International Conference on Stochastic Processes in Systems Biology, Genetics & Evolution

August 21-25, 2012

Hosted by the

Center for Theoretical Biological Physics
Department of Statistics
Office of Research

RICE

Rice University
Houston, Texas

ICSP2012

Welcome!

Welcome to the **2012 International Conference on Stochastic Processes in Systems Biology, Genetics, and Evolution** (ICSP2012) August 21-25, 2012 on the campus of Rice University, This meeting continues a long tradition of workshops and conferences organized, in part, by the **Center for Theoretical Biological Physics** (CTBP). This conference, ICSP2012, represents the collaborative efforts of CTBP, the Department of Statistics and the Office of Research at Rice University.

Stochastic processes are an important tool for building models of dynamic phenomena in biology, which include a random component. Systems biology has emerged as an important scientific discipline focused on understanding the functional properties of complex biological systems. Within an individual cell or a larger tissue, normal biological functioning depends on the interaction and signaling between cellular components and/or individual cells. The field of systems biology brings challenges not only in characterizing the essential structure of multi-scale phenomena but also the intrinsically stochastic (random) nature of the biological system. It is difficult to name a specific topic in systems biology in which probabilistic and/or statistical analysis do not play a major role.

Data-sets produced by large-scale DNA-sequencing efforts such as the Human Genome Project and recently, the Tumor Genome Atlas Project have revolutionized the long-standing fields of genetics and evolution. In particular, the sub-disciplines of population genetics, phylogenetic analysis continue to undergo a renaissance as these methods can shed light and understanding on the biological data-sets being generated in abundance. Biological applications have stimulated the development of analytical methods in stochastic process theory such as branching processes, Markov chains, models of diffusion and other categories of processes. The synergy has been present from the beginnings of modern biology, but now it undergoes an explosive growth.

This conference will focus on emerging trends within the field of systems biology with a focus on the statistical methodologies and probability models that are most valued within the field. Special attention will be given to emerging challenges in systems biology, such as exploring the role of cancer stem cells in tumor development and progression, characterizing the systems pathways in inflammation which trigger sepsis, models of antibiotic resistance, and many other challenges in genetics and evolution.

ICSP2012 incudes 7 symposia (42 short and long talks) and a poster session. We are complimenting the intensive research agenda of the conference with an opportunity for some social-professional networking by hosting a general “meet-n’-greet” reception on Tuesday evening, and another reception during the poster session on Friday afternoon. We invite all participants to attend each of the receptions.

On behalf of all our symposia organizers, and the members of the organizing committee, we hope everyone enjoys the conference.

ICSP2012 Local Organizing Committee

Marek Kimmel
Herbert Levine
Christopher M. Smith

ICSP2012

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Local Organizing Committee

Marek Kimmel, PhD
Professor of Statistics
Department of Statistics, and Bioengineering
Rice University
Houston, Texas (USA)

Herbert Levine, PhD
Professor of Bioengineering
Co-Director, Center for Theoretical Biological Physics
Department of Bioengineering
Rice University
Houston, Texas (USA)

Christopher M. Smith, PhD
Executive Director, Center for Theoretical Biological Physics
Associate Vice Provost for Research Initiatives & Outreach
Rice University
Houston, Texas (USA)

Oleg Igoshin, Rice University
Stephanie Hicks, Rice University
Sriram Iyengar, University of Texas
Ines Maria del Puerto, University of Extremadura, Spain

Scientific Committee

Seth Corey, Northwestern University

Michael W. Deem, Rice University, USA

Miguel Gonzalez, University of Extremadura, Spain

Shachi Gosavi, National Center for Biological Sciences, Bangalore, India

Patsy Hakkou, Leiden University, Netherlands

Oleg Igoshin, Rice University

Christine Jacob, INRA, Jouy-en-Josas, France

Peter Jagers, Chalmers University, Sweden

Marek Kimmel, Rice University

Amaury Lambert, Universite Paris 6, France,

Herbert Levine, University of California at San Diego

Gordon Mills, U.T. MD Anderson Cancer Center

Suhita Nadkarni, Salk Institute

José Onuchic, Rice University

David Rand, University of Warwick, UK

Yousif Shamoo, Rice University

ICSP2012

Conference Sponsors

This conference would not have been possible without the generous support of:

National Science Foundation, Division of Mathematical Sciences

National Science Foundation, Division of Physics

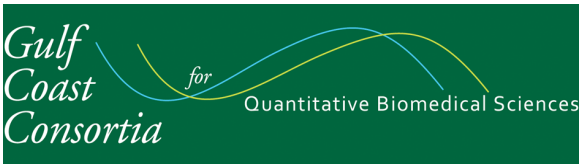
Center for Theoretical Biological Physics – Rice University

Department of Statistics – Rice University

Gulf Coast Consortium for Quantitative Biomedical Sciences

Office of Research – Rice University

Bioscience Research Collaborative – Rice University



This conference was supported in part by NSF awards **DMS-1217525** (Kimmel, Rice U) and **PHY-0822283** (Onuchic, UCSD/Rice U).

ICSP2012

General Information

All **ICSP2012** conference activities will be held at the Rice University Bioscience Research Collaborative (BRC) building 6500 Main Street, Houston. This building is on the far south end of campus (see the maps on the following pages), or you can visit:

http://www.rice.edu/maps/maps.html

Conference Registration Desk

The conference registration desk will be located in the BRC 1st Floor Lobby area just outside the Auditorium

Hours of Operation: 3:00 PM – 5:00 pm, August 20, Monday
7:00 AM – 5:00 pm, August 21, Tuesday
7:00 AM – 6:00 pm, August 22, Wednesday
7:00 AM – 6:00 pm, August 23, Thursday
7:00 AM – 5:00 pm, August 24, Friday
7:00 AM – 5:00 pm, August 25, Saturday

Your **conference program** and **nametag** can be picked up at the registration desk. In addition, registration desk staff will be able to help with most logistics issues.

Air Travel

Houston has two airports: William P. Hobby (HOU; 11 miles to the south of campus), and the George Bush Intercontinental (IAH; 24 miles to the north of campus. Intercontinental is a hub of global travel. Hobby is a hub for regional, domestic travel. Together they offer 1,000 flights a day in and out of Houston. Visit http://www.fly2houston.com/ for more information.

Ground Travel (To/From the Airports)

Taxi. Taxi fares in Houston are charged by zones and by meter. You may catch a taxi outside of the terminal. Anticipate taxi fares are about $28 from Houston Hobby and about $52 from George Bush Intercontinental, one way fares.

Shuttle Service. SuperShuttle (http://www.supershuttle.com/) provides one-way and round-trip service from both area airports. Reservations from the airport are preferred. Reservations for pick-up and transport to the airport are required. For more information call +1 713.523.8888 or visit www.supershuttle.com. The typical airport-Rice round-trip fare is ~$50.

Rental Cars. Information on rental car companies that serve the Houston area can be found on the airport Web site noted above. For more information, visit http://www.fly2houston.com/iah-Rental-Cars .

Driving Directions

Directions from both area airports to Rice University, along with campus maps, can be found on the Rice website at http://futureowls.rice.edu/futureowls/How_to_Get_Here.asp.

Public Transportation

Public transportation is available via the Houston Metro Light Rail. The closest stops are 'Museum District' and 'Memorial Hermann Hospital/Houston Zoo'. For more information on Metro Light Rail, visit http://www.ridemetro.org.

Participant Parking

Off-campus attendee's can park in the BRC garage for $11/day. **NOTE:** There are NO in-n'out privileges with the BRC garage.

Speaker Parking

Hilton Hotel

Speakers lodging at the Hilton Hotel Houston Plaza can park in the hotel without charge.

Local/Commuting Speakers:

Speakers from the Houston/Texas area commuting to the conference will be provided day passes (white credit card size tickets) to park in the Hilton Hotel Houston Plaza or BRC garages. **NOTE:** There is NO in-n'out service with the BRC garage, but there is at the Hilton Hotel garage. If you think you'll need to leave during the conference and return the same day ("in-n'-out" garage service), we highly recommend that you park at the Hilton Hotel garage.

For BRC garage: When you **initially** arrive at the BRC you'll need to use a personal credit card to gain entrance to the BRC parking garage. Then you'll need to pick-up a parking pass/ticket from the registration desk. When you leave for the day, insert your white parking ticket into the gate meter, then insert the credit card that you used to gain entrance in earlier in the day. **NOTE**: There is NO in-n'-out service with the BRC garage.

For Hilton Hotel garage: When you **initially** arrive at the hotel garage, be sure to get a gate ticket as you enter the garage. Then you'll need to pick-up a parking pass/ticket from the registration desk. IF you think you'll need in-n'-out garage service, ask for additional hotel parking passes. When you leave the hotel garage give your gate ticket and the white parking pass/ticket to the gate attendant. Repeat this process for in-n'-out service, using a new parking pass each time.

Lost-n'-Found

For lost or found items, please see the registration desk.

Speaker Talk/Slide Prep

We will make available the BRC auditorium on Monday, August 20, 3:00 – 5:00 pm and each conference day after the last talk of the day for speakers who wish to view/prep their presentation talks on the auditorium A/V equipment. There may be additional prep time made during the lunch hour, pending staff availblility.

A/V Service in Sessions

Each symposium session will have a dedicated A/V support person to assist and/or rectify any A/V issues. Most rooms are equipped for computer projection and audio, and a wireless microphone for the speaker. Although we will have available a collection of various VGA to HDMI/mini Display port connectors, we may not have your particular connector, so speakers are encouraged to bring the connector appropriate for their particular laptop. The later is particularly true for Apple computers.

Rice No-Smoking Policy

Rice maintains a tobacco-free policy. There is no smoking in any building on campus, and smoking outside must be at least 20 feet from any building egress (doors, windows, etc.).

Printing Travel Electronic Boarding Passes

There will be a computer and printer available at the registration desk to print electronic airline boarding passes.

Poster Session – Posting/Removing Posters

Poster presenters may begin posting Thursday afternoon (August 23). Please see a staff member at the registration desk for the mounting tape that you will use to mount your poster to the lobby walls. No other tape, pins, tacks, etc., are allowed to mount your poster to the wall. If you have issues mounting your poster, please see someone at the registration desk. Mount your poster to the space below and to the right of the poster number (already pre-mounted on the wall).

All posters need to be removed by Saturday (August 25) after the last session. We highly recommend that you or a colleague remove your own poster. Any posters remaining after the deadline will be removed and disposed. We do not have the resources to store and/or ship posters for those who do not retrieve their posters.

Weather/Attire

You can expect hot temperatures (90^{o}F+ / 32^{o}C+), humidity (~70%) and lots of sun during the day. Temperatures and the humidity during the evenings/nights will be slightly lower (but not by much). BRC, as are most all other buildings in Houston, are air-conditioned.

Internet (Wi-Fi) Service

Wi-Fi Internet service is generally available (without charge) anywhere on campus, if you log-in/register as a "Guest" when start your web browser. For information on wireless access at Rice University, please visit. If you have any issues with your wireless access, please see a staff member at the registration desk.

Cell Phones, Pagers, PDA & Other Electronic Devices

As a courtesy to other meeting attendees and your conference speakers, electronic devices must be operated in silent/vibrate mode will in all sessions. Cell phone conversations are not allowed during any symposia session. If you must take a call, please take your call out of the auditorium.

Contact Information

Christopher Smith (conference logistics, speaker/scholarship hotel reservations)
(713) 348-8160, cmsmith@rice.edu

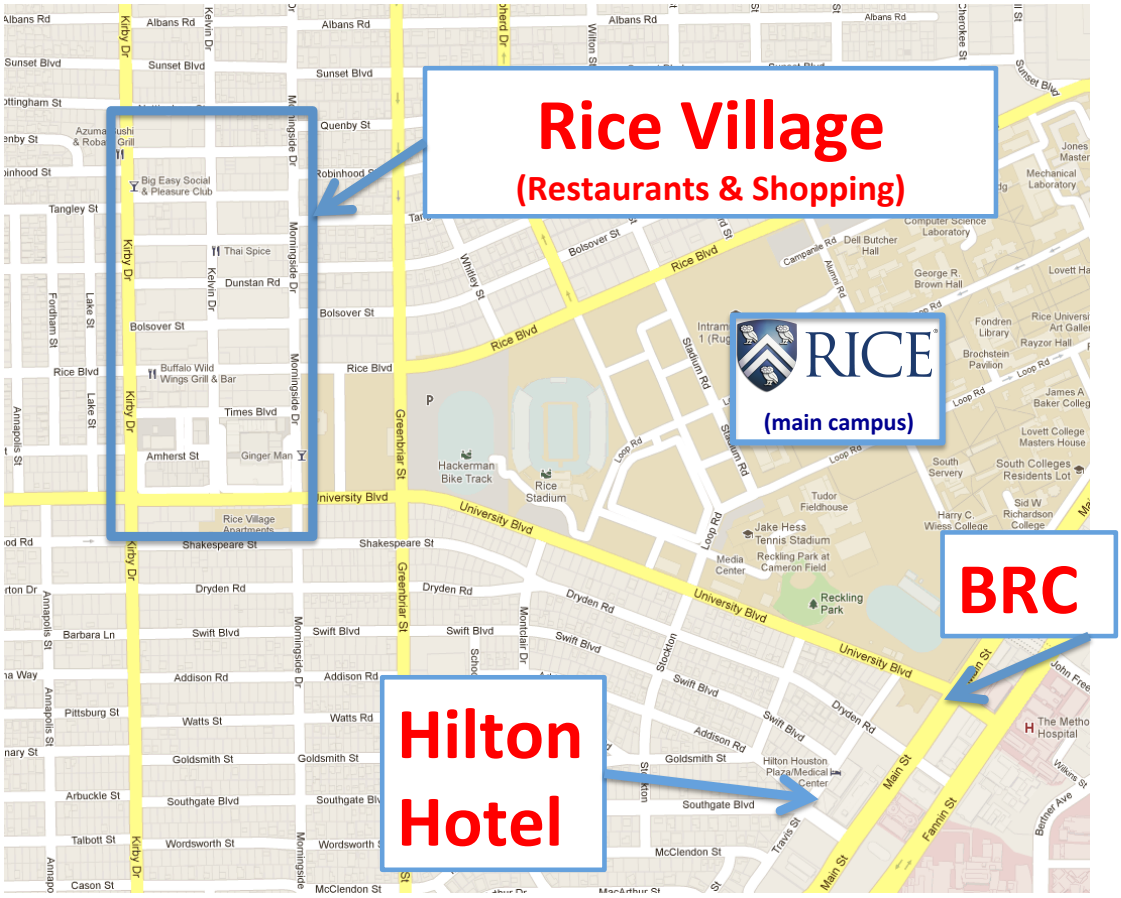
Local Area Map for ICSP2012 (@ BRC-Rice)

FOOD (lunch): For a relatively quick lunch there are a few "take-out/eat-in" eateries in the block highlighted in blue, bordered by Main Street, Dryden Rd and Fannin Street.

Local Area Map for ICSP2012

Dinner

Shopping



Rice Village is a muli-block collection of:

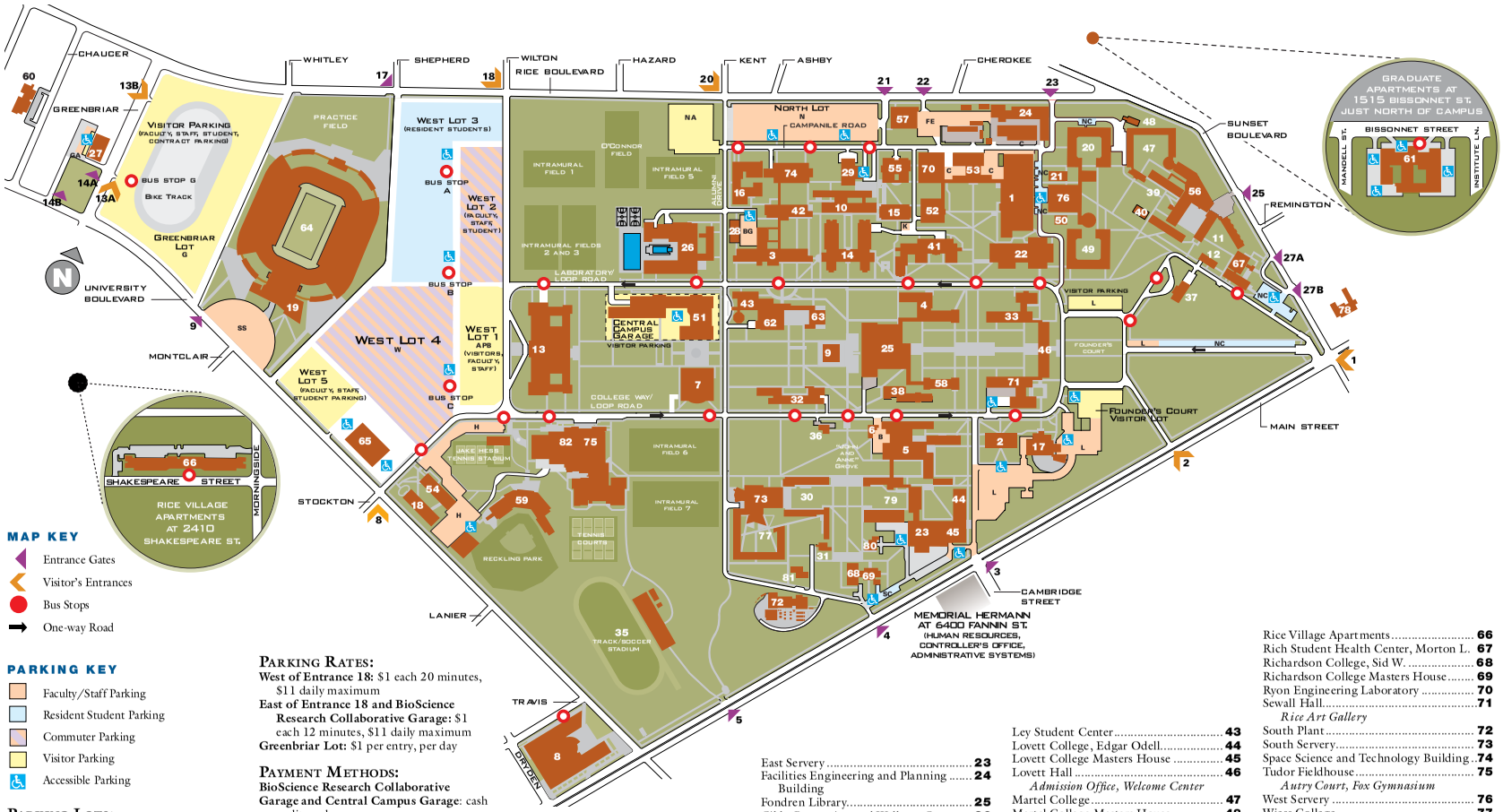
restaurants: http://www.ricevillageonline.com/dining.php

boutiques/shops: http://www.ricevillageonline.com/shopping.php

The variety of restaurants here make it an ideal spot for dinner.

