

Workshop 5: Treatment, Clinical Trials, Resistance
(February 16-20, 2015)

Organizers: Mariam Eljanne (National Institutes of Health), Peter Shields (The Ohio State University), Jack Tuszynski (University of Alberta), Larry Nagahara (National Cancer Institute), and Kristin Swanson (Northwestern University)
Report by: Marcio Duarte Albasini Mourao, Karly Jacobsen, Leopold Matamba Messi

MONDAY, FEBRUARY 16, 2015

Computational approaches to the discovery of new cancer drugs: The story of Colchicine and its derivatives
Jack Tuszynski (Cross Cancer Institute, Edmonton, Canada)
Dr. Tuszynski's presentation focused on how the role of computational approaches in drug discovery pipeline. The drug discovery process is a multiphase process (04 phases) that begins with target identification and validation and ends with the approval process by a regulatory agency prior to drug commercialization. He argued that each phase of the drug discovery pipeline could benefit significantly from computational approaches. However, the initial phase stands to benefit the most from computational studies as it relates to the identification of metabolic and pharmacologic actions and the determination of the side effects associated with various doses and evidence of effectiveness. Dr. Tuszynski concluded the talk with an example of computational framework used in the discovery process of the cancer drug *Colchicine* and suggested a well developed simulation platform (ADMET™) for drug discovery.

Using networks models to genetically map biologic process to complex phenotypes
Kenneth Buetow (Arizona State University)
Dr. Buetow's presentation focused on network models to better leverage and understand cancer. These networks models account for the individual heterogeneity in underlying etiology as well as the diversity and interaction of events underpinning the complex phenotype that is cancer. His group has developed distance based approaches with the assumption that individuals should share genetic variability based on shared traits, and proposed a network analysis method: *Pathway of Distinction Analysis (PoDA).* PoDA provides a means to map differences in genome-wide constitutional variation observed in networks to phenotypes of interest. For example when applied to breast cancer and hepatocellular carcinoma, PoDA has identified networks important in the etiology of these cancer not seen through single gene analysis. Dr. Buetow concluded with an overview of a new computation framework: *ASU Next Generation Cyber Capability*. The new framework extends PoDA to include all measured inherited variability observed in the pathways and is enabled and searches for the smallest collection of such variation with the network required to significantly classify alternative phenotypes.

Platform clinical trials in oncology and neurology
Donald Berry (MD Anderson Cancer Center)
Dr. Berry spoke about platform clinical trials: a novel approach to drug development that seeks to address the issue of developing drugs in diseases that are less prevalent while the cost of developing a drug continues to increase. He argued that increase granularity of biomarkers may necessitate speed up and redesign of drug development pipelines as well as modernizing the tools that are used in evaluating drugs for regulatory purposes. A platform trial seeks to find the best treatment for a disease by simultaneously investigating multiple treatments, using specialized statistical tools for allocating patients and evaluating results. Dr. Berry succinctly described key steps of a platform trial in the following way. At the beginning of a platform trial, patients are assigned to treatments with equal randomization probabilities. The accumulated outcome data is then used to adjust randomization probabilities and assign new patients to better performing treatments. This adaptive process improves

treatment outcomes for patients within the trial, improves the information available on treatment effects and side effects, reduces the evaluation time for the best treatments, and may identify effective combination therapies. He concluded the talk with several examples of ongoing clinical trials that are utilizing the platform trials methodology and alluded to ongoing lobbying efforts to get the FDA to beginning accepting Bayesian analysis for demonstrating the effectiveness of new drugs.

The timing of resistance medicated treatment failure
Kevin Leder (University of Minnesota)
Many treatment modalities lose their effectiveness due to acquired resistance. One way the resistance comes about is the evolution of mutant strains that are resistant to the prevalent therapy. Dr. Leder presented a mathematical model of acquired resistance to treatment incorporating a mechanism of resistance. He discussed how such a model could be used to predict the timing of treatment failure due to acquired resistance. Dr. Leder formulated concepts that may be used to evaluate treatment failure: timescale to extinction, turnaround time, and crossover time. In order to evaluate the efficacy of a drug associated with a given therapy, he studied large population asymptotics of the latter measures. Dr. Leder presented an analysis of the application of his framework to a therapy for Non-Small Cell Lung Cancer. By studying the distribution of turnover time to extinction time ratio, He could predict that with continued application of the drug, the resistance is highly likely if not a certainty. Furthermore, the model does not support a strategy that would consist in withdrawing the drug at turnaround time to guard against the resistance. Dr. Leder concluded by presenting versions of the model are used to study the correlation between crossover time and population characteristics.

Biophysical subtypes of pancreatic cancer
Eugene Koay (MD Anderson Cancer Center)
Survival rates for pancreatic cancer patients have been stagnant for decades, partly due to the complex biology of the disease and its significant heterogeneity between patients. Personalized approaches to therapy may help accelerate progress, but requires the identification of robust biomarkers. Dr. Koay presented his efforts to establish robust biomarkers to quickly identify whether a patient is responding to a specific treatment regimen. The novel approach pioneered in his lab involves analyzing physical properties of pancreatic tumors that can be measured from CT scans. This approach supports the notion that the multiscale mass transport properties of pancreatic cancer influence the natural history of the disease and its sensitivity to cytotoxic therapies. Dr. Koay presented the transport oncophysics methodology used to derive physical properties of cancer cells from imaging data using optimal transport methods. He presented several case studies of the transport oncophysics approach to study intratumoral heterogeneity of *gemcitabine* delivery and its correlation to drug delivery, response to treatment and outcome in humans. He demonstrated that changes in transport oncophysics correlate with local control of pancreatic tumors and posited that mass transport properties derived from CT scans could be used as biomarkers of pancreatic cancer progression.

Personalizing chemotherapy treatment using systems engineering tools and model-based dynamic optimization
Robert Parker (University of Pittsburgh)
Oncologist are challenged to balance efficacy and toxicity for their patients. Dr. Parker spoke about a framework developed in his lab that incorporates patient-level data with mechanistic models of toxicity to determine treatment schedule with the goal of minimizing drug-dependent toxicity. His team has developed a decision support system that combines pharmacokinetics and pharmacodynamic models, including drug-dependent toxicity, for the purpose of designing novel treatment regimens for chemotherapeutics. Dr. Parker presented a case study of this approach with docetaxel as the antitumor

agent and neutropenia as proxy for determining the toxicity. Efficacy is measured using a power-law structure and the model-based mixed-integer dynamic optimization returns dosing schedule that provides antitumor effect equivalent to the maximum used in the clinic, but with a toxicity profile that is controlled to be no greater than Grade 3 acutely, and not to exceed Grade 2 for more than 6 consecutive days. Dr. Parker concluded with insights on how the model-based treatment design framework advocated by his team can address combination therapy using drugs with overlapping toxicity and can respond to patient-specific changes on drug efficacy and toxicity during cyclic chemotherapy.

Using mathematical models to design mixed treatment strategies
Ami Radunskaya (Pomona College)
Combined treatment regimens are now frequently used in treating some cancers. However, the determination of treatment schedule in such regimens remains a challenge. Dr. Radunskaya spoke about ongoing modeling frameworks that may be used in clinical settings to suggest treatment schedules and doses for combination chemotherapies, monoclonal antibody treatments and vaccine therapies. For vaccine therapies in cancer, she constructed a two populations (CD4+, CD8+) delayed differential equation model of T-cell activation that included self-regulation of the immune system. She based her strategy on the observation that cancer vaccines are weak antigens that are further limited by self-regulation and used the model to suggest an optimal vaccination schedule with the goal to maximize immune response. The model was calibrated with experimental data from mice and a genetic algorithm was used to find the optimal dosage and schedule.

Dr. Radunskaya noted that the tumor microenvironment is essentially immunosuppressive and combination therapies are essential to inhibit the immunosuppressive effect in many cancers. However, as in vaccine therapies, the effectiveness of combined therapies may also hinges on finding optimal schedules. The heterogeneity of cancer also requires that these schedules be patient-specific. She presented a framework for determining optimal schedules for combination therapies against melanoma. The framework is built around a mathematical model of melanoma that incorporates immune response, tumor growth and circulation. Finally, She concluded the talk by looking at monoclonal antibodies (mAB) and chemotherapy combined treatments for colorectal cancer. She developed a mathematical model including five populations of cells, mAB treatment and chemotherapy. As in the previous two cases, the model was then used within an optimization procedure to suggest doses and a schedule of when to administer each of the drugs.

TUESDAY, FEBRUARY 17, 2015

Mathematical modeling as a tool to generate biologically conformal radiotherapy dose plans for glioblastomas
Corbin Rayfield (Northwestern University)
Dr. Rayfield started with a discussion of the current status of glioblastoma multiforme (GBM) treatment and the yet to be realized potential of personalized medicine. Clinicians are still using a very blunt approach to stratify patients based on age, debilitation, etc. which does not allow for identification of GBM phenotype or a hypothesis of the efficacy of treatment. Dr. Rayfield believes that modeling can provide a critical contribution towards improving patient stratification. He continued with a quick introduction to radiation biology, explaining direct and indirect action, the four different cellular effects, the basics of the cell survival curve and fractionation, the focus of the present work. He then presented a model which incorporates a spatial dependency of the effectiveness of radiation based on the oxygen

enhancement ratio. Subsequently, an ideal model-driven clinical trial was developed which seeks to optimize radiation treatment plans based on pre-treatment FMISO PET scans. By incorporating the scans which delineate the sub-volume of hypoxic tumor, model predictions can be made on the effect of dose/fraction modulations for different treatment plans. The clinician can then compare and select a dose paint treatment plan based on the maximal amount of days gained.

Mathematical modeling as a tool to generate biologically conformal radiotherapy dose plans for glioblastomas

Alicia Martínez González (Universidad de Castilla-La Mancha)

Dr. Martínez González spoke about targeting hypoxia in glioma and whether the impact of hypoxia is irreversible. She presented a reaction-diffusion model for normoxic and hypoxic cells incorporating a go-or-grow phenotypic dichotomy. The model was able to replicate the behavior of pseudopalisades which are generated by vascular damage and drive glioma invasion. An experiment was designed using a microfluidic device where vaso-occlusion was imitated by blocking a channel. Their model simulations successfully reproduced the qualitative results of the experiment; they are currently designing further experiments which incorporate therapies. Next, she addressed the question of whether or not the impact of hypoxia is irreversible by introducing an antioxidant therapy which increases the rate of hypoxic cells developing a normoxic phenotype. Antithrombotic (AT) and antioxidant (AO) therapies were combined into a more sophisticated model, the results of which showed that a lower tumor volume is always achieved with the combination therapy, sometimes in a synergistic manner. *In vivo* mice xenograft experiments confirmed the effect on tumor volume and visual inspection of the tumors revealed low-grade glioma characteristics.

A bleaker view, more clearly: Applying evolutionary dynamics modeling to cancer

Arijit Chakravarty (Takeda Pharmaceuticals Co.)

Dr. Chakravarty began by introducing the differing views of cancer as driven by oncogenes, metabolism or an evolutionary process. A subscriber to the evolutionary view, he believes cancer is a process of somatic Darwinian evolution within each patient driven by genetic variation, selective pressure and differential fitness. The presentation focused on the rich body of evidence for each of these three elements which point to cancer as an evolutionary disease. Cells in tissue culture frequently missegregate their chromosomes; chromosomal instability is a common source of the genetic variance observed in tissue culture cells. Molecular evolutionary analysis of cancer cell lines found evidence of selection pressure (e.g. ratio of synonymous to nonsynonymous mutations in coding regions). Clinical data also supports heterogeneity within a single patient as sequences of primary tumor and metastases showed a very different spectrum of mutations. Dr. Chakravarty presented the evolution of chronic myeloid leukemia in response to treatment as evidence of selection pressure. He continued by discussing the implications of cancer evolution and the different questions that arise for drug development, including comparison of a growth rate inhibition metric to a change from baseline metric. He also considered how evolutionary dynamics can be used in the preclinical setting. Rates derived from kinetic colony growth assays were used in a simple dynamic model which considered how a reduction in the growth rate of the fastest growing colonies affects the overall growth rate. He concluded by stressing the need for a discipline-level shift in thinking and the fundamental insights into cancer behavior provided by evolutionary biology.

Interplay between molecular imaging and tumor modeling of anti-angiogenic therapies

Robert Jeraj (University of Wisconsin)

The speaker began with an overview of molecular imaging, tumor angiogenesis, and anti-angiogenic therapies, focusing on the clinical challenges of vascular endothelial growth factor receptor (VEGFR)

tyrosine kinase inhibitors (TKI) due to withdrawal phenomenon characterized by proliferative and vasculature flares. Clinical trials show heterogeneity among patients; comparison of the dynamics of the flare between responders and non-responders were studied to determine appropriate timing of drugs. Evidence showed that chronic VEGFR TKI exposure leads to increased plasma VEGF. A build-up of resistance was demonstrated in patients with no clinical benefit during three cycles of treatment. The effects of direct blockade were also tested by introducing Bevacizumab during the VEGFR TKI break. To understand the clinical data through modeling, a Monte Carlo approach was employed which used PET/CT imaging data and incorporated three layers (tissue, cellular, and molecular) and two modules (imaging and therapeutic). Sensitivity analysis revealed that critical parameters in the model are the initial oxygen partial pressure in the tumor, cell cycle time and daily vascular growth fraction and daily vascular regression fraction. Dr. Jeraj concluded by emphasizing the power of the marriage between molecular imaging and tumor modeling.

Patient-Specific Mathematical Neuro-Oncology: Every cancer patient deserves their own equation
Kristin Swanson (Northwestern University)
Dr. Swanson began her lecture with an introduction to gliomas, an overview of the problem from diagnosis to the treatment of the disease, and the existing four grades of survival. In her introduction, she explained how the current imaging procedures (obtained by MRI) only reveal the tip of the iceberg of the actual disease and provided a case for why we need more information. Dr. Swanson used two patients as case studies while providing answer for the following questions: What patients respond to therapy; How much response occurs?; Can we optimize survivorship for each patient? She proceeded by talking about 3D reconstruction of brain tumors, which provides a great deal of information, including the observation that cells appear to be diffusing.

Dr. Swanson then introduced a two dimensional reaction-diffusion model of cell migration versus proliferation rates. Here, MRI allows the estimation of patient specific invasion and proliferation kinetics. With differential gene expression one can connect molecular profiles with patient specific rates, which led to the discovery of the IDH1 mutation. This mutation is associated with malignant progression (they diffuse a lot more), below the threshold of detection. She found that seizure incidence correlates with lower size but diffuse tumors.

Dr. Swanson then went back to the two patients of the beginning of the presentation: what can be done? How do you approach the two patients differently, knowing that one has nodular and the other has diffusive cancer? She spoke about the need of having a different approach, when resection margin is needed to remove 99% of the tumor for both patients. She also spoke about the ability to predict patient benefits from resection (75% survival: 8 months more on the nodular); classification of the success of the treatment based on the tumor size evolution over time (before and after treatment); the radius of the tumor versus the diagnosis time; and using patient specific virtual controls to detect impact of gene therapy (phase I clinical trial). Dr. Swanson concluded her talk discussing surgery versus radiation versus chemotherapies.

Clinically targeted mathematical modeling to study response, resistance and recurrence of glioblastoma brain cancer
Russell Rockne (Northwestern University)
Dr. Rockne started his talk with an introduction to GBM (Glioblastoma), a lethal primary brain tumor that often recurs after treatment. His stated goal is to combine information from several clinical levels (cell, imaging and population). Here, MRI is the main approach to monitor the progression of the disease.

Dr. Rockne introduced a two-dimensional reaction-diffusion model based on the MRI that is patient-specific, with the goal of studying the spatial-temporal evolution of the GBM and how the phenotype and the kinetics of the disease are changed by therapy. He uses the mathematical model to understand radiation response factors. One of the parameters for radiation response is alfa, which he estimates using simulations and matching with data. He finds that faster proliferating tumors have a bigger response to therapy. He then proceeds by quantifying the role of hypoxia in determining resistance to radiation therapy for individual patients. Incorporation of hypoxia increases performance of the fitting: it diminishes the resistance, but only one patient was tested.

Dr. Russel Rockne talk addressed specific effects of chemotherapy, which induce genetic alterations that may change phenotype in GBM patients. He shows that recurrent cancer has a different phenotype, where proliferation is diminished and invasion is increased. Since treatment is changing phenotypes, he argues for different treatments and more realistic models (hybrid models or stochastic models). He concludes by presenting some potential future directions. These include adaptive clinical treatment via patient-specific modeling and a multi-evolutionary algorithm.

Personalized therapeutic regimes in multiple myeloma
Ariosto Silva (H. Lee Moffitt Cancer Center & Research Institute)
Dr. Silva described how particular features of cancer, combined with flawed paradigms and bad habits widespread in cancer research, prevent us from curing cancer. He then proposed how one may overcome these challenges by combining biological models from biomedical sciences, clinical data, and evolutionary dynamics into a mechanistic framework capable of predicting clinical response. He and his collaborators use their work in multiple myeloma, a treatable but incurable cancer of the bone marrow, as a proof of principle for adaptive personalized medicine. In his summation: The right drug combination at the right dose and schedule, for the right patient, at the right time, and for the right duration of time, adjusting any of these elements as needed, aiming to maximize survival and quality of life.

WEDNESDAY, FEBRUARY 18, 2015

Predicting the Response of Breast Cancer to Neoadjuvant Chemotherapy Using a Mechanically Coupled Reaction-Diffusion Model
Jared Weis (Vanderbilt University)
Dr. Jared Weis started his talk by providing a motivation for the use of neoadjuvant chemotherapy (NAC) in breast cancer: NAC was found to reduce tumors to a point where they become amenable to surgery (during the period 8-12 weeks). Changes to the tumor are measured in the tumor longest dimension (RECIST) and placed in one of four response categories. His goal is to use mathematical models to predict patient response early in the course of therapy.

Using a detailed mathematical model as a 'negative' example, where too many parameters with no information for them exist, Dr. Weis proposes a different approach: adopt a patient-scale spatio-temporal modeling framework. Here, he proposes to use quantitative imaging to inform constraints in models of tumor growth. Dr. Weis presents a reaction-diffusion logistic growth model with migration and proliferation terms, using imaging to obtain parameters of the model. He provided further insights into the mechanics of cancer, and using an example of cancer diffusion, showed that tumors are sensitive to the mechanical micro-environment.

Using a T1-weighted high-resolution isotropic volume examination (THRIVE), a contrast enhanced MRI to detect the tumor and a diffusion-weighted MRI to get diffusion values, Dr. Weis designed a study where 33 patients underwent NAC. He imaged time points and performed parameter reconstruction from a pair of images to make a prediction of what the tumor looks like before surgery and then compare with the actual experimental data (validation of the method). Preliminary prediction results provide agreement with clinical response observations (used as a predictive indicator of response to therapy).

Multiscale modeling of cell populations in a consistent computational framework: progress and challenges

Alexander Fletcher (University of Oxford, Oxford, UK)

Dr. Fletcher spoke about the computational framework developed at Oxford for efficient simulation of cardiac and cell population dynamics. Alongside experimental and clinical approaches, such a tool could be effectively used to unravel the complex interactions between processes across multiple scales. He began the talk with an overview of various area of research at Oxford that greatly utilize computational methods and emphasized the issue of reproducibility in such studies which is mostly due to the variety of computational tools and implementation of the algorithms. Dr. Fletcher presented a C++ library in development at Oxford to address some of these challenges for Cardiac, Heart and Soft Tissue research. The library has been dubbed *Chaste* as in Cardiac, Heart and Soft Tissue Environment. He detailed the challenges that arise with developing such a library and shared the technical details of how the team try to circumvent these challenges by employing best practices in software development.

Predicting response to hormone therapy in advanced prostate cancer patients by integrating a mathematical mechanistic model tumor progression with data from clinical trials

Zvia Agur (Institute of Medical BioMathematics, Israel)

Dr. Agur presented a framework that integrates mathematical models with patient data to predict the response to hormone therapy for advanced prostate cancer. She began the talk with statistics on the prevalence of prostate cancers around the world and described the various stages of progression of the disease. These include: the local stage treatable with surgery and radiation therapy; the hormone sensitive stage treated with androgen deprivation therapy; and the castrate resistant stage which develops over a longer time span and is treated with chemotherapy. She argued that being able to predict the time of disease progression through the stages would give clinician better planning tools during treatment. Dr. Agur spoke about the integrated framework that she has developed to help determine the progression of the disease as well patient response to treatment. The framework is composed of a mechanistic model of tumor growth including tumor dormancy and treatment effects. The model is supplemented with statistical analysis of patient's data to identify covariate variables and construct patient specific models. Finally the model was used to predict time to biochemical failure of androgen deprivation therapies and time to onset of castrate resistant prostate cancer with the prediction cross validated on patient data. Dr. Agur modeling framework suggests the existence of a complex tumor growth law and at least two distinct mechanisms to androgen radiation therapy resistance operating on two different time scales.