Rice University Campus Map

6/2011



MAP KEY

- Entrance Gates
- Visitor's Entrances
- Bus Stops
- One-way Road

PARKING KEY

- Faculty/Staff Parking
- Resident Student Parking
- Commuter Parking
- Visitor Parking
- Accessible Parking

Parking Lots:

APB Alice Pratt Brown Hall Lot
B Baker College–Housing & Dining Lot
BG Biology–Geology Lot
BRC BioScience Research Collaborative Garage
C Campanile Lot
CG Central Campus Garage
FE Facilities, Engineering and Planning Lot
G Greenbriar Lot
GA Greenbriar Annex
H Hess Court Lot
K Keck Lot
L Lovett Lot
N North Lot
NA North Annex Lot
NC North Colleges Residents Lot
SC South Colleges Residents Lot
SS South Stadium Lot
W West Lot

Parking Rates:

West of Entrance 18: $1 each 20 minutes, $11 daily maximum
East of Entrance 18 and BioScience Research Collaborative Garage: $1 each 12 minutes, $11 daily maximum
Greenbriar Lot: $1 per entry, per day

Payment Methods:

BioScience Research Collaborative Garage and Central Campus Garage: cash or credit card
Greenbriar Lot, Founder's Court, North and West Lots Visitor Section: credit card

BUILDINGS

Abercrombie Engineering Laboratory 1
Allen Business Center 2
President's Office
Anderson Biological Laboratories, M.D. 3
Anderson Hall, M.D. 4
Dean of Architecture
Baker College 5
Baker College Masters House 6
Baker Hall, James A. III 7
Dean of Social Sciences, James A. Baker III Institute for Public Policy
BioScience Research Collaborative 8
Brochstein Pavilion, Raymond and Susan 9
Brockman Hall for Physics 10
Brown College, Margarett Root 11
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Dean of Wiess School of Natural Sciences
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ACADEMIC SCHOOLS

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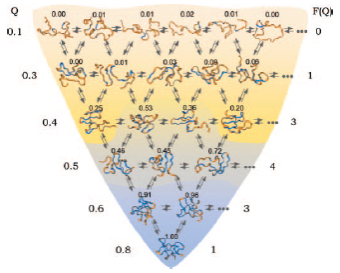
Continuing Studies, Susanne M. Glasscock School of 18
Engineering, George R. Brown School of 22
Humanities, School of 38
Music, The Shepherd School of 13
Natural Sciences, Wiess School of 14
Social Sciences, School of 7

Center for Theoretical Biological Physics

Rice University – Houston, Texas

The field of biological physics seeks to explain biological phenomenon through precise quantitative descriptions and modeling. Quantitative descriptions are based upon fundamental concepts and laws defined in engineering, physics, chemistry, etc. Therefore, biological physics research requires the expertise and approaches of a number of scientific and mathematical disciplines. CTBP biological physics research is an active collaboration between experimentalists (biochemists, geneticists, biologists) generating biological data in the laboratory, and theoreticians (physicists, mathematicians, chemists) who develop quantitative models to explain observed biological phenomena.



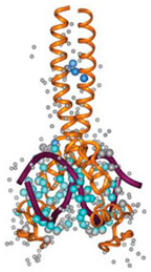
The **Center for Theoretical Biological Physics (CTBP)** is a consortium of researchers from Rice University, the University of California, San Diego, and the the Salk Institute for Biological Studies. Center research revolves around three synergy themes – ***Cellular Tectonics***, the dynamic mesoscale structure of the intracellular milieu (e.g., protein structure); ***Computational Approaches to Intracellular and Intercellular Communication,*** chemical-based reaction-diffusion governed communication across complex spaces (e.g., cell communication); and **Gene Regulatory Networks**, genetic/signaling networks that exhibit specificity and robustness in the face of intrinsic stochasticity, and yet retain evolvability (e.g., gene regulation).

CTBP **Graduate Students** are recruited through faculty in various academic departments at Rice University, the University of Houston, Baylor College of Medicine, the Salk Institute for Biological Studies, and the University of California, San Diego.

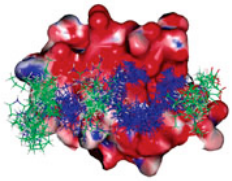
Post-Doctoral Scholars are recruited year-round. Although CTBP offers several CTBP PD fellowships, but most CTBP PD are supported by extramural awards to CTBP faculty. Regardless of CTBP, all PD involved in a CTBP core reaserch project enjoy the benefits and priviledges of the being an associate of the Center.

CTBP routinely hosts 2-3 ***Visiting Faculty Scholars*** each year for short visits and longer-term sabaticals to conduct collaborative research with CTBP faculty.

The Center is always recruiting undergraduate research interns, graduate students, postdoctoral fellows, and visiting faculty scholars. There are currently more than 110 undergraduate and graduate students, postdoctoral fellows and faculty associated with the Center. If you have additional questions or are interested in any of our research opportunities, please visit our web site or contact:



Christopher M. Smith, PhD.
Center for Theoretical Biological Physics, Rice University
6100 Main Street MS-654, Houston, Texas 77005
(713) 348-8160 cmsmith@rice.edu



http://ctbp.rice.edu

CTBP is a Physics Frontiers Center of the National Science Foundation

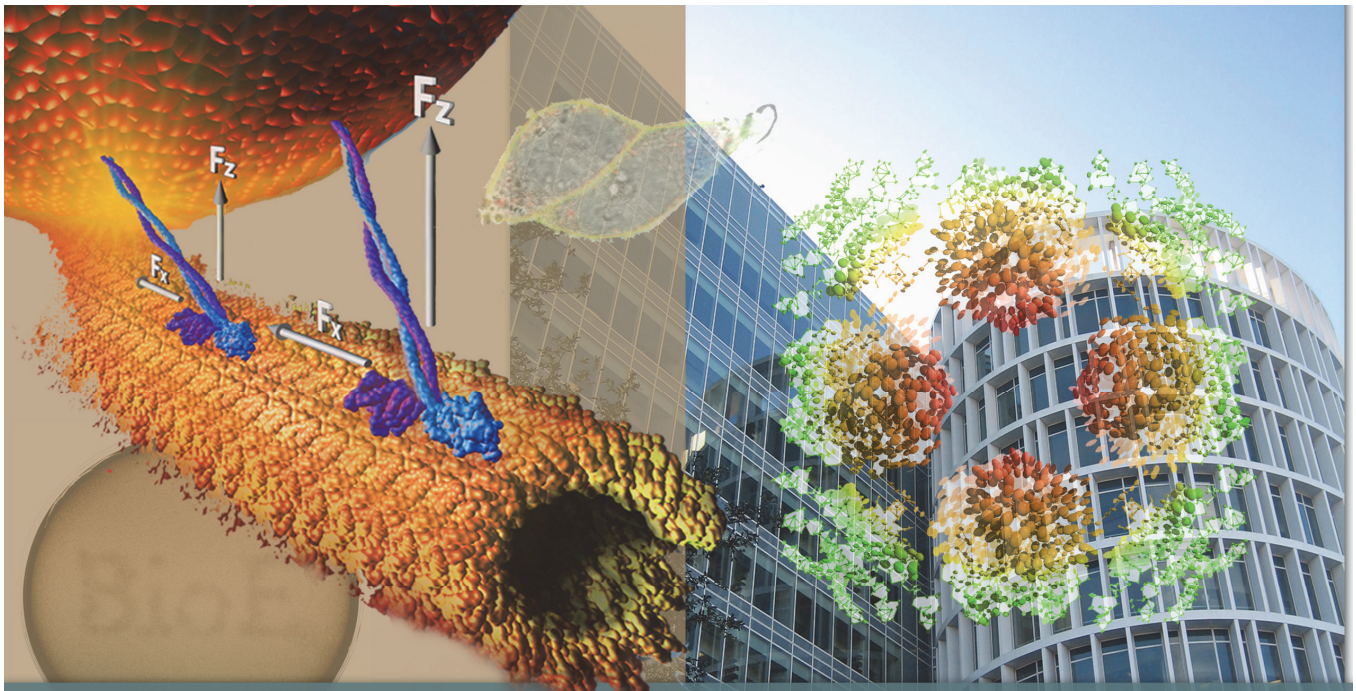
The Department of Statistics

The Department of Statistics at Rice University was founded in 1987 within the School of Social Science. In 1990, the Department transitioned to the School of Engineering rejoining the computational engineering faculty at Rice. In 1996 we moved from Herman Brown to the new computational engineering building, Duncan Hall, where we still reside today. In its initial stages, the Department of Statistics consisted of four core faculty, seven joint faculty and eight adjunct faculty with a graduate student body of fifteen students. The department has grown to a core faculty of ten, ten joint faculty and eighteen adjunct faculty with a Ph.D. student body of forty-five students and an undergraduate program that graduates five students per year.

In addition to the undergraduate B.A. degree, students may work towards one of the three graduate degrees offered: the professional master's degree, M.Stat (thesis not required); the research master's degree, M.A. (thesis required); and the doctoral degree Ph.D.

For additional information on the Statistics program at Rice, visit:

http://www.statistics.rice.edu/



Graduate Studies in Systems, Synthetic, and Physical Biology

sspb.rice.edu

Major breakthroughs in 21st century science and engineering will occur in research areas that lie at the interface of traditional disciplines. Systems and synthetic biology combine approaches from engineering, mathematics and computer science to fundamental and applied bioscience.

Rice University anticipates the launch of a new interdisciplinary Ph.D. program in Systems, Synthetic, and Physical Biology (SSPB) with enrollment beginning in the fall of 2013. The program will train students to combine principles from science, technology, engineering and mathematics to make transformative discoveries and advances in biological engineering. SSPB students will be highly interdisciplinary, with strong foundations in the quantitative and life sciences.

What is systems and synthetic biology?

Systems biology is the study of emergent properties of biological systems that cannot be understood by considering their parts in isolation. Synthetic biology is the purposeful design of unnatural biological systems using molecular genetic parts.

What is physical biology?

Physical biology is an integration of biology with chemistry, physics, mathematics, and computer science to provide a highly quantitative approach to problems in biology, biomedicine and biotechnology. By taking an interdisciplinary and mathematical approach to biology, the physical and chemical properties of molecular structures can be linked directly to their role within the organism.

Faculty

SSPB faculty come from eight departments across the George R. Brown School of Engineering and the Wiess School of Natural Sciences.

Genevera Allen, Statistics
George Bennett, Biochem & Cell Bio
Matthew R. Bennett, Biochem & Cell Bio
Cecilia Clementi, Chemistry
Dennis Cox, Statistics
Michael W. Deem, Bioengineering
Michael Diehl, Bioengineering
Ramon Gonzalez, Chem & Biomol Eng
Oleg A. Igoshin, Bioengineering
Lydia E. Kavraki, Comp Sci
Ching-Hwa Kiang, Physics & Astronomy
Herbert Levine, Bioengineering
Marek Kimmel, Statistics
Michael H. Kohn, Eco & Evol Bio
Anatoly B. Kolomeisky, Chemistry
Herb Levine, Bioengineering
Jianpeng Ma, Bioengineering
John T. McDevitt, Chemistry
Deepak Nagrath, Chem & Biomol Eng
Luay K. Nakhleh, Comp Sci
Jose Onuchic, Physics & Astronomy
George Phillips, Biochem & Cell Bio
Nicholas H. Putnam, Eco & Evol Bio
Amina A. Qutub, Bioengineering
Robert Raphael, Bioengineering
Ka-Yiu San, Bioengineering
Laura Segatori, Chem & Biomol Eng
Yousif Shamoo, Biochem & Cell Bio
Jonathan Silberg, Biochem & Cell Bio
Junghae Suh, Bioengineering
Jeffrey J. Tabor, Bioengineering
Peter Wolynes, Chemistry
Weiwei Zhong, Biochem & Cell Bio

RICE

Graduate Studies in Systems, Synthetic, and Physical Biology

sspb.rice.edu

Curriculum

The curriculum includes a newly developed *Fundamentals of SSPB* course designed to provide students from diverse backgrounds with exposure to a breadth of biological and quantitative topics. This includes at least two advanced courses in computer science, physics, applied mathematics or statistics, and two courses that focus on a biological subject within the area of a student's dissertation research. Students joining the SSPB program are expected to have prior training in biology, chemistry, computer science, engineering, mathematics, statistics, or physics.

Advanced classes

Experimental Synthetic Biology • Metabolic Engineering • Introduction to Computational Systems Biology Modeling • Design Principles of Biochemical Networks • Systems Biology of Blood Vessels • Gene Therapy • Macromolecular Systems Bioengineering • Computational Molecular Bioengineering / Biophysics • Protein Engineering • Systems Biology of Human Diseases • Biophysical Chemistry • Bioinformatics: Sequence to Structure • Bioinformatics: Sequence Analysis • Bioinformatics: Network Analysis • Evolution of Genes and Genomes • Evolutionary Bioinformatics • Topics in Evolutionary Biology - Graduate • Probability in Bioinformatics and Genetics • Probability and Statistics for Systems Biology

Major research areas

- Systems engineering in regenerative medicine
- Metabolic disease modeling
- Vaccines and the immune system
- Physical theories of evolution
- Membranes and molecular motors
- Regulatory network of embryonic stem cells and cancer stem cells
- Evolutionary analysis of genetic and proteomic circuits
- Computational modeling of the vasculature
- Algorithms relating clinical data with intracellular networks
- Synthetic gene circuits
- Engineering pattern formation
- Systems biology of proteostasis

RICE

2012 International Conference on Stochastic Processes in Systems Biology, Genetics and Evolution

Gulf Coast Consortia for Quantitative Biomedical Sciences

GCC, created in 2001, fosters interdisciplinary approaches to biomedical science to breakdown barriers and build bridges, increase cooperation and collaboration, and train young scientists for the future.

GCC, located in the BioScience Research Collaborative, is committed to building strong, interdisciplinary training opportunities as well as critical collaborative research groups across its six member institutions. Noted for creating an extraordinarily impactful and innovative collaboration, GCC was chosen as a finalist for the 2011 Collaboration Prize from more than 800 candidates.

Individual centers of research form **GCC Research Consortia**, research arm of GCC. These consortia catalyze cross-institutional interactions, provide a support for collaborative research, acquire funding for research centers and shared facilities and equipment, and sponsor workshops and conference that foster collaboration.

- GCC for Bioinformatics; Chair: Olivier Lichtarge, Baylor College of Medicine
- John S. Dunn GCC for Chemical Genomics; Chair: Peter Davies, Institute for Biosciences & Technology, Texas A&M Health Science Center
- John S. Dunn, Sr. GCC for Magnetic Resonance; Chair: David Gorenstein, UTHealth
- GCC for Protein Crystallography; Chair: Robert O. Fox, University of Houston
- GCC for Theoretical & Computational Neuroscience; Chair: Steve Cox, Rice University
- GCC for Translational Pain Research; Chair: Patrick Dougherty, M. D. Anderson Cancer Center
- Gulf Coast Cluster for Early Disease Detection; Chair: John McDevitt, Rice University
- GCC Coast Cluster for Translational Addiction Sciences; Chair: Kathryn Cunningham, UT Medical Branch at Galveston

As the training arm of GCC, the **Keck Center** (organized in 1990) maintains multiple inter-institutional training programs designed to address national shortages of interdisciplinary bioscience researchers. These seven training programs, comprised of more than 60 trainees and 450 faculty from GCC member institutions, provide a uniquely rich intellectual environment where novice and experienced researchers are encouraged to pursue interdisciplinary science. There are additional summer programs for undergraduates.

- Training Program in Patient Safety and Quality; PI: Dean Sittig, UT Health Science Center-Houston; AHRQ
- Biomedical Informatics & Computational Biology; PI: Tony Gorry, Rice University; NLM
- Computational Cancer Biology; PI: Monte Pettitt, University of Houston; CPRIT
- Interdisciplinary Graduate Nanobiology; PI: Rebekah Drezek, Rice University; NIBIB
- Molecular Biophysics Program; PI: Ted Wensel, Baylor College of Medicine; NIGMS
- Pharmacological Sciences; PI: John F. Hancock, UT Health Science Center-Houston; NIGMS
- Theoretical & Computational Neuroscience; PI: Peter Saggau, Baylor College of Medicine; NIBIB

For more information, contact Karen S. Ethun, Executive Director, GCC, kethun@rice.edu.

PO Box 1892, MS 141, Houston, Texas 77251-1892 *www.gulfcoastconsortia.org*

A collaboration of:
Baylor College of Medicine
Rice University
University of Houston
University of Texas Health Science Center at Houston
University of Texas Medical Branch at Galveston
University of Texas MD Anderson Cancer Center

ICSP2012

Conference Schedule

Tuesday – Saturday

*All **symposium sessions** will be held in the Bioscience Research Collaborative Auditorium (1st Floor)*

*The **poster session** will be held in the Bioscience Research Collaborative Lobby (1st Floor)*

*The **"Meet-n'-Greet" Reception** (Tuesday) will be held in the Bioscience Research Collaborative 2rd Floor Patio*

Tuesday, August 21
Schedule

7:30 Coffee (BRC 1st Floor Foyer)

8:00 Welcome (BRC Auditorium, 1st Floor)
Marek Kimmel, Prof Statistics
Herbert Levine, Prof Bioengineering & Co-Director, CTBP
Vicki Colvin, Prof, Chemical & Biomol Engineering & Vice Provost for Research
Katherine Ensor, Prof & Chair, Statistics
Michael Deem, Prof Bioengineering

8:30 – 12:20 **Morning Symposium** (BRC Auditorium, 1st Floor)

Systems Biology, Genetics and Evolution: New Challenges for Stochastic Dynamics (Michael Deem)

8:30 **Imaging Dynamics and Heterogeneity in Cell Signaling and Transcription**
Michael White, University of Manchester

9:10 **A Systems Biology Approach to Drug Development and Implementation**
Gordon B. Mills, MD Anderson Cancer Center

9:50 **Sorting Variation Outcomes: A Perturbative View of the Genotype-Phenotype Relationship**
Olivier Lichtarge, Baylor College of Medicine

10:30 Session Break

11:00 **Evolution Modularity in Biological Systems**
Michael Deem, Rice University

11:40 **Geometry, Epistasis, and Developmental Patterning**
Eric Siggia, Rockefeller University

12:20 – 2:00 Session Break – Lunch

[*Tuesday schedule (afternoon) continued on next page*]

2:00 – 5:50 **Afternoon Symposium** (BRC Auditorium, 1st Floor)

Stochastic Processes for New Biology (Christine Jacob)

2:00 **Population Genetics Stochastic Process Models Forward and Backward in Time**
Robert Griffiths, University of Oxford

2:40 **A Phylogenetic Confidence Interval for the Optimal Trait Value**
Serik Sagitov, Chalmers Institute of Technology

3:20 Session Break

3:50 **Information Transmission in Small Gene Regulatory Networks**
A**leksandra Walczak**, Ecole Normale Supérieure

4:30 **Limit Models for a General Class of Branching Processes with Memory and Population Dependence in Large Populations**
Christine Jacob, French National Institute for Agricultural Research

5:10 **Discovery of Mechanisms and Prognosis of Cancers from Mathematical Modeling of Large-Scale Molecular Biological Data**
Orly Alter, University of Utah

6:00 **Reception** (BRC 2nd Floor Patio)

Wednesday, August 22
Schedule

8:30 Coffee (BRC 1st Floor Foyer)

9:00– 12:10 **Morning Symposium** (BRC Auditorium, 1st Floor)

Stochasticity of Cell Differentiation and Cell Fates (Seth Corey)

9:00 **Stem Cell Fate in Hematopoiesis = Determinism + Stochasticity**
Seth Corey , Northwestern University

9:40 **An Endogenous Accelerator for Gene Expression provides a Fitness Advantage**
Leor Weinberger , University of California San Francisco

10:20 Session Break

10:50 **On Passenger and Driver Mutations: A Mathematical Modeling Approach**
Cristian Tomasetti , Harvard University

11:30 **Heterogeneity and Nonlinear Dynamics in Single Cells and Biofilms**
Gürol M. Süel, University of Texas Southwestern Medical Center

12:10 – 2:00 Session Break – Lunch

2:00 – 5:00 **Afternoon Symposium** (BRC Auditorium, 1st Floor)

Stochastic Processes of Cancer (Marek Kimmel)

2:00 **Cancer as a Complex System: Insights from Stochastic Modeling**
Natalia Komarova, University of California Irvine

2:40 **Stem Cell Dynamics in Normal Human Colon Crypts and the Progression to Colon Cancer**
David Axelrod, Rutgers University

3:20 Session Break

3:50 **Hijacking Homeostatsis: How Heterogeneity Drives Tumor Progression and Treatment Failure**
Alexander R. A. Anderson, Moffitt Cancer Center

4:30 **The Genomic Landscape of DNA Double-Strand Breaks Induced by Replication Stress**
Maga Rowicka, University of Texas Medical Branch

Thursday, August 23
Schedule

8:30 Coffee (BRC 1st Floor Foyer)

9:00– 12:20 **Morning Symposium** (BRC Auditorium, 1st Floor)

Stochastic Gene Expression and Intracellular Signaling I (Tomasz Lipniaki)

9:00 **Information Capacity of Signaling Networks: Where are the Bottlenecks?**
Andre Levchenko, John Hopkins University

9:40 **Heterogeneity of Proliferating Cell Populations: Models and Data**
Marek Kimmel, Rice University

10:20 Session Break

10:50 **Networks, Noise and Evolution: Lessons from Synthetic Gene Circuits**
Gábor Balázsi, The University of Texas MD Anderson Cancer Center

11:30 **Ultrasensitivity and Stochasticity of the *Bacillus subtilis* Sporulation Decision**
Oleg Igoshin, Rice University

12:10 – 2:00 Session Break – Lunch

2:00 – 5:30 **Afternoon Symposium** (BRC Auditorium, 1st Floor)

Stochastic Gene Expression and Intracellular Signaling II (Andre Levchenko)

2:00 **Sex and Arithmetic in Nematodes**
Scott Rifkin, University of California San Diego

2:40 **Computational Model for Autophagic Vesicle Dynamics in Single Cells**
William Hlavacek, Los Alamos National Laboratory

3:20 Session Break

3:50 **Next Generation Sequencing for Metagenomics: Bioinformatics Challenges**
Yuriy Fofanov, University of Houston

4:30 **State-Space Collapse in Modeling Stochastic Phenomena**
Adam Bobrowski, Lublin University of Technology

4:50 **Stochastic NF-κB Activation via Autocrine TNFα Signaling**
Tomasz Lipniacki, Institute of Fundamental Technological Research

Friday, August 24
Schedule

8:30 Coffee (BRC 1st Floor Foyer)

9:00– 12:30 **Morning Symposium** (BRC Auditorium, 1st Floor)

Self Organization, Epigenetics & Evolution (Oleg Igoshin)

9:00 **A Quantitative Narrative for the Living Cell: From Precise Measurements to General Principles**
Ido Golding, Baylor College of Medicine

9:40 **Demographic Noise in Darwinian Evolution: Application to Bacterial Competence**
Herbert Levine, Rice University

10:20 Session Break

10:50 **Cancer Attractors and Non-Genetic of Cancer Cell Population Heterogeneity – Implications for Mutation-Less Progression of Cancer**
Sui Huang, Institute for Systems Biology

11:30 **Multicellular Organization of Capillary Development**
Amina Ann Qutub, Rice University

12:10 **Identifying the Dynamic States of the 3D Genome Organization**
Andrzej Kudlicki, University of Texas Medical Branch

12:30 – 2:00 Session Break – Lunch

2:00 – 5:00 **Afternoon Symposium** (BRC Auditorium, 1st Floor)

Poster Session & Reception

Saturday, August 25
Schedule

8:00 Coffee (BRC 1st Floor Foyer)

9:00 – 12:30 **Morning Symposium** (BRC Auditorium, 1st Floor)

Branching Processes in Population Biology & Genetics (Peter Olofsson)

9:00 **Controlled Branching Processes in Varying Environment**
Inés M. del Puerto, University of Extremadura

9:40 **AIDS: The Mismanagement of the Epidemic in the United States**
James R. Thompson, Rice University

10:20 Session Break

10:50 **General Branching Processes and Cell Populations**
Peter Oloffson, Trinity University

11:30 **The Signature of Selective Sweep: Learning from a Warfarin Resistance Locus in Rats**
Shuwei Li, Rice University

11:50 **Sex-linked Branching Processes**
Miguel González, University of Extremadura

12:30 – 2:00 Session Break – Lunch

2:00 – 4:50 **Afternoon Symposium** (BRC Auditorium, 1st Floor)

Stochastic Theory for Biochemical Systems (Marek Kimmel)

2:00 **Limiting Behavior of Chemical Reaction Systems**
Denis Cox, Rice University

2:40 **Modeling And Parameter Estimation Of Feedback Loops In NF-κB Signaling**
Allan Brasier, University of Texas Medical Branch

3:20 Session Break

3:50 **Systems Biology Analyses of Inflammatory Signaling in Time and Space**
Pawel Paszek, University of Manchester

4:10 **Solution Surfaces of Genetic Networks and Applications**
Gemunu H. Gunaratne, University of Houston

4:30 **Computation of Most Likely Genetic Evolution Paths for Bacterial Population Models**
Robert Azencott, University of Houston

ICSP2012

Symposium Sessions

Speaker Abstracts

Tuesday – Saturday

Bioscience Research Collaborative
Auditorium (1st Floor)

Systems Biology, Genetics and Evolution: New Challenges for Stochastic Dynamics

Tuesday, August 21, 8:30 – 12:30
Session Chair: Michael Deem

Imaging Dynamics and Heterogeneity in Cell Signaling and Transcription

Michael White
Faculty of Life Sciences
University of Manchester
Manchester, United Kingdom

Cell populations are almost always heterogenous in their function and fate. To understand cell fate decisions, it is vital to measure quantitively and dynamically the molecular processes that underlie cell-fate decisions in single cells. Early signalling events often occur within seconds of stimulation, whereas intracellular signalling and transcriptional changes may take minutes or hours. Cell-fate decisions, such as whether a cell divides, differentiates or dies, can take many hours or days. Multiparameter experimental and computational approaches to integrate quantitative measurements and mathematical simulations are required to understand the highly dynamic mechanisms that control cell fate.

We measured transcription dynamics using combined fluorescence and luminescence imaging (Harper *et al.,* (2011) *PLOS Biology*, **9**(4):e1000607). Regular pulses (oscillations) of transcription can arise from single gene copies. Timing of oscillations in prolactin promoter-directed expression showed low correlation between single gene copies in the same cell. These cycles appeared to arise from periods of chromatin opening and closing and the cyclicity appeared to result from a refractory period that could represent chromatin remodelling. These data suggest that stochastically-phased oscillatory cycles of transcription might arise from single gene copies in the absence of regulatory feedback loops.

We have observed NF-κB nuclear cytoplasmic oscillations (Nelson *et al.,* (2004) *Science* **306**: 705) and have observed that their frequency can control the pattern of downstream gene expression (Ashall *et al., Science,* (2009) **324**: 242). I will discuss the control of dynamics and cell-to-cell heterogeneity (Paszek P *et al. (2010) Proceedings of the National Academy of Sciences of the United States of America* **107**:11644-11649) in the timing of NF-κB oscillations as well as their potential functional importance.

A Systems Biology Approach to Drug Development and Implementation

Gordon B. Mills
University of Texas M. D. Anderson Cancer Center
Houston, Texas USA

The realization of the promise of personalized molecular medicine will require the efficient development and implementation of novel targeted therapeutics. The goal will be to deliver the right drug to the right patient at the right time at the right dose. This effort will require a integration of information from the DNA, RNA and protein level into predictors of which patients are likely to respond to particular therapies. The overall likelihood of response to particular drugs represents the interaction between predictors of sensitivity with predictors of resistance. Efficient clinical trials testing these precepts will require the development and implementation of novel trial designs. It is likely that we will need to increase the size of phase I and II trials to allow the identification and validation of molecular markers at the same time as the initial evaluation the toxicity and efficacy of targeted therapeutics. This will come with the advantage of being able to deliver targeted therapeutics to enroll a much smaller population of patients selected for the likelihood to respond in phase III trials accelerating the approval of effective targeted therapeutics.

The phosphatidylinositol 3'kinase (PI3K) pathway is aberrant at multiple levels across a wide variety of tumors making it the most common activating aberration in cancer. This has led to the development and now early clinical testing of drugs targeting multiple components of the pathway. The efficient utilization of these drugs will require the ability to accurately determine mutation and activation status in tumors as well as determining the interaction between the PI3K pathway and other pathways in driving tumor pathophysiology. Using a novel accurate and sensitive mass spectroscopy based sequencing approach, we have evaluated mutations in the PI3K pathway across more than 500 breast cancer samples. We have also implemented a high throughput functional proteomics approach designated reverse phase protein arrays to characterize the level and activity of multiple signaling pathways. We demonstrate than an integrated analysis of mutation, proteins levels and protein activity is able to predict lack of response to trastuzumab in patients and to novel drugs targeting the PI3K pathway in vitro. This demonstrates that the response to targeted therapeutics is due to an interaction of markers of sensitivity and markers of resistance and provides important approaches for patient selection.

The PI3K pathway is critically important to cellular function and is thus under exquisite homeostatic control. The feedforward and feedback loops in the pathway determine the response to perturbation of the pathway by mutation or therapeutic intervention. Strikingly inhibition of the pathway at the level of mTOR or AKT results in the activation of potent feedback loops resulting in activation of multiple cell surface tyrosine kinases, PI3K itself and in the case of mTOR inhibitors, AKT. This may contribute to the observation that mTOR inhibitors appear to make some patient tumors grow more rapidly an unexpected and disappointing consequence of targeted therapeutics. Our preliminary systems biology-based mathematical and experimental models of the PI3K signaling network accurately predict these consequences as well as the biochemical processes involved. Further, the models suggest combinations of targeted therapeutics likely to reverse the negative effects of the mTOR inhibitors converting the outcome from negative to positive in terms of tumor growth.

Systems biology is the study of the emergence of functional properties that are present in a biological system but that are not obvious from a study of its individual components. Systems biology is a data-driven process requiring comprehensive databases at the DNA, RNA, and protein level to integrate systems

biology with cancer biology. Combining these patient and model-based databases with the ability to interrogate functional networks by a systematic analysis using siRNA libraries and chemical genomics provides an ability to link in silico modeling, computational biology, and interventional approaches to develop robust predictive models applicable to patient management.

Sorting Variation Outcomes: A Perturbative View of the Genotype-Phenotype Relationship

Olivier Lichtarge
Baylor College of Medicine
Houston, Texas, USA

The genotype-to-phenotype relationship is central to life. Its response to variations impacts health in the short term and evolution over the long term. Yet, the unique structural and cellular context of any given mutation has precluded direct mathematical modeling thus far. Here, we propose a first principles equation for the action of genotype variations on protein molecular phenotype. A central component of this equation is the evolutionary gradient, which is a quantitative measure of evolutionary importance that identifies key determinants of molecular function. More broadly, the action of mutations predicted by the whole equation correlates with the effects of missense mutations in vitro and in vivo, and it sorts the impact of protein coding variations across the human population as well as in some specific diseases. In theory, this analytic view of evolution suggests a tie between evolution and traditional variational principles while, in practice, having broad practical applications to annotate and engineer proteins and to interpret human variations in health and disease.

Evolution of Modularity in Biological Systems

Michael W. Deem
Departments of Bioengineering and Physics & Astronomy
Rice University
Houston, Texas USA

I will discuss the evolution of modularity in examples from the natural world. Dynamical systems typically evolve in a changing environment, and I will show that the level of modularity correlates with the rapidity and severity of environmental change. Emergence of modularity is driven by noise in the environment and is facilitated by horizontal gene transfer. This mechanism is evident in a number of systems, from viruses and bacteria to development and physiology. Bacterial metabolic networks show increasing modularity as the physical environment or horizontal gene transfer rate increases, and experimental protein interaction data shows that protein networks have become increasingly modular over the last four billion years. More recently, modularity provides early warnings in the evolution of influenza flu strains and in heart rate anomalies in physiology. I will describe a quasispecies theory for the evolution of modularity. Techniques from field theory will be used to provide an analytic solution to this theory.

Geometry, Epistasis, and Developmental Patterning

Eric Siggia
Rockefeller University
New York, New York USA

Developmental signaling networks are composed of dozens of components whose interactions are very difficult to quantify in an embryo. Geometric reasoning enumerates a discrete hierarchy of phenotypic models with a few composite variables whose parameters may be defined by in vivo data. Vulval development in the nematode *Caenorhabditis elegans* is a classic model for the integration of two signaling pathways; induction by EGF and lateral signaling through Notch. Existing data for the relative probabilities of the three possible terminal cell types in diverse genetic backgrounds as well as timed ablation of the inductive signal favor one geometric model and suffice to fit most of its parameters. The model is fully dynamic and encompasses both signaling and commitment. It then predicts the correlated cell fate probabilities for a cross between any two backgrounds/conditions. The two signaling pathways are combined additively, without interactions, and epistasis only arises from the nonlinear dynamical flow in the landscape defined by the geometric model. In this way, the model quantitatively fits genetic experiments purporting to show mutual pathway repression. The model quantifies the contributions of extrinsic vs. intrinsic sources of noise in the penetrance of mutant phenotypes in signaling hypomorphs and explains available experiments with no additional parameters. Data for anchor cell ablation fix the parameters needed to define Notch autocrine signaling.

Stochastic Processes for New Biology

Tuesday, August 21, 2:00 – 5:10
Session Chair: Christine Jacob

Population Genetics Stochastic Process Models Forward and Backward in Time

Robert Griffiths
University of Oxford
Oxford, United Kingdom

Classical stochastic process models in population genetics describe how a population of genes evolves forward in time under random drift, mutation, selection and recombination. Examples are the Wright-Fisher diffusion process; Moran models, which are birth and death processes; and Cannings models, where parents have an exchangeable offspring distribution. Coalescent models, which are random trees or graphs, describe the ancestral lineages of samples of genes back in time. These backwards and forwards models belong together technically as dual stochastic processes. This talk will discuss examples of forwards and backwards in time models. Forwards the models are the Wright-Fisher diffusion process; Fleming-Viot diffusion process describing DNA sequence evolution; and Moran models with multiple offspring and selection. The backwards models describing ancestral lineage history are respectively the Kingman coalescent process; Gene trees, which are perfect phylogenies constructed from mutation patterns on DNA sequences; and branching coalescing lineage graphs.

A Phylogenetic Confidence Interval for the Optimal Trait Value

Serik Sagitov
Chalmers Institute of Technology
Gothenburg, Sweden

We consider a model for adaptive evolution of a phenotype across a family of n related species with unknown phylogeny. The unknown species tree is modeled by the Yule process conditioned on having n tips. The trait value is assumed to evolve along a lineage as an Ornstein–Uhlenbeck process characterized by a certain adaptation rate and unknown optimal trait value. For the vector of n trait values describing the outcome of such an evolution we study the moments of the sample mean and sample variance. Our analytical and simulation results lead to a simple confidence interval for the optimal trait value when the adaptation rate is larger than half the speciation rate.

This is a joint work with Krzysztof Bartoszek.

Information Transmission in Small Gene Regulatory Networks

Aleksandra Walczak
Laboratoire de Physique Théorique
Ecole Normale Supérieure
Paris, France

Many of the biological networks inside cells can be thought of as transmitting information from the inputs (e.g., the concentrations of transcription factors or other signaling molecules) to their outputs (e.g., the expression levels of various genes). On the molecular level, the relatively small concentrations of the relevant molecules and the intrinsic randomness of chemical reactions provide sources of noise that set physical limits on this information transmission. Given these limits, not all networks perform equally well, and maximizing information transmission provides a optimization principle from which we might hope to derive the properties of real regulatory networks. Inspired by the precision of transmission of positional information in the early development of the fly embryo, I will discuss the properties of specific small networks that can transmit the maximum information. Concretely, I will show how the form of molecular noise drives predictions not just of the qualitative network topology but also the quantitative parameters for the input/output relations at the nodes of the network. I will show how the molecular details of regulation change the networks ability to transmit information.

Limit Models for a General Class of Branching Processes with Memory and Population Dependence in Large Populations

Christine Jacob
Department of Applied Mathematics and Informatics
French National Institute for Agricultural Research
Joey-e-Josas, France

We consider a general class of multitype branching processes in discrete time with memory and population size dependence, that may be particularly useful in population dynamics. In this general setting the long term behavior of this class of processes is an open difficult question. So we rather consider the limit models of this process, as the initial population size tends to ∞, either when normalized by the current size of the whole population, or without normalization, considering then only rare types of the process. In the first setting, we show that the normalized process, as long as it is not extinct, has some asymptotic behavior as the corresponding deterministic dynamical system on individual probabilities. In the second setting, we show that the limit process concerning the rare types, may be reduce to a memory-dependent Bienaymé-Galton-Watson process (extension of the classical singletype BGW process). We study the asymptotic time behavior of this class of processes. Moreover, in the subcritical case, we give the distribution of the extinction time and of the size of the tree until extinction. In both settings (nonrare types or rare types), we give a upper bound of the error between the original process (or its transitions) and the limit.

Discovery of Mechanisms and Prognosis of Cancers from Mathematical Modeling of Large-Scale Molecular Biological Data

Orly Alter
USTAR Associate Professor of Bioengineering and Human Genetics
Scientific Computing and Imaging Institute
University of Utah
Salt Lake City, Utah USA

In my Genomic Signal Processing Lab, we develop generalizations of the matrix and tensor computations that underlie theoretical physics, and use these computations to create models that compare and integrate different types of large-scale molecular biological data. We use our models to computationally predict physical, cellular and evolutionary mechanisms that govern the activity of DNA and RNA. Experimental results verify our computational prediction of a global causal coordination between DNA replication origin activity and mRNA expression, demonstrating that matrix and tensor modeling of DNA microarray data can be used to correctly predict previously unknown biological modes of regulation. We believe that future discovery and control in biology and medicine will come from the mathematical modeling of large-scale molecular biological data, just as Kepler discovered the laws of planetary motion by using mathematics to describe trends in astronomical data.