Design principles for cancer therapy guided by changes in complexity of protein-protein interaction networks

Edward Rietman (Newman-Lakka Institute, Massachusetts, USA)

Dr. Rietman discussed applications of some measure on graph that could be used to further our understanding of the relationships and dependencies within protein interaction networks. He presented topological measures (Betti numbers) and thermodynamical measures that could successfully be exploited to further our understanding of cancer dynamics. By exploring published protein-protein

interaction (PPI) networks of several cancers, Dr. Rietman provided evidence that the Betti numbers of the underlying interaction graphs correlates linearly with survival and can be used to predict survival gain/losses produced by a targeted inhibition of specific proteins in a cancer PPI network. He posited that interpolating Betti numbers on cancer survival curves could be explored with therapeutic intent and help clinicians in selecting therapies. He suggested that combining Betti numbers with thermodynamic measures on graph such as the Gibbs free energy of a network may provide new insights applicable to personalized medicine.

Predicting the differential localization of metastases to the brain
Pamela Jackson (Northwestern University)
Dr. Pamela Jackson started her talk with an introduction to brain tumors (50% are metastatic). She described current therapies for brain metastasis: chemotherapy where applicable; surgery; radio surgery (most common). The main point was that brain metastases are treated the same way regardless of primary histology. She provided examples of malignant melanoma (located near large vessels) and explained how gray/white matter junctions are seeds of metastatic cells.

She proceeded by describing two main tumor approaches to growth, whereby one is the cooptive (feeds off existing cells) and the other is angiogenic (recruits new vessels). Lung, breast and melanoma represent the highest incidence of brain metastases and demonstrate differential angiogenic biology. This differential may affect differential therapeutical approaches. The main question addressed in Dr. Jackson's talk is: can we assess spatial localization and differential growth strategies based on tumor angiogenic biology?

Dr. Jackson described a multi-scale agent-based spring model with growth of individual cells; random and directed cell movement and cellular interactions. She also described how untreated lung cancer grows in both gray/white matter while untreated melanoma grows preferentially in the grey matter. The questions are: 1) do lung and melanoma metastases seed at different distances from the cortex? 2) Do lung and melanoma metastases exhibit different patterns of edema? Dr. Jackson concluded by describing a current study of patient data with the goal of providing answers to these questions.

Evaluating treatment response in glioblastoma multiforme: improvement by incorporating anatomical boundaries
Josh Jacobs (Northwestern University)
Dr. Jacobs started his talk with an introduction to glioblastomas (GBM) and its associated mortality. He then described how diffusion and migration rates are calculated, i.e., by calculating the radius from imaging at different time points.

He described a model for the glioma growth (Komolgorov model) with diffusion (invasion) and proliferation. Importantly, the tumor diffuses faster in white matter than grey matter. He compares the isotropic (very linear profile in tumor growth) with anatomic variations in invasion by simulations. The latter does not provide close results to experimental data.

Dr. Jacobs preliminary results showed that the model worked for some patients but not for others. For small tumors, both simulations and patient data showed non-linear tumor growth behavior that cannot be recovered by the model. That may explain the differences observed on same patients. He concluded with a summary and future work.

Using bioengineered tissues to build computational models of tumor dynamics in human tissues

Farzin Ghaffarizadeh (University of Southern California)
In this talk, Dr. Farzin Ghaffarizadeh discussed his study on colon cancer metastases in the liver using bioengineered tissues. He described two primary platforms: liver discs for in vitro studies and liver organoids in bioreactors. He then proceeded by providing a description of the anatomy of the liver and by characterizing cancer cell behavior in liver tissues. The goal of the bioengineering is to mimic cell behavior on the liver discs. He also described the goal of correlating cell behavior to ECM density by simulating light transmission microscopy to quantify the disc ECM structure.

Dr. Ghaffarizadeh described the application of the Pierre-Francois Verhulst population growth model to the population on disc, providing cell counts on and off disc over time (days). The parameters of the model were obtained by fitting the model to the data. The speaker then proceeded by describing steps towards the creation of 3D digital liver tissues: Mark CVs in histology; Estimate lobule geometry via Voronoi decomposition; Place PVs (Veins) and Pas (Arteries) at vertices; Add sinusoids, choose ROI; and fill the region with hepatocytes.

Dr. Ghaffarizadeh described the simulation of substrate distribution in digital liver tissue. He provided examples with oxygen and glucose (both dimensionless). We concluded with a description of future work: insert simulated cells in the digital liver tissue; and a visualization of a simulation video with 500k cells.

THURSDAY, FEBRUARY 5, 2015

Radiotherapy planning based on the biologically equivalent dose model
Jan Unkelbach (Harvard Medical School)
Dr. Unkelbach discussed radiotherapy planning including development of treatment planning systems. He focused on the biologically equivalent dose (BED) model which describes the BED as a quadratic function of the dose per fraction and takes into account sensitivity to fractionation. Optimal fractionation scheme problems address the inherent trade-off between minimizing BED for the normal tissue and maximizing BED in tumor. The speaker discussed extensions of the BED model, such as those including incomplete repair, multiple compartments, hypoxia, and cell cycle effects. However, he emphasized that these extensions are not able to be implemented in clinical practice. As such, he proceeded to demonstrate that the standard BED model can give rise to non-uniform radiotherapy fractionation schemes when the objective function describes the cumulative BED instead of the physical dose. Dr. Unkelbach then presented an example of a spinal metastasis treatment with two beams which sought to administer a prescribed dose to tumor while minimizing the dose to kidney, spinal cord and normal tissues. They considered two different fractions and optimized the non-uniform treatment plan by seeking to improve the kidney dose, resulting in an inhomogeneous total physical dose which reduced the BED in the entrance region, reduced the kidney mean dose by 25%, and reduced the skin mean dose by 13%. Dr. Unkelbach concluded by discussing applications of the BED model to concurrent chemoradiation.

Stochastic models for tumor control probability (TCP) and normal tissue complication probability (NTCP)
Thomas Hillen (University of Alberta)
Dr. Hillen presented several mechanistic stochastic models for tumor control probability (TCP), the probability that a given treatment will eradicate a tumor, and for normal tissue complication probability (NTCP) which quantifies the risks of side effects. Six TCP models were presented: a Poissonian TCP which is equivalent to the biologically equivalent dose model, a birth-death model using a master

equation approach, a model from Monte Carlo simulations, and extensions of each of the three models which incorporated two compartments in the cell population, taking into account cell-cycle dynamics and varying sensitivity of active and quiescent cells to radiation. The six models were directly compared in a prostate cancer application; in some cases the results for one and two compartment models differed, implying that less sensitive cell populations are important to consider if they exist. Several NTCP models were also presented; the model with a logistic birth-death formulation for NTCP admitted straightforward mathematical approaches, including the method of characteristics to solve a hyperbolic PDE, to identify where the NTCP transition occurs. A rigorous ODE optimization problem could then be formulated for simultaneously maximizing TCP and minimizing NTCP.

An edema-based model for diffuse low-grade gliomas under radiotherapy
Mathilde Badoual (Paris Diderot University)
Dr. Badoual presented a model for the effects of radiotherapy on grade II gliomas, low-grade tumors which are characterized by a lack of angiogenesis. An anaplastic transformation triggering angiogenesis transforms these tumors into more aggressive forms. Understanding of the regrowth delay after radiotherapy allows for a prediction of the gain of lifetime due to treatment. Clinical histological samples were analyzed and the amount of edema was correlated with T2 MRI signal abnormalities. An initial diffusion proliferation model was formulated and showed decent agreement to data under the assumption that the diameter is an iso cell density curve. Motivated by heterogeneity in clinical times of regrowth delay, a model with edema was developed which was informed by the patient sample observations and accounted for production and draining of edema by tumor cells. The effect of radiotherapy was included, characterized by a parameter which is the fraction of cells killed by radiotherapy. Sensitivity analysis was performed on the gain of lifetime and regrowth delay; the most critical parameter was determined to be the radiotherapy fraction. When all parameters were fit for each patient a very good correlation was demonstrated between fitted and measured tumor radius, even considering the large variability in dynamics. If all parameters were fixed, a good agreement was shown with the regrowth delay but the model was not as predictive for the gain of lifetime.

Chalkboard to bedside: translating insights from multi-scale evolutionary models to the clinic
Jacob Scott (H. Lee Moffitt Cancer Center & Research Institute)
Dr. Scott discussed evolutionary drug resistance with a model exploration of how treatment plans could be “steered" in genotype space. He argued that failure of targeted therapy is a conserved evolutionary phenomenon, citing melanoma, chronic myeloid leukemia and gastrointestinal cancer. Hidden randomness between fitness landscapes limits reverse evolution. A stochastic model was presented where genotype was represented by a hypercube and mutations corresponded to a Hamming distance of one. The model analysis was driven by the question of whether there are trajectories under one drug treatment that are irreversible under a second; Cefotaxime, Piperacillin, and a hypothetical third drug were considered. To simplify the discrete time population dynamics, the genotype-phenotype mapping was mapped to a biased uphill Markov chain based on fitness. An empirical dataset for fifteen landscapes in E. coli was used. From their analysis they concluded that evolution does not commute; that is, the order that drugs are prescribed matters in terms of the irreversible evolutionary trajectories.

“I have a Ph.D. in mathematics and I’m here to help” - Contributions to cancer research
Larry Nagahara (National Cancer Institute, NIH)
Dr. Nagahara spoke about the changing landscape of cancer research in the big data era and the efforts of the National Cancer Institute (NCI) to support the applied mathematics community. The speaker emphasized the need for mathematical models arising from both successes and failures in the clinic. The Goldie-Coldman and Norton-Simon hypotheses from the 1970s were cited as examples

demonstrating the need to accelerate the process from a model-driven hypothesis to clinical trial results. The complexity of the tumor microenvironment was discussed along with the difficulties of modeling complex processes such as immunotherapy and stem cell therapy. Finally, Dr. Nagahara spoke about the physical sciences-oncology network of the NCI and presented a new call for proposals for centers and projects to support the advancement of applied mathematics cancer research including an ideas lab to build convergence translational research teams.

Phase i trials in melanoma: optimizing order and timing of combination therapy
Alexander Anderson (H. Lee Moffitt Cancer Center & Research Institute)
Dr. Alexander Anderson started his talk describing the push for Integrated Mathematical Oncology (IMO), to better understand, predict and treat cancer. The goal is to build biologically relevant models, which necessarily have to include the fact that the cancer is multi-scale. However, bridging scales, from molecular to cellular to organism, is a fundamental problem. He proceeded by providing images of targeted therapy of metastatic melanoma with relapse after 23 weeks (after 15 weeks appears to be almost completely normal). Can they help with the decision of when and how to act?

Dr. Anderson continued describing good responses after treatment with a combination of chemotherapy and an AKT inhibitor in patients with metastatic solid tumors including melanomas. Their experiments showed that these treatments differentially induces autophagy in cells and that autophagy modulates treatment responses. So, the combination separated the populations into responsive and non-responsive to treatment. Dr. Anderson proposed the hypothesis that autophagy has 2 states: proliferative and non-proliferative autophagy. To address this hypothesis, they developed a compartment model comprising a system of ordinary differential equations. The model is comprised by 3 ODEs, one for non-autophagy and the other two for the states mentioned above. They calibrated the model with a genetic algorithm (for 9 days) from data of several patients (each for each cell line).

The model predicts that the standard of care combination therapy is effective in short term tumor control but the treatment will eventually fail. Nevertheless, schedules can be optimized mathematically and applied to extend response. Dr. Anderson also provided a description of a phase i virtual clinical trial. Their analysis emphasized the relevance of selecting patients based on autophagy transition rates and growth rates. He concluded by providing challenges and describing future work.

Molecular Epidemiology and Breast Cancer Risk
Cenny Taslim (The Ohio State University)
Dr. Cenny Taslim started her talk with a present and a future timeline for cancer as well as a description of conventional and evolved practices. She argued for a systems biology approach, with a combination of data at several different scales. Using mRNA, DNA methylation and miRNA data, Dr. Taslim's overall goal is to determine if miRNA can be used to predict breast cancer risk.

Dr. Taslim proceeded with an explanation of miRNA biogenesis, indicating that miRNA negatively regulates gene expression and also have many biological targets. She provided a summary of an analysis done on women using miRNA expression. This analysis was done using a projection based multivariate classification method based on an extension of a partial least square regression. The approach used cross-validation to identify 41-miRNA panel classifying women with high and low risk for breast cancer. They validated their results with a different cohort study. Dr. Taslim concluded with a describing of future work, where she argued for the need of testing their approach in a higher study cohort.

RECIST vs change in tumor growth rate (TGR) to evaluate treatment efficacy

Serge Koscielny (Institut Gustave Roussy)
Dr. Serge Koscielny began by addressing the importance of evaluating tumor response to therapy. Tumor response is often evaluated with RECIST, but RECIST takes into account only tumor growth during treatment, and it is impossible to distinguish the effect of treatment from the intrinsic characteristics of a tumor. The goal is then to provide a quantitative approach and integrate data before and after the clinical trials.

Dr. Koscielny described incorporating pretreatment data to measure treatment effect as the difference between the tumor growth rate (TGR) measured before and after treatment. He assumed an exponential growth for tumor lesions and compared RECIST and TGR using data from patients treated mostly in phase I trials. He then simulated the impact of the accuracy of tumor size measurement on both TGR and RECIST evaluations.

Results show that TGR is independently associated with prognosis (overall survival and progression free survival) in the entire trial. Dr. Koscielny then described some pros and cons of TGR. One pro is that it is based on conventional metrics and technology. Also, each patient is considered as its own control. A con is on the implementation of the TGR where additional imaging is needed: CT scan before treatment onset. TGR also provides useful info for drug development.

Workshop 6: Targeting Cancel Cell Proliferation and Metabolism Networks

(March 23-27, 2105)
Organizers: Baltazar Aguda (Disease Pathways, LLC), Robert Gatenby (Moffitt Cancer Center), Vito Quaranta (Cancer Cell Biology, Vanderbilt), Santiago Schnell (Molecular & Integrative Biology, U of Michigan)
Report by: Jae Kyoung Kim, Richard Buckalew

Monday, March 23, 2015

The Metabolism of Proliferating and Leukemic Lymphocytes
Jeffrey Rathmell (Duke University)
Dr. Rathmell discussed the immune response of cells, focusing on metabolism. Immune response of normal cell populations consist of pathogen sensing, expansion, contraction and memory. However, leukemic cells remain in the proliferative phase. He tried to answer how do cells know when, what, and how much to build or tear down? It turns out glycolytic switches and T cell activation play critical roles. He found that T Cell stimulation dramatically increases Glucose uptake, and T Cells express a subset of regulated Glucose transport mainly via GLUt1. Furthermore, he found that Tcells differentiate into metabolically distinct effector or regulatory subsets. Finally, he also presented why Lukemia cells behave differently from T cells regarding aerobic glycolysis. The difference is due to the mTor-signaling pathway involving AMPK.

p53 regulation of Mitochondria
Paul Hwang (Center for Molecular Medicine, NIH)
Dr. Hwang talked about how p53 regulates the function of Mitochondria. p53 is one of the most commonly mutated tumor suppressor genes in human cancers and thus a guardian of the genome. It is known that p53 regulates mitochondria through multiple pathways in particular via SCO2 and TFAM. p53 also can translocate into mitochondria. He had interest in why p53 regulates mitochondrial respiration. It has been known than p53 regulation of respiration as part of its antioxidant function. Furthermore, p53 promoting

mitochondrial respiration increases aerobic exercise capacity that parallels the strong inverse relationship between cardio-respiratory fitness and cancer-free survival observed in large epidemiologic studies. Interestingly, he found that mutant p53 can also increase oxidative metabolism. These disparate findings can be explained by the dissociation of the cell cycle and mitochondrial activities of p53. This finding is also consistent with the growing evidence that cancer cells depend not only on aerobic glycolysis but also on mitochondrial metabolism which may contribute to tumorigenesis in the setting of defective cell cycle regulation by mutated p53.

Modeling metabolic networks with an ensemble evolutionary flux balance analysis approach
Riccardo Colombo (University of Milan)
Dr. Colombo talked about his new method for flux balance analysis (FBA). FBA is a constraint-based method that optimizes the reaction flow of a network. FBA relies on stoichiometric constraints and quasi-steady state and does not need kinetic parameters. Due to this FBA is computationally less inexpensive than mechanism based method. He presents how to use FBA to answer to which are the network flux distributions that explain specific property or phenotype. Specifically, he used ensemble evolutionary FBA approach based on genetic algorithm and clustering algorithm. This method is applied to identify the core metabolic model of yeast for Crabtree+/- phenotypes. He also presented a new software that visualizes molecular interaction networks and biological pathways.

Adaptive resistance and fractional response of cancer cells to cancer drug
Mohammad Fallahi-Sichani (Harvard)
Dr. Fallahi-Sichani presented a systemic identification for cancer drug sensitivity. While EC50/IC50 are mainly used to represent the drug effect, via multi-parametric approach, he found that variation in Emax and slope of dose-response curve are important factor to determine drug efficacy. He exemplifies this result with Akt/PI3K/mTOR inhibitors and RAF/MEK inhibitors. He also discussed why treatment of $BRAF^{V600E}$ melanomas with drugs, such as vemurafenib, that inhibit RAF/MEK signaling is effective in the short term, but remission is not durable. He found that drug resistance appears to involve short-term adaptive responses that compensate for RAF/MEK inhibition via up-regulation of other pro-growth mechanisms. With a systematic approach to studying the responses of human melanoma cell lines to various RAF and MEK inhibitors, he found that responses to RAF inhibitors are remarkably diverse and involve multiple pathways that can be up or down-regulated over time, with significant variability across cell types and individual cells. Specifically, he have identified a role for JNK/c-Jun signaling in altering the cell-cycle distribution of melanoma cells, causing apoptosis-resistant cells to accumulate and drug maximal effect (E_{max}) to fall; co-drugging with RAF and JNK inhibitors or JUN knockdown reverse this effect. His study shows that a systems-level approach (combining high density time-dependent measurements, quantitative modeling and single-cell analysis) provide a general framework for evaluating new drugs with adaptive and paradoxical response and for identifying potentially useful combination therapies.

Massive re-organization of the liver chromatin landscape following metabolic and inflammatory signals
Ido Goldstein (NCI, NIH)
Dr. Goldstein discussed how fuel production is temporally regulated in liver during fasting at the transcriptional level. The response to fasting is temporally organized in the process of glycogen break down, gluconeogenesis and ketogenesis. These changes are mediated by alterations in chromatin structure and transcription factor occupancy. To evaluate the alterations in chromatin landscape and gene expression following fasting, he analyzed livers from fasted mice with three assays: DNasel-seq and H3K27Ac Chip-seq and RNA-seq assays. As a result, he found ~4,000 sites in liver chromatin in which accessibility was altered following fasting. Interestingly, these binding site are for PPARa, GR and CREB.

He concluded that these three components play the critical role in regulating the temporally organized fasting response in liver.

Tuesday, March 24, 2015

Modeling targeted therapy response in oncogene addiction
Vito Quaranta (Vanderbilt)
Dr. Quaranta discussed the source of heterogeneity in observed cancer drug effects. With a high-throughput colony Fractional Proliferation (cFP) assay, he simultaneously tracks in real-time the proliferation dynamics of hundreds to thousands of single-cell derived clones in a cell population exposed to drugs. The widespread heterogeneity of drug response is captured by a new metric, the drug-induced proliferation (DIP) rate, which encapsulates single-cell variation into a dynamic measure of drug response outcomes. Interestingly, the variation of DIP rates from colony to colony in PC9 is approximately normally distributed, a strong indication it arises from stochastic sources. Similar distributions were obtained from many additional oncogene-addicted cell lines, rigorously re-derived from single cells. Thus, a mutated driver oncogene does not ensure cell-to-cell homogeneity of response, even when genetic background diversity is minimized. To explore whether these distributions are of consequence to treatment, he constructed a Polyclonal Growth (PG) mathematical model able to incorporate theoretical or experimental DIP rates as parameters. Interestingly, with the DIP rate distribution parameters as input, a completely different result was obtained: the size of the erlotinib treated population rebounded to initial values after ~11 days, after an initial drop to half the value at 5 days. He concluded that it is unlikely that conventional acquired resistance was responsible for the rebound and even in the absence of acquired genetic resistance, heterogeneity of drug response promotes rebound of the treated population.

How Many MTDNA's Does It Take to Make a Tumor?
Ed Reznik (Sloan Kettering Institute)
Dr. Reznik discussed about the relationship between the copy number of mitochondrial DNA (MTDNA) and tumor. He analyzed MTDNA copy number variation across 21 distinct solid tumor types, examining over 8,000 samples of tumor and adjacent normal tissue profiled with next-generation sequencing methods. With this survey, he found that in a subset of tumor types, including kidney chromophobe and adrenocortical carcinomas, MTDNA copy number is significantly associated to patient survival. He also found that MTDNA copy number is correlated to the expression of mitochondrially-localized metabolic pathways, suggesting that MTDNA accumulation and depletion reflect gross changes in mitochondrial metabolic activity. He also identified a subset of tumor-type-specific somatic alterations, including IDH1 and NF1 mutations in gliomas, whose incidence is strongly correlated to MTDNA copy number. These results indicate than intimate connection between MTDNA content and the molecular events underlying the initiation and progression of tumors.