Our recent generalized singular value decomposition (GSVD) modeling of just two patient-matched genomic datasets uncovered a previously unknown global pattern of DNA aberrations that is correlated with, and possibly causally related to, brain cancer survival [Lee,* Alpert,* Sankaranarayanan and Alter, PLoS One 7, e30098 (2012); http://dx.doi.org/10.1371/journal.pone.0030098]. This new link between a glioblastoma multiforme (GBM) brain tumor's genome and a patient's prognosis offers insights into the cancer's formation and growth, and suggests promising targets for drug therapy. The best prognostic predictor of GBM prior to this discovery was the patient's age at diagnosis. Our recently formulated higher-order GSVD is the only mathematical framework to date that enables comparison of more than two patient-matched genomic datasets [Ponnapalli, Saunders, Van Loan and Alter, PLoS One 6, article e28072 (2011); http://dx.doi.org/10.1371/journal.pone.0028072]. Ultimately we hope to bring physicians a step closer to one day being able to predict and control the progression of cancers as readily as NASA engineers plot the trajectories of spacecraft today.

Stochasticity of Cell Differentiation and Cell Fates

Wednesday, August 22, 9:00 – 12:10
Session Chair: Seth Corey

Stem Cell Fate in Hematopoiesis = Determinism + Stochasticity

Seth J. Corey
Departments of Pediatrics and Cell & Molecular Biology
Northwestern University
Evanston, Illinois USA

The constant, error-free production of blood cells constitutes a complex, dynamic system. Its components exist within a narrow range, yet their production must respond quickly to challenges of blood loss, hypoxia, and infection. How the blood cell production is regulated remains a great mystery. Are hematopoietic growth factors instructive or permissive? Is hematopoiesis deterministic or stochastic? Do hematopoietic stem cells constitute discrete subsets or a continuum? Does the modeling of normal hematopoiesis provide insights into life-threatening disease states of hypoproduction or leukemia?
Hematopoietic growth factors such as granulocyte colony-stimulating factor (GCSF) are pleiotropic. They promote cell cycle division, survival, resistance to apoptosis, differentiation, and, sometimes, influence end-cell function. Hematopoietic commitment ultimately depends on gene transcription involving master switches. For granulopoiesis, this involves SCL, PU.1, C/EBPa, CREB, and Gfi-1, which are either activators or repressors of gene expression. How much of these transcriptional factors are regulated by growth factors through their cognate receptors? We hypothesize that the function of hematopoietic growth factors as instructive or permissive depends on their dose. As concentration of growth factor becomes lower, stochastic events become more common.

Since the discovery of hematopoietic growth factors, this question has been rephrased as whether growth factors are instructive or permissive. Hematopoietic growth factors, with the exception of erythropoietin, are produced locally for the target tissues. Circulating levels, reflecting spillover, are sub-nanomolar. Receptor affinities are nanomolar or sub-nanomolar. T cells, macrophages, fibroblasts, and endothelials chiefly produce hematopoietic growth factors upon stimulation. Thus, growth factor production is pulsatile. Experimental data suggest stochastic processes play a role in determining cell fate from daughter cells of a stem cell. What proportion of stem cell fate is due to probabilistic events? By addressing the first question experimentally in association with modeling, we hope to replace this question with a more specific question of where stochasticity operates in GCSF-driven granulopoiesis.

Recent systemic and modeling studies of dynamics of signaling pathways in cells at various stages of hematopoiesis, underscore the role of bistable (or even multistable) switches, which can direct the cell towards "fates" such as differentiation in various directions, proliferation, or possibly apoptosis. These switches, as they are described and modeled, are essentially deterministic circuits, displaying a series of stable and unstable steady states. The stable steady states (work regimes) correspond to distinct patterns of expression of target genes, characteristic of a given cell "fate". Small change in initial conditions at individual cell's level or in type or strength of receptor activation results in switching from one stable work regime to another.

However, that paradigm, although it explains the interplay of positive and negative feedbacks in cells, does not explain the intrinsic stochasticity, which is implied by both classical and more recent experiments on hematopoietic cells. Independently, there exists a sizeable body of evidence that eukaryotic cells may make

individual decisions based on nondeterministic rules. The sources of intrinsic stochasticity in eukaryotic cells are related to processes in which a small number of interacting molecules may trigger a large-scale effect. Stochastic effects may provide robust evolutionarily adaptive mechanisms. One might consider a fundamental of hematopoiesis, the ability to protect against environmental insults (e.g. infection or blood loss) requires a design feature incorporating stochastic dynamics. Only through systems analysis based on multi-scale modeling will greater understanding of the complexity and dynamics of hematopoiesis be achieved.

An Endogenous Accelerator for Gene Expression Provides a Fitness Advantage

Leor Weinberger
Department of Biochemistry and Biophysics and QB3
University of California San Francisco
San Francisco, California USA

Signal-transduction circuits have long been known to differentiate between signals by amplifying inputs to different levels. I will describe our findings of a novel transcriptional circuitry in a human herpesvirus that dynamically converts greater inputs into faster rates without amplifying the final equilibrium level (i.e. acceleration without amplification). This acceleration is generated by a highly self-cooperative transcriptional negative-feedback circuit (Hill coefficient ≈ 7) and produces a significant replication advantage. Mutation of the accelerator circuit into an amplifier generates a severe fitness cost, even for synthetic accelerator circuits outside the context of infection. The virus partially buffers against loss of accelerator circuitry by reducing transcriptional strength but this compensation decelerates expression and carries a heavy fitness cost for the virus. In general, accelerators may provide a mechanism for signal-transduction circuits to respond quickly to external signals without increasing steady-state levels of potentially cytotoxic molecules.

On Passenger and Driver Mutations: A Mathematical Modeling Approach

Cristian Tomasetti[1], Bert Vogelstein[2], and GiovanniParmigiani[1]
[1]Department of Biostatistics and Computational Biology, Dana-Farber Cancer Institute and Department of Biostatistics, Harvard School of Public Health, Boston, Massachusetts USA
[2]Ludwig Center for Cancer Genetics and Therapeutics, and Howard Hughes Medical Institute, Johns Hopkins Kimmel Cancer Center, Baltimore, Maryland USA

Important progress has been made in our understanding of cancer thanks to the ever growing amount of data originated by sequencing technologies. However, the ability to differentiate between driver and passenger mutations found in cancer tissues is critical and it remains a great challenge. One useful approach is given by the integration of sequencing data on the somatic mutations found in cancer tissues with mathematical modeling. This system biology approach enables us to investigate the heterogeneity found in cancer cell populations and provides us with estimates for the dynamics of passengers and drivers. In this talk I will highlight the main results of my current work, which sheds light on how to better estimate passenger mutation rates. Furthermore, a general principle for improving the detection of driver mutations by reducing the amount of noise" caused by the passengers will be introduced.

Heterogeneity and Nonlinear Dynamics in Single Cells and Biofilms

Gürol M. Süel
Green Center for Systems Biology, Department of Pharmacology
University of Texas Southwestern Medical Center
Dallas, Texas USA

Stochastic Models of Cancer

Wednesday, August 22, 2:00 – 5:20
Session Chair: Marek Kimmel

Cancer as a Complex System: Insights from Stochastic Modeling

Natalia Komarova
University of California Irvine
Irvine, California USA

In this talk, I will describe a number of mathematical tools which help obtain new insights into the processes of cancer initiation, progression and treatment. The main idea is to study cancer as an evolutionary stochastic dynamical system on a selection-mutation network. I will discuss the following topics: Cooperation in cancer: a new engine of evolution; and Stem cells, control, and tissue architecture.

Stem Cell Dynamics in Normal Human Colon Crypts and the Progression to Colon Cancer

David E. Axelrod[1,2] & Rafael Bravo[1]
[1]Department of Genetics, Rutgers University, Piscataway, New Jersey USA
[2]Cancer Institute of New Jersey, University of Medicine Dentistry of New Jersey, New Brunswick, New Jersey USA

There are about 140,000 new cases of colon cancer in the U.S. each year, and about 50,000 deaths. Understanding and detecting the earliest stages of colon cancer could contribute to reduced mortality. However, the earliest stages are not usually observable.

In order to elucidate these earliest stages of colon cancer we have developed agent-based models of colon crypts and simulated tumor progression. The models are being used to infer the stochastic dynamics of stem cell division and differentiation, as well as the spatial consequences of cell movement. The models are based on our measurements of the numbers and spatial distribution of stem cells, transient amplifying cells, and differentiated cells in a set of normal colon crypts in human biopsy specimens.

In silico experiments (simulations) with the "virtual crypts" are achieved by changing the properties of each cell, e.g. division, differentiation, and death. These properties depend upon a cell's position in the extracellular microenvironment of the crypt, both in the stem cell niche and along the crypt axis. The resulting cell dynamics, and emergent properties of the crypts, are displayed as movies of different colored cell types at different positions, as plots of cell numbers as a function of time, and as tables of parameter values at each iteration.

These experiments are yielding information about (1) the range of parameter values for cell division, differentiation, and death that result in maintenance of the normal quasi-stationary state of numbers of each different cell type, (2) the location at which a cell mutation results in monoclonal conversion of a crypt, (3)

the effect of different forms of microenvironment gradients on crypt dynamics, (4) the "mutated" parameter values that result in tumor progression from normal crypts to polyps, and (5) the effects of radiation and chemotherapeutic agents that can suggest novel targets for therapy

Hijacking Homeostatsis: How Heterogeneity Drives Tumor Progression and Treatment Failure

Alexander R. A. Anderson
Moffitt Cancer Center
Tampa, Florida USA

Heterogeneity in cancer is an observed fact, both genetically and phenotypically. Cell-cell variation is seen in almost all aspects of cancer from early development all the way through to invasion and subsequent metastasis. Our current understanding of this heterogeneity has mainly focused at the genetic scale with little information on how this variation translates to actual changes in cell phenotypic behavior. Given that many genotypes can lead to the same cellular phenotype, it is important that we quantify the range and scope of this heterogeneity at the phenotypic scale as ultimately this variability will dictate the aggressiveness of the tumor and its treatability. Central to our understanding of this heterogeneity is how the tumor cells interact with each other and with their microenvironment. Since it is these very interactions that drive selection and that ultimately define the ecology of the tissue in which the tumor is developing. Considering an organ as an ecological system, means that we should view normal tissue homeostasis as equilibrium that cancer cells must disrupt if they are to be successful. Disruption of this equilibrium is often one of the first events in cancer development, as the normal control mechanisms of the tissue are damaged or ignored. We will discuss the interplay between homeostasis, heterogeneity, evolution and ecology in cancer progression and treatment failure with an emphasis on the metabolism of breast cancer.

The Genomic Landscape of DNA Double-Strand Breaks Induced by Replication Stress

Maga Rowicka, Nicola Crosetto‡, Abhishek Mitra‡, Maria Joao Silva, Norbert Dojer, Magda Bienko, Philippe Pasero, Ivan Dikic
University of Texas Medical Branch
Galveston, Texas USA

In spite of extensive knowledge on their causes and repair mechanisms, the genomic landscape of DNA double-strand breaks (DSBs) – "breakome" – remains largely unexplored. Here, we present a genome-wide approach to map DSBs at nucleotide resolution by direct in situ labeling, enrichment on streptavidin, and next-generation sequencing (BLESS). We used BLESS to globally map DSBs in human cells exposed to replication stress. We found 2,307 non-uniformly distributed breaking hotspots, with high fragility in repetitive regions prone to form secondary structures including centromeric satellites and Alu repeats. DSBs hotspots were abundant in chromosomal regions rearranged in human cancers and in known cancer. We have also estimated breaking probability for every human gene and have shown that genes often rearranged in cancer are more fragile than average. Our study reveals landscape of genomic fragility related to DNA replication, characterizes highly fragile regions and provides rich resource for future studies.

Stochastic Gene Expression and Intracellular Signaling Pathways I

Thursday, August 23, 9:00 – 12:10
Session Chair: Tomasz Lipniaki

Information Capacity of Signaling Networks: Where are the Bottlenecks?

Andre Levchenko
John Hopkins University
Baltimore, Maryland USA

We are faced with a major paradigm shift in cell biology, akin to the turn of the 20th century dramatic reformulation of the basic physics. As in physics of that time, we need to deal with inherent unpredictability: uncertainty of cell behavior, particularly in terms of cell decision making. Given the variability of their properties, even in isogenic populations, can living cells be expected to make high fidelity, robust decisions, and if so how informed can these decisions be by the environmental inputs? Using a combination of novel experimental and theoretical approaches, i will address these questions in the context of several signaling networks, featuring most prominently the NF-kappaB/JNK signaling network triggered by TNF. i will explore in particular, the conditions under which the fidelity of cell signaling and decision making can be improved through feedback regulation, redundancy, time integration and multicellular processing.

Heterogeneity of Proliferating Cell Populations: Models and Data

Marek Kimmel
Departments of Statistics and Bioengineering,
Rice University, Houston, Texas USA

Recent years brought a deluge of technologies to observe biological processes at single-cell and sometimes at single-molecule levels. These include high-content microscopy as well as microfluidics and insertion of engineered fragments of genetic material into cells. Stochastic models introduced 20 or 30 years ago suffered from paucity or absence of such data. These models can be now re-thought and re-applied in the new context. The talk, idiosyncratically, reviews some of models conceived over past 20 years and confronts them with recent biological findings. This includes the pseudo-stochastic model of unequal division of cells, and the branching process model of gene amplification. Biological phenomena discussed include self-renewal and maturation of stem cells, variability of abundance of proteins in cells and carcinogenesis.

Networks, Noise and Evolution: Lessons from Synthetic Gene Circuits

Gábor Balázsi
The University of Texas MD Anderson Cancer Center
Houston, Texas USA

Genes are templates for protein synthesis. Proteins determine how cells behave. Therefore, genes should determine how cells behave. However, genes do not act in isolation: they alter each other's protein producing capacity through complex regulatory networks. Moreover, genes and proteins are present in small numbers and move around stochastically inside minuscule cellular volumes, giving rise to stochastic reactions and randomly fluctuating protein levels that can affect cell division rates, thereby modulating fitness. We connect stochastic molecular events to cell population fitness and long-term evolution by designing synthetic gene networks that control the noise of proteins relevant in well-defined environments where cells evolve.

Ultrasensitivity and Stochasticity of the *Bacillus subtilis* Sporulation Decision

Jatin Narula[1], Seram N. Devi [2], Masaya Fujita*[2], **Oleg A. Igoshin***[1]

[1]Department of Bioengineering, Rice University
[2]Department of Biology and Biochemistry, University of Houston
Houston, Texas USA

Starving *B. subtilis* cells execute a gene-expression program resulting in formation of stress-resistant spores. Sporulation master regulator, Spo0A, is activated by a phosphorelay and controls the expression of a multitude of genes, including the forespore-specific sigma factor s^F and the mother-cell specific sigma factor s^E. We use synthetically rewired phosphorelay network to uncover how cells make reliable decisions despite molecular noise. By inducing expression of phosphorelay kinase KinA we observe a switch-like increase in the number of sporulating cells above certain threshold. Using a combination of stochastic modeling and single-cell microscopy we investigate the origin and physiological significance of this ultrasensitive threshold. The results indicate that the phosphorelay is unable to achieve sufficiently fast and ultrasensitive response via its positive feedback architecture, suggesting that the sporulation decision is made downstream. In contrast, activation of s^F in the forespore and of s^E in the mother-cell compartments occurs via a cascade of coherent feed-forward loops and thereby can produce fast and ultrasensitive responses as a result of KinA induction. Unlike s^F activation, s^E activation in the mother-cell compartment only occurs above the KinA threshold, resulting in completion of sporulation. Thus ultrasensitive s^E activation explains the KinA threshold for sporulation induction. We therefore infer that under uncertain conditions cells initiate sporulation but postpone making the sporulation decision in order to average stochastic fluctuations and to achieve robust population response.

Stochastic Gene Expression and Intracellular Signaling Pathways II

Thursday, August 23, 2:00 – 5:50
Session Chair: Andre Levchenko

Sex and Arithmetic in Nematodes

Scott Rifkin
University of California San Diego
San Diego, California USA

Although the sex of an organism is commonly encoded genetically, sex determination itself is a developmental process. The encoded information must be read, interpreted, and acted upon. *Caenorhabditis elegans* has chromosomal sex determination where worms with two X chromosomes become hermaphrodites and the rare worm with only one X chromosome becomes male. Worms precisely measure the ratio of X chromosomes to autosomes (non-sex chromosomes) by a game of molecular tug-of-war. Regulators on the X chromosomes try to repress the key gene xol-1 while regulators on the autosomes try to activate it. The competition takes place largely at the xol-1 promoter and is focused on transcription. In this talk, I will discuss three questions about C. elegans sex determination using measurements of gene expression with single molecule resolution: (1) When does a worm decide what sex it is? (2) Does each cell make this decision on its own? (3) What are the dynamics of the regulatory tug-of-war?

Computational Model for Autophagic Vesicle Dynamics in Single Cells

William Hlavacek
Los Alamos National Laboratory
Santa Fe, New Mexico USA

Macroautophagy (autophagy) is a cellular recycling program essential for homeostasis and survival during cytotoxic stress. This process, which has an emerging role in disease etiology and treatment, is executed in four stages through the coordinated action of over thirty proteins. An effective strategy for studying complicated cellular processes, such as autophagy, involves the construction and analysis of mathematical or computational models. When developed and refined from experimental knowledge, these models can be used to interrogate signaling pathways, formulate novel hypotheses about systems, and make predictions about cell signaling changes induced by specific interventions. Here, we present the development of a computational model describing autophagic vesicle dynamics in a mammalian system. We used time-resolved live-cell microscopy to measure the synthesis and turnover of autophagic vesicles in single cells. The stochastically simulated model is consistent with data acquired during conditions of both basal and chemically-induced autophagy. The model was tested by genetic modulation of autophagic

machinery and found to accurately predict vesicle dynamics observed experimentally. Furthermore, the model generated an unforeseen prediction about vesicle size that is consistent with both published findings and our experimental observations. Taken together, this model is accurate and useful and can serve as the foundation for future efforts aimed at quantitative characterization of autophagy.

Next Generation Sequencing for Metagenomics: Bioinformatics Challenges

Yuriy Fofanov
Center for BioMedical and Environmental Genomics
University of Houston
Houston, Texas USA

Fast and accurate identification of organisms or functional signatures (genes) of interest in environmental samples is difficult, since they occur in complex backgrounds of genomic material. Knowledge of the total genomic diversity, microorganism interactions, and functional organization of the microbial communities in the clinical, environmental (air, water, soil, or surface) or food samples, can provide critically important information allowing to improve the quality of virtually all nucleic acid-based identification approaches, including PCR, RT-PCR, High Throughput Shotgun Sequencing, and DNA microarrays. Most importantly, it can also dramatically increase overall understanding of the organization and evolution of microbial/viral communities, particularly in response to external factors, such as the release of chemical and biological agents, or natural and man-made disasters.

Over the last five years, in collaboration with Midwest Research Institute, Johns Hopkins Applied Physics Lab, LLNL, Loyola University (Chicago), and Sandia National Lab, we have collected, sequenced (using Illumina GIIx) and analyzed hundreds of environmental and clinical metagenomic samples, including air, soil, as well as fresh and sea water under normal and disaster conditions (Hurricane Ike in Houston 2008, BP Oil Spill in 2010 in Golf of Mexico), to name a few.

This talk will focus on bioinformatics challenges and solutions associated with the use of NGS sequencing platforms (Illumina, Roshe 454, SOliD, and Ion Torrent) for analysis of metagenomic sequencing data; various (non-16S rRNA-based) approaches to compare and characterize metagenomic samples; as well as challenges associated with pathogen detection in the presence of complex backgrounds. Biases in the NGS sequencing data associated with sample preparation, sequencing platforms, data analysis algorithms, and interference introduced by large amount of background genomic material will be also discussed.

Presented work was supported by the DHS Science and Technology Directorate (Chemical and Biological Division), DTRA, NIH/MLM, and University of Houston and UH CBMEG.

State-Space Collapse in Modeling Stochastic Phenomena

Adam Bobrowski
Lublin University of Technology
Lublin, Poland

In modeling one often encounters a situation where a sequence of stochastic processes converges in a sense to a process with `much smaller' state-space. This is in particular the case when a more complicated model is replaced by a simpler, or `averaged' one. For example, one of the coordinates of a point in the state-space may in the limit become irrelevant, equal to another coordinate, or be a function of other coordinates. Some points may also get `lumped' together. Mathematically, this often boils down to a singular perturbation of the differential equation related to the stochastic processes. Looking from the perspective of the theory of semigroups of operators, I will discuss several examples of such phenomena and ways of proving the related convergence theorems. The examples include models of gene regulation and expression, fish dynamics, hereditary processes, queues, fast neurotransmitters, etc.

Stochastic NF-κB Activation via Autocrine TNFα Signaling

Tomasz Lipniacki
Institute of Fundamental Technological Research
Polish Academy of Sciences

NF-κB is a key transcription factor controlling innate immune responses. Its activity is tightly controlled by the numerous feedback loops, including two negative loops mediated by the NF-κB inducible inhibitors, IκBα and A20, which assure oscillatory responses, and positive feedback loops arising due to paracrine and autocrine regulation via TNFα and other cytokines. We demonstrated that positive autocrine regulation via TNFα leads to sustained oscillations in WT cells characterized by significant TNFα and TNFα receptors expression. These oscillations can start spontaneously even in unstimulated cells due stochastic fluctuations. In A20 deficient cells even small TNFα expression and secretion qualitatively influences kinetics leading to prolonged NF-κB activation in response to pulse TNFα stimulation. As a result cells with increased TNFα secretion or with impaired A20 expression are expected to have elevated NF-κB activity, which may lead to a chronic inflammation and promote cancer.

Self Organization, Epigenetics and Evolution

Friday, August 24, 9:00 – 12:30
Session Chair: Oleg Igoshin

A Quantitative Narrative for the Living Cell: From Precise Measurements to General Principles

Ido Golding
Baylor College of Medicine
Houston, Texas, USA

The goal of my lab is to form a quantitative narrative for the fundamental processes driving the living cell. This narrative is built upon precise measurements performed in individual cells, at the level of individual molecules and discrete events in space and time. To achieve this level of detail, we are using a synthesis of approaches: classical molecular biology and biochemistry; single-cell and single-molecule fluorescence microscopy; advanced image- and data analysis algorithms. By using simple, coarse-grained theoretical models, we are able to distill our result into general principles, which can then be directly compared to findings in other model systems. I will present a few examples from our work.

Demographic Noise in Darwinian Evolution: Application to Bacterial Competence

Herbert Levine
Department of Bioengineering
Rice University
Houston, Texas USA

Motivated by experiments on laboratory-scale evolution in both microorganisms and biomolecules, we introduce and study a class of multi-locus evolution models. For these models, the population advances via being dragged forward by its most fit members and can be quantitatively studied using ideas from the theory of non-equilibrium spatially-extended processes. A key finding is the anomalously large dependence on population size and the related anomalously large usefulness of genetic recombination. Using this approach, insight can be obtained regarding the indirect selection for mechanisms which speed up adaptation, including becoming mutator-like and going into a state competent for genetic exchange. One surprising finding is the advantage of a mixed-strategy, where only a subset of the population goes into the competent state.

Cancer Attractors and Non-Genetic of Cancer Cell Population Heterogeneity – Implications for Mutation-Less Progression of Cancer

Sui Huang
Institute for Systems Biology
Seattle, Washington USA

An elementary process in metazoan development and disease is the transition of one cell phenotype A to phenotype B. At molecular resolution, this process is in essence the transition from one gene expression profile S (=a cellular state vector defined by the specific configuration of the activity of N= ~ 20,000s loci in the genome) into another one. Thus formally, the cell undergoes a "high-dimensional" state transition in an N-dimensional state space, from state S_A to state S_B. This transition of course is regulated, or better, "channeled", by the gene regulatory network in that the individual gene loci cannot change their activity independently of each other because of regulatory (trans) interactions between the loci that heavily constrain the dynamics of S in each cell. Such constrained dynamics of gene regulatory networks, dS/dt = F(S) has been studied in the past decade in systems biology, leading to the formal explanation of Waddington's "epigenetic landscape" whose topography reflects these developmental channeling constraints that are imposed by the interactions of the gene regulatory networks encoded in the genome and that guide development. Herein, "valleys" are the attractor states that represent the observable phenotypic states A, B, C - the normal cell types of the metazoan body. Thus, a given genome maps into a specific landscape. The landscape picture offers a sense of the global "relative stability" of phenotypic states (attractors) with respect to noise-driven attractor transitions for systems with more than two attractor states. Herein, the "elevation" at state S is a quasi-potential function U(S) that can be precisely defined even in non-integrable systems F(S) and permits the prediction of the transition probability between any two attractor states. This formalism affords a conceptual framework for understanding how cell population heterogeneity affects cell phenotype transitions. We apply this to the study the mutation-independent aspects of cancer progression that has escaped attention in cancer biology. In this model the cancerous cell phenotypes are sets of unoccupied and un-evolved attractors in the uncharted regions of the epigenetic landscape of the genome, and cancer progression is epitomized by attractor transitions between these pathological attractors – a purely "epigenetic" event. We show by modeling and experimental validation in an in vitro single-cell resolution cell population dynamics model that development of drug resistance may be initiated via a Lamarckian instruction by an environmental stress that induces a (stem-cell like) drug resistant state. Thus, the inexorable and rapid evolution of resistance to drugs may not simply be a consequence of Darwinian selection ("survival of the fittest") but may be helped by another, perhaps ubiquitous mechanism in the inevitable fraction of cancer cells that are not killed by the drug and that adhere to F. Nietzsche's principle "What does not kill me makes me stronger".

Further reading:

S. Huang. (2011). On the intrinsic inevitability of cancer: From foetal to fatal attraction. Semin Cancer Biol 21, 183-99

S. Huang. (2012). Tumor progression: Chance and necessity in Darwinian and Lamarckian somatic (mutationless) evolution. In press - Prog Biophys Mol Biol

Multicellular Organization of Capillary Development

Byron Long, Rahul Rekhi, Amada Abrego, and **Amina Ann Qutub**
Department of Bioengineering,
Rice University
Houston, Texas USA

The ability to control capillary regrowth (or angiogenesis) can lead to new treatments for stroke and cancer. To systematically control angiogenesis, we need a means to understand the complex ways growth factors can influence cell behaviors and spatial organization. To that end, we developed a scalable computational model that describes capillary growth in terms of patterns of basic endothelial cell behaviors when stimulated by angiogenic and neurotrophic factors. We introduce a "Rules-as-Agents" method for rapid comparison of cell behavior hypotheses to our in vitro angiogenesis experiments. Endothelial cells are represented as finite state machines, and their properties are explored by a search algorithm. We then score, rank and quantify differences between competing hypotheses about cell behavior. Results predict how endothelial migration, proliferation, branching, and elongation integrate to form capillary structures within a 3D matrix in the presence of varying growth factor concentrations. This work offers the ability to understand – and ultimately engineer – human cell behavior at the microvasculature.

Identifying the Dynamic States of the 3D Genome Organization

Andrzej Kudlicki
University of Texas Medical Branch
Galveston, Texas USA

Chromatin capture experiments (4C, Hi-C) allow genome-wide mapping of physical interactions between chromosomal loci.
We discuss the impact that stochastically non-homogeneous subpopulations of cells contained in an experimental sample may have on the results of a chromatin capture experiment.
We propose a method allowing to identify this phenomenon by analyzing statistical and geometrical properties
of chromatin capture measurements. By applying the algorithm to published experimental data, we demonstrate that subpopulations with different chromatin conformations are indeed present and their influence on the results is significant.

Finally, we present an algorithm that reconstructs the chromatin conformations in each subpopulation by applying graph-theoretic considerations. We demonstrate that the results are consistent with several subpopulations of cells executing significantly different transcriptional programs.

Branching Processes in Population Biology and Genetics

Saturday, August 25, 8:30 -12:20
Session Chair: Peter Oloffson

Controlled Branching Processes in Varying Environment

Manuel Mota, **Inés M. del Puerto**, Alfonso Ramos
Department of Mathematics
University of Extremadura
Badajoz, Spain

Branching processes are regarded as appropriate probability models for the description of the extinction/growth of populations (see [1]). The oldest and simplest discrete time branching process is the standard Bienaymé-Galton-Watson branching processes, that describes the evolution of a population in which each individual, independently of the others, gives rise to a random number of offspring (in accordance with a common reproduction law), and then dies or is not considered in the following counts. This simple model is not always adequate to describe actual phenomena, thus there are many variants of this model to deal with important properties of real-world populations. In particular, controlled branching processes are useful to model some situations where some kind of control is required. For example, in an ecological context there are invasive animal species that are widely recognized as a threat to native ecosystems, but eradication plans can create controversy. In such cases, it is better to control the population, although it could suppose periods of culling of animals.

The evolution of a controlled branching process is developed into two phases: a reproductive phase where individuals give birth to their offspring according to a probability distribution, called reproduction law, and a control phase where some individuals are introduced or removed according to other probability distribution, called control law.

In the literature on controlled branching processes (see [2] and [3], and references therein), the control phase is assumed to depend on the population size. On the other hand, in the vast majority of works, the reproduction law is assumed to be the same for every individual in any generation. However, it seems reasonable to think that the reproductive abilities of the individuals of a population may vary from one generation to another, because of factors such as food supply or weather conditions. One can find many published papers regarding standard or multitype Galton--Watson processes whose reproduction laws vary with the generation, usually referred as varying environment. But, until now, this possibility has not been considered in the class of the controlled branching processes, at least from a general viewpoint.

It is the aim of this paper to introduce and research inhomogeneous controlled branching processes or also called controlled branching processes in varying environment. In particular, conditions for extinction or growth to infinity to be the only long--term possibilities are stated and the extinction problem is tackled. Moreover the study of the rate of convergence of the process on the non--extinction set is considered.

References:

[1] Haccou, P., Jagers, P. and Vatutin, V. (2005) Branching processes: Variation, growth and extinction of populations, Cambridge University Press.
[2] González, M., Molina, M. and del Puerto, I. (2005) Asymptotic behaviour of critical controlled branching process with random control function. J. Appl.Probab. 42, 463-477.
[3] Yanev, G.P. and Yanev, N.M. (1989) Conditions for extinction of controlled branching processes. Math. Ed. In Math. 1, 550--555.

AIDS: The Mismanagement of the Epidemic in the United States

James R. Thompson
Noah Harding Professor of Statistics
Rice University
Houston, Texas USA

Starting 30 years ago, the author published a series of articles and book chapters and gave numerous talks indicating how a simple shutdown of centers facilitating high frequency gay male sex would drive the epidemic down to endemic levels. Extreme isolation measures, such as those practiced for a time in Cuba and a few European countries, were not necessary. The sociological disruption would be minimal. Generally speaking, these shutdowns were carried out in the rest of the First World, but not in the United States. The United States has long since passed the 600,000 deaths resulting from that bloodiest of American wars, the War Between the States. The United States has the overwhelming majority of First World AIDS cases. The rest of the First World has defacilitated the high contact centers and suffered much less from AIDS than the United States.

General Branching Processes and Cell Populations

Peter Olofsson
Trinity University
San Antonio, Texas USA

General branching processes provide an excellent framework to investigate properties of *in vitro* cell populations. A brief overview of such processes and their main results is given, and a few recent applications are surveyed. In particular, an application to the desynchronization of an initially synchronized cell population is presented in detail. Work presented is joint with Alison Bertuch, Suzanne Sindi, and Thomas O. McDonald.

The Signature of Selective Sweep: Learning from a Warfarin Resistance Locus in Rats

Shuwei Li, Zhenjiang Lan, Ying Song, Michael H. Kohn
Department of Ecology and Evolutionary Biology
Rice University
Houston, Texas USA

Selective sweeps describe the spread of a beneficial allele and the hitchhiking of adjacent neutral sites. By detecting the unique patterns, the presence of adaptive variants can be inferred. However, it is not always straightforward to detect (or more difficult to decipher) the complex patterns that are a result of demographics and often, a prior, unknown modes of selection. Here we revisit the selection of warfarin poison (since 1950s) at the resistance gene *Vkorc1* (vitamin K epoxide reductase subunit 1), which has been a textbook example of heterozygote advantage. We decode the sweep signals using forward simulation in Norway rat (Rattus norvegicus) populations from Germany where an Y139C mutation in *Vkorc1* has spread over vast areas to examine three fundamental questions in adaptation:
1. Is there a sweep after selection and what is the strength of selection?
2. What is the mode of selection (directional or balancing selection)?
3. Is the adaptive SNP (Y139C) a de novo mutation or a standing variation?
We estimated the strength of warfarin selection as ~0.3, found support for the balancing selection model, and we suggested that the Y139C allele has arisen de novo or was introduced by migration into the resistance area ~10 years past the introduction of warfarin.

Sex-linked Branching Processes

Miguel González, Cristina Gutiérrez, Rodrigo Martínez and Manuel Mota
Department of Mathematics
University of Extremadura
Badajoz, Spain

It is well-known that in human and some animal populations the sex of the individuals is determined by a pair of chromosomes X and Y. A female has XX chromosomes, while a male has XY chromosomes. Certain characteristics are due to genes carried on the X chromosome (X-linked). Others due to genes carried on the Y chromosome (Y-linked) and still others to genes carried on both chromosomes (XY-linked). From a practical viewpoint, it is of interest to model and analyze the evolution of sex-linked genes from generation to generation.

First, focusing our attention in the Y-chromosome, it is worth mentioning that some of the Y-linked genes are expressed in males and play a relevant role in the mating of these males, whereas some others (really, the majority) are not expressed or if they are, they do not play any role in their mating. Recently, in [1] and [2] two different multitype two-sex branching processes have been introduced to analyze the evolution of the number of carriers of both types of Y-linked genes. In the first one it is assumed the preference of females for males with a specific genetic characteristic determined by an allele of the gene. The second model considers that females choose their mates blindly, without caring the genotype they have.

In this talk we review the main probabilistic and inferential results obtained until now for these models (including modifications allowing mutations). The probabilistic results are related to the extinction and/or survival of the Y-linked genes and to their growth rates into the population. In general, the behavior of such genes depends on the average number of female and male offspring per mating unit. These parameters of the offspring distributions have been estimated in a Bayesian context, using Monte-Carlo Markov Chain methodology, and also in a frequentist framework through Expectation-Maximization method.

Second, we deal with some particular X-linked branching models. Concretely, we focus on a mutitype two-sex branching process which allows us to model the evolution of the number of individuals carrying the alleles, R and r, of a gene linked to X chromosome. The R allele is considered dominant and the r allele is assumed to be recessive and lethal. Then, females can have two genotypes: homozygous, RR, and heterozygous, Rr, whereas only R males are able to live. Homozygous and heterozygous females have identical phenotypes so males do not know the genotype of their mates, it can be said that they made a ``blind'' choice among the two genotypes. We use this model to study the extinction probability of one of these lethal alleles, i.e. under which conditions it will eventually disappear and when it will survive along the generations.

References:

[1] González, M., Hull, D.M., Martínez, R. and Mota, M. (2006). Bisexual branching processes in a genetic context: the extinction problem for Y-linked genes, Mathematical Biosciences, 202, 227-247.

[2] González, M., Martínez, R. and Mota, M. (2009). Bisexual branching processes to model extinction conditions for Y-linked genes, Journal of Theoretical Biology, 258, 478-488.

Stochastic Theory for Biochemical Systems

Saturday, August 25, 2:00 - 4:50
Session Chair: Marek Kimmel

Limiting Behavior of Chemical Reaction Systems

Dennis D. Cox
Department of Statistics
Rice University
Houston, Texas USA

We review the "standard" model for meso-scale chemical reaction systems typically used in cell level systems biology models and derive a panoply of limiting behaviors. A sketch of a possible general theory is presented, and we indicate the obstacles to that development. In the limit, different subsystems behave as discrete processes, diffusion processes, or deterministically, conditional on other subsystems. It will be shown that these results are useful for developing faster simulation algorithms.

Modeling And Parameter Estimation Of Feedback Loops In NF-κB Signaling

Brasier, AR, Kalita, MR, Choudhary, S, Zhao, Y.
Sealy Center for Molecular Medicine, Institute for Translational Sciences,
University of Texas Medical Branch
Galveston, Texas USA

The Nuclear Factor-κB (NF-κB) signaling pathway controls gene networks important in the innate immune response. Upon pathway activation, NF-κB/RelA is released from cytoplasmic inhibitors, from where it translocates into the nucleus. Here, NF-κB/RelA activates negative feedback loops that produce damped nucleo-cytoplasmic dynamics, or feed-forward loops that control distinct arms of innate signaling. We report our experience using measures of cellular geometry and quantitative estimates of translocated NF-κB/RelA as priors in Bayesian inference to estimate other biophysically realistic parameter values of the pathway. Because the sources of cell-to-cell variability are not well understood, we performed Bayesian inference on dynamic single cell imaging data of fluorescently labeled RelA, where we were able to identify a subpopulation of cells exhibiting distinct kinetic profiles was identified that corresponded to differences in the IκBα translation rate. These studies indicate that cellular geometry, initial- and total NF-κB concentration, IκBα translation and IκBα degradation rates account for distinct cell-to-cell differences in canonical NF-κB translocation dynamics. In follow up studies, we have used quantitative proteomics to identify a feed-forward pathway that links the canonical to the noncanonical NFkB pathways. These approaches will accelerate parameter estimation and model refinement in signaling pathway modeling studies.