Reprogramming of metabolism in tumors by somatic copy number co-alteration of proximal enzyme coding and cancer causing genes
Ashwini Kumar Sharama (German Cancer Research Center)
Dr. Sharama talked about how linear proximity of metabolic gene and cancer-causing genes in the chromosomes can lead to metabolic remodeling. For this, he developed the analysis pipeline, Identification of Metabolic Cancer Genes (iMetCG). These tools can be used to investigate such events by integrating data for 19 different cancer types from TCGA that led to the identification of novel metabolic cancer genes. Furthermore, with iMetCG, he found that metabolic and cancer-causing genes

are approximately located in chromosomes. This provides a rationale for why deregulation of metabolism is an emerging hallmark of cancer.

Metabolic rewiring in cancer cells

Daniela Gaglio (Institute of Bioimaging and Molecular Physiology – CNR, Segrate (Milan))

Dr. Gaglio discussed using metabolomics to integrate experimental data with the goal of reconstructing metabolism networks that have been altered by cancer. Metabolomics provides information at a finer detail than genomics that allows specific mechanisms to be detected. For example, oxidative phosphorylation behaves heterogeneously among cancers, reflective of adaptation to different environments. Metabolomics allows researchers to identify these differing phenotypes more accurately. Using the tools of metabolomics, Dr. Gaglio identified S-phase arrest as the mechanism by which glucose/glutamine starvation kills cancer cells. More generally, her team was able to construct an accurate "CWR" (rewiring) map identifying specific adaptations to deal with the increased ROS damage from cancer proliferation.

Landcape and flux of cellular networks

Jin Wang (Stony Brook University)

Dr. Wang presented a vector field decomposition method for analyzing chemical reaction networks and applied it to two published models. The method is essentially the Helmholtz decomposition, whereby a vector field F is decomposed as $F = -\nabla U + \nabla \cdot V$. The 'gradient component' U provides an energy landscape where local minima correspond to fixed points of F. The 'curl component' V represents a motive force for traversing the landscape. Traditionally, trajectories on energy landscapes are posed as an optimization problem, or alternatively as the limit of small noise systems. Dr. Wang showed that his approach is equivalent to these approaches.

Dr. Wang performed this decomposition on a vector field F in many dimensions, representing the cell cycle. He presented a 2 dimensional projection with variables representing Cyclin A and Cyclin B. The resulting landscape resembled a 'mexican hat' with deep wells representing G0 and G1 and a barrier representing the G1/S transition. The curl part of the decomposition was a rotational vector field in the direction of cell cycle progression. He also showed a decomposition of a cancer network (made continuous using Hill functions), where the resulting landscape had three deep wells representing normal cells, cancer cells, and apoptosis. By adjusting rate parameters to reflect known therapeutic and pathologic mechanisms, he showed that these wells can be made more shallow, moved, or eliminated entirely.

This decomposition method allows for perturbation analysis, by identifying 'markers' (e.g. local minima) and seeing how they change with parameters. There are also potential applications for dimension reduction.

Reverse engineering crosstalk in the signaling network

Lani Wu (University of California San Francisco)

Dr. Wu is interesting in reducing complex networks to understandable motifs ('crosstalk') governing cellular behavior, with the goal of identifying good targets for therapeutic intervention. Her main method is perturbation analysis in an experimental setting. She demonstrated results of this approach applied to human neutrophils.

In neutrophils, the PRN is highly modular, with an identifiable front F, middle M, and back B. These subnetworks are characterized by activity of actin, tubulin, and myosin, respectively, and can be individually up- and down-regulated. By perturbing each of the units separately and recording changes in fluorescence in the others over time, then retaining only those links which were persistent across time points, Dr. Wu identified a motif whereby the front and the back modules were mutually inhibitive.

She then constructed a PDE model based on this motif with the goal of identifying altered networks underlying pathological phenotypes. She made many different versions of the model with altered topologies (introducing new excitatory / inhibitory links) and compared model outputs qualitatively with experimental data. This process was effective in identifying a new link that existed in each matching model (and only in matching models), which provided a target for new experiments.

Wednesday, March 25

High glygolytic metabolism in stem-like cancer cells: Regulation by glucose in the microenvironment and therapeutic implications

Peng Huang (The University of Texas MD Anderson Cancer Center)

Glioma cells can be reliably classified as stem-like cells using metabolic phenotype. This phenotype emerges in U87 cultures after subcutaneous implantation in mouse models. Such cells exhibit a large change in respiration and overexpress CD133 compared with normal culture. These stem-like cells have higher respiration and glycolosis along with higher drug resistance.

Using ABCG2 as a marker to reliably identify stem-like (SL) cells, Dr. Huang's team studied the effect of glucose starvation on tumor populations. SL cells are eliminated while other cells persist at lower rates. However, restoration of glucose reversed the effect, with new stem-like cell lines emerging. Thus tumor phenotypes are dynamic and highly adaptive to their microenvironment.

Dr. Huang identified Akt as a key link in the proliferation of glioma cells. Akt is upregulated by ATP mediated AMPK downregulation. Blocking glycolosis blocks the chain upstream of Akt upregulation. Using 3-BrPA (or 3-BrPE in vivo), Dr. Huang's team reduced ATP by 80%, effectively targeting SL cells.

Dr. Huang identified SL subpopulation dynamics after application of the standard therapeutic drug Dox. Although Dox reduces tumor mass, he found that stem-like cell numbers increased after therapy, indicating that Dox alone is completely ineffective in removing cancer. In contrast, a Dox-3-BrOP cocktail was more effective than either alone, suggesting that subpopulation phenotype is an important consideration in formulating therapeutic techniques.

Cancer cell metabolism and the tumor microenvironment

Siv Sivaloganathan (University of Waterloo)

Dr. Sivaloganathan is concerned with integrating dynamics at several scales to understand biology. In this talk he discussed μm scale modeling of pO_2 and pH surrounding blood vessels, to better understand the tumor microenvironment. The main topic of the talk was a plateau in pH contrasted with steadily decreasing pO_2 as distance from the tumor increases, and his goal was to describe and understand this phenomenon.

To address the question, Dr. Sivaloganathan constructed a hybrid ODE / cellular automaton model representing the metabolism of individual tumor cells. Inputs to the model are nutrient availability, which he adjusted to match experimental data. The model showed that as distance from a blood vessel increases, oxidative respiration and aerobic glycolosis reverse in importance, and that the point where this occurs corresponds to the observed pH plateau. The conclusion is that metabolic byproducts of the less efficient glycolosis underly the phenomenon.

Oncogenic disruption of circadian rhythm and opportunity for chronotherapy

Brian Altman (Abramson Family Cancer Research Institute, University of Pennsylvania Perelman School of Medicine)

Circadian rhythm modulates the cellular processes involved in cancer pathology, and Dr. Altman argues that effective cancer treatment must take these effects into account. He also suggests that a principal component of cancer pathology is disruption of normal circadian processes.

To support the latter argument, Dr. Altman identified a circadian effect of MYC which is overexpressed in many cancers. MYC binds to the same sites as CLOCK, a key gene in circadian rhythm. This may explain the apparently paradoxical overexpression of MYC, which also upregulates tumor suppressors downstream of it in the network. By disrupting the circadian rhythm, MYC prevents the normal 'resting' phase of cells and promotes proliferation. To support this argument, Dr. Altman assayed MYC knockout and MYC+ mutants, finding ATP / AMP oscillation in the knockout which were not present in the MYC+ model. Overall, there were many fewer proteins that oscillate in the MYC+ cells.
Current chronotherapy is aimed at making traditional chemotherapy less toxic to the patient. By identifying the phase of protein oscillation in MYC-overexpressing cells, Dr. Altman argues that chronotherapy also provides a way to more directly target tumor cells with chemotherapy.

Modeling glycolosis of cancer cells
Rafael Moreno-Sánchez (Instituto Nacional de Cardiologia and Universidad Nacional Autonoma de Mexico)
Dr. Moreno-Sánchez began by addressing the "Warburg Hypothesis," that cancer is caused by the replacement of respiration by glycolysis. After confirming that glycolytic metabolism is increased in cancer cells, he then presented lots of data showing that respiration is also increased. The conclusion is that mitochondrial damage likely plays a much smaller role in cancer pathology than previously thought.
In the second part of his talk, Dr. Moreno-Sánchez presented a kinetic model of glycolosis, describing the key steps in its construction:

- Determination of forward and backward rate constants in the relevant kinetic equations
- Scaling the model for consistent units, distinguishing between mg cytosolic protein and total cellular protein
- Calibrating activity levels for the correct cancer to be modeled
- Constructing rate equations using reversible Michaelis-Menten formalism and Hyperbolic models
- Using COPASI software to implement and analyze the model
- Iterating these steps until the model is accurate

Dr. Moreno-Sánchez finished his talk by emphasizing that for glycolosis dependent cancers, rate constants must be measured because they are likely to differ from those in healthy cells.

Stoichiometric and ensemble modeling of respiro-fermentation
Krishna Mahedevan (University of Toronto)
Dr. Mahedevan presented results from metabolic modeling at the genome scale, with stoichiometric constraints. The model he described includes all known chemistry involved in a given genetic network, including intermediate steps, and enforces a stoichiometric balance constraint on the variables. Such constraints allow solutions of the model to be cast as optimization problems, where the variable to optimize is chosen to be growth in the case of cancer modeling.
The model predicts that the balance between glycolysis and respiration is limited by the fixed surface area of a cell; glucose uptake replaces much of the oxygen intake in the tumor cell environment. Dr. Mahedevan went on to suggest that surface area constraints may have been an early factor in the evolution of mitochondrial membranes. Dr. Mahedevan then described attempts to explain the Crabtree Effect using such 'membrane economy' models, as well as studies to find effective targets for cancer therapy.
The final portion of the talk addressed the concept of an ensemble model, where unknown rate parameters are sampled randomly to create many different models. The models are then screened

according to experimental data to find particular combinations of parameters which produce 'good' output. This provides a basis for further experimentation.

Systems biology and the challenges for elucidating the role of biological networks in cancer
Osbaldo Resendis-Antonio (Computational Genomics Consortion, Instituto Nacional de Medicina Genomica)
Dr. Resendis-Antonio placed the modern 'tsunami of data' in the context of rapid advances in technology, and described approaches for integrating such large data sets, including thermodynamic, 'top-down', and 'bottom-up' approaches. He also described methods for detecting 'module structures' within biological networks (essentially cluster detection). Dr. Resendis-Antonio's talk was largely an overview of many types of models that have been developed at many different scales, including the evolution of cancer models over time.

Thursday, March 26

Relating cancer cell heterogeneity to drug resistance
Steven Altschuler (University of California, San Francisco)
Cancer cell populations can be highly heterogeneous. In this talk, Dr. Altschuler discussed progress in understanding the origins of this heterogeneity and its implications in predicting drug response.

Warburg and Tumor Metabolism Revisited – Hexokinases, Glycolosis, and the Metabolic Gestalt of the Cell
R. Brooks Robey (Research & Development Service, Veterans Affairs Medical Center)
Nearly a century has elapsed since Warburg and colleagues first applied contemporary manometric techniques to the biochemical characterization of cancer metabolism. Their studies identified several cardinal features of tumor metabolism, most notably increased glucose-derived lactate generation in the presence, as well as the absence, of O2 - or so-called aerobic glycolysis. Recent advances in our understanding of the relationship between metabolism and cell survival and a resurgent interest in targeting cancer metabolism for therapeutic benefit have refocused attention on the characteristic features of cancer that Warburg described, as well as their mechanistic underpinnings. Hexokinases catalyze the first committed step of glucose metabolism, are overexpressed in cancer, and have emerged as important mediators of the anti-apoptotic effects of growth factors and Akt. They also directly contribute to the signature glycolytic phenotype of tumors. The ability of hexokinases to prevent apoptosis is mediated, in part, by direct physical and functional interaction with mitochondria and competition with pro-apoptotic Bcl-2 proteins for binding to common mitochondrial target sites. Bound hexokinases also facilitate the exchange of adenine nucleotides and other anionic metabolites into and out of mitochondria, thereby promoting mitochondrial integrity and directly coupling the metabolism of glucose in the cytosol to terminal substrate oxidation and oxidative phosphorylation within mitochondria. This and closely related forms of metabolic crosstalk play important roles in the coordination and control of intra- and extramitochondrial amphibolic metabolism and contribute to the characteristic proliferative and metabolic phenotypes of cancer cells. Considered in the context of the metabolic gestalt of the cell, these coupling mechanisms may also constitute attractive potential targets for therapeutic cancer intervention.

The influence of mathematics on medicine and public health
Avner Friedman (The Ohio State University)
In this talk Dr. Friedman gave two examples: atherosclerosis/cholesterol modeling, and kidney fibrosis, based on two papers we published this year with MBI postdoc Wenrui Hao. The first paper develops

cholesterol guidelines (we call it "risk map") more refined than those suggested by the American Heart Association. The second paper opens the possibility of monitoring the disease of kidney fibrosis without the need to do repeated biopsies. Both models are described by systems of PDEs. The models also offer possible treatments, but human data will be needed in order to verify the conclusions of the models.

Phenotypic diversity and population growth in fluctuating environments
Christian Mazza (University of Fribourg)
Organisms in fluctuating environments must constantly adapt their behavior to survive. We consider strategies where cells switch their phenotypes randomly or use costly sensing mechanisms to respond optimally to environmental changes . The strategies are compared using net growth rates and Lyapunov exponents for models involving random differential equations and branching processes in random environments.

Quantitative imaging to drive biophysical models of tumor growth
Thomas Yankeelov (Vanderbilt University)
The ability to identify, early in the course of therapy, patients that are not responding to a given therapeutic regimen is highly significant. In addition to limiting patients' exposure to the toxicities associated with unsuccessful therapies, it would allow patients the opportunity to switch to a potentially more efficacious treatment. In this presentation, we will discuss ongoing efforts at using data available from advanced imaging technologies to initialize and constrain predictive biophysical and biomathematical models of tumor growth and treatment response.

Evaluating glutamine addiction in gliomas using PET imaging
Sriram Venneti (University of Michigan)
Cancer cells commonly undergo metabolic reprograming enabling increased nutrient use to fuel their growth and proliferation. The Warburg effect is the classic example wherein tumors exhibit enhanced glucose uptake and metabolism through aerobic glycolysis. This increase in glucose uptake can be evaluated in vivo using positron emission tomography (PET) imaging with the glucose analogue 18F-fluorodeoxyglucose (18F-FDG). 18F-FDG PET imaging is a valuable clinical tool and is routinely used in diagnosing, grading and staging cancers. However, 18F-FDG is of limited value in evaluating gliomas in vivo due to high background glucose metabolism in the normal brain resulting in suboptimal tumor delineation. Glutamine is the most abundant amino acid in the plasma and many cancers are addicted to glutamine for their survival. We have recently developed 4-18F-(2S,4R)-fluoroglutamine (18F-FGln) for PET imaging in vivo. We evaluated glutamine uptake using PET imaging with 18F-FGln in vivo in glioma animal models to demonstrate that 18F-FGln showed high uptake in gliomas but minimal uptake in the normal brain, enabling clear tumor visualization. We translated these findings to human glioma subjects where 18F-FGln showed high tumor/background ratios in human glioma patients with progressive disease in contrast to that observed with 18F-FDG. These data suggest that 18F-FGln is specifically taken up by gliomas, can be used to assess metabolic nutrient uptake in gliomas in vivo and may serve as a valuable tool in the clinical management of gliomas.

Metabolic Pathways and the Restriction Point in the Cell Cycle
Baltz Aguda (Founder & CEO, Disease Pathways, LLC)
The Restriction Point (RP) is a checkpoint in G1 phase that marks the transition from growth factor-dependent to growth factor-independent cell cycle progression. Its core switching mechanism involves cyclin E/CDK2, the retinoblastoma protein, and transcription factors E2F and MYC. Models of RP dynamics that we and others have proposed earlier do not explicitly consider the bioenergetic and biosynthetic

processes that drive the cell cycle. In this talk, I will discuss the links among RP, glycolysis and glutaminolysis, and then explore the potential control points in the expanded network.

Friday, March 27

Reverse engineering signaling pathways in cancer cells: Effects of honokiol on the notch signaling pathway as a case study
Santiago Schnell (University of Michigan)
The ability to accurately infer an intracellular network from data remains a significant and difficult problem in molecular systems biology. We developed a novel network inference methodology that integrates measurements of protein activation from perturbation experiments. The approach was validated *in silico* with a set of test networks and applied to investigate the effects of honokiol on the notch signaling pathway in SW480 colon cancer cells. Our methodology relies on logic-based networks to provide a predictive approximation of the transfer of signals in a network. The method can also be leveraged to identify additional perturbation experiments needed to distinguish between a set of possible candidate networks. The development of methodologies that permit the accurate prediction of connectivity in dysregulated pathways may enable more rational determination of what therapy is best for a patient.

Modeling intermitotic time distributions
Rachel Leander (Middle Tennesee State University)
Cell division is one of the most fundamental processes of life, yet it is subject to significant random variation. Experiments have shown that, even in a population of homogeneous cells, the distribution of intermitotic times (IMTs) is highly variable. Furthermore, IMT distributions exhibit interesting temporal dynamics, especially in response to perturbations such as drug treatment. Using a top-down approach, we have developed a stochastic model of the cell cycle that is based on the cell cycle check point. This model enables us to frame the problem of determining a cell's IMT as a first exit time problem, through which we derive an expression for the distribution of IMTs. This distribution can be analyzed in order to relate distribution properties and dynamics to model parameters.

Workshop 7: Stem Cells, Development, and Cancer
(April 13-17, 2015)
Organizers: Heiko Enderling (Moffitt Cancer Center), Thomas Hillen (University of Alberta), John Lowengrub (University of California, Irvine)
Report By: Joshua Chang, Kimberly Fessel, and Jae Kyoung Kim

MONDAY, APRIL 13, 2015

Development undone: How cancer cells hijack stem cell pathways to sustain plasticity
Lynne-Marie Postovit (University of Alberta)
Dr. Postovit began her talk by providing an overview of the metastatic process. She explained that metastasis is highly inefficient in that many cells die during the transition between the primary and secondary tumor sites; survival of this process requires cells to possess many strong attributes, perhaps most importantly adaptability. Cancer cells achieve this adaptability by promoting plasticity (pluripotency) and thus obtain a selective advantage. Dr. Postovit's work focuses on specifically how cells acquire and sustain plasticity, and she claims that the signaling factor Nodal is critical to this process leading to tumor aggressiveness. Her biological experimentation has shown that Nodal enriches for cancer stem cell phenotypes, that blocking Nodal reduces tumor invasion, and that Nodal increases

micrometastatic growth. She concluded her talk with a discussion about why Nodal is overexpressed in these aggressive cells, particularly due to hypoxia and microenvironmental stress. She also mentioned that Nodal is not regulated by Lefty proteins in tumor progression, as it is in embryonic development, and thus leads to uncontrolled cancer growth.

Cancer stem cells discovered… Mathematically
Leonid Hanin (Idaho State University)
Cancer stem cells are considered highly tumorigenic with self-renewal and metastatic capabilities. To study these properties, Dr. Hanin has proposed a model for primary and secondary tumor growth. He bases his probabilistic model on clinical realities, including such values as minimal tumor detection size, and he composes an explicit formula for the probability distribution of the expected sizes of metastatic growths. Since his model includes many parameters, he has also considered parameter identifiability, and he ultimately optimizes his parameter set with a maximum likelihood estimate using patient-specific data. His findings indicate that a small self-renewing subpopulation must exist; that is, he demonstrates the existence of cancer stem cells mathematically. His other results predict that a large primary tumor may actually suppress small lung metastases and that metastases often occur before the primary tumor is detectable. This latter discovery implies that early detection with resection alone will not help some patients since secondary tumors have already begun forming; rather, a systemic approach should be used at the beginning of treatment in these cases.

Mathematical models of chronic lymphocytic leukemia (CLL)
Dominik Wodarz (University of California, Irvine)
Dr. Wodarz characterized chronic lymphocytic leukemia (CLL), which is the most common form of leukemia in adults and usually presents asymptomatically. The varying forms of this disease result in different levels of impairment, and Dr. Wodarz has built a mathematical model to determine why some instances lead to a chronic disease state while others are transient. His resulting model for the cancer lineage subpopulations uses telomere length to classify cells and to quantify risk. He investigates disease kinetics with this model and assesses CLL treatments virtually. One type of CLL therapy he studies is the chemo-immunotherapy drug ibrutinib, which causes temporary increases of CLL cells in the blood but eventual decline. He seeks to understand if the CLL cells actually die or if they are merely redistributed during treatment. He further considers the evolutionary dynamics of ibrutinib drug resistance with a stochastic form of his CLL model on virtual patients. Overall, Dr. Wodarz achieves a wide variety of relapse times for his virtual population but can predict more accurate personalized times via his mathematical model.

Stem cell dynamics in human colon crypts and the therapy and prevention of cancer
David Axelrod (Rutgers University)
Cells in the human colon crypt are spatially stratified. Quiescent stem cells lie near the bottom of the crypt, followed by proliferating stem cells, and then differentiated cells near the top. Dr. Axelrod seeks to quantify the number and location of each of these groups using an agent-based model in the form of a virtual crypt. He specifies rules for the proliferative capacity and movement of each cell type and then observes the emergent behaviors. Dr. Axelrod explained that, in the context of his model, cell type (stem, non-stem, etc.) is not an intrinsic property, but rather a response to microenvironmental cues. For parameter quantification, he uses specimens biopsied by a collaborator to calibrate his virtual crypt. He then looks at model applications for cancer therapy and prevention. From this, Dr. Axelrod can suggest effective schedules for fractionated radiation therapies or perhaps the use of oral pharmaceuticals to increase death of mutated colon cells near the top of the crypt thereby avoiding cancer formation.