Systems Biology Analyses of Inflammatory Signaling in Time and Space

Pawel Paszek
University of Manchester
Manchester, United Kingdom

Our immune system must be able to rapidly fight against pathogens, but at the same time be tightly regulated to prevent harmful autoimmune and allergic responses. This intricate balance is controlled by a cellular and molecular system involving specialized immune cells as well as signalling networks incorporating key transcription factors such as Nuclear Factor kappa B (NF-κB) and Signal Transducers and Activators of Transcription (STATs). We use a multidisciplinary system biology approach involving mathematical modelling, cutting-edge live-cell-imaging, molecular cell biology and immunology to resolve the underlying complex nonlinear and stochastic dynamics in space and time. A new quantitative understanding of these processes will move us towards better therapeutic strategies for inflammatory disease.

Solution Surfaces of Genetic Networks and Applications

Gemunu H. Gunaratne
Department of Physics
University of Houston
Houston, Texas USA

Living systems maintain their physiological state under environmental changes and isolated genetic mutations through feedback within highly connected networks of genes, proteins, and other bio-molecules. Unfortunately, this robustness also makes it difficult to correct defects such as hereditary diseases, as evidenced by the surprising lack of efficacy of single target drugs that were designed to act on specific molecular targets. Side-affects from medications are another consequence of the connectivity in underlying networks. If accurate models of gene networks were available, they could be used to compute how effective therapies for diseases can be designed. Unfortunately, it is very difficult to construct sufficiently accurate models.

We propose to use ^{3}solution surfaces^{2} of the gene network associated with a biological process. In principle, they can be obtained by sequencing many biologically perturbed mutants. However, studies of model networks and nonlinear electronic circuits show that the solutions surfaces are smooth; hence, good approximations can be obtained from expression data of a handful of mutants. Furthermore, as we show through several examples, biologically relevant issues can be addressed in this approach. Specifically, we can compute how the state of a gene network can be moved to a pre-specified state. As an example, we have used the methodology to compute how the brain transcriptome of Drosophila can be altered in order to move the animal to a sleep-deprived like state. Experiments are being conducted to verify our predictions. Interestingly, this biologically motivated approach to study networks may have applications in other disciplines; some examples will be discussed.

Computation of Most Likely Genetic Evolution Paths for Bacterial Population Models

Robert Azencott
Department of Mathematics
University of Houston
Houston, Texas USA

We consider stochastic models for bacterial population evolution experiments where dayly deterministic growth alternates with selection of a fixed size random subpopulation. Multiple genotypes may emerge by random mutations, and emerged genotypes with high selective advantage tend to reach fixation . We have developed new algorithms to compute the most likely succession of genotype fixations within a small pool of potential genotypes.

Our approach involves rare events analysis and large deviations theory. We present numerical results based on E. Coli evolution experiments performed in Tim Cooper's laboratory (UH Biology Dept).

ICSP2012

Poster Presentation Session & Reception

Bioscience Research Collaborative
First Floor Lobby
2-5 pm

Beverages
Warm/Cold Hor D'ourves

Poster Abstracts

P1

Comparing gene expression pattern in the *skn-1* intestinal developmental network in *C. briggsae*, *C. remanei*, and *C. elegans* to gain insights into the dynamical functional roles of orthologous genes

Allison C.Y. Wu, Lawrence Du, Scott A. Rifkin
University of California San Diego

Previous studies have shown that, in the *C.elegans skn-1* network, the most downstream gene *elt-2* determines the onset of gut development while *end-3*, *end-1*, and *med-1/2* constrain the gene expression variability. Inboth *C. briggsae* and *C. remanei*, there has been a large amount of copy number evolution in this network: there are 5 functionally similar *med* paralogs in *C. remanei* , 4 *med* paralogs in *C. briggsae* and two orthologs of *end-3* in *C. briggsae*. These potentially functionally similar homologs add extra connections to this intestinal specification network. We want to know how and why these redundant genes are preserved, whether these seemingly redundant connections are really redundant, and whether these connections add to or strengthen specific dynamical network properties, such as buffering of noise or environmenal variation or feedback strength.

In this study, we use single-molecule fluorescence *in situ* hybridization (smFISH) to measure the expression pattern of genes in the *skn-1* network in these three species, including *end-3* orthologs, *end-1* and *elt-2*. By quantitatively measuring the expression dynamics of these genes, we willustrate the dynamical roles these orthologs play in the intestine development in different nematode species and reveal the effects of gene duplication on dynamical network properties.

P2

Offspring Variance Estimators in Branching Processes with Time Non-Homogeneous Immigration

George Yanev[1] & Ibrahim Rahimov[2]
[1]Department of Mathematics, University of Texas – Pan American, Edinburg, Texas (USA), [2]Department of Mathematics and Statistics, Zayed University, Dubai (UAE)

One instance in which branching processes with non-homogeneous immigration are relevant is within models of the dynamics of renewing cell populations where the experimentally observable cells are supplemented by an influx of unobservable cells (e.g., stem cells). This study considers conditional least squares estimators (CLSE) for the offspring variance in critical discrete-time branching processes with non-homogeneous immigration. The asymptotic behavior of the estimators is established under some additional moment assumptions on both reproduction and immigration. The models considered allow the immigration distribution to vary with time such that its mean increases to infinity at a speed that could correspond to a near-critical branching population. Thus, the results obtained are an extension of Winnicki's (Probability Theory and Related Fields, 88 (1991), 77-106) findings in the critical case. The derived limit theorem completes the results of Rahimov (Stochastic Processes and Applications, 118 (2008), 1892-1908) in which the limiting distribution of the CLSE for the offspring mean depends on the offspring variance. The proofs make use of martingale techniques as well as results from the theory of weak convergence in Skorokhod spaces.

P3

The signature of selective sweep: learning from a warfarin resistance locus in rats

Shuwei Li, Zhenjiang Lan, Ying Song, Michael H. Kohn
Department of Ecology and Evolutionary Biology, Rice University, Houston, Texas (USA)

Selective sweeps describe the spread of a beneficial allele and the hitchhiking of adjacent neutral sites. By detecting the unique patterns, the presence of adaptive variants can be inferred. However, it is not always straightforward to detect (or more difficult to decipher) the complex patterns that are a result of demographics and often, a prior, unknown modes of selection. Here we revisit the selection of warfarin poison (since 1950s) at the resistance gene *Vkorc1* (vitamin K epoxide reductase subunit 1), which has been a textbook example of heterozygote advantage. We decode the sweep signals using forward simulation in Norway rat (Rattus norvegicus) populations from Germany where an Y139C mutation in *Vkorc1* has spread over vast areas to examine three fundamental questions in adaptation:

1. Is there a sweep after selection and what is the strength of selection?
2. What is the mode of selection (directional or balancing selection)?
3. Is the adaptive SNP (Y139C) a de novo mutation or a standing variation?

We estimated the strength of warfarin selection as ~0.3, found support for the balancing selection model, and we suggested that the Y139C allele has arisen de novo or was introduced by migration into the resistance area ~10 years past the introduction of warfarin.

P4

Estimated noise-driven phenotypic switching rates depend on cell division rates

Rhys M. Adams[1] and Gábor Balázsi[1]
[1]Department of Systems Biology – U950, The University of Texas MD Anderson Cancer Center, Houston, TX, USA, E-mails: rhysm.adams@gmail.com, gbalazsi@mdanderson.org

Introduction: The capacity of cells to change their phenotype can significantly affect the overall fitness of a cell population. For a cell population, environmental cues may provide the signals by which cells commit to a phenotype. However, even isogenic cells within a static environment may commit to drastically different phenotypes due to noisy gene expression.

Biochemical processes involved in gene expression include (but are not limited to) the production and degradation/dilution of mRNA and protein molecules. The stochastic nature of these processes is commonly assumed to determine the rates of stochastic phenotype switching and the distributions of gene products within a cell population. We sought to solve the reverse problem: to infer the rates at which cells switched stochastically between different phenotypes based on their stationary distributions. We found that stochastic switching rates could be inferred from stationary distributions only after accounting for state-dependent differences in cell division rates.

METHODS & RESULTS: We observed experimentally stochastic phenotype switching of yeast cells with chromosomally integrated inducible synthetic gene circuits. The gene circuits consisted of the reverse tetracycline Trans-Activator (*rtTA*) activating its own expression and the expression of a fluorescent reporter gene from identical promoters in the presence of the inducer ATc. Cells grown in constant levels of inducer relaxed to stationary bimodal fluorescence distributions. Traditional techniques (neglecting inducer-dependent differences in growth rates) incorrectly predicted the rates of switching between high- and low-expressor subpopulations based on these distributions.

Since we observed a decrease in overall cell population division rates with rtTA expression, we developed a new method to estimate switching rates by incorporating this information. We modeled cell division rates as a decreasing function of ATc activated rtTA and estimated the rate at which cells crossed an arbitrary fluorescence boundary. This net “cellular current” resulted from movements towards decreasing and increasing fluorescence. For cells whose division rates are unaffected by their cell state, the increasing current is equal to the decreasing current. However, when cell division rate changes with the cell state, disequilibrium between the increasing and decreasing currents arises, which was quantified

based on our model of cell division rates.

We inferred the decreasing currents by assuming that concentrations of stable proteins (such as GFP) decreased due to dilution from cell growth. We calculated the increasing current from the net current arising from cellular fitness differences. Finally, we used these currents to estimate the rate at which cells leave a given state. Tiny differences in cell division times more than one order of magnitude shorter than stochastic switching times masked large differences between stochastic switching rates.

We developed models of growing cell populations incorporating division rates and protein production/dilution rates that recaptured experimental distributions. Intriguingly, these stochastic models implied that bimodal distributions may emerge even for deterministically mono-stable systems.

CONCLUSION: Expression-dependent differences in growth rates can drastically alter estimated rates of stochastic switching.

P5

Mathematical model of stem cell differentiation and tissue regeneration with stochastic noise

Przemysław Rafał Pazdziorek, Institute of Mathematics of the Polish Academy of Sciences / Institute of Applied Mathematics and BIOQUANT, University of Heidelberg.

Differentiation and self-renewal of stem cells are essential processes to maintain a supply of well-specialized cells for every tissue. The promising medical applications and the complexity of those processes encourages to implement numerical and mathematical methods to understand better the mechanisms which regulate stem cells behaviour. Environmental perturbations may have an influence on the death rate, proliferation rate and on the fraction of self-renewal at every stage of differentiation.

We investigate the system of Ito stochastic differential equations with linear diffusion coefficients based on the deterministic model of multistage cell lineages proposed by Anna Marciniak-Czochra. We present some numerical simulations of the stochastic model for a different number of stages of differentiation. The interactions between the noises, added to the different stages, are characterised using numerical simulation. The long-time behaviour of the two-dimensional version of the model is well discovered, asymptotic stability of the related Markov semigroup is proved using the theory of the Markov semigroups and the method of the Hasminskiı function.

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Joint project with Anna Marciniak-Czochra[1] and Ryszard Rudnicki[2]
[1] University of Heidelberg, [2] Institute of Mathematics of the Polish Academy of Sciences

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P6

A Path-Based Approach to Sequence Evolution

Michael Manhart[1] and Alexandre V. Morozov[1,2]
[1]Department of Physics and Astronomy, [2]BioMaPS Institute for Quantitative Biology,
Rutgers University, Piscataway, NJ (USA)

We develop a computational approach to studying Markov processes using a path-based decomposition of the master equation. This method is generally applicable to any discrete state space and continuous time Markov process, but here we focus on its application to sequence evolution. Standard tools to infer biologically-meaningful parameters from sequence data using evolutionary models crucially rely on the assumption of site-independence, which limits their use in studying complex fitness landscapes and correlations among sites. Our path decomposition method, however, requires no such restrictions, and therefore permits analysis of more realistic models, especially those that account for the physics of protein folding and DNA-protein interactions in sequence fitness. Our efficient implementation of this formalism allows for calculation of several quantities of interest, including time-dependent transition probabilities, mean first-passage times, and statistics of evolutionary trajectories. This has many applications in phylogenic inference from sequence alignments, especially inference of fitness landscapes and properties of evolutionary trajectories and distances.

P7

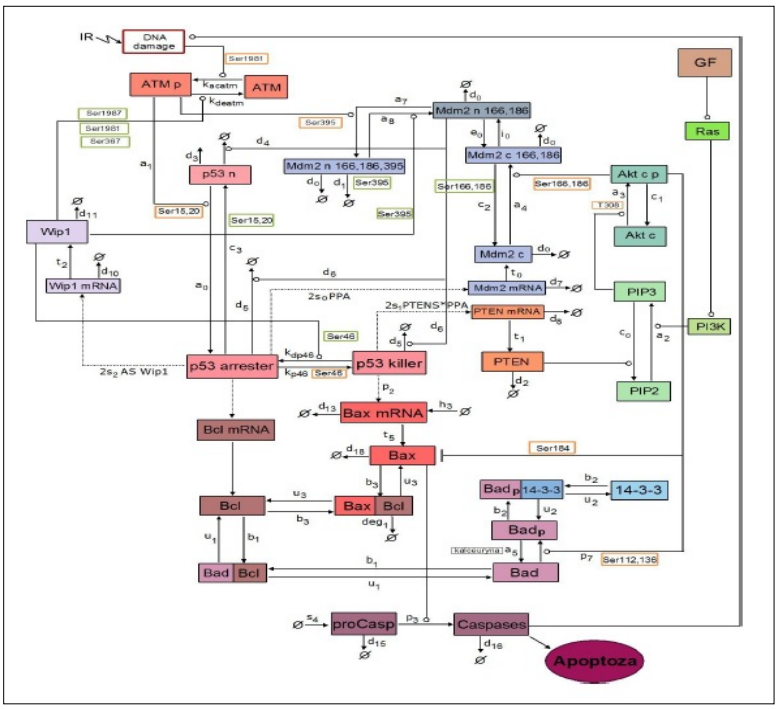
Bistability and Oscillations in p53 Interaction Network

Marta Bogdał[1,2], Beata Hat[1], Marek Kochańczyk[1] & Tomasz Lipniacki[1]
[1]Insitute of Fundamental Technological Research – Polish Academy of Sciences,
Warsaw, Poland
[2]University of Warsaw, Warsaw, Poland

The transcription factor p53 is responsible for cell cycle regulation as a tumor suppressor. In response to DNA damage p53 activates and initiates different transcriptional programs that result in cell cycle arrest, cellular senescence or apoptosis. We proposed a model of p53 regulatory pathway based on our prior model (Puszynski 2008), which includes the additional module of the detection of DNA damage due to ionizing radiation (IR), and distinguishes two forms of p53 protein with opposing functions: p53 'arrester' and p53 'killer'. p53 arrester is responsible for cell cycle arrest and DNA damage repair acting in negative feedback loops with its transcriptional targets and main “inhibitors”, phosphatase Wip1 and protein Mdm2. On the other hand, p53 killer is responsible for activation of the apoptotic pathway, and for transcription of its main “activator” phosphatase, PTEN, forming a positive feedback loop. The resulting model thus includes four negative and two positive feedback loops. DNA damage leads to oscillations of p53 levels and activation of DNA damage repair; if the damage is small, the system recovers to the initial state (survival), but if the damage is large and cannot be repaired sufficiently fast, p53 killer reaches stable high level and initiates apoptosis. The analysis of the model shows that the critical dose of radiation initializing apoptosis is dependent on expression level of phosphatases Wip1 (an anti-apoptotic agent) and PTEN (a pro-apoptotic agent). This observation suggests differential sensitivity to ionizing radiation of cancer cell lines, depending on the relative expression levels of Wip1 and PTEN in their respective primary lines; these levels have been reported to vary widely between different cell types with potential impact on the efficacy of radiotherapy.

We also analyzed the apoptotic module separately. It is based on interactions among BCL family proteins, that play pro-apoptotic (Bax, Bad) and anti-apoptotic (Bcl) roles. We propose it to function as a logical gate with the initial levels of p53 killer and dephosphorylated Akt kinase, serving as inputs, and with apoptosis or lack thereof as the output. This could be either an OR or AND gate, depending on whether a single or both inputs are required for apoptosis. We have managed to obtain both behaviors from the model by varying its parameters.

All in all, we developed an expanded model of p53 cancer signaling that allows making useful radiotherapeutic predictions based on the endogenous levels of relevant regulators as well as shedding light on the cellular logic of committing to apoptosis.



P8

Langevin Modeling for Extrinsic Fluctuations: Approximation Method and Statistical Properties

Yoshihiko Hasegawa[1] & Masanori Arita[1]
[1]Department of Biophysics and Biochemistry,
The University of Tokyo, Tokyo (Japan)

Noise-induced phenomena are attracting much attention not only for engineering applications but also in molecular biology. Molecular systems function in nanoscale environments and are subject to multiscale noise through thermal and other environmental fluctuations. A recent single-cell observation of *Escherichia coli* revealed that the protein copy number does not strictly obey the gamma distribution, and its stationary distribution was modeled by superstatistics (i.e., the superposition of multiple statistical models). Likewise, many theoretical studies suggest that biochemical noise is not Gaussian and consequently facilitates enhanced functionality. All these observations indicate the importance of temporal noise-intensity fluctuations in studying biological mechanisms. In applied physics, superstatistics with temporal and/or spatial fluctuations is used to explain non-Gaussian stationary distributions. This concept is also applied to stochastic processes in which noise-intensity fluctuations are accounted for in a static way. We consider temporal noise-intensity fluctuations as dynamic fluctuations and modulated the intensity of white Gaussian noise by the Ornstein-Uhlenbeck process in overdamped Langevin equations:

$$\dot{x} = f(x) + g(x)s\xi_x(t), \quad \dot{s} = -\gamma(s-\alpha) + \sqrt{\gamma}\xi_s(t). \qquad (1)$$

Here, $f(x)=-\partial_x V(x)$ ($V(x)$ is the potential), α is the mean of the Ornstein-Uhlenbeck process, γ is the relaxation rate ($\gamma>0$), $g(x)$ is an arbitrary function representing a multiplicative term, $\xi_x(t)$ and $\xi_s(t)$ denote white Gaussian noise with the correlation: $\langle\xi_x(t)\xi_x(t')\rangle=2D_x\delta(t-t')$ and $\langle\xi_s(t)\xi_s(t')\rangle=2D_s\delta(t-t')$. We call the term $s\xi_x(t)$, the stochastic intensity noise (SIN) because the noise intensity is governed by a stochastic

process. Figure 1 shows examples of SIN with ρ=0.01 and ρ=100, where ρ denotes the squared variation coefficient of SIN defined by $\rho=D_s/\alpha^2$ [(a) and (b) are time course of SIN and (c) and (d) are their histograms].

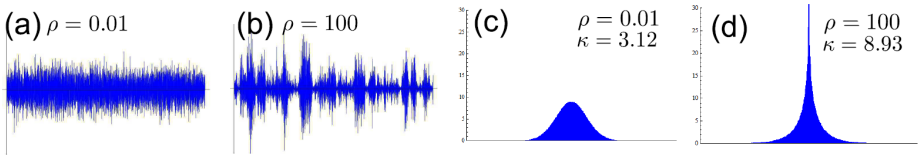


Fig. 1 (a)-(b) Time course of SIN and (c)-(d) histograms. ρ and κ denote the squared variation coefficient and kurtosis.