Major genes in colorectal cancer

Avner Friedman (Mathematical Biosciences Institute, Ohio State University)

Genes are considered major if they are necessary and sufficient for disease causation; scientists associate five such genes with colorectal cancer including p53, APC, and SMAD. Furthermore, patients with ulcerative colitis or Crohn's disease carry a higher risk for colon cancer due to disruptions in the colon mucosa. Dr. Friedman mathematically models the early stages of colon cancer in these patients by investigating how mucosa deterioration depletes the body's natural protection from tumor formation. He considers a simplified geometry where the middle of colon crypt is represented by flat layers. Using a system of coupled ordinary differential equations to track inflammation, MUC1, MUC2, beta-catenin, and the size of the cancer, Dr. Friedman finds the number of cells mutated at the p53 gene to be a highly important parameter. Various checkpoints for cellular overpopulation and hypoxia exist within the body; however, cancer appears to evade these controls. Dr. Friedman incorporates genetic mutations to APC as a disruption to the population-size checkpoint while mutations to SMAD cause a disruption of the oxygenation checkpoint. In his PDE, free-boundary model, he has shown that if both mutations occur, the colon tumor can grow indefinitely. Mutations to only one of these controls, however, may lead to a roughly constant-sized tumor.

TUESDAY, APRIL 14, 2015

Analysis of mutations leading to the myelodysplastic syndrome (MDS) using modified Moran models

Marek Kimmel (Rice University)

Dr. Kimmel's research focuses on how various types of mutations give rise to the development of myelodysplastic syndrome (MDS), in particular, how driver and passenger mutations lead to different varieties of this disease. Dr. Kimmel introduces compartments for bone marrow, peripheral blood, and body tissues in his model for MDS, and he uses his system of equations to explain the disease phases: birth, early severe congenial neutropenia (SCN), intermediate SCN, and eventual acute myeloid leukemia (AML). He additionally investigates the application of hormone therapy, which yields changes in the cellular proliferation rate. Using a discretized Moran process, Dr. Kimmel finds two absorbing states and then determines the expected time to fixation. He calculates the most probable paths for the order of the mutations and likely temporal trajectories for the size of the mutant population. Dr. Kimmel has also extended his model to include spatially heterogeneous bone marrow, and he concluded his talk by showing that there exists a trade off between the selective advantage of mutated cells and the separation of various cell types.

The dynamic complexity of brain tumor stem cells

Jeremy Rich (Cleveland Clinic)

Dr. Rich is a medical doctor specializing in neuro-oncology research. He addressed the audience with a clinical description of brain tumors and cancer stem cells. Though researchers have stratified brain tumors into four different types, these grades do not truly correlate with patient prognoses—primarily because metastatic events are known to cause most cancer-related deaths. Metastasis formation appears to be linked to neoplastic cancer cells, and moreover, the molecular regulators associated with induced pluripotency (dedifferentiation) are also linked with cancer. Unfortunately, blocking specified dedifferentiation pathways might not eliminate the risk of cellular reprogramming because cells may find a new path to the same pluripotent state. Nonetheless, Dr. Rich investigates the differences between normal and cancerous stem cells including changes to the STAT3 pathway and the output of gaseous signaling molecules, such as nitric oxide. Dr. Rich closed by reviewing several key properties (such as feedback cues, pH, and mitochondria life cycles) that may prove crucial in the development of effective

cancer therapies. He also called for the consideration of these features in future models for cancer stem cell activity.

New open source tools for simulating large 3D multicellular systems on the desktop
Paul Macklin (University of Southern California)
Cell and tissue mechanics within solid tumors are incredibly complicated, and models of such may require incorporation of necrosis, calcification, hypoxia, inflammation, and cellular signaling as well as a host of other biological phenomena. Dr. Macklin presented his numerical framework for investigating tumor evolution via agent-based models. His program, PhysiCell, offers many capabilities for tackling off-lattice models, fluid and solid ODE models, computational parallelization, and the wide range of parameters necessary for characterizing necrosis, apoptosis, etc. Dr. Macklin's technique can handle both large numbers of cells and complicated geometries, and he verified these assets by demonstrating one simulation that tracked 500,000 cells and another that detailed a glandular structure. He also described his finite-volume method, BioFVM, for realistic biological problems such as modeling colon cancer metastases in the live. Lastly, Dr. Macklin explained MultiCellDS, a data library being developed to encourage researchers to explicitly organize and share their multicellular modeling efforts. He ended by asking for audience feedback and suggestions for database design.

Replicative senescence and cancer
Ignacio Rodrigues-Brenes (University of California, Irvine)
Dr. Rodrigues-Brenes talked about the role of replicative senescence in cancer. Replicative senescence is the loss of cell division caused by shortage of telomeres. Since telomerase enzyme can extend telomere length, stem cells and majority cancer cells express the enzyme, explaining their unlimited division. Thus, replicative senescence can act as a potent tumor suppressor pathway. To investigate this, he developed the cell-lineage model based on concepts of fitness in evolutionary theory and cellular replication limits. He found transient and persistent nature of cell-lineage. By using a Moran process, he found that replication limits reduces the chance of 2^{nd} mutations during first year and after 10 years with no rep limit, the mutation chance increases. This result is also confirmed via agent model validation. Furthermore, he found that if the mutation originates in stem-cells long-term persistence is likely, which poses a significant risk for progression to cancer. On the other hand, if the mutation originates in progenitor cells, the presence of mutation is likely to be transient, which reduces the risk of disease development. Finally, he discussed about the anti-telomerase therapy.

Modeling effects of the tumor microenvironment on brain tumor stem cell phenotypes
Anita Hjelmeland (University of Alabama)
Dr. Hjelmeland talked about how physiological microenvironment can be a marker for brain tumor stem cells. First, she talked about the benefits and challenges in collaboration between biologists and mathematicians and listed the measurable parameters in vitro and in vivo. Then, she talked about a cancer stem cell marker for glioma, Sox-2. Using this marker, she was able to find that glioma stem cells reside in niches. She also found that microenvironments present in the niche regulate glioma stem cell phenotypes: hypoxia. Furthermore, she found that low glucose levels indicate tumor in brain, and reprogramming events occur more rarely in non-GSCs. This is further validated with multiphoton imaging of glioma stem cells glucose uptake in brain. Finally, to find a novel target of glucose restriction, she used Knome Arrays and found preferential effects of a small molecule inhibitor in restricted glucose. Since glioma stem cells are radioresistant, targeting glioma stem cells can provide a novel therapy.

Mathematical models of oncolytic virus therapy and characterization of the invasive and non-invasive glioma: How to eradicate invasive glioma cells?

Yangjin Kim (Konkuk University)
Dr. Kim talked about a mathematical model of Chase-ABC mediated oncolytic virus therapy targeting cancer stem cells and glioma infiltration. Oncolytic virus therapy uses engineered virus to kill cancer cells while having minimal damage on normal cells. To make the oncolytic virus therapy effective, the virus should spread in cancer cells, which can be inhibited due to glioma external cellular materials (ECM). Thus, Chase-ABC, a bacterial enzyme has been proposed to remove the ECM, helping the spread of the viruses. He presented a mathematical model describing the effect of the Chase-ABC on the oncolytic virus treatment for glioma. With this model, he discussed various treatment options.

WEDNESDAY, APRIL 15, 2015

Reconstructing the in vivo dynamics of stem cells from telomere length distributions
Benjamin Werner (The Institute of Cancer Research)
Dr. Werner talked about how telomere length distribution can be used to reveal the stem cell dynamics. Specifically, he discussed about the stem cell divisions in the human hematopoietic system throughout life. By analyzing the shape of telomere length distributions underlying stem cell and using the mathematical model, he can reveal the initial telomere length and progressive telomere lose. These match with data from adult, but not young age people. While finding the reason for the observed discrepancy, he was able to find that an increasing stem cell pool during childhood and adolescence. This method also allows the detection of individual differences from a single tissue sample. Furthermore, he discusses how his work can be used to understand the acute promyelocytic leukemia, which occurs dominantly in early age.

Neurogenesis and tumor metastasis: Myth or reality?
Arianna Bianchi (Heriot-Watt University)
Dr. Bianchi examined the role of the autonomic nervous systems in tumor development and metastasis. She presented that the nervous systems affects the tumor development both indirect and direct ways. Indirect regulation includes perineural invasion, and immunosuppression. Direct regulation includes neurotransmitters, which inducing proliferation and migration of tumors. Tumors also can affect the development of nervous systems via NGF (nerve growth factor) and AGM (Axon guidance molecule). Based on these interactions, she developed the first model of the neuro-neoplastic synapse, giving good qualitative results although it is simple.

Stochastic models of stem cell dedifferentiation in cancer
Sasha Jilkine (University of Notre Dame)
Dr. Jilkine talked about the effect of dedifferentiation of progenitor cells on cancer. Specifically, she tried to answer, “which is more likely cancer cell of origin between stem cells or dedifferentiation of progenitor cell?” Via comparing the models having different regulations of homeostasis of stem cells, she found that the effect of dedifferentiation depends on how the stem cell numbers are controlled. That is, she found that if homeostasis is regulated tightly via asymmetric divisions, the dedifferentiation has little effect. However, if the stem cells can divide via both symmetric and asymmetric, the dedifferentiation can slows down cancer cell onset and lead to exponential growth of cell population. Finally, she also discussed the effect of negative feedback loops from the progenitor population on stem cell population.

Acute and fractionated irradiation differentially modulate glioma stem cell division kinetics
Heiko Enderling (Moffitt Cancer Center)
Dr. Enderling discussed the radiation response of glioblastoma multiforme (GBM). GBM is one of the most aggressive human malignancies with a poor patient prognosis. Specifically, he investigated how tumor

grows and radiation response change in the presence of glioma stem cells (GSC), which have ability to self-renew and repopulate the tumor and have been reported to be less sensitive to radiation- induced damage. For this, he used integrated approach between modeling and experiments. He found that his agent based model, which consist of glioma cell and glioma stem cell, behave very different depending on parameter selection. Thus, experiments were used to calibrate parameters (e.g. proliferation rate and migration rate). Based on this, the model allows the estimation for the frequency of symmetric GSC division events. Furthermore, to explain the discrepancy between simulations and experimental data regarding fractionated radiation dose response, he found that increased self-renewal rate upon DNA damage is required in the model. Thus, the model hypothesize a constitutive activation of stem cell division kinetics signaling pathways during fractionated treatment, which contributes to the frequently observed accelerated repopulation after therapeutic irradiation.

Mathematical models for anisotropic glioma invasion: a multiscale approach
Christina Surulescu (Felix-Klein-Zentrum fur Mathematics)
Dr. Surulescu presented her multiscale model of glioma invasion. Glioma is a broad class of brain and spinal cord tumors arising from glia cells, which are the main brain cells that can develop into neoplasms. Since they are highly invasive they are hard to remove by surgery, the understanding of glioma spread patterns is hence essential for both radiological therapy as well as surgical treatment. Thus, she developed multi-scale mathematical model describing the glioma-spread patterns. The model describes the microscopic dynamics, including receptor binding, and mesoscopic dynamics, such as cell migration. Furthermore, go-or-grow type mechanisms are included to describe the tumor proliferation. By deriving the effective model on the macroscale, she was able to simulate the evolution of the tumor cell population.

The Role of Wnt Signaling in Stem Cells and Early Colorectal Cancer
Helen Byrne (Oxford University)
Dr. Byrne talked about mathematical models of Wnt signaling, with particular focus on the intestinal crypt, stem cells and the early stages of colorectal cancer. Wnt signaling regulates the proliferation, apoptosis, migration and differentiation of epithelial cells that line intestinal crypts. First, she found that the intestinal crypts are monoclonal by using the multiscale model describing the mechanistic interactions among neighboring cells and Wnt signal depending stochastic cell division. She also discussed what properties mutant cell need to establish itself in the crypt. Finally, she talked about how cross talk between Wnt and Delta-Notch signaling affects the dynamics of normal and mutant cells.

THURSDAY, APRIL 16, 2015

Parameterizing spatial-temporal models from image information
Dirk Drasdo (Institut National de Recherche en Informatique et en Automatique (INRIA))
In his talk, Dr. Drasdo discussed how image data can be used to test hypotheses of biological systems, guide experimental strategies, and predict in-vivo behavior given in-vitro observations. His main example was understanding liver damage due to acetaminophen overdose. From confocal micrographs, three-dimensional volume datasets are constructed. Then, specific physical parameters are extracted from the images. The extracted parameters, and/or the reconstructed image, are then used in the multi-scale agent-based model simulations. These simulations were used to examine several different hypotheses. The simulations validate the hypothesis that hepatocyte division occurs along the closest blood vessel. They also examined HGF-dependent DNA synthesis in order to more-understand the timing of hepatocyte proliferation. They used this theoretical work to compute the most-likely shape of liver lobules. Combining the growth models for all the various cell-types produces a multi-scale tissue

model that Dr. Drasdo's group simulated. They used this model to examine the question of the HFG source and the timing of its release. They found that the HGF source is likely from the portal vein. They also found that the timing of the release is fairly early, about six hours. His group also found that cell cycle reentrance depends on metabolic factors such as ECM and ATP, and death depends on ATP and waste.

Empirical sampling of single cell events predicts xenograft behavior
Alexander Pearson (University of Michigan)
In this talk, Dr. Pearson discussed issues around evaluating treatment strategies for ovarian cancer. The primary tool used in the research presented in this talk was xenografts of cancer cells grown in cellular media. Using a single-cell microfluidics capture chamber, single cell divisions are visible under different combinations of treatment media and stem cell markers. Under these experimental set-ups, kinetic parameters of cell division are easily measured. These parameters can be used in modeling efforts to determine tissue-level growth of tumors, for instance using stochastic Markov chains or deterministic ordinary differential equations. Using a combination of these methods, Dr. Pearson's group looked at the development of ALDH+ primary ovarian cancer cells, compared to the ALDH- control group. They were about to compute growth curves for each of these groups under various treatments.

An in-silico investigation of niche-driven cancer stem cell plasticity
Noemi Picco (Moffitt Cancer Center)
In this talk, Dr. Picco examined the question of what induces and maintains the "stemness" nature of cancer cells. Dr. Picco devised a hybrid agent-based model where cells move divide and differentiate subject to external environmental cues that are represented by continuous variables. In this model, cells sit at positions in a two dimensional lattice. The continuum models are associated with reaction diffusion equations. The ECM is also modeled in this framework, and motion is subject to ECM integrity. The model parameters relate to dedifferentiation threshold, persistence, and memory, which is linearly related to the threshold. In these models, the signal for dedifferentiation is invoked by cell death. As an example, Dr. Picco simulated a well-differentiated breast cancer where there is very high threshold before dedifferentiation and low memory. In this case, there is not enough dedifferentiation to sustain a stem cell niche. In the second case, for a moderately differentiated breast cancer where the threshold is not as high, there is enough signal of dedifferentiation locally to trigger "stemness" and feedback towards more stemness. In the final extreme case where the threshold is low, all cells always proliferate and maintain the stemness property. Dr. Picco explored the entire parameter space and characterized each combination of the three parameters in terms of the three different types of outcomes.

Data-driven mathematical modeling of mammary ductal elongation
Michael Lewis (Lester and Sue Smith Breast Center)
In this talk, Dr. Lewis gave an overview of breast cancer, noting that breast cancer is not a single disease but a combination of many separate disease processes. Cancer can be thought of as a continuum of diseased states. As related to breast cancer, Dr. Lewis gave an overview of the development of the breast, including the various cell types that differentiate in order to produce the mammary glands. Different cancer types arise as a result of different origin cells. Ductal elongation is a phenomenon that occurs often in breast cancer. A model of ductal elongation, tracking birth, death, and migration of cells was presented. The model was parameterized using measurements of mammary glands, taken for several weeks. The mathematical model, compared to the results of experiments, indicated that the understanding of cell death as represented in the model is incomplete. This model was substantially improved by incorporation of structural growth bifurcations. Through modeling, his group also determined that tumor-initiating cells lie close to blood vessels.

Mathematical models of heterogeneity, clonal selection and therapy resistance in acute leukemias
Anna Marciniak-Czochra (Heidelberg University)
Acute Myeloid Leukemia (AML) is associated with the presence of clonal selection. Dr. Marciniak-Czochra presented her work focused on a particular cell lines involved in AML. Experiments have found that all cells contributing to the cancer model originate from as little as three to five clones. It has also been shown that during relapse, the number of clones is similarly small, and not necessarily the same as the clones involved in the original cancer diagnosis. In her models, healthy cells and leukemic cells are tracked. Behaviorally, a Lyapunov function was found and non-trivial steady states and stability were assessed. The models indicated that self-renewal is essential for cancer. Self-renewal of the cancer cells destabilized the healthy steady state condition, leading to the development of cancer. This model was used to examine various therapies. Clonal selection is likely due to non-local feedback, and therapy can lead to the selection of more-aggressive clones. The model indicates that a lower-dose treatment introduced iteratively can be a good option for treating cancer without relapse.

Evolution and phenotypic selection of cancer stem cells
Jan Poleszczuk (Moffitt Cancer Center)
Cancer cells, even within the same tumor, can vary wildly in the kinetics of their population dynamics. Some of the sources of this variation include age and origin tissue. Different organs of different have an intrinsic set of kinetics that dictates their behavior. Transformation into cancer cells will inherit these kinetics that determine initial cell and tumor population progression dynamics. The question then is how a clinician can optimally perform a biopsy to obtain a relevant sample of the growing tumor. In Dr. Poleszczuk's talk, he discussed how sampling angle affects the type of sample obtained in a biopsy. Different angles tend to give different types of cells - more glancing angles tend to give samples that contain the more-malignant cells. The clonal diversity that is captured in a single typical tumor biopsy represents only a small proportion of the total phenotypes present in a cancer. The optimal sampling strategy hence samples not perpendicular to the edge of the tumor, but has good representation of the radial components.

FRIDAY, APRIL 17, 2015

Mathematical modeling of phenotypic switching in cancer
Mohammad Kohandel (University of Waterloo)
In his talk, Dr. Kohandel presented a nuanced discussion of the cancer stem cell (CSC) hypothesis. According to the CSC hypothesis, in addition to their self-renewal, CSCs, as defined by their biomarkers, can undergo symmetric or asymmetric "unidirectional" divisions to generate daughter cells with low tumorigenic potential (non-CSCs). Furthermore, cancer stem cells are often believed to the sole source of malignant cancer cells. Using stochastic simulations, Dr. Kohandel's group studied the CSC hypothesis in the context of tumor hypoxia and treatment. The cancer stem cells were given different treatment sensitivities relative to the non-stem cancer cells. Similarly, the dynamics of the cells in the hypoxic niches were modified. A similar model using a system of ODEs also included dedifferentiation. It found that there is a shift towards higher expression of particular cell markers. Yet, there are also other cancer stem-like mimicry cells that proliferate without presenting the classical stem cell markers. Due to death of non-resistant cells, these cells proliferate even in treatment conditions. As a result, there is an overall phenotypic switch in the tumor.

On a mathematical model of cancer stem cells with non-local terms
Jose Ignacio Tello (Universidad Complutense de Madrid)

Metastasis is the process of the escape of cancerous cells from tumors to surrounding tissue. In this talk, Dr. Tello presented a hybrid Eulerian-Lagrangian model for cancer stem cell metastasis. They key feature of his model is a stem cell niche, which maintains the population of stem cells. These cells are given a small probability of escaping the niche, whereby they follow chemical gradients and move along blood vessels. After leaving the niche, hematopoietic cells can leave the blood vessels and return to the niche, affecting the equilibration of osteoblasts in bone, potentiating bone mineralization. Another key feature of this model is fluid in the bone, whose velocity is modeled. The resulting coupled system of PDEs for progenitor cells, differentiated cells, and cancer stem cells had coefficients that were determined through balance arguments and from patient data. Numerical simulations showed that cell populations tend to go to more-homogeneous distributions, while the tumor grows exponentially.

Mathematical modelling of the tumor growth paradox and more…
Thomas Hillen (University of Alberta)
The tumor growth paradox is a name given to counter-intuitive phenomenon of persisting post-treatment cancer cells growing to tumors of sizes larger than the pretreatment tumor. In this chalk talk, Dr. Hillen discussed this paradox using mathematical modeling and associated analysis. The tumor growth paradox was given as a mathematical definition by linking death rate of non-stem tumor cells to resulting tumor growth rates. A tumor is said to satisfy this paradox if there exists a tuple of death rates such that the larger death rate is associated with quicker tumor growth. As a model to investigate this paradox, Dr. Hillen introduced the birth-jump process. This process is a system of two integro-differential equations where the integral kernels represent growth of the tumor in the presence of crowding effects. Numerical investigation of these equations showed the existence of solutions satisfying the paradox. Reduction of this system to ordinary differential equations greatly simplified the analysis, and a proof of existence of this paradox was given. Dr. Hillen presented results of these models as applied to head and neck cancers. His group investigated the benefit gained by coupling a differentiation promoter combined with radiation. They found that a differentiation promoter can have a drastic effect, allowing for reduction in radiation.