Two dimensional Fokker-Planck equation (FPE) of Eq. (1) is given by $P(x;s;t)=L_{FP}P(x;s;t)$, where L_{FP} is an FPE operator. We developed an approximation scheme for the FPE, which casts the two dimensional equation into one dimensional equation in terms of x, by using the adiabatic elimination. The obtained equation is given by

$$\partial_t P(x;t) = [-\partial_x f(x) + \{D_x(D_s + \alpha^2)\}\Delta_g + \{(D_x^2 D_s(4\alpha^2 + D_s))/\gamma\}\Delta_g^2]P(x;t) \qquad (2)$$

where Δ_g is a differential operator defined by $\Delta_g=\partial_x{}^2 g(x)^2-\partial_x g'(x)g(x)$. Because Eq. (2) includes derivatives higher than the second order, it is called higher-order Fokker-Planck equation (HFPE). We have solved Eq. (2) with perturbation expansion and show that it can be applied to several nonlinear systems including a gene expression mechanism.

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P9

Absorbing Markov Chain as a Model of Protein-Ligand Interaction

Marcin Pacholczyk[1] & Marek Kimmel[2]
[1]Institute of Automatic Control, Silesian University of Technology, Gliwice, Poland
[2]Department of Statistics, Rice University, Houston, Texas (USA)

Analysis of protein - small molecule interactions is crucial in the discovery of new drug candidates and lead structure optimization. Small biomolecules (ligands) are highly flexible and may adopt numerous conformations upon binding to the protein. Scoring functions are traditionally used in many docking protocols and have key impact on a quality of structure-based virtual screening. A correct scoring function should be able to guide search algorithm to find and recognize native-like docking poses. In ideal case scoring function should be able to predict binding affinity. Despite extensive research, scoring remains a major challenge in structure-based virtual screening. We apply Stochastic Roadmap Simulation (SRS) and finite absorbing Markov chain theory to build a model of protein-ligand binding process [1,2]. We propose a computational quantity – time to escape (TTE) from a funnel of attraction around binding site as a measure of binding affinity. The results based on PDBBind CoreSet [3] show statistically significant correlation between actual binding affinity and calculated TTE.

Stochastic Roadmap Simulation

Each node of a roadmap represents one conformation of a ligand. Formally, each conformation of n parameters is represented by a vector q. The set of all possible conformations forms the conformational space C. SRS assumes that the interactions are described by an energy function $E(q)$, which depends only on the conformation q of the ligand. A pathway in C represents motion of the ligand around protein. A roadmap may be considered a directed graph G encoding many pathways in C. Each node of a roadmap is a randomly selected conformation q from C with associated energy $E(q)$. Each directed edge between two nodes v_i and v_j has associated weight, which is equal to the probability of transition between the two nodes [1].

Time to Escape
Time to escape is expressed as a minimal number of simulation steps needed to escape from the funnel of attraction around the protein binding site. The funnel of attraction F_i is defined as the set of conformations within 10 Å RMSD of the bound conformation. TTE can be regarded as a mean time to absorption in finite absorbing Markov chain and can be easily calculated using general tools from Markov chain theory [1, 2].

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P10

Timing and variability of metabolic gene activation depend on the rate of environmental change

Truong Nguyen[1], Bo Ma[1], Yu-Yu Cheng[1] & Matthew R. Bennett[1]
[1]Department of Biochemistry and Cell Biology, Rice University, Houston, Texas (USA)

Modulation of gene network activity allows cells respond to changes in environmental conditions. For instance, activation of the galactose-metabolic pathway (the GAL network) allows *Saccharomyces cerevisiae* to metabolize galactose in the absence of glucose. In contrast, this network is strictly repressed when both glucose and galactose are available and thus, is only activated when glucose is completely depleted from the environment. In this project, we examined how the time rate of change of the environmental glucose level affects induction of the GAL network. We use custom-design microfluidic chips to change glucose level at different time-dependent rates, and combined with fluorescent microscopy at single cell level to track the expression of the fluorescent-tagged *gal1*, encoding galactose kinase. Our data show that the time it takes to induce *gal1* expression is in inverse relationship with the glucose-depletion rate. In fact, this induction time was largest when glucose was withdrawn instantaneously from the environment. Furthermore, we show that the variability of the induction time depends non-monotonically on the rate of glucose depletion and exhibits a minimum at intermediated rates. Thus, the time-scales over which environmental factors change can affect single cells differently within the isogenic population. Our mathematical modeling suggests that pleiotropic effects of the metabolic transition from glucose to galactose are likely responsible for the variations of the GAL network's activation. These findings shown the dynamics of environmental factors can determine the phenotypic outcome at single cell and population level.

P11

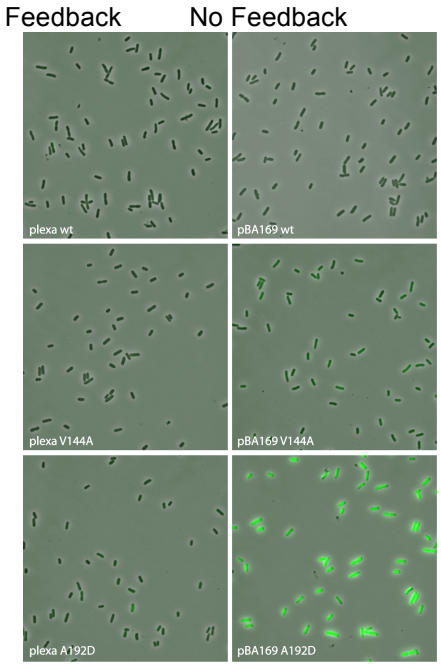
Genetic Feedback Provides Robustness To Mutation

David C. Marciano[1,2], Rhonald Lua[1,2], Teng-Kuei Hsu[1,2,3], Panagiotis Katsonis[1,2], Shivas R. Amin[1,2], Christophe Herman[1] & Olivier Lichtarge[1,2,3]

[1]Department of Molecular and Human Genetics, [2]Computational and Integrative Biomedical Research Center, [3]Verna and Marrs McLean Department of Biochemistry and Molecular Biology, Baylor College of Medicine, Houston, Texas (USA)

The *E. coli* LexA repressor is a model system for understanding how bacteria use a genetic switch to respond to DNA damage and develop resistance to antibiotics. However, the evolutionary constraints on the LexA protein structure as they relate to genetic switch function are not well understood. Here we provide an evolutionary model that attributes mutational robustness of a gene to its negative feedback

mechanism. We used a computational tool for sequence analysis to identify LexA residues under evolutionary selection and targeted those residues for mutagenesis. We find that the impact of these mutations is dependent on the genetic architecture of the system. In the absence of negative feedback, a majority of these substitutions reduce steady-state expression levels and reduce *in vivo* repressor function. However, in the context of the negative feedback loop, the impact of these mutations is mitigated (see figure). In our model, deleterious mutations that reduce cellular LexA levels also reduce auto-repression and consequently cause up-regulation of LexA gene expression. The result is a self-correcting system that buffers against mutations perturbing repressor stability. This suggests negative feedback provides a direct selective advantage for the gene that is manifest in ~40% of transcription factors in *E. coli* having this genetic architecture.



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P12

Construction of a "Waddington landscape" for Stochastic Cell Differentiation and Cell State Transitions

Joseph Xu Zhou[1,2,4], Erik Aurell[3,4], Sui Huang[1,2,4]
[1]Institute for Systems Biology, Seattle, WA, USA, [2] Institute for Biocomplexity and Informatics, University of Calgary, Calgary, Alberta, Canada;[3] Department of Computational Biology, KTH, Stockholm, Sweden,[4] Kavli Institute for Theoretical Physics China, CAS, Beijing, China

Developmental dynamics of multicellular organism is a process that takes place in a multi-stable system in which each attractor state represents a cell type and attractor transitions correspond to cell differentiation paths. This new understanding has revived the idea of a quasi-potential landscape, first proposed by Waddington as a metaphor. To describe development one is interested in the "relative stabilities" of N attractors (N>2). Existing theories of state transition between local minima on some potential landscape deal with the exit in the transition between a pair of attractors but do not offer the notion of a global potential function that relate more than two attractors to each other. Several *ad hoc*

methods have been used in systems biology to compute a landscape for non-gradient systems, such as gene regulatory networks. Here we present an overview of the currently available methods, discuss their limitations and propose a new decomposition of vector fields that permit the computation of a quasi-potential function that is equivalent to the Freidlin-Wentzell potential but is not limited to two attractors. As an example shown in Figure below, the quasi-potential function U^{norm} of a dynamical system with four attractors is derived from the normal decomposition. Both vector fields of the gradient component and the remaining normal component are plotted on the contour plot of U^{norm}. The results are compared with the quasi-potential calculated from U~-lnP with various noise levels. The validity of various constructions of quasi-potential functions is discussed. The significance of a correct quasi-potential function for cell differentiation and cell state transitions is demonstrated in these examples and discussions.

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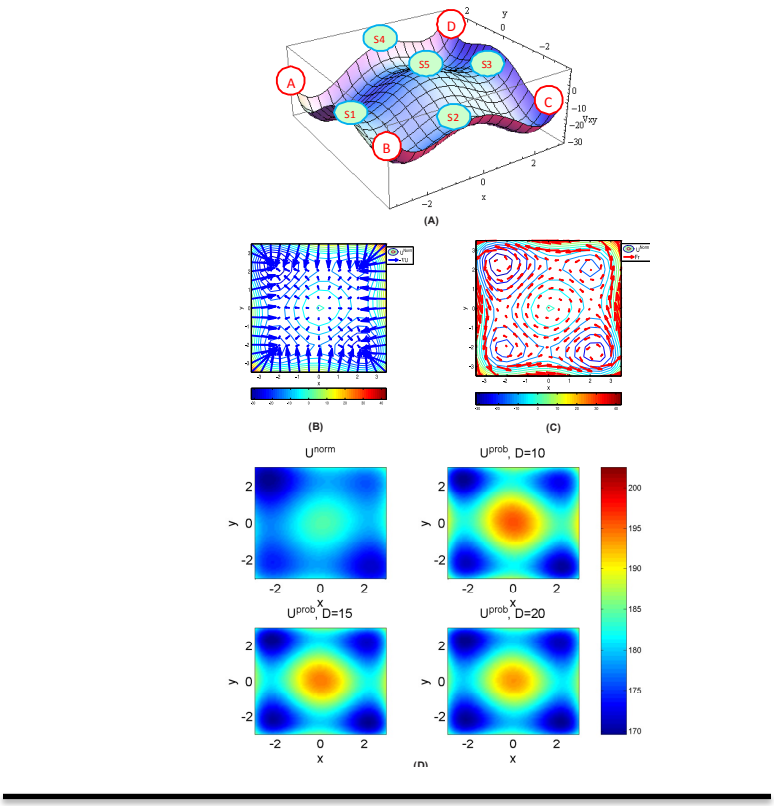

P13

The ERK-induced Repression of MEK1 and MEK2 in the MAPK Cascade Dynamics

Pawel Kocieniewski[1] & Tomasz Lipniacki[1]
[1]Insitute of Fundamental Technological Research – Polish Academy of Sciences, Warsaw, Poland

The Raf/ERK pathway belongs to the MAPK family and is important in regulating proliferation and differentiation. Its core comprises a cascade of kinases: Raf, Mek, and Erk, all of which have isoforms. As discovered recently there exist regulatory differences between MEK1 and MEK2 isoforms. In particular, MEK1 has unique phosphorylation site (Thr292), which is phosphorylated by ERK, leading to MEK1 and MEK2 accelerated inactivation. Catalanotti et al. 2009 reported that ablation of MEK1 lead to unexpected prolonged activation of ERK and MEK2 in Mouse Embryonic Fibroblasts (MEFs) [1]. They found that the Thr292-dependent negative feedback regulation of MEK1 is transferred to MEK2 due to these isoforms' heterodimerization. We incorporated these interactions to investigate their role and provide a more complete model of the ERK cascade.

The model comprises all levels of the cascade from the EGFR membrane receptor to ERK. Upon binding the ligand, EGFR receptors dimerize and undergo phosphorylation. Phosphorylated protomers subsequently bind and activate an adapter protein Sos1. Sos1 then activates Ras, which in turn activates the Raf/MEK/ERK cascade. MEK1 and MEK2 can homo- and heterodimerize. MEK1 can be phosphorylated by ERK at Thr292. We propose that this creates a binding site for the MEK-specific phosphatase, which upon binding dephosphorylates both protomers within the dimer. The model also includes the classical negative feedback to Sos1 from ERK; phosphorylated Sos1 cannot bind the receptor and activate RAS. The model has been implemented using BioNetGen rule-based environment [2], and is defined by 41 rules generating 108 species.

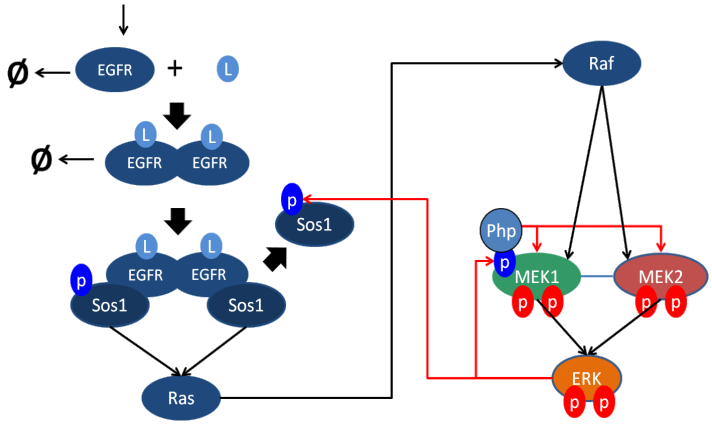

Fig.1 MEK1/2 Heterodimerization Model. The red arrows represent negative feedback

The model correctly reproduces the observed profiles of MEK and ERK activation profiles obtained in the experiments with WT and KO MEFs [1]. In particular, the model reproduces prolonged activity of ERK and MEK due to ablation of the negative feedback by (1) MEK1 knockout, (2) mutation of Thr292, and (3) disruption of MEK1/2 heterodimerization. Interestingly, ERK activity profile requires MEK2 to have kinase activity several times greater than MEK1. In summary, MEK isoforms play distinctive roles in the MAPK cascade and their dimerization is functionally important. The isoform specificity was reported for other MAPK kinases and deserves investigation.

P14

Power-law distributions arise from maximizing entropy subject to cost-sharing constraints

G. Jack Peterson and Ken A. Dill
Laufer Center for Physical and Quantitative Biology, Stony Brook University, NY (USA)

Power-law distributions are commonly observed in social and biological systems – the distributions of city sizes, scientific citations, numbers of protein interactions, metabolic network degree, etc. We are developing a framework for expressing power-laws in terms of a 'cost-sharing' rule combined with the principle of Maximum Entropy. We consider communities of 'social particles', where the cost of adding a particle to the community is shared between the particle joining the community and the particles that are already members of the community. Power-law community size distributions arise as a natural consequence of the maximization of entropy, subject to this cost-sharing rule. Our probability distribution has one free parameter, and interpolates smoothly between exponential and power-law distributions, as a function of sharing inequality. We have fit our theoretical distribution to data from 26 real-world data sets, which range from exponential to power-law. This method relates the probability distribution to simple observable quantities, which may be useful for systems where limited observations are available.

P15

Type of noise determines cell decision - analysis of the toggle switch model

Joanna Jaruszewicz[1] & Tomasz Lipniacki[1,2]
[1]Division of Modeling in Biology and Medicine, IPPT PAN, Warsaw, Poland, [2]Department of Statistics, Rice University, Houston, Texas, USA

The bistable regulatory elements enhance heterogeneity and may allow cells in multicellular organism to specialize and specify their fate. Our study demonstrates that in systems with the underlying bistability, like genetic switches, the noise characteristic controls in which of the epigenetic attractors cell population will settle.

In the model of the toggle switch we consider three types of noise: gene switching noise, transcriptional noise and dimerization noise. We calculated impact of each noise parameter on the stationary probability distribution (SPD). We found that the change of noise parameters for any of two genes (U or V) alters the protein SPD, influencing probability mass fraction in each of two basins of attraction. Interestingly, decrease of noise associated with a given gene can promote activation of that gene or the other, depending on the type of noise.

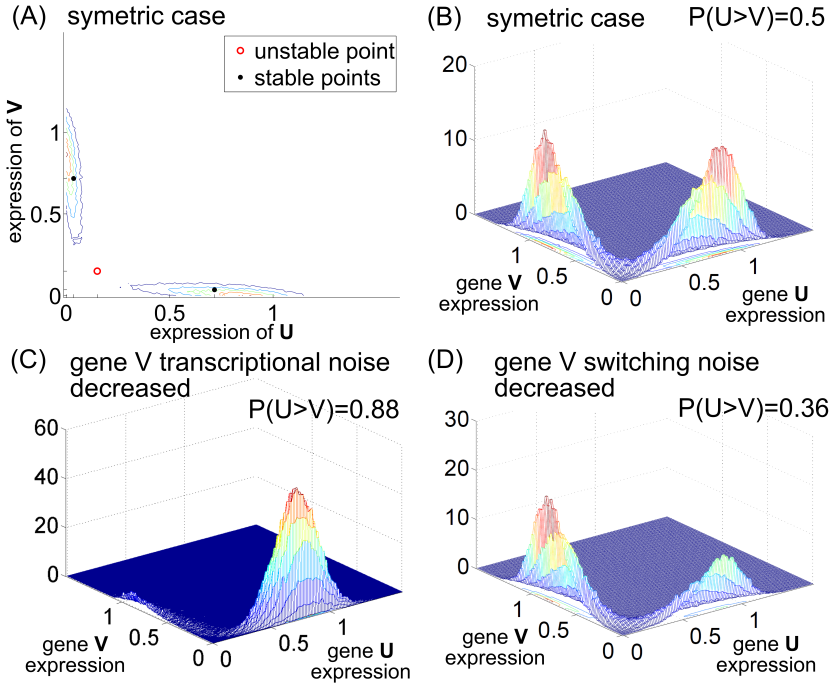

Figure 1
The protein SPD for the toggle switch model. (A) and (B) – contour plot and corresponding mesh plot; Parameters for gene U equal to that for gene V. (C) – 5-fold decrease of the transcriptional noise of gene V leads to gene U activation. (D) – in turn 5-fold decrease of the gene switching noise of gene V leads to gene V activation (64% of probability mass concentrates in the state in which gene is active).

P16

Stochastic traveling waves in a bistable reaction system on the plasma membrane

Marek Kochańczyk[1], Paweł Żuk[2], Joanna Jaruszewicz[1] & Tomasz Lipniacki[1,3]
[1]Institute of Fundamental Technological Research, Warsaw, Poland, [2]Interfaculty College of Science, Warsaw University, Poland, [3]Department of Statistics, Rice University, Houston, Texas, USA

A living cell can be considered as a stochastic biochemical reactor, wherein possible cell fates are associated with attractors of an underlying dynamical system. In perfectly mixed systems, transitions between attracting states may occur due to the presence of noise, while in spatially structured systems they can be associated with the propagation of heteroclinic traveling waves.