CTW Evolutionary Game Theory
April 27 – May 1, 2015

Organized by: Andrew Belmonte (Pennsylvania State University), Vlastimil Krivan (University of South Bohemia), John Nagy (Scottsdale Community College), Zhijun Wu (Iowa State University)
Reported by: Noelle Beckman, Leili Shahriyari, and Richard Buckalew

Monday, April 27, 2015

Maynard Smith & Parker's (1976) Rule Book for Animal Contests, Mostly
Susan Riechert (University of Tennessee)
Maynard Smith & Parker's 1976 paper on asymmetric games offered animal behaviorists and behavioral ecologists a theoretical framework/guide to understanding animal behavior in competitive contexts. Dr. Riechert traced the influence of this 'contest rule book' from the factors that led the two researchers to develop a treatise on the logic of the asymmetric game to empirical tests of the contest rules and theoretical additions made to the basic model and its underlying assumptions. Over a thousand studies cite this paper directly and thousands more cite work spurred by the original paper. The vast majority of these studies confirm the evolutionarily stable strategy (ESS) predictions made by Maynard Smith & Parker. Theoretical and empirical deviations from EES can largely be explained by the need for further

structuring of the analyses into sub games and investigation of less obvious asymmetries than apparent size and resource value. To date, much progress has been made in three areas of interest to behaviorists: (1) understanding of the strategic nature of repeated contests between conspecifics over limited resources; (2) modelling developments that deal with how information about potential asymmetries is gained; and (3) evaluation of the question of honest signaling with specific reference to threat displays. Dr. Riechert proposed suggestions for future work, such as analysis of ESS in natural populations and extensions to interspecific, predator-prey, and non-conflict contexts. She also suggests modeling the entire game series beyond the focal game. Much of this will either require collaboration with mathematicians, or require that students interested in animal behavior obtain a strong foundation in biomathematics.

Plants play games too: How the tragedy of the commons explains much about the vegetation we see
Joel Brown (University of Illinois at Chicago)
Plant communities offer conspicuous displays of woody stems, masses of leaves, and often several layers of such vegetation. Plants in their quest to compete and reproduce seem to produce a lot of biomass. Plants play games for nutrients (belowground) and light (aboveground). The solutions to these games result from three sources of a tragedy of the commons. First, the plants over-produce roots to pre-empt each others access to water and nitrogen. Second, the plants do the same with their leaves to pre-empt access to light. And third, the plants may invest heavily in stems because the lion's share of light goes to the tallest plant. Dr. Brown and colleagues began with a simple game of belowground root production and then examine how asymmetric competition for light amplifies the tragedy of the commons. Using a Cobb-Douglas production function, they integrate roots, leaves and stem into a single model of resource allocation in response to competition. Such models can be placed within the context of population dynamics, plant number, total plant biomass and ultimately new avenues for species coexistence. Not only does evolutionary game theory assist in understanding plants, arguable a game theoretic approach may be the only way to understand some of the most important features of plants and their communities.

Foraging games between gerbils and their predators
Burt Kotler (Ben-Gurion University)
Sand dune dwelling gerbils interact with foxes, owls, and horned vipers in an environment in which resource patches renew and deplete daily. There, gerbils face tradeoffs of food and safety and must use the tools of time allocation and vigilance to manage risk. Predators must contend with gerbil behavior and manage fear using the tools of time allocation and daring. For gerbils, this means optimal patch use and optimal vigilance levels in a depleting environment over the course of the night, i.e, their harvest rates in resource patches must balance energetic, predation, and missed opportunity costs throughout the night, and their vigilance levels must balance predator encounter rate, predator lethality, and the effectiveness of vigilance and decline throughout the night as resources deplete. For predators, this means that they must choose their activity to equalize opportunity throughout the night. The consequences are that gerbil activity declines throughout the night in lock-step with predator activity and the apprehensiveness of the gerbils. Furthermore, a complete theory the predator-prey foraging game in gerbils needs to account for the following. 1. Foraging decisions of gerbils are responsive to their own state and that of their predators; owls are responsive only to their own state. 2. The state of a gerbil affects it foraging decisions, and it foraging decisions affect its state. This feedback is necessary to understand risk management by gerbils over a lunar cycle. 3. Gerbils enjoy safety in numbers, and gerbils show density-dependent patch use and habitat selection. This creates a 'risk pump' across habitats as gerbils carry safety with them as they alter habitat use. 4. Sight lines affect the quality of vigilance and risk management in response to different predators.

Different approaches to modeling foraging and predator-prey games among animals
Amos Bouskila (Ben-Gurion University)
Understanding principles and processes in ecology and evolution is not easy. Generating hypotheses and predictions in these disciplines is often not intuitive due, in part, to the many factors that may affect the outcomes of processes. Moreover, some of the situations involve games among various organisms that may lead to unintuitive results. Theoretical models may not provide proofs that we reached full understanding of the system, but they can generate testable hypotheses and predictions and can assist in the understanding of experimental results. Dr. Bouskila described different modeling approaches he and colleagues have used to investigate animal decisions in regard to foraging under the risk of predation in two systems. In the first, they interpreted the escape strategy of a lizard from an avian predator with a simple decision tree model. The second system described games among rodents and between rodents and their predators. This system begs for a game theoretic model, and two approaches will be exemplified. A static game has the advantage of simplicity. It can often be solved analytically and its results are relatively easy to interpret. Nevertheless, the simplicity has its costs in terms of realism. Some simplifications embedded in the static approach can be relaxed in a dynamic state-variable game model. These models provide refined insights and more specific predictions, taking into consideration variation in the state of the animals and its temporal dynamics.

Game theory of interactions among predators and groups of prey
Bill Mitchell (Indiana State University)
Predators allocate time among different patches of prey. Prey may move between refuges and exposed feeding areas or form a group. Dr. Mitchell used a continuous Markov process and an adaptive dynamics approach to explore the decision mechanism for group formation and movement. He found that the benefit of being in a group depends on the responsiveness of the predator, the predator's detection of prey, and the prey's detection of the predator as well as whether the dilution effect is perfect or imperfect, the distribution of food between the two patches, and the killing efficiency.

Cooperation, cheating, and collapse in biological populations
Jeff Gore (Massachusetts Institute of Technology)
Natural populations can suffer catastrophic collapse in response to small changes in environmental conditions, and recovery can be difficult even after the environment is restored to its original condition. Dr. Gore and colleagues used laboratory microbial ecosystems to directly measure theoretically proposed early warning signals of impending population collapse based on critical slowing down. Their experimental yeast populations cooperatively break down the sugar sucrose, meaning that below a critical size the population cannot sustain itself. The cooperative nature of yeast growth on sucrose makes the population susceptible to "cheater" cells, which do not contribute to the public good and reduce the resilience of the population. He used a game theoretic approach to address the influence of negative frequency dependent interactions on the presence of mixed strategies and found that negative frequency dependence is a driver of phenotypic heterogeneity in yeast.

Tuesday, April 28, 2015

Testing games of habitat selection
Douglas Morris (Lakehead University*)*
All organisms use habitat, so it is reasonable to assume that most, if not all, species engage in evolutionary games of habitat selection. A large variety of taxa occupy habitat in ways consistent with theory; thus, habitat selection appears universal, at least for motile organisms with sensory capabilities.

All organisms also consume resources, so it should be possible to test theories of habitat selection with foraging behavior. Coarse-grained field experiments confirm that invasion landscapes based on foraging behavior predict the relative abundance of meadow voles in replicated habitats. But foraging behavior in fine-grained experiments that manipulated the risks and rewards of foraging patches was not uniquely predicted by the activity-density of the voles. Harvest rates in safe versus risky patches within foraging sites mirrored visitation rates to those patches, but not at the intermediate scale where a habitat's quality was determined by more than one site. Variation in density thus appears to dictate foraging behavior at coarse-grained scales where habitat selection is resolved through dispersal from one habitat to another. At fine-grained scales, however, variation in risk and reward appear to dictate local patch use.

Optimal information use in habitat selection
Ted Galanthay (Ithaca College)
How might organisms constrained by perceptual limitations or imperfect information use available information optimally in habitat selection? To begin to answer this question, Dr. Galanthay and colleagues study a general ordinary differential equation model of a single species in a two-patch heterogeneous environment in which organisms have access to resource information. There exists a global evolutionarily stable strategy, which depends on the magnitude of the constraints and the heterogeneity of the resources, which leads to the ideal free distribution (IFD). When organisms pay a cost to travel between patches, this strategy is no longer evolutionarily stable, but a strategy that incorporates these costs and does not lead to the IFD is convergent stable.

The rock-paper-scissors game is everywhere in nature
Barry Sinervo (University of California, Santa Cruz)
The rock-paper-scissors game (RPS) in its pure form has each strategy losing to one strategy, while beating another. Here Dr. Sinervo showed that this one-population game is often modified by another population that can leverage fitness by varying present-generation choices, given the highly predictable nature of RPS cycles at future time points. For example, females should be selected to prefer rare sires to produce rare sons, given their higher fitness than common sons in the next generation of RPS competition. The action of the second population's choices can often convert the RPS game in the RPS population to an apostatic RPS game in which rare strategies are favored, but the three strategies still exhibit RPS intransitivity. Dr. Sinervo developed analytical tools for analyzing such two population interactions, and review the literature for other 3 population games. Several fish species, two birds, insects, isopods and literally hundreds of lizard species all play variations of the RPS. Dr. Sinervo also showed how other two population games generate conditions whereby one population can enforce an RPS in the other population. An example of predators feeding on cryptic types, aposematic model (defend warning coloration) and aposematic mimic (undefended cheater) was shown to perhaps reflect an RPS game when viewed from the predators perspective.

Spatial patterns and interactions in public goods games
Andrew Belmonte (Pennsylvania State University)
Dr. Belmonte started his talk by explaining The Tragedy of the Commons. Should we invest in something that is shared while we can get benefit without contributing? He then explained the mathematical set up of the public goods game. After that he presented a model that has been developed for the public goods games by Hauert, Holmes & Doebeli (2006). He also explained the model for spatial evolutionary games developed by Nowak and May (1992). Dr. Belmonte then discussed his model for the spatial evolutionary games and his developed fitness gradient equation. Then he mentioned the models by Hauert, Holmes & Doebeli (2008) and Wakano, Nowak & Hauert (2009) and compared his results with

theirs. He concluded that fitness gradient flux extends stability of Turing patterns, accelerates traveling fronts, and leads to new complex states.

Spatial Evolutionary Games
Rick Durrett (Duke University)
Dr. Durrett started his talk by introducing some examples of spatial games; Prisoner's Dilemma / Altruism, Snowdrift game, Battle of the sexes, and Stag hunt. He then explained some models for evolutionary games in cancer. He also talked about the non-spatial generalized Rock-Paper-Scissors game. He explained the voter model on d-dimensional lattice developed by Holley and Liggett (1975) and explained how recent work of Cox, Durrett, and Perkins for voter model perturbations can be applied to study spatial evolutionary games in which all relative fitness are close to 1, a situation which covers many applications to cancer. The main result was that the effect of space is equivalent to (i) changing the entries of the game matrix and (ii) replacing the replicator ODE by a related PDE. He mentioned the first idea is due to Ohtsuki and Nowak (for the pair approximation) while the second one is well known in the theory of stochastic spatial processes. Also, the limiting PDE depends on the kernel which dictates the interaction between players only through the values of two simple probabilities associated with it (an idea initially proposed by Corina Tarnita et al). However, when there are three strategies the limiting object is a system of reaction diffusion equations.

ESS for dispersal in heteregeneous environments
Yuan Lou (Ohio State University)
Dr. Lou started the talk by asking the following question "What kind of the movement strategies are optimal?" He continued by explaining the logistic model and the competition models developed by Hasting (1983) and Dockery et al. (1998). Then he presented a question asked by Fretwell and Lucas in 1970 "How should organisms distributed in heterogeneous habitat?". He discussed some recent developments on the evolution of dispersal, focusing on finding evolutionarily stable strategies for dispersal. He mentioned that the solution of the logistic models cannot reach an ideal free distribution; however, by modifying the dispersal strategies he could produce an ideal free distribution.

Understanding the occurrence of cry-wolf plants in a tri-trophic system
Kateřina Staňková (Maastricht University)
Dr. Stankova explained a tri-trophic system consisting of plants, herbivores and predators, in which plants release herbivory-induced chemical signals betraying herbivores to their predators. In this system, so-called "cry wolf" plants occur, which produce signals even when they harbor no or only few herbivores. She has developed three models using game theory, where three types of plants are players. One model is "the naive model", which is the first model related to their tri-trophic system. She has used Hamilton-Jacobi-Bellmann approach to solve this problem. The next model focuses only on the optimal behavior of predator, while this behavior is defined as probability of the signal of the cheating plant. She solved this problem in reverse time using H-J-B approach. For most parameter domains, the predator should go to the cheating plants only if the expected number of offspring from visiting cheating plants outweighs the expected number of offspring from visiting the honest plants. In the last model, she added plants as a leading player in a Stackelberg game. Then she talked about her preliminary results which were typical optimal strategies for plants and predator. The optimal strategy was "plants should all be honest or neutral. The predator's strategy should be almost immediately go to honest plants". Also in the optimal strategy, plants should have a very small portion of cheaters and gradually have only honest plants (cheaters will die anyway, but not also with some herbivores).

Wednesday, April 29, 2015

Evolutionary branching in the multivariate case

Johan Metz (Institute of Biology, Mathematical Institute, Leiden University)

After mentioning that fitness of the individuals depends on the environment in which they live, Dr. Metz talked about the characteristics of a branching point and types of singular points. He then presented monomorphic fitness functions and initial options for polymorphism. He also went over the differential equations for the trait vectors. Then he calculated the dynamics of the trait deviations, and an explicit expression for dimorphism. He proved locally-enduring coexistence under some conditions. Then he showed simulations for quadratic fitness functions with a specific set of parameters where the trajectory leaves the coexistence set. In particular, Dr. Metz showed that, as long as the evolutionary trajectory stays within the reign of the local quadratic approximation of the fitness function, any initial small-scale polymorphism around an attracting invadable evolutionarily singular strategy will evolve towards a dimorphism. That is, if the trajectory does not pass the boundary of the domain of dimorphic coexistence and falls back to monomorphism (after which it moves again towards the singular strategy and from there on to a small scale polymorphism, etc.).

Origin and Structure of Social Networks Based on Cooperative Actions

Christoph Hauert (University of British Columbia)

Dr. Hauert started by explaining simple games with infinite and finite populations. He then reviewed some of the most well known models, including the lattice game by Nowak & May (1992), and network games by Jackson et al. (2012). Some analytical results for the network games have been obtained; pair approximation by Ohtsuki et. al. (2006), inclusive fitness by Taylor et. al. (2007), and amalgamation by Debarre et. al (2014). In all of these models the separation of strategy and structure is the common. He proposed that cooperative action represented as directed links, individuals control actions and choose targets (freedom of action, Hume 1748), and then resolve dichotomy between strategy and structure. Moreover, he explained his model using strategy space and strategic types. In this model the structure encodes strategy. He then presented the results of the theoretical model for different parameter sets. They had done a social experiment with 9 groups of 20-50 students (247 total) playing donation game. Participants see only their local neighborhood, 60 rounds, and up to two adjustments of links. He concluded with the following observations: if we focus on actions instead of interactions, we will get new ways of modeling; vicarious reciprocity drives emergence of networks; and inequity aversion drives links in the experimental social network.

Modelling evolution in structured populations involving multi-player interactions

Mark Broom (City University London)

Dr. Broom started his talk by explaining territorial behavior, using wild dogs as a specific example. He then presented a model based on the evolution on graphs. This model includes the birth-death process, which has two absorbing states: no mutants, or the whole population become mutants. Dr. Broom then considered a population of N individuals who can move to M distinct places with some certain probabilities. The population follows the random process. He then went over examples of the territorial interaction model and the territorial raider model. Moreover, he explained the evolutionary dynamics of population in the proposed model. Finally he showed the results of Hawk fixation probability in a Dove population, and Dove fixation probability in a Hawk population. In summary, they have developed a new framework for modeling game theoretical interactions in a structured population which incorporates three key components. An important future step is to more fully incorporate evolutionary dynamics in the new framework.

The Emergence of Stable Non-Selfish Behaviors in Evolutionary Games because of External Influences

Christopher Griffin (Pennsylvania State University)
Dr. Griffin's objective is to understand how cooperation can evolve through external pressure: why do certain social sites have a lot of rolls and others don't, and can we say something about moderation policies in such situations. He then presented a multi-species model in which several population may interact with each other through an evolutionary game. In this model, two species (predator and prey) each play a prisoner's dilemma game within species. They interact with each other through a zero-sum game whose outcome affects intra-species strategic choice and generalizes the notion of a Bayesian game. Dr. Griffin then extended this model to settings with dynamic population size and more complex strategy spaces and illustrated the resulting strategy evolution. Finally, he mentioned some future directions for this research, including time-varying behavior types.

Evolution and co-evolution of habitat choice in stochastic environments
Sebastian Schreiber (University of California, Davis)
Dr. Schreiber divided his talk into two parts: single species results and two species results. He defined the ideal free distribution (IDF) and mentioned the well known studies on IDF. He then explained his model which is based on stochastic differential equations. He modified his model by coupling spatially and explained the evolution of patch selection. He defined the evolutionary stable strategy (ESS), and obtained the conditions for both pure and mixed ESS. In the second part of the talk, he talked about the model on predator-prey coevolution, and the modified version which included mutant prey and invasion exponents. He has also obtained the expression of the mixed ESS for this model. In summary, a population exhibits an IDF if the per-capita growth rates in all occupied patches are equal and individuals move to an unoccupied patch. Stochastic fluctuations in prey demography can exaggerate contrary choice. Stochastic fluctuations in predator demography can select against enemy-free space and select for congruent choices.

Evolution of Social Cliques
Zhijun Wu (Iowa State University)
This talk is based on maximizing the social contacts in the social network. Dr. Wu defined the social network, the social clique, and the connectivity matrix. He asked several questions, including: Is a social clique an equilibrium state/optimal strategy of the evolutionary game? Are there equilibrium states/ optimal strategies on non-clique subgraphs? He then defined symmetric evolutionary games (SEgame) and illustrated necessary & sufficient conditions for the equilibrium state of SEgame. He also defined the generalized knapsack problem (GKproblem) and explained the first order necessary conditions under which GKproblems have optimal solutions, i.e. local maximizer. Then, he compared SEgames and GKproblems. Afterward, Dr. Wu moved to the proposed social network model and proved that a maximal clique is an equilibrium state; however, an equilibrium state may not necessary be over a maximal clique. Moreover, in most cases, population over a maximal clique is a local maximizer.

Unifying adaptive dynamics and inclusive fitness: Evolution of dispersal and cooperation in an extended Hamilton-May model
Kalle Parvinen (University of Turku (Finland))
The concepts of Inclusive Fitness and Adaptive Dynamics are two ways to analyze models of evolution. Inclusive fitness is very good in simple models, but can be difficult to define when metapopulations are considered. By contrast, adaptive dynamics are harder to interpret and analytically mostly intractable. Dr. Parvinen used an adaptive dynamics approach to analyze a simple model and compared with the results obtained by inclusive fitness.

Metapopulation models arise when there is assortment into groups by behavior or spatial location. Dispersal becomes important in this type of model as population and environmental dynamics can affect dispersal in complex ways.
Adaptive dynamics generates a fitness gradient along which individuals evolve. Their knowledge is extremely local and this approach describes the effect of small mutations. Inclusive fitness takes into account the effect of a mutation on 'nearby' individuals such as kin, and follow's Hamilton's rule: altruism can evolve if the benefit to others times a relatedness factor outweighs the cost of the mutation. This rule is difficult to apply to complex systems.
Dr. Parvinen presented an extended Hamilton-May type model of cellular autonoma which disperse randomly, and with some cost. His model allows n individuals per patch, and produces n new adults at each iteration; constant population size was kept for comparison to the base model. He showed how R_0 can be generated for the extended model by calculating the transition matrix and performing several transformations on it.
Dr. Parvinen then showed that through a lengthy calculation, earlier explicit results from less general models could be recovered.

Thursday, April 30, 2015

Game Theory in cancer at the societal and cellular level
Robert Austin (Princeton University)
Dr. Austin's talk was in two parts; in part 1 he described the choice between patient-centered care and profit-centered care as a prisoner's dilemma, whereby universities and medical firms mutually support one another in the profit-based system. To support this claim he showed that institutions can profit from cancer while providing no net benefit, pointing to ad buys, NCI funding, and university income from drug patents.
In the second part of the talk, Dr. Austin described a simple 2×2 game modeling the interaction between multiple myeloma (MM) and stromal (ST) cells in a tumor. Using predator-prey like interaction terms, he classified equilibrium solutions of the resulting system by describing the payoffs to each organism and thus the game that results in each solution, concluding that coexistence is possible due to hawk-dove like interactions between MM and ST cells.
In an effort to increase predictability of a disease course given initial data, Dr. Austin developed a biochip which he calls an "evolution accelerator". The chip consists of a large number of reservoirs with small connections between them, and on which a gradient is imposed (in this case a chemotherapeutic drug). By measuring growth constants of MM and ST cells in such an experiment, he estimated the parameters governing the predator-prey type interaction described above, and used this to generate a velocity field. He then analyzed how these parameters are affected by the presence of the chemotherapeutic drug in an attempt to optimize treatment.

Evolutionary Game Theory as a 1st order approximation to cancer
David Basanta (Moffitt Cancer Center)
Dr. Basanta began by describing cancer as a heterogeneous collection of individual cells, and his focus is on the interactions between them. Specifically, Dr. Basanta is interested in understanding the process by which tumors (for instance prostate tumors) metastasize and migrate throughout the body.
He first presented an agent-based model of bone metastasis following RANKL, TGFβ, and Bone Remodeling Factor. The model provides some insight into how a tumor takes hold in bone, where the BRF is manipulated to promote cancer invasion.
Next, Dr. Basanta introduced a 3×3 game between MM (myeloma), ST (stromic), and I (independent cancer) cells in an attempt to explain the presence of both stromagenic and stroma independent

cancers. By targeting just the MM cells, tumor size initially decreases but I cells eventually explode. The conclusion was "what you don't select against, you select for."
Finally, he demonstrated how slowly adding complexity to a minimal model is preferable to starting with an unwieldy, complex one. First Dr. Basanta presented an agent-based model based around a 2×2 game between proliferators and invaders. Extending the results to a spatial model produced little change. However, further adding variable neighborhood size (to model physical boundaries) produced an emergent selection for motility at the edge of a tumor, providing a possible explanation for metastasis.

Coevolution of cancer hallmarks
John Nagy (Scottsdale Community College)
Dr. Nagy began his talk by showing examples of Shionogi tumors in mouse models, a type of hormone-dependent tumor used to model human prostate cancer. In the control, microvessels permeate the tumor. Castration to remove testosterone from the tumor environment resulted in decreased vasculation, which led to a significant reduction in tumor size. However, once normal vasculature was restored, the cancer returned but was no longer hormone-dependent.
The interaction between proliferation and angiogenesis was cast as a game theoretic interaction, in which angiogenesis provides a group benefit but at significant cost just to the individual, and further requires cooperation to succeed. The strategies available to cells were defined as the fraction of energy devoted to proliferation and angiogenesis. In order to produce an accurate model, Dr. Nagy described a complex interaction between AMP, ADP, and ATP and energy use in cells.
Once ATP was properly accounted for, the model was cast in the adaptive dynamics setting, and was shown to have no evolutionary singular strategies. The result is that proliferation is strongly selected for and subsets of the tumor forgo angiogenesis entirely. Remarkably, such "hypertumors"lead to so called evolutionary suicide and prevent the tumor from growing to lethal sizes. The question then becomes why cancer is so often fatal to the host, and Dr. Nagy suggested that this is because a tumor lifespan is quite long and most human tumors exist in a transient phase of increased angiogenesis.

Playing games in the mud: interactions between shorebirds and their benthic prey
Jan van Gils (Royal Netherlands Institute for Sea Research)
Dr. van Gils studies red knots, a species of seabird that undergoes large migrations, nesting in the arctic and generally wintering in the tropics, as well as in the Netherlands. He first demonstrated "sequential density dependence" whereby density effects in one location carry over to produce effects in another location. He illustrated this by pointing to population mortality rates during and after destructive dredging of the knots' feeding ground. Due to increased selection pressure, mortality rates increased during the winter but there was a concomitant decrease in mortality once the birds returned to the arctic. This effect can be interpreted as a perturbation of a population dynamic steady state.
Through laboratory simulations with captive animals as well as observation in the wild, Dr. van Gils and collaborators observed feeding behavior of the birds, classifying behavior as "Search", "Move", or "Handle" and generating a markov chain model of the transitions between these behaviors. Specifically, they studied the effect of density on the transition probabilities, showing that nutritional intake is negatively correlated with population density.
Next Dr. van Gils described "interference competition", where the birds must choose between two species of bivalves to eat. One species, Loripes, has an easily digestible thin shell and a high flesh to shell ratio but toxic levels of sulfides due to environmental interaction. The second species, Dosinia, is not toxic but has a lower flesh to shell ratio. The birds prefer Dosinia when it is plentiful, especially when they have previously been sick from eating Loripes.

By analyzing toxin constraints as well as elevated shell content constraints, Dr. van Gils was able to calculate "depletion lines", whereby the population trajectories of Loripes and Dosinia could be predicted based on initial conditions, including bird population data. He then showed that these depletion lines accurately reflect empirical data over many years. Using this method, he claimed that recent decrease in red knot populations are most likely due to a decline in the Dosinia population.

Mechanistic population games and seasonal migration

Tim Reluga (Pennsylvania State University)

Dr. Reluga is interested in age-related properties of infectious disease. He began his talk by showing a stark difference in mortality – age curves for the 1918 Spanish flu and a standard year in the late 1920s. He then presented a two-patch (old, young) SIR model intended to address the question: under what circumstances should a person attempt to maximize or minimize their susceptibility to infection? For example, common wisdom holds that children should be exposed to chicken pox early, as it becomes much more dangerous later in life.

To answer the question Dr. Reluga used ideas from economics, including lifetime utility and future discounting, which gives fitness as an integral over future states. He then incorporated uncertainty into the model by using Markov decision process theory, using the transition matrix to calculate an expected lifetime utility.

When juvenile virulence is large in the model, the Nash Equilibrium is to reduce individual transmission rates as much as possible. However, when juvenile virulence is low, two Nash Equilibria appear: get the disease as early as possible or avoid it completely. Dr. Reluga claimed this may explain the rise of Polio as a public health problem at the same time that public health was improving generally, as children were getting the disease later than they had been historically.

He then showed how to obtain a variation of the basic reproduction number,R_d could be obtained from the model. By taking a "capital" approach to fitness, he demonstrated R_d for a model of seasonal migration. By varying the amount of "future discounting" (long term planning), solutions to a periodic, quadratic-cost model provided varying fitness to individuals. He then applied these concepts to a model of red crab migration.

Multiscale Evolutionary Game Theory modeling of food webs

Rosalyn Rael (Tulane University)

Dr. Rael studies the evolution of food webs in the context of game theory. In the models she presented, the strategy of an organism is population average body size, since organisms tend to prefer food at least an order of magnitude smaller than itself. Body size works as a proxy for growth rate and energy needs as well as other biological descriptions of an organism.

She first presented a two-level and then three-level adaptive dynamics model based on logistic growth at the bottom and metabolic decay in the second and third levels of the hierarchy. For both models, initial conditions were chosen to maximize carrying capacity, and in both models adding evolution benefited the basal species but not the second-tier species. The top tier species, when present, also benefited from the addition of evolutionary dynamics into the model.

In the second part of her talk, Dr. Rael described a model of complex food web evolution. In her model, she started with a small number of species, connected in a food web according to the niche model. She then added dynamics to this network and allowed the system to run until approximate equilibrium. At this point, a single species is chosen to produce a mutation: a new species that is nearby to its parent in parameter space, and thus exhibits similar predator / prey connections in the web. Repeating this process 500 times results in webs that show interesting diversity and some parallels to empirical data. In many such models, the system crashes before the simulation is finished. In most models the top two tiers crash, leaving only plants. When various parameters of the models are considered with respect to

the connectance of the webs, the simulation results have distributions that are quite similar to empirical data.

Friday, May 1, 2015

Strategy dependent time delays in replicator dynamics
Jacek Miękisz (University of Warsaw)
Classical evolutionary game theory, in the form of replicator dynamics, ignores time scale separations and delay effects, and is also deterministic. Dr. Miękisz's work attempts to include these effects into the basic framework of replicator dynamics. He classified delay into three basic types: social, biological, and strategy dependent. In all of these cases, he studied the effect of the delay on evolutionarily stable strategies (ESSs)
Social delay means replication at time t is based on an individual's payoff at time $t - \tau$. The modified evolution equation includes a sort of "average" payoff across populations that includes terms that are mixed in time. The result is that the ESS in the original model remains asymptotically stable for small time delay, and undergoes a hopf bifurcation as the delay grows.
In biological delay, birth occurs at a time τ after the parents have 'played'. In this case, the evolution equation no longer has mixed terms. Here, the dynamics are implicit in one equation and the population must be solved as a system of equations. Now the interior ESS remains globally asymptotically stable for any τ.
Strategy dependent delay is a modification of biological delay where the time from playing until birth may depend on the strategy chosen. In this case, the stationary solution is highly dependent on these delays. Dr. Miękisz presented simulations showing the convergence of well known 2×2 games to various equilibria, where the distance from the base ESS increases as the difference between the delays increases. He then compared these results to a 'mean-field' expression via Taylor expansion in τ, and showed that for small delay there is strong agreement.
Dr. Miękisz also addressed the question of why oscillations occur in games. He presented a three-player $2 \times 2 \times 2$ game with a simple payoff structure and 3 Nash equilibria. In the no noise regime, adding small delay retains local asymptotic stability around the mixed ESS, but large delay shifts the system to a globally attracting pure strategy ESS. When noise is added to the system, small delay results in a stochastically stable cycle around the mixed ESS. Again, large delay pushes the system to a pure strategy ESS.

The habitat selection game
Vlastimil Krivan (Ceske Budejovice (Czech Republic)
Dr. Krivan presented several models of two-patch population dynamics in order to study how populations distribute themselves spatially. The model includes a patch preference for each population as well as a cost of dispersal. The addition of dispersal makes the equilibrium solution evolutionarily unstable unless the payoff functions are exactly balanced for the two patches.
Dr. Krivan is interested in the distinction between evolution and plasticity in a population; the first is assumed to operate on large time scales and to be homogeneous within a population, while the second acts faster and produces varied behavior within a population. Using a logistic growth model, he showed that both approaches lead to the ideal free distribution but in very different ways and on very different time scales.
Dr. Krivan then presented a Lotka-Volterra type model to investigate when two species can coexist in both patches. In particular, he found that including dispersal in this model can ruin the stability of such an equilibrium. He then compared predictions of the model to experiments on bacterial populations which matched very well.

Variation, social information use and personality
Sasha Dall (University of Exeter)
Dr. Dall is interested in the evolution of personality in (both human and nonhuman) populations. He defined personality as 'stable, consistent individual differences in behavior within a population'. He noted that empirically, personalities vary along just a few axes. He contrasted the usual interpretation of game theory, which selects for unpredictability in strategy, with empirical observations that personality exists among many vastly different types of organisms.
To account for the contradiction, Dr. Dall described a game he called "Hawk-Dove with Eavesdroppers", where a third strategy is available to the players. The eavesdropper strategy is to present as a hawk only if one's opponent lost in its last game, and otherwise play as a dove. Interestingly, the standard ESS remains an ESS but variation in aggressiveness selects for a stable, nonzero population of eavesdroppers. In other words, if there is information available, then it can pay to use that information.
Next Dr. Dall described a similar variation in the "Trust Game". This game includes variation in the cooperativity of responders as well as a skepticality parameter for initiators. Again, variance in opponent's behavior selects for more sophisticated players; in this case the variance must be relatively high before 'Sampling' behavior gains positive utility. Simulations of the game show that such sophisticated sampling can in fact select for dimorphism in responder population, encouraging some degree of cooperation in addition to defectors.

Emergent node tree structures for multiscale modeling of the dynamics of interacting agents
Ruchira Datta (The Ohio State University)
Dr. Datta's main research goal is the simplification of complex games with many players. To motivate this goal, she described several examples of complex systems gone wrong, including her time working on Google's search feature and recently implemented online healthcare marketplaces. The solution is modularity and integration of those modules, and this is the overall framework of emergent node tree structures (ENTs).
She provided several examples of complex interaction systems such as saboteurs, tumor microenvironments, and pollination in a meadow. Her examples illustrated that ENTs need not reflect cooperativity and may not reflect intuitive notions of how a system may be modularized.
Dr. Datta then presented the mathematical structure of an ENT in terms of multilinear mappings of (n, m)-type tensors across populations. She defined the game theoretical concept of a "Hierarchically perfect Nash Equilibrium", in which all nodes, including emergent nodes, are playing their best reaction to each other's' strategies.
She finished her talk by noting that a generic tensor in $C^3 \otimes \mathrm{C}^3 \otimes C^3$ has rank 5 rather than the expected rank 27. This means that modularity is likely a property of most n-player games, and indicates that ENTs may be a valuable structure for studying such games.

Workshop on Topics in Applied Dynamical Systems: Equivariance and Beyond
(May 24-27, 2015)
Organizers: Pietro-Luciano Buono (University of Ontario Institute of Technology), Martin Krupa (Paris-Rocquencourt Centre, INRIA), Maria Leite (University of South Florida), Yuan Lou (The Ohio State University), Yunjiao Wang (Texas Southern University)

The purpose of this four day workshop was to reflect on the state of equivariant dynamical systems and coupled cell systems theory, focusing on a selection of interconnected research directions. The workshop featured some of the main contributors to the theory and its numerous applications, highlight

promising future directions, and mark the contribution of Professor Martin Golubitsky as one of the leaders of the field on the occasion of his 70th birthday.
Themes:

- Equivariant dynamics and applications
- Coupled cell systems and applications
- Pattern formation in natural sciences
- Network Dynamics Mathematical Neuroscience

This workshop was co-sponsored by the OSU Department of Mathematics and The Institute for Mathematics and its Applications (IMA).

Workshop on Spatially-varying Stochastic Differential Equations with Applications to the Biological Sciences
(July 7-10, 2015)
Organizers: Peter Craigmile (The Ohio State University), Radu Herbei (The Ohio State University)

In biology, ecology, and public health there has been a growth in the use of stochastic differential equations (SDEs) to model scientific phenomena over time. SDEs have the ability to simultaneously capture he known deterministic dynamics of the variable of interest (e.g., chemical levels within a cell, the chemical or physical characteristics of a river, the presence, absence and spread of a disease), while enabling a modeler to capture the unknown dynamics or measurement processes in a stochastic setting.

In this four-day workshop, participants learned about the use of SDEs to model physical phenomena in the biological sciences. Students learned how to define and manipulate SDEs, and understood the difficulties in performing statistical inference on the parameters of SDEs using data. They related the modeling of SDEs to the theory of spatial and temporal data analysis, and carried out a small group project to discover and investigate how to model data from various disciplines within the biological sciences.

The lectures were taught by a selection of external and internal speakers, each of which had a different experience in different aspects of modeling using SDEs, as well as in spatial and temporal data analysis. Students were educated on the material through practical exercises.

Students came to the workshop with two years of graduate experience in Statistics or equivalent. They were comfortable with statistical models and theory, likelihood inference, and had some exposure to Monte Carlo techniques. Students should have taken a course in linear models, and had knowledge of the statistical software package called R (http://www.r-project.org). Some exposure to time series analysis and spatial statistics is helpful, but not essential.

The workshop was also supported by STATMOS, a NSF-funded Research Network for Statistical Methods for Atmospheric and Oceanic Sciences.

Summer Undergraduate Programs
June 8-August 14, 2015

The goal of this program was to introduce students to exciting new areas of mathematical biology, to involve them in collaborative research with their peers and faculty mentors, and to increase their

interest in mathematical biology. The program consisted of three parts - each including a mix of educational and social experiences: a one-week introduction to mathematical biology (June 8-12, 2015); an eight-week individualized research experience as part of a research team at one of the eight participating host institutions; and a week-long Capstone Conference (August 10-14, 2014).

The one-week program was held June 8-12, 2015 and featured tutorial lectures, computer labs, lab tours, and short-term team efforts designed to introduce students to a variety of topics and methods of research in mathematical biology. The lectures were given by several distinguished researchers. The goal of this MBI NSF-funded program is to introduce students to exciting new areas of mathematical biology, to involve them in collaborative research with their peers and faculty mentors, and to increase their interest in mathematical biology. During the one-week program, the students toured labs that use quantitative methods in the biological and medical sciences.

For the MBI supported students, the end of the one-week program marked the start of their summer-long projects at one of the host institutions. This part of the program was held June 15-August 7, 2015 and the host institutions included projects at: Arizona State University, Indiana University – Purdue University Indianapolis, The Ohio State University, The Pennsylvania State University, University of Pittsburgh, and the Virginia Bioinformatics.

The Summer Undergraduate Program ended with a weeklong Capstone Conference which was held August 10-14, 2015. It celebrated all of the nationwide efforts of undergraduate researchers in the mathematical biosciences – not just those of the MBI sponsored REU students. This student-centered conference featured a graduate studies recruitment fair for Institute Partner Schools; panel discussions on career and graduate opportunities in mathematical biology; keynote talks from prominent mathematical bioscientists geared toward student interests; an opening reception and a mid-week social event at the Columbus Zoo & Aquarium followed by a dim sum banquet dinner. Most importantly, the capstone conference offered undergraduate students doing research projects in the mathematical biosciences and opportunity to present their work on the national stage. This included 25 half-hour oral presentations and 30 poster presentations on individual and team projects. This next generation of mathematical biologists were all actively engaged in the lively discussions around each topic and made the conference a terrific success.

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

MBI-CAMBAM-NIMBios Summer Graduate Program
Nonlinear Dynamics in Biological Systems
June 1-12, 2015
Organizers: Anmar Khadra (McGill University), Santiago Schnell (University of Michigan Medical School)

Quantitative bioscience is the application of mathematics, physics and numerical computations to all spheres of biology. It provides a common currency to the understanding of life at the microscopic and macroscopic level, from single molecules to complex ecosystems. It underlies the development of personalized biomedical devices, optimized drug delivery to patients and the prediction of ecosystem health in changing environments. While these challenges are typically addressed within each research area, the required quantitative (mathematical, physical and computational) tools are shared across all areas. The rich stream of experimental data has made it possible for bioscientists to build testable and

predictive models that are based on sound data. It is these models, accompanied by statistical and computational approaches that have provided a platform for experimentalists to understand the dynamics of their respective biological systems and to guide new experiments. As a result, the field of mathematical and computational modeling has been felt strongly across the biological sciences, including neuroscience, cancer biology, immunology, epidemiology, ecology, and evolutionary biology. In this summer school, we aim to provide a new generation of trainees with the opportunity to learn more about the basics of this field and give them an overview of the latest advancements made in quantitative biosciences.

Aims of the Summer School:
1. Introduce students (at the graduate and undergraduate level) and postdoctoral fellows to the fields of mathematical biology and nonlinear dynamics through daily lectures and tutorial sessions.
2. Teach them how to use certain mathematical methods and computational tools to analyze various physiological processes (e.g., in neuroscience, immunology, cardiology) and ecology.
3. Provide them with proper training in research methodologies through group projects supervised by the instructors of the summer school.
4. Teach them how real experimental data is collected and analyzed, and how it is used to foster collaborations with traditional experimental-based research laboratories.
5. Improve their presentation skills through feedback during project presentations.

The lecturers:

- Leon Glass (McGill University)
- Jacques Bélair (University of Montreal)
- Michael Guevara (McGill University)
- Michael Mackey (McGill University)
- Frédéric Guichard (McGill University)
- Santiago Schnell (University of Michigan)
- Lea Popovic (Concordia University)
- Anmar Khadra (McGill University)
- Erik Cook (McGill University)

Sponsors:

- Center for Applied Mathematics in Bioscience and Medicine (CAMBAM)
- Mathematical Biosciences Institute (MBI)
- National Institute for Mathematical and Biological Synthesis (NIMBioS)

F. <u>COMMUNITY INVOLVEMENT IN MBI PROGRAMS</u>

The Director and Associate Directors were in continuous contact with the mathematical and bioscience communities in order to identify areas of opportunity in the mathematical biosciences. To insure that MBI programs have a sustained strong impact, the Director and Associate Directors continue to identify areas for industrial and government participation. They have started to build a stronger Institute Partner Program and they are working to develop corporate relationships while strengthening the sponsored postdoctoral program.

Sponsored Postdoctoral Fellows
MBI expects to have a portion of its postdocs sponsored by a company, institute, or bioscience department. Each sponsor pays a percentage of the postdoc's compensation, benefits and overhead, and in return, gets an equal percentage of time and effort from the postdoc. The sponsored postdocs are appointed for one to three year periods. In 2014-2015, MBI had one sponsored postdoc: Michal Seweryn, who began his term in 2012, was cosponsored by the OSU College of Public Health. In 2014-2015, MBI had four sponsored postdocs: Duan Chen, who began his term at MBI in 2011, was cosponsored by Michigan State; Paul Hurtado, who began his term at MBI in 2011, was cosponsored by the OSU Department of Evolution, Ecology and Organismal Biology; Jincheol Park, who began his term in 2012, was cosponsored by the OSU Department of Statistics; and Michal Seweryn, who began his term in 2012, was cosponsored by the OSU College of Public Health.

Institute Partners
MBI welcomes the participation of other academic institutions in the MBI Institute Partner (IP) Program. The goals of the IP program are to help enable researchers from partner institutions to participate in MBI programs and to increase the national and international impact of MBI programs while encouraging scientific activity and the growth of mathematical biosciences at partner institutions.

IPs are universities, government labs and companies. Typically, a single department (but sometimes a group of departments) enters into an agreement with MBI to become an IP. The IP designates a contact person who is charged with making decisions on behalf of the IP.

The IP program uses MBI matching funds to subsidize the travel expenses of IP member researchers to allow their participation in MBI programs. In addition, each year MBI provides up to $15,000 to support conferences in mathematical biology held at IP institutions. IP representatives are invited to annual meetings to explore research and educational opportunities and provide input for future institute programs. IP members also receive MBI newsletters, proceedings, and annual reports.

2014-2015 Institute Partners
1. Arizona State University
2. Battelle Memorial Institute
3. Boston University
4. Case Western Reserve University
5. Cornell University
6. Daegu University
7. Drexel University
8. Duke University
9. Florida State University
10. Howard University
11. IBM Corporation
12. Indiana University--Purdue University
13. Instituto Gulbenkian de Ciencia
14. Iowa State University
15. Konkuk University
16. McGill University
17. Michigan State University
18. Mississippi State University
19. Moffitt Cancer Center

20. Mount Sinai School of Medicine
21. National Autonomous University of Mexico (UNAM)
22. National Tsing Hua University
23. New Jersey Institute of Technology
24. Ohio University
25. Pennsylvania State University
26. Princeton University
27. Rutgers University at New Brunswick
28. Rutgers University at Camden
29. Texas Tech University
30. The Ohio State University
31. Trinity University
32. Tulane University
33. University of Alberta
34. University of Bath
35. University of California, Davis
36. University of California, Irvine
37. University of California, Los Angeles
38. University of California, San Diego
39. University of Cincinnati
40. University of Exeter
41. University of Georgia
42. University of Glasgow
43. University of Houston
44. University of Iowa
45. University of KwaZulu-Natal
46. University of Maryland
47. University of Maryland Baltimore County
48. University of Miami
49. University of Michigan
50. University of Minnesota
51. University of Notre Dame
52. University of Nottingham
53. University of Oxford
54. University of Pittsburgh
55. University of Southern California, Los Angeles
56. University of Twente
57. University of Utah
58. University of Washington
59. University of Waterloo
60. University of Wyoming
61. Vanderbilt University
62. Virginia Commonwealth University
63. Virginia Polytechnic Institute and State University

Workshops at Institute Partners

MBI helped support four workshops held at MBI partner institutions in 2014-2015:

1. The Ohio State University, May 24-27, 2015: "Workshop on Topics in Applied Dynamical Systems: Equivariance and Beyond"
2. University of Glasgow, June 10-12, 2015: "Glasgow 2nd Workshop on Soft Tissue Modeling"

Corporate Involvement
As an extension of the IP program, MBI is working to develop corporate relationships among pharmaceutical and bioengineering companies. The goal of corporate involvement is to identify areas where mathematical sciences can be helpful to nonacademic businesses. In building corporate involvement, companies are invited to present industrial challenges and problems to MBI audiences and to participate in MBI programs and workshops. Discussions were held to expand MBI's corporate interactions which include a postdoc visitation program and mentoring opportunities with corporate partners. Current nonacademic IP members include Battelle and IBM. In the past, MBI had corporate partnerships with Eli Lilly Company, GlaxoSmithKline, Legacy Good Samaritan Hospital, and Pfizer, Inc.

G. DIVERSITY EFFORTS

The MBI diversity mission is to help shape the mathematical biology community in a way that represents the diversity of our society. Enhancing representation will ensure that the Math Biology community benefits from a diversity of ideas, research approaches, and educational strategies. Historically, women, African-Americans, Hispanics, Native American, and Alaskan Natives have been underrepresented in the mathematical biology community, and our efforts target individuals from this group. MBI works at two levels:

- It is MBI policy that each of its programs should actively seek diversity among its participants in gender and ethnicity.
- MBI will sponsor activities that promote mathematical biology and its opportunities in the academic community and will do so in ways that reach the broadest number and types of individuals.

To be most effective, these activities should reach early career students including undergraduates and contribute to increasing the diversity of future mathematical biologists.

Diversity Committee
The Diversity Committee provides consultation and ideas, and helps MBI to carry out its diversity mission.

Current members of the Diversity Committee are:
1. Erika Camacho (Arizona State – Glendale)
2. Ricardo Cortez (Tulane)
3. Holly Gaff (Old Dominion)
4. Maeve McCarthy (Murray State)
5. Kim Weems (NC State)
6. Aziz Yakubu (Howard)

Former members are:
1. Helen Chamberlin (Ohio State, ex officio)
2. Carlos Castillo-Chavez (Arizona State)
3. Joan Herbers (Ohio State)

4. Trachette Jackson (Michigan)
5. Yi Li (Iowa)

Visiting Lecturer Program
The MBI Visiting Lecturer Program sponsors visits of mathematical biologists to institutions that have large numbers of undergraduate students who are members of groups that are under- represented in the mathematical sciences community. The purpose is to encourage members of these groups to go to graduate school and to consider careers in the mathematical biosciences. In addition to delivering a lecture on mathematical biology that is accessible to an undergraduate audience, the lecturers meet with individual students and with groups of interested faculty and students to further this purpose. There have been eight lectures in the three and a half years that the program has existed. The 2014-2015 lecturers are listed in Section A2.

MBI Conference Awards
MBI has started a new diversity program whereby MBI offers full travel support to winners of a presentation award at conferences that serve minority communities. MBI had presented 4 conference awards 2014-2015, the recipients are listed in Sections A2. The math institutes have also started their own conference award program modeled on the MBI program.

MBI Capstone Conference Awards
The Capstone Conference Awards are modeled on the MBI Conference Awards, and are made to underrepresented minority students nominated by their mentors. The award enables the participation of recipients in the MBI REU Capstone Conference and includes reimbursement of travel expenses (round-trip economy class airfare, ground transportation, etc), and direct-billed accommodations. The MBI Diversity Committee selects three winners each year.

2015 Capstone Conference Award recipients:
1. Dominic G. Gray, Norfolk State University
2. Luis Mestre, Universidad Metropolitana, Puerto Rico

Math Institutes Diversity Programs
The MBI is actively involved in the Mathematical Sciences Institutes Diversity Committee, which includes participants from all NSF supported math institutes. A major aim of the committee is the development, organization and sponsorship of national events and programs that foster diversity in the mathematical sciences, and build community. We have worked with other Math Institute Diversity committee members to obtain support for events and fellowships in support of underrepresented minorities.

MBI representatives participate in conferences and workshops sponsored by the Math Institutes Diversity Committee and its collaborators. Examples of involvement include:
- MBI representatives (Postdocs and Associate Director) attend the annual Modern Math Workshop to provide scientific talks and to advertise MBI programs
- MBI representatives attend SACNAS, to serve as poster judges, mentors to early career trainees and to coordinate the Math Institutes Booth
- MBI postdocs attend the Field of Dreams conference, to offer scientific talks and to mentor early-career trainees

I. EVALUATION OF MBI PROGRAMS

MBI formally evaluates its programs in two ways. First, starting in 2010 with funding from the current grant, MBI has had a contract with Strategic Research Group (SRG, http://www.strategicresearchgroup.com/) to perform an independent evaluation of MBI programming based on online questionnaires and personal interviews. Second, every 2-3 years, MBI sends e-mails to former participants and visitors to collect specific information on outcomes from their respective visits, including collaborations, papers written or significantly influenced, and many others. Informally, MBI staff and directors are listening and watching for information that can improve MBI programs, and many improvements have been made this way.

The evaluation process with SRG

SRG independently conducts the evaluation of MBI programming. Evaluation begins with SRG Partner/Principal Investigator Kathleen Carr meeting with Golubitsky and Nance to discuss scope and goals. SRG then designs and implements the evaluation instruments, collects and houses the resulting data, performs in-house analysis, and issues reports to MBI.

SRG meets three to four times a year with MBI Directors to discuss results. SRG's general expertise provides MBI with both the information and analysis that influence MBI programming, and does so in a way that MBI would not be able to do on its own.

How working with SRG has helped MBI

MBI has made adjustments based on SRG reports and information and MBI has also learned what it is doing well that should not be changed. This has happened on levels ranging from the big picture (postdoctoral mentoring; the attitudes and involvement of bioscientists) to the small (afternoon snacks and better coffee at events). Here are some ways in which SRG evaluations have helped change MBI programs.

Post-doc program

- Influenced changes to the post-doc career ("professional") mentoring program
- Influenced changes and clarifications to post-doc scientific mentoring
- Led to clarification of post-doc teaching opportunities

Biosciences participants

- We learned that our bio-based visitors were often hesitant about coming to a math institute. We are now asking our workshop organizers to take this into account in their programming.
- MBI is starting to ask workshop organizers to create tutorials aimed at participants from the biosciences that will be on the web before the workshops

Logistics

- Tentative schedules are now online earlier
- Use social media better
- Consider shorter workshops
- Pointed out inadequacies in MBI online registration, which are being addressed

REU & Capstone Conference

- We changed and improved logistics of this complex program, including our internal funding model, handling of travel for the students, and the logistics for the Capstone Conference.

Positive reinforcement: workshop participants like

- The extra discussion time in our workshop schedules
- The diverse communities that speak and participate
- The number of participants
- The logistics, support, and general staff interaction

Moving forward with SRG

In the new grant, SRG will continue evaluating MBI programs (workshops, post-docs, long-term visitors, and Capstone Conference). In addition, MBI expects to work with SRG to learn more about the long-term impact of MBI programs, and to better evaluate the Institute Partner program and MBI web initiatives. Also, locally, Nance will write a formal summary for each of the reports received from SRG.

No Cost Extension Year - Annual Report for DMS-09311642 For Year 2015-2016

Summary of MBI Programs in Academic Year 2015-2016

MBI hosted two Emphasis Semester programs in 2015-2016: the Autumn 2015 Emphasis Semester was on *Mathematical Molecular Biosciences* and the Spring 2016 semester was on *Dynamics of Biologically Inspired Networks*.

The Organizing Committee for the **Autumn 2015 Semester** consisted of **Emil Alexov** (Computational Biophysics and Bioinformatics, Clemson University), **Ridgway Scott** (Computer Science and Mathematics, University of Chicago), **Reidun Twarock** (Mathematics and Biology, University of York), and **Guowei Wei** (Mathematics, Michigan State University).

This one-semester program brought together researchers from mathematics, chemistry, physics, biology, computer science, and engineering to explore new ways to bridge these diverse disciplines, and to facilitate the use of mathematics to solve open problems at the forefront of the molecular biosciences.

With the availability of modern biotechnologies, an important trend in traditional life sciences disciplines (such as physiology, plant biology, neuroscience etc.) is a fundamental transition from macroscopic phenomenological disciplines to molecular based biosciences ones. In parallel with this development, a major change in the life sciences in the 21st century is the transformation to quantitative and predictive sciences. Revolutionary opportunities have emerged for mathematically driven advances in biological research. In the past few decades experimental exploration of self-organizing molecular biological systems (such as HIV viruses, molecular motors and proteins in Alzheimer's disease) are examples of dominating driving forces in scientific discovery and innovation. However, the emergence of excessive complexity in self-organizing biological systems poses fundamental challenges to their quantitative description, because of the excessively high dimensionality and the complexity of the processes involved. Mathematical approaches that are able to efficiently reduce the number of degrees of freedom, and model complex biological systems, are becoming increasingly popular in molecular biosciences. Multiscale modeling, manifold extraction, dimensionality reduction and machine learning techniques have been introduced to reduce the complexity of biomolecular systems while maintaining

an essential and adequate description of the biomolecules of interest.

Currently, a major barrier for mathematical scientists to work in this field is the lack of knowledge in molecular biology, while a major barrier for biologists is the lack of knowledge about modern mathematical tools and techniques that have been developed in the past 20 years. This semester workshop program was designed to help bridge gaps between molecular biologists and mathematical scientists and to facilitate their collaborations. There is enormous potential in this area for integrative interdisciplinary research in which theoreticians and experimentalists develop solutions to challenging problems in tandem. This program acted as a catalyst to exploit these synergies and to create a network of collaborations that will sustain future activities in this area beyond the duration of this program.

Autumn 2015 Emphasis Semester Workshops

1. Workshop on Omics Data Analysis (September 16-18, 2015)
2. Workshop 1: Geometric and Topological Modeling of Biomolecules (Sept 28 – Oct 2, 2015)
3. Workshop 2: Multiple Faces of Biomolecular Electrostatics (Oct 12-16, 2015)
4. Workshop 3: Modeling and Computation of Transmembrane Transport (November 16-20, 2015)
5. Workshop 4: Mathematical Challenges in Drug & Protein Design (Dec 7-11, 2015)

Autumn 2015 Current Topic Workshops

1. Uncertainty, Sensitivity and Predictability in Ecology: Mathematical Challenges and Ecological Applications (October 26-30, 2015)
2. Foundations Meet Translation (December 2, 2015)

The Organizing Committee for the **Spring 2016 Emphasis Semester** on *Dynamics of Biologically Inspired Networks* consisted of **Pete Ashwin** (College of Engineering, Mathematics and Physical Sciences, University of Exeter), **Nina Fefferman** (Ecology and Evolutionary Biology, University of Tennessee), **Martin Feinberg** (Chemical Engineering & Mathematics, The Ohio State University), **Leon Glass** (Department of Physiology, McGill University, Macdonald Campus), **Adilson Motter** (Physics, Northwestern University), **Mason Porter** (Mathematical Institute, University of Oxford), and **Ruth Williams** (Mathematics, University of California, San Diego).

The MBI network program is part of a yearlong cooperative program with IMA. To see the fall 2015 IMA network workshops go to http://www.ima.umn.edu/2015-2016/ima-mbi-program.html.

Networks and deterministic and stochastic dynamical systems on networks are used as models in many areas of biology. This underscores the importance of developing tools to understand the interplay between network structures and dynamical processes, as well as how network dynamics can be controlled. The dynamics associated with such models are often different from what one might traditionally expect from a large system of equations, and these differences present the opportunity to develop exciting new theories and methods that should facilitate the analysis of specific models. Moreover, a nascent area of research is the dynamics of networks in which the networks themselves change in time, which occurs, for example, in plasticity in neuroscience and in up regulation and down regulation of enzymes in biochemical systems.

There are many areas in biology (including neuroscience, gene networks, and epidemiology) in which network analysis is now standard. Techniques from network science have yielded many biological insights in these fields and their study has yielded many theorems. Moreover, these areas continue to be exciting areas that contain both concrete and general mathematical problems. Workshop 1 explored

the mathematics behind the applications in which restrictions on general coupled systems are important. Examples of such restrictions include symmetry, Boolean dynamics, and mass-action kinetics; and each of these special properties permits the proof of theorems about dynamics on these special networks.

Workshop 2 focused on the interplay between stochastic and deterministic behavior in biological networks. An important related problem is to understand how stochasticity affects parameter estimation. Analyzing the relationship between stochastic changes, network structure, and network dynamics poses mathematical questions that are new, difficult, and fascinating.

In recent years, an increasing number of biological systems have been modeled using networks whose structure changes in time or which use multiple kinds of couplings between the same nodes or couplings that are not just pairwise. General theories such as groupoids and hypergraphs have been developed to handle the structure in some of these more general coupled systems, and specific application models have been studied by simulation. Workshop 3 brought together theorists, modelers, and experimentalists to address the modeling of biological systems using new network structures and the analysis of such structures.

Biological systems use control to achieve desired dynamics and prevent undesirable behaviors. Consequently, the study of network control is important both to reveal naturally evolved control mechanisms that underlie the functioning of biological systems and to develop human-designed control interventions to recover lost function, mitigate failures, or repurpose biological networks. Workshop 4 will address the challenging subjects of control and observability of network dynamics.

Spring 2016 Emphasis Semester Workshops

1. Workshop 1: Dynamics in Networks with Special Properties (Jan 25-29, 2016)
2. Workshop 2: The Interplay of Stochastic and Deterministic Dynamics in Networks (Feb 22-26, 2016)
3. Workshop 3: Generalized Network Structures and Dynamics (Mar 21-15, 2016)
4. Workshop 4: Control and Observability of Network Dynamics (Apr 11-15, 2016)

Spring 2016 Current Topic Workshops

Modeling and Inference from Single Molecules to Cells (Feb 8-12, 2016)

Educational Programs

Joint 2016 US-Canadian Institutes Epidemiology Graduate Summer School: Mathematical Modeling of Infectious Disease (hosted at MBI) (June 13-22, 2016)

Graduate students from the mathematical and life sciences, public health, and related fields were encouraged to apply to the 2016 Graduate Summer School on Mathematical Modeling of Infectious Disease Spread, to be held at MBI. The program for this 10-day summer school will feature researchers from the mathematical and biological sciences, who will deliver lectures, case study presentations, and mentor the school participants in special project groups. The case study lectures will focus on public health issues, and will be open to the university community. During the summer program each student will work on a research project in a team of approximately five participants. Topics to be covered include: deterministic and stochastic frameworks for modeling disease dynamics; disease dynamics on social networks; metapopulations; host behavior and disease evolution; vector-borne diseases; zoonotic diseases; pathogen dynamics and co-infection.

The 2016 summer school focused on the mathematical modeling of infectious diseases, a field that is growing in importance because of the many issues in disease spread and control arising from new or newly emerging diseases (e.g., SARS, Ebola, West Nile virus), and because new data sources are now available to study disease transmission, pathogen evolution, and the impact of the social behavior of hosts (e.g., genotyping databases, cell phone networks and air travel tickets, social networks). Capitalizing on new data sources to understand and control these impacts on disease spread requires detailed modeling of interactions amongst pathogens and hosts, the training of sophisticated modelers, and the development of new mathematics. This summer school prepared students to study such models in their future research.

No tuition was charged to summer school participants. Financial support for local expenses for 50 students was made available through co-sponsorship by the National Institute for Mathematical and Biological Synthesis (NIMBioS, Tennessee –Knoxville), the Army Research Office (ARO), the Fields Institute (Toronto), the Centre for Disease Modelling (CDM, York University), the Centre for Applied Mathematics in Bioscience and Medicine (CAMBAM), the Society for Mathematical Biology (SMB), and the Atlantic Association for Research in the Mathematical Sciences (AARMS). The Ohio State University and the National Science Foundation (DMS/NSF) have provided additional support.

Undergraduate Program (June 6 - August 12, 2016) [Mostly supported by a separate NSF-REU grant]
This innovative program for 12 fully supported students consisted of three parts:

1. An introductory one-week program (June 6-10, 2016): Tutorials, computer labs, and short-term team efforts designed to introduce students to a variety of topics in mathematical biology.
2. An eight-week REU Program (June 13 – August 5, 2016): individualized research experience as part of a research team at one of the participating host institutions. Host institutions are: Arizona State University, Indiana University – Purdue University Indianapolis, New Jersey Institute of Technology, The University of Notre Dame, The Ohio State University, and Penn State University.
3. A one-week *Capstone Conference* (August 8-12, 2016): A student centered conference featuring talks and posters by students (usually 50 students participate) doing research in mathematical biology, keynotes by prominent mathematical biologists, a graduate studies recruitment fair, and other special features.

MBI Postdoctoral Training

The goal of the MBI Postdoctoral Fellow program is to produce scientists with an independent research program; the MBI mentoring program is aimed at helping to accomplish this goal. The MBI training program prepares postdoctoral fellows for jobs in university or college teaching, industry, and national labs. The MBI mentoring program has a number of distinctive features.

1) Each postdoctoral fellow has two designated scientific mentors: one in the mathematical sciences and one in the biosciences. The scientific mentors serve as senior collaborators who facilitate the scientific progress of the post-docs, as well as serve as professional mentors and role models. The scientific mentors are chosen in cooperation with the Directorate and the mentors may change from time to time.
2) MBI approved scientific mentors are researchers at either Ohio State or at one of the MBI Institute Partners; MBI funds face-to-face contacts with external mentors.

3) Each postdoctoral fellow receives $2,500 per year for professional travel. These funds facilitate professional development by supporting their participation in professional meetings or their travel to work with collaborators other than the designated mentors.
4) A unique feature of the MBI postdoctoral fellow experience is the networking capabilities afforded to each post-doc because of the large number of MBI visitors. We set up opportunities for the post-docs to interact with many of our visitors.
5) To support self-reflection and oversight by the MBI director, each post-doc writes an annual report describing his or her accomplishments of the previous year and his or her expectations for the next year. The reports are reviewed in a formal meeting with two members of the Directorate.
6) To foster collaboration and offer opportunities to practice presentations of different types, each MBI post-doc gives (at least) one scientific talk each year in the Post-Doc Seminar and poster presentations at the annual Institute Partner Meeting and the annual Scientific Advisory Committee Meeting.
7) Each MBI postdoctoral fellow is encouraged to teach one course while at MBI. MBI has arrangements with the Mathematics Department to make this possible; opportunities in other departments are handled on a case-by-case basis. Post-docs are observed and provided with teaching feedback and coaching by departmental faculty or MBI directors.
8) MBI postdoctoral fellows are encouraged to participate as mentors in the MBI graduate and undergraduate summer schools; some post-docs participate as mentors for Ohio State undergraduate research projects in mathematical biology.
9) The post-docs receive professional mentoring in two ways:
    a. Monthly meetings of the post-docs with Mike Reed (Senior Scientific Advisor) and Tony Nance (Deputy Director). These meetings discuss grant writing, elevator talks, department politics, among many other topics.
    b. In informal discussions with members of the MBI Directorate
10) Collectively the post-docs have several responsibilities that allow them to practice their communication and organizational skills.
    a. They help write reports for the MBI scientific workshops (each workshop report is written by a group of three post-docs; each post-doc writes two reports). This activity provides an opportunity to practice writing and summarizing for a broader audience.
    b. The MBI post-docs organize the annual *Workshop for Young Researchers in Mathematical Biology* (WYRMB) with two post-docs chosen to take the lead.
    c. Each year one MBI post-doc represents the post-docs on the MBI Colloquium Committee. The post-docs are in charge of taking colloquium speakers to lunch.
    d. An MBI post-doc is asked to give a talk at the annual SACNAS meeting; occasionally other post-docs speak at other diversity meetings.

MBI Postdoctoral Fellows

MBI NSF Supported Postdoctoral Fellows 2015-16. In [...] we indicate the next positions for Post-docs who have finished their stay at MBI in 2016

1. **Casper Woroszylo**
2. **Leili Shahriyari**
3. **Matt Oremland [**Process data scientist: Regeneron Pharmaceuticals, Inc.]
4. **Farrah Sadre-Marandi**
5. **Wenrui Hao** [Assistant Professor: Math, Penn State U]
6. **Kim Fessel** [Data Scientist: Breaktime Media, Boston]

7. **Karly Jacobsen** [Applying for job in industry]
8. **Reginald McGee**
9. **Richard Buckalew** [Assistant Professor: Math, Minnesota - Duluth]
10. **Jeff Gaither**
11. **Min Wang**
12. **Joy Zhou** [Assistant Professor: Math, Lafayette]
13. **Marcio Duarte Albasini Mourao** [Data Science Consultant/Database Engineer: U Michigan, Consulting for Statistics, Computing and Analytics Research]

MBI Postdoctoral Fellow Hires from September 2016

1. **Punit Gandhi** (Physics, University of California at Berkeley)
2. **Colby Long** (Mathematics, North Carolina State University)
3. **Omar Saucedo** (Mathematics, University of Florida)
4. **Yangyang Wang** (Mathematics, University of Pittsburgh)

Post-doc Professional Development Seminar: This monthly meeting, led by **Mike Reed** and **Tony Nance,** gives postdoctoral fellows the chance to practice talks of all descriptions and to discuss career-related issues (such as grant writing, job application material, networking, etc.).

Short Course: In Autumn 2015 MBI Long Term Visitor **Ridgway Scott** (Computer Science and Mathematics, University of Chicago) presented an eight-lecture short course on *The Digital Nature of Biology* to MBI post-docs and visitors. More details about this course can be found at https://mbi.osu.edu/event/?id=991.

External Evaluation of MBI

MBI has a contract with Strategic Research Group (http://www.strategicresearchgroup.com/index.htm) to perform an independent evaluation of MBI programming based on online questionnaires and personal interviews.

Early Career Awards in 2015-16

ECA are competitively awarded annually by MBI to enable untenured tenure-track faculty to participate in MBI emphasis programs by **spending three-four months in residence at MBI.**

1. **Guang Lin**, Mathematics, Purdue University, Sep 25, 2015 – Dec 25, 2015
2. **Xueying Wang**, Mathematics, Washington State Univ, Jan 1 - May 31, 2016
3. **Casian Pantea**, Mathematics, West Virginia University, Jan 11 – May 10, 2016
4. **Rajeev Azad**, Biological Sciences, U North Texas, Jan 21 – May 18, 2016

Early Career Awards currently expected for 2016-17

1. **Lin Wan,** Chinese Academy of Sciences
2. **Juan Calvo,** University of Granada – Spain
3. **Nessy Tania**, Smith College
4. **Alan Veliz-Cuba**, University of Dayton
5. **Hye-Won Kang**, University of Maryland, Baltimore County
6. **Thomas Woolley**, Oxford University

Long Term Visitors in 2015-2016

1. **Fernando Antoneli**, Universidade Federal De São Paulo, Jan 23 – Mar 31, 2016
2. **Robert Eisenberg**, Molecular Biophysics and Physiology, Rush University Medical Center, Aug 17 – Oct 16, 2015
3. **Cheol-Min Ghim**, Physical Biology Biological Physics, Ulsan National Institute of Science and Technology, Aug 10, 2015 – Jul 9, 2016
4. **Kesh Govinder**, Mathematical Sciences, University of KwaZulu-Natal, Mar 1 – Dec 20, 2016
5. **Jae Kyoung Kim**, Department of Mathematical Sciences, Korea Advanced Institute of Science and Technology (KAIST), Jan 11 – Feb 28, 2016
6. **Xiulan Lai**, Renmin University of China, Jan 14 - May 1, 2016
7. **Ka Yin Leung**, Mathematical Institute, Utrecht University, Jan 21 – Apr 16, 2016
8. **Tong Li**, Department of Mathematics, University of Iowa, Sep 15 – Oct 15, 2015
9. **Zhiming Li**, Central China (Huazhong) Normal University, Sep 18 – Dec 16, 2015
10. **Jinn-Liang Liu**, Cell Biology and Applied Mathematics, National Hsinchu University of Education, Aug 13 – Nov 1, 2015
11. **Bibo Lu**, Mathematics, Michigan State University, Aug 20 – Dec 20, 2015
12. **Philip Maini**, Wolfson Centre for Mathematical Biology, University of Oxford, Jan 26 – Feb 28, 2016
13. **Maya Mincheva**, Northern Illinois University, Jan 24 – Feb 27, 2016
14. **Duc Nguyen**, Mathematics, Michigan State University, Aug 20 – Dec 20, 2015
15. **Eddie Nijholt**, Mathematics, University Amsterdam, Feb 22 – Mar 25, 2016
16. **Tatiana Orlova**, Computer Science, U Chicago, Sep 21 – Dec 14, 2015
17. **Maciej Pietrzak**, Biostatistics, Ohio State University College of Public Health, August 2015 - August 2016
18. **Mason Porter**, Mathematical Institute, University of Oxford, Mar 19 – Apr 16, 2016
19. **Ridgway Scott**, Computer Science and Mathematics, University of Chicago, Sep 14 – Dec 12, 2015
20. **Yane Wang**, Shaanxi Normal University, March 2016 - March 2017
21. **Guowei Wei**, Department of Mathematics, Michigan State University, Aug 22 – Dec 12, 2015
22. **Jacek Wesolowski**, Department of Probability and Mathematical Statistics, Warsaw University of Technology, Apr 2-29, 2016
23. **Dexuan Xie**, Department of Mathematical Sciences, University of Wisconsin-Milwaukee, Aug 31 – Dec 15, 2015
24. **Hyunmo Yang**, Physics, Ulsan National Institute of Science and Technology, Sep 1, 2015 – June 30, 2016

Long Term Visitors currently expected for 2016-17

1. **Yane Wang**, Shaanxi Normal University
2. **Kesh Govinder**, University of Kwa Zulu Natal
3. **Boseung Choi,** Korea University Sejong Campus
4. **Bill Kalies**, Florida Atlantic University
5. **Abel Palafox Gonzalez**, CIMAT – Mexico
6. **Konstantin Mischaikow**, Rutgers University
7. **Tomas Gedeon**, Montana State University
8. **Kelly Spendlove,** Rutgers University
9. **Yury Garcia Puerta,** CIMAT – Mexico
10. **Marcio Gameiro**, University de Sao Paulo at Sao Carlos

11. **Xiulan Lai**, Renmin University – China
12. **Mason Porter,** Oxford University
13. **Yangjin Kim**, Konkuk University – Seoul, Korea
14. **Arnd Scheel**, University of Minnesota
15. **Blerta Shtylla**, Pomona College
16. **Philip Maini**, Oxford University

Short Term Visitors in 2015-2016

1. **Caleb Bastian**, Princeton University, Nov 30 – Dec 6, 2015
2. **Ariel Fernandez**, AF Innovation, Nov 3-8, 2015
3. **Giuliana Indelicato**, Mathematics, University of Torino, Sep 27 – Oct 12, 2015
4. **Reidun Twarock**, Mathematics and Biology, U York, Sep 25 – Oct 15, 2015
5. **Eunok Jung,** Mathematics, Konkuk University, June 12-22, 2016

Ohio State University Course Release Visitors in 2015-2016

Fall Semester

1. **Ching-Shan Chou** (Math)
2. **Avner Friedman** (Math)
3. **Chuan Xue** (Math)

Spring Semester

4. **Adriana Dawes** (Math)
5. **David Terman** (Math)
6. **Daniel Thompson** (Math)
7. **Joe Tien** (Math)
8. **Catherine Calder** (Statistics)
9. **Shili Lin** (Statistics)
10. **David Sivakoff** (Statistics)
11. **Yunzhang Zhu** (Statistics)

MBI hosted three seminars each semester weekly during non-workshop weeks: The MBI Colloquium, the Postdoc Seminar, and the Long Term Visitor Seminar.

MBI Colloquium

The MBI Colloquium brings in prestigious researchers from around the world to give high-level talks to non-expert scientists as well as spend time with the MBI post-docs. The 2015-2016 MBI Colloquium speakers were:

1. **Tim Elston**, Applied Mathematics, University of North Carolina Chapel Hill
2. **Haim Bar**, Statistics, University of Connecticut
3. **Seth Sullivant**, Mathematics, North Carolina State University
4. **Marsha Rosner**, Ben May Department for Cancer Research, University of Chicago
5. **Paul Stoodley**, Microbial Infection and Immunity, Ohio State University
6. **Santiago Schnell**, Molecular & Integrative Biology; Computational Medicine & Bioinformatics; Brehm Center for Diabetes Research; University of Michigan
7. **Marty Golubitsky**, Mathematics and Mathematical Biosciences Institute, Ohio State University
8. **Luis Carvalho**, Mathematics and Statistics, Boston University
9. **Andrew Noymer**, Public Health, University of California – Irvine
10. **Michael Summers**, Chemistry and Biochemistry, University of Maryland

11. **Domitilla Del Vecchio**, Mechanical Engineering, Massachusetts Institute of Technology
12. **Arni S.R. Srinivasa Rao**, Biostatistics and Epidemiology, Augusta University
13. **Giovanni Parmigiani**, Biostatistics, Harvard University
14. **Herschel Rabitz**, Chemistry, Princeton University

MBI Post-doc Seminar

MBI Post-docs and visiting post-docs give a research talk in this seminar each year. In addition to the 13 supported MBI post-docs two additional visiting post-docs, Maciej Pietrzak and Ruchira Datta, spoke in the MBI Post-doc Seminar.

MBI Long Term Visitor Seminar

With the number and scientific breadth of visitors (of all varieties) seen above, MBI added a 3rd seminar series featuring talks by MBI Long Term Visitors. The 2015-2016 MBI Long Term Visitor Seminar speakers were:

1. **Bob Eisenberg** (Molecular Biophysics and Physiology, Rush University Medical Center)
2. **Jinn Liang Liu** (Applied Mathematics, National Hsinchu University of Education)
3. **Gunjan Agarwal** (Biomedical Engineering, Ohio State University)
4. **Tong Li** (Mathematics, University of Iowa)
5. **Guowei Wei** (Mathematics, Michigan State University)
6. **Chuan Xue** (Mathematics, Ohio State University)
7. **Ching-Shan Chou** (Mathematics, Ohio State University)
8. **Guang Lin** (Mathematics, Purdue University)
9. **Dexuan Xie** (Mathematical Sciences, University of Wisconsin-Milwaukee)
10. **David Terman** (Mathematics, Ohio State University)
11. **Cheol-Min Ghim** (Life Sciences, Ulsan National Inst of Science and Technology)
12. **Philip Maini** (Wolfson Centre for Mathematical Biology, University of Oxford)
13. **Janet Best** (Mathematics, Ohio State University)
14. **Fernando Antoneli** (Mathematics, Universidade Federal de Sao Paulo)
15. **David Sivakoff** (Statistics and Mathematics, Ohio State University)
16. **Xueying Wang** (Mathematics, Washington State University)
17. **Mason Porter** (Mathematical Institute, University of Oxford)
18. **Joe Tien** (Mathematics, Ohio State University)
19. **Jacek Wesolowski** (Mathematical Institute, Warsaw University of Technology)
20. **Rajeev Azad** (Biological Sciences, University of North Texas)

MBI Series Books Published by Springer in 2015-16

The Mathematical Biosciences Institute Lecture Series
Series Editors: **Marty Golubitsky, Michael Reed**
http://www.springer.com/series/13083

Volume 1: *Stochastics in Biological Systems*, Editors: **Michael Reed, Richard Durrett**

Volume 1.1 *Branching Process Models of Cancer* by **Richard Durrett**
Volume 1.2 *Stochastic Analysis of Biochemical Systems* by **David F. Anderson, Thomas G. Kurtz**
Volume 1.3 *Stochastic Population and Epidemic Models* by **Linda J.S. Allen**
Volume 1.4 *Stochastic Models for Structured Populations* by **Vincent Banseye, Sylvie Meleard**

Volume 1.5 *Stochastic Neuron Models* by **Priscilla E. Greenwood, Lawrence M. Ward**
Volume 1.6 *Probabilistic Models of Population Evolution* by **Etienne Pardoux**

MBI Institute Partners in 2015-2016

MBI currently has 64 Institute Partners (IPs), including the withdrawal of Rutgers University at Camden and the addition of two IPs added in 2015-2016:

1. University of Chicago
2. University of Wisconsin-Milwaukee

See https://mbi.osu.edu/participate/institute_partners/ for a complete list of MBI IPs.

Public Lecture series

MBI continued to be instrumental in the Science Sundays Public Lecture Series at OSU, including sponsoring a lecture by **Jill Pipher**. Science Sundays lectures are held monthly during the academic year, usually attract 150-250 individuals, and provide a forum to interest, engage, and inform the public about a wide range of current and emerging issues in science that touch our everyday lives.
http://artsandsciences.osu.edu/science-sundays

Workshops at IPs

From August 2015 – July 2016, MBI helped support two workshops held at MBI partner institutions.

1. **Howard University**, April 9, 2016: Travel Grant for young researchers to attend "Precision Medicine"
2. **Virginia Commonwealth University**, May 20-22, 2016: Travel Grant for young researchers to attend "BAMM! Biology and Mathematics through Medicine"

Diversity Initiatives:

Visiting Lecturer Program

The Visiting Lecturer Program (VLP) sponsors visits of mathematical biologists to institutions that have large numbers of undergraduate students who are members of groups that are under-represented in the mathematical sciences community. The purpose is to encourage members of these groups to go to graduate school and to develop careers in the mathematical biosciences. This program is one of the initiatives suggested by the MBI Diversity Committee. http://mbi.osu.edu/education/visiting-lecturer-program/ the 2015-2016 VLP lectures were:

1. **Talitha Washington**, Truman State University, April 15-16, 2016
2. **Talitha Washington**, CSU Channel Islands, April 29, 2016

MBI Conference Awards

The MBI Conference Award is a full travel award for an untenured junior faculty, postdoc, or graduate student to attend one MBI workshop of the winner's choice. MBI has worked with organizers to set up an evaluation procedure to identify winners at national meetings, including the SACNAS Modern Math Workshop, Blackwell-Tapia Conference, AWM Poster Sessions at JMM and the SIAM Annual Meeting, and NAM's annual Granville-Brown-Hayes Session at JMM. All of our award winners can be seen at http://mbi.osu.edu/about/diversity-statement/conference-award-winners/ .

Program Initiatives
2016-2017 Emphasis Programs

The theme for the **Autumn 2016 Emphasis Program** is *Analysis of Complex Data in Biological Systems*.

Within the next few years all fields of mathematical biology will be impacted by large amounts of complex data. Because of this, there are many new mathematical questions to be addressed. Should old simple models be thrown out and should we begin again with newer complex models? Or are there mathematical ways to use the new data to determine parameters in the old models more accurately and thus allow their parameters to be updated automatically in real time as the data stream in. These questions are fundamental to medical practice in acute crises, to the dynamical behavior of cells, to policy decisions about vaccination and epidemic spread, to the effects of climate change on ecological niches, and to our understanding of brain function.

Scientists now have huge amounts of data about processes that are only partially known or unknown. The question is: How can we use the data to gain new mechanistic understanding about how biological systems work? Some examples are:

- New techniques in imaging allow the collection of large amounts of patient data. Monitors give huge amounts of data on real time about organ and whole body physiology, as well as microbiomes. We can now understand better how we are different as well as how we are similar, and what consequences these differences have.
- Sensors can track individual animals and reveal complicated changes in ecological environments due to climate change. Cell phones can record geospatial information that can be useful when trying to understand the spread of diseases.
- New techniques allow biologists to observe subcellular behavior in real time.
- Moreover, these data can be connected in important ways. The evolution over relatively short times of pathogens within individuals affects the spread of disease in populations. So population dynamics is related to immune system dynamics.

This MBI emphasis program will explore new mathematical techniques that can be used in the analysis of complex data in a variety of biological systems and settings. Fields that can be expected to contribute to the understanding of complex data are combinatorics, probability theory, statistics, geometry, algebraic topology, control theory, and ordinary and partial differential equations.

The program will consist of four workshops. Workshop 1 will focus on geometric and topological methods of data analysis. Workshop 2 will focus on mathematical methods for analyzing data sets in cancer biology. Workshop 3 will discuss the ways of linking complex data with dynamical systems models in neuroscience. Workshop 4 will be devoted to the impact of new streaming data collection techniques on population biology from the cellular, the organismal, to the ecological level, with special emphasis on the dynamics of disease spread in real time.

Organizing Committee

- **Konstantin Mischaikow**, Mathematics, Rutgers
- **Qing Nie**, Biomedical Engineering & Mathematics, Univ of California, Irvine
- **Horacio Rotstein**, Department of Math Sciences, New Jersey Institute of Tech
- **Terence Speed**, Bioinformatics, Walter & Eliza Hall Institute of Medical Research
- **Vladimir Vacic**, Computer Science, University of California, Riverside
- **Michael Waterman**, Biological Sciences, Mathematics, and Computer Science, University of

Southern California

Planned Workshops for Autumn Semester 2016

1. *Topological, Geometric, and Statistical Techniques in Biological Data Analysis* (September 12-16, 2016)
2. *Models for Oncogenesis, Clonality and Tumor Progression* (Sept 26-30, 2016)
3. *Dynamical Systems and Data Analysis in Neuroscience: Bridging the Gap* (October 17-21, 2016)
4. *Population Models in the 21st Century* (November 14-18, 2016)

The theme for the **Spring 2017 Emphasis Program** is *Growth and Morphogenesis.*

Morphogenesis, the origin of form during the development of an organism, constitutes the processes by which simple cellular arrays are transformed into highly structured and often complex tissues, organs and appendages. The mechanisms of morphogenesis are exceptionally complex and diverse, and are only partially understood. There is a large experimental literature on how various genetic, physiological and morphological perturbations alter morphogenesis, but the interpretation of those results is largely done through verbal, conceptual and diagrammatic models. Although such models have an internal logic they are not quantitatively rigorous and typically do not suggest specific mechanisms other than simple single-level biological processes like transcription or translation. Mathematical modeling has played an important role in developing a deeper understanding of the capacities and limitations of various mechanisms. Problems in morphogenesis have also led to the development of new mathematics such as Turing systems and the development of multiscale modeling approaches.

Traditionally, mathematical modeling has focused on one particular spatial scale. However, we know that biological function arises from the integration of processes acting across multiple scales. In many cases, these scales are intimately coupled so that a separation of scales is not possible. This leads to the problem of how to couple models of different forms (deterministic, stochastic, agent-based) across scales and also the challenge of how to analyze them, both mathematically and computationally.

To have impact in biology, mathematical models must be validated and then used to make biologically testable predictions, or to help explain biological phenomena. To date, biological data have been quite coarse and rather static (especially in development), so high-level modeling involving partial differential equations has, by and large, been appropriate. However, we are now at the dawn of a new era in which, for the first time, we have spatiotemporal data. Thus the new challenges facing us are:

- How to collect robust summary statistics from biological data, ranging from expression of biomarkers to the structural changes in the morphology of growing tissues?
- What is the appropriate level of model description consistent with the data available?
- How do we integrate multimodal, multiscale data to allow us to determine parameter values in our models and subsequently validate our models?

To achieve advances in these areas requires a broad range of expertise and we propose three workshops which will bring together experts from a number of different disciplines to present the state of the art in their fields and to work together to arrive at a consensus on what are specific, focused challenges that can be addressed over the next five years.

This emphasis program was inspired by the upcoming 100th anniversary of the publication of D'Arcy Thompson's book *On Growth and Form*.

Organizing Committee

- **Tomas Alarcon**, Mathematical Biology, Centre de Recerca Matemàtica
- **Philip Maini**, Wolfson Centre for Mathematical Biology, University of Oxford
- **Frederik Nijhout**, Biology, Duke University
- **Pablo Padilla**, Institute for Applied Mathematics, National Autonomous University of Mexico (UNAM)

Planned Workshops for the Spring Semester 2017

1. *The biological Challenges in Morphogenesis* (February 20-24, 2017)
2. *Modelling of Tissue Growth and Form* (March 6-10, 2017)
3. *Hybrid Multi-Scale Modelling and Validation* (March 27-31, 2017)
4. *Women Advancing Mathematical Biology: Understanding Complex Biological Systems with Mathematics* (April 24-28, 2017). Sponsored in part by Microsoft Research.