In this study we analyze the interplay between the two modes of steady state transition. As an example we consider a bistable spatially-extended model of kinase-phosphatase interactions on the plasma membrane. The bistability of the system arises from the assumption that kinase molecules activate each other and that they can be in one of the three states: unphosphorylated, single or doubly phosphorylated. Catalytic activity of kinases increases with their phosphorylation level. The system is analyzed with the help of numerical Monte Carlo simulations, performed using SpatKin, our software designed to simulate reaction-diffusion processes on the lattice.

As one could expect, in the limit of infinite diffusion the probability density (PD) obtained in the spatially-extended system converges to PD of the perfectly mixed system obtained in Gillespie algorithm simulations. However, for finite diffusion the behavior of the spatially-extended system differs qualitatively from the behavior of the perfectly mixed system.

First, at small (physiological) diffusion the phosphorylation mode changes from distributive to (more effective) processive, which leads to the system activation. Second, even in the parameter range in which a small isolated subcompartment remains mostly inactive, the traveling activatory waves may propagate leading to persistent activation of a larger compartment. Interestingly, these waves can arise spontaneously after a small subvolume is activated due to stochastic fluctuations (figure 1). Local activation probability is dramatically enhanced in subdomains characterized by slower diffusion.

This shows that the local immobilization of substrates can lead to the global activation on the plasma membrane in the mechanism which involves stochastic fluctuations and semi-deterministic traveling wave propagation. There exist an optimal diffusivity range, where the signal initiation and transduction over the membrane is most efficient.

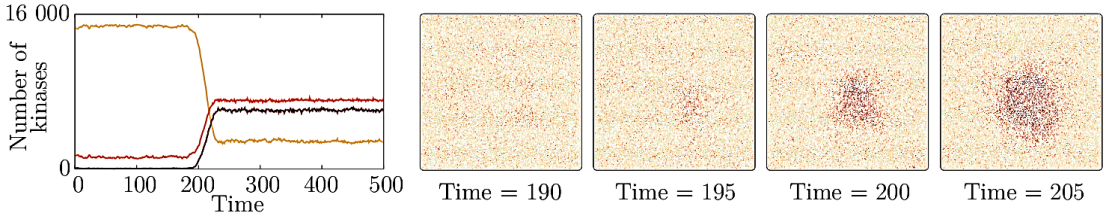

Figure 1. Time profile and four sample snapshots. Color key: kinases: unphosphorylated – orange, single phosphorylated – red, doubly phosphorylated - brown; phosphatases – pale green.

P17

The dependence of expression of NF-κB – dependent genes: Statistics and evolutionary conservation of control sequences in the promoter and in the 3' UTR

Marta Iwanaszko[1], Marek Kimmel[1,2],
[1]Department of Automation Control, Silesian University of Technology, Gliwice, Poland,
[2]Department of Statistics, Rice University, Houston, Texas (USA)

BACKGROUND

The NF-κB family plays a prominent role in innate (early) immune response and has impact on other processes such as cell cycle activation or cell apoptosis. The dynamics of NF-κB translocation has been studied both experimentally and using mathematical and computer modeling [1,2]. Once in the nucleus, NF-κB activates transcription of approximately 90 genes, some of which trigger further stages of the immune response [3]. NF-κB-dependent genes can be categorized, based on the timing of their activation counted from NF-κB translocation into the nucleus, as Early, Middle and Late genes. It is not obvious what mechanism is responsible for segregation of the genes' timing of transcriptional response. One likely hypothesis might be that the later the gene is, the more cofactors are required to activate it. Another control sequences are AU - rich elements (ARE) located in 3'UTR. AREs target mRNA for rapid degradation and inflict mRNA instability. Recent studies show that genes transcribed with unstable mRNA have different transcription dynamic which also divides genes to Early, Middle and Late group [4].

SUMMARY

It is likely that the differences in timing are reflected in differences in the structure of promoter regions of genes in different categories. Specifically, this might concern differences in number and type of transcription factor binding motifs, required for NF-κB itself as well as for the putative cofactors. Using this approach we analyzed if gene's assignment to the Early, Middle or Late group based on expression pattern, is connected with special features in promoter structure. This connection may be one of the mechanisms underlying the different patterns of gene expression control. We also compare Tian's results with Hao and Baltimore work on mRNA stability inflicting different transcription kinetic patterns. Both issues are best considered in the evolutionary framework, first, since functional binding sites are likely to be conserved in evolution and second, since the patterns of evolutionary change of promoter regions are not very well-known and are of serious interest.

CONCLUSION

Wider phylogenetic analysis of NF-κB dependent genes provides insight into the degree of cross – species similarity found in the Early genes, opposed to many differences in promoter structure that can be found among the Late genes. This suggest that activation and expression of the Late genes is much more species – specific than in the Early genes [5]. Based on the promoter structure and ARE content Middle genes can be divided into two subgroups which show similarities to Early and Late genes.

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P18

Stochastic competitive population dynamics: A study on evolutionarily stable dispersal rate in heterogeneous spaces

Yen Ting Lin[1], Hyejin Kim[2] & Charles R. Doering[1,2,3]
[1]Department of Physics, [2]Department of Mathematics,
[3]Center for the Study of Complex Systems, University of Michigan, Ann Arbor, MI (USA)

We propose two individual-based patch models to study competitive population dynamics of two species with identical birth and death rates, but distinct dispersal rates and compete for limited resourses in heterogeneous environments. The objective is to explore whether the evolutionarily stable dispersal rate exists, and if so, how it depends functionally on various parameters of the systems. Combining conventional asymptotic analysis with a novel asymptotic analysis proposed by Lin et al, we obtained closed forms of asymptotic solutions of both systems, as well as the insight of the detail dynamical mechanisms.

The essential parameter of the system is identified to be the carrying capacity of each patch times the environmental variance. The conclusions are: (1) Given fixed dispersal rates of both species, the slower dispersers will always have evolutionarily advantage over a long period of time if the parameter is greater than a critical value that depends upon the ratio of the birth/death rates and the dispersal rates. In other words, slower dispersers have evolutionary advantages in more heterogeneous environments, as well as in a system with larger characteristic population size, and vice versa. (2) The evolutionarily stable dispersal rate exists only when the parameter is greater than a uniquely defined critical value which depends solely on the ratio of the birth/death rates. (3) We obtained asymptotically closed form of the evolutionarily stable dispersal rate as the response of various parameters of the systems. Most importantly, we understand how the evolutionarily stable dispersal rates depend on environmental variance.

Demographic fluctuations, which are often neglected in deterministic models, are identified to be the fundamental mechanisms for such regime shifts. Our analytical results are supported by large-scale exact numerical simulations. The limit behaviors reported by previous studies published by J. Dockery et al, D. Kessler & L.M. Sander, as well as J.N. Waddell et al confirm our general analysis, which provides a comprehensive understanding of such type of individual-based competitive population dynamics.

P19

Coloured gene expression noise endows in silico cell populations with drug resistance independently of mutations

Daniel A. Charlebois[1,2], Nezar Abdennur[2,3] & Mads Kærn[1,2,3]
[1]Department of Physics, University of Ottawa, [2]Ottawa Institute for Systems Biology, [3]Department of Cellular & Molecular Medicine, University of Ottawa, Ontario (Canada)

Gene expression is a stochastic process which can generate phenotypic variability within a population of otherwise identical cells. This epigenetic variability can be beneficial to a cell population experiencing an acute stress by providing a temporary basis for natural selection. Based on experimental observations, it has been proposed that budding yeast possess long-term epigenetic memory. Specifically it was observed that yeast populations were able to adapt to a drug-induced stress by shifting gene expression levels towards those more favourable for growth. Consistent with a memory effect, this shift was reversible, with population wide gene expression returning to pre-treatment levels upon removal of the drug. Such a mechanism may contribute to the development of drug-resistant tumours in absence of genetic mutations. We use individual-based simulations of heterogeneous cell populations to explore this hypothesis.

First, we show that the time-scale of epigenetic memory has a significant effect on reproductive fitness. Surprisingly, even relatively short-lived fluctuations in gene expression can ensure long-term survival of a drug-resistant population. Then we apply our approach to the development of drug-resistant cancer cells by incorporating drug-induced mutagenesis, and explore how tumour growth rates and the probability of remission depend on the mutation rate, the initial number of dividing cancer cells, and the time-scale of gene expression noise. We found that the time-scale of epigenetic memory for a drug-resistant cell population to develop independently of mutations was comparable to that measured for certain genes in human cancer cells.

Our results indicate that permanent drug-resistance is an inherent property of coloured gene expression noise, and may arise even in the absence of mutations. We anticipate that the future development and analysis of corresponding analytical models will led to a better understanding of this phenomena and ultimately to novel experiments and treatment regimes.

*Daniel A. Charlebois, Nezar Abdennur, Mads Kærn. (2011) "Gene Expression Noise Facilitates Adaptation and Drug Resistance Independently of Mutation", Physical Review Letters, 107(21), doi: 10.1103/PhysRevLett.107.218101.

P20

Universality of Poisson indicator and Fano factor of transport event statistics in ion channels and enzyme kinetics

Srabanti Chaudhury[1,2], Jianshu Cao[3,], & Nikolai A. Sinitsyn[1,2]
[1]Theoretical Division, Los Alamos National Laboratory, Los Alamos, NM(USA), [2]New Mexico Consortium, Los Alamos, NM(USA), Department of Chemistry, Massachusetts Institute of Technology, Cambridge, MA (USA)

The key measurable quantity in ion channel transport had been the steady state flux through a single channel in a membrane that separates two compartments with different solute concentrations. In addition to average fluxes single-channel ion current measurements allow to study fluctuations, for example, the most accessible characteristics of fluctuations in molecular transport are related to second moment of the turnover time statistics and current distribution such as the Poisson Indicator and the Fano Factor. We consider a generic stochastic model of ion transport through a channel with arbitrary internal structure and kinetic rates of transitions between internal states. We show that measurement of statistics of single molecule transition time through the channel contains only restricted information about internal structure of the channel. The Poisson Indicator and the Fano Factor as function of solute concentration depend only on three parameters in addition to the parameters of the Michaelis-Menten curve that characterizes average current through the channel. This makes statistics of ion fluxes in the model of transport thought an ion channel effectively equivalent to the one in the simple kinetic model with only two internal states. On one hand, this universality imposes intrinsic restrictions on the information about the structure of a studied ion channel that can be obtained by measuring variance of transport characteristics. On the other hand, it identifies the new information that can be obtained from such measurements and provides its interpretation in terms of effective kinetic rates in an effective two-state system.

P21

Random Time Changes and Poisson Processes: An Application Using Skorohod-Type Topology in Fast-Slow Reactions

Casper Woroszylo, Dennis Cox
Department of Statistics, Rice University, Houston, Texas (USA)

This work builds on results by Tom Kurtz on Poisson representations of chemical reaction systems. In particular, we make use of the almost sure approximation of discrete jump processes by corresponding deterministic formulations in the thermodynamic limit. For a particular example, we partition the set of reactions into "fast" and "slow" reactions, i.e. infinite and finite reaction rates, respectively, and formulate a piecewise deterministic approximation for the system. This approximation is shown to converge almost surely in a sequence of Skorohod type metric spaces in the thermodynamic limit.

P22

Bernoulli mixture models in application of the evaluation of algorithms estimating functionality of missense mutations

Stephanie Hicks[1], **Sharon E. Plon**[2], **Marek Kimmel**[3]
[1]Department of Statistics, Rice University, Houston, Texas (USA), [2]Departments of Pediatrics and Human and Molecular Genetics, Baylor College of Medicine, Houston, Texas (USA)

Background
Whole genome and whole exome sequencing projects yield thousands of missense mutations with unknown functionality. Direct estimation of the sensitivity and specificity of bioinformatic algorithms predicting the impact of missense mutations on protein function requires a "gold standard" or set of mutations with known functionality. In the absence of a "gold standard", additional statistical methods are needed to estimate the accuracy of these algorithms. It has been shown informative predictions depend on the algorithm and sequence alignment employed and often algorithms disagree as to which mutations are predicted deleterious or neutral (Hicks et al., 2011, *Hum Mut*).

Materials and methods
To investigate the level of agreement, disjoint categories of sets of mutations are defined depending on which algorithms predict which mutations to be deleterious or neutral. We develop two statistical models called Bernoulli Mixture (BM) and Augmented Bernoulli Mixture (ABM) based on the capture-recapture technique which employ these disjoint categories. Application of these models allows us to jointly estimate the sensitivities and specificities of each algorithm considered without the use of a gold standard and to estimate the proportion of deleterious mutations in a given set. These estimates may then be used to calculate the posterior probability of a given variant being deleterious. When considering n algorithms, there are 2^n disjoint categories employed by the ABM model which includes $2n + 3$ parameters and the BM model is a special case of the ABM model which includes $2n + 1$ parameters. We use the Expectation-Maximization algorithm for parameter estimation.

Results
We apply the models to two types of predictions of functionality: simulated and real predictions. Using simulated predictions, we accurately recover the true sensitivity and specificity values and report confidence regions. We show example posterior probabilities of a given variant being deleterious. When a gold standard is available, we show the sensitivity and specificity estimates reported the BM and ABM models closely match the sensitivity and specificity estimated directly using the true functionality status. To test our models on mutations without known functionality, we apply the models to mutations obtained from the exomes of four individuals which were sequenced at the Human Genome Sequencing Center at Baylor College of Medicine to identify cancer susceptibility genes for acute lymphocytic leukemia and

lymphoma in children. Within each individual, we estimate posterior probabilities for each variant being deleterious and apply an intersection filter to look for deleterious mutations shared by the three affected individuals, but not in the unaffected individual.

Conclusions
The BM and ABM models may be used to estimate the sensitivity and specificity of algorithms predicting the functionality of mutations without the use of a gold standard and to calculate posterior probabilities of a given variant being deleterious which may be used downstream in application of finding causal variants in next-generation sequencing.

Acknowledgements
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P23

On the Evolution of Breakpoint Hotspots of Somatic Copy-number Alterations in Human Cancer

Yudong Li[1,2], Li Zhang[1], Robyn L. Ball[3], Xinle Liang[2], Jianrong Li[2], Zhenguo Lin[4] & Han Liang[1]

[1]Department of Bioinformatics and Computational Biology, The University of Texas MD Anderson Cancer Center, Houston, Texas (USA), [2]Department of Food Sciences and Biotechnology, Zhejiang Gongshang University, Hangzhou (China), [3]Department of Statistics, Texas A&M University, College Station, Texas (USA),[4]Department of Ecology and Evolution, The University of Chicago, Chicago, Illinois (USA)

Somatic copy-number alterations (SCNAs) play a crucial role in the development of human cancer. However, it is not well understood what evolutionary mechanisms contribute to the global patterns of SCNAs in cancer genomes. Taking advantage of data recently available through The Cancer Genome Atlas, we performed a systematic analysis on genome-wide SCNA breakpoint data for eight cancer types. First, we observed a high degree of overall similarity among the SCNA breakpoint landscapes of different cancer types. Then, we compiled 19 genomic features and evaluated their effects on the observed SCNA patterns. We found that evolutionary indel and substitution rates between species (i.e., humans and chimpanzees) consistently show the strongest correlations with breakpoint frequency among all the surveyed features; whereas the effects of some features are quite cancer-type dependent. Focusing on SCNA breakpoint hotspots, we found that cancer-type–specific breakpoint hotspots and common hotspots show distinct patterns. Cancer-type–specific hotspots are enriched with known cancer genes but are poorly predicted from genomic features; whereas common hotspots show the opposite patterns. This contrast suggests that explaining high-frequency SCNAs in cancer may require different evolutionary models: positive selection driven by cancer genes, and non-adaptive evolution related to an intrinsically unstable genomic context. To the best of our knowledge, this is the first comprehensive analysis on the largest SCNA dataset of human cancer. Our results not only present a systematic view of the effects of genetic factors on genome-wide SCNA patterns, but also provide deep insights into the evolutionary process of SCNAs in cancer.

P24

Mapping the regulatory structure between two key transcription factors in a breast cancer cell line

Jinho Lee[1,3], Victor Shum[1], Michael Mancini[2], Oleg Ighosin[3] & Gábor Balázsi[1]
[1]Department of Systems Biology, UT MD Anderson Cancer Center, [2]Department of Molecular and Cellular Biology, Baylor College of Medicine, [3]Department of Bioengineering, Rice University, Houston, Texas (USA)

Estrogen receptor alpha (ERα) expression is an important classifier for breast cancer patients. Therefore, understanding ERα regulation can be important for improving the efficiency of current therapeutic strategies for breast cancer. ERα and another transcription factor, GATA3 were suggested to have mutual regulatory positive feedback loops, which may contribute to the ERα expression pattern. By measuring the response of the ERα-GATA3 regulatory network to various perturbations and fitting a set of quantitative gene regulation models to the data, we identified the regulatory structure between ERα and GATA3. Furthermore, we measured ERα and GATA3 protein and mRNA expression level in single cell or single nucleus using flow cytometry, Immunofluorescence and mRNA FISH, which will reveal the stochasticity in this system. Our results suggest possible regulatory modes that may exist between ERα and GATA3 in the T47D breast cancer cell line.

P25

CanDrA: Cancer-Specific Driver Missense Mutation Annotation with Optimized Descriptors

Yong Mao[1], Han Chen[1], Han Liang[1], Funda Meric-Bernstam[2], Gordon Mills[3] & Ken Chen[1]
Departments of [1]Bioinformatics and Computational Biology, [2]Surgical Oncology, [3]Systems Biology, The University of Texas M.D. Anderson Cancer Center, Houston, Texas (USA)

Driver mutations are somatic mutations that provide growth advantage to tumor cells, while passenger mutations are those that are not functionally implicated in oncogenesis. Predicting driver mutations is challenging because they occur much less frequently than passengers, they turn to have low prevalence across cancer sample cohort and their function determination is multifactorial. Missense mutations have been considered more practical driver candidates for cancer target discovery and development, because they have well-recognized roles in many genetic diseases, are widespread in the cancer genome and potentially more druggable than other types of mutations. Although a dozen of computational methods have been developed for predicting the functional impact of missense mutations, only a few were specifically designed for identifying drivers. Since more missense mutations are identified by large-scale cancer genome sequencing projects and more powerful predictive factors are designed, development of accurate model through systematic data integration and optimization under specific cancer background becomes within reach. Here, we present such a cancer-specific driver annotation system as in Figure 1, called CanDrA that has outperformed other tools on the glioblastoma multiforme and the ovarian carcinoma data from The Cancer Genome Atlas (TCGA) and the Cancer Cell Line Encyclopedia project. Our analyses indicate that (1) modelling real passenger mutations is important to achieve specificity, (2) culling mutations across different conditions is important to achieve sensitivity, and (3) large-scale functional screening experiments such as those performed by the Cancer Target Discovery and Development (CTD²) Network will be essential for further advances.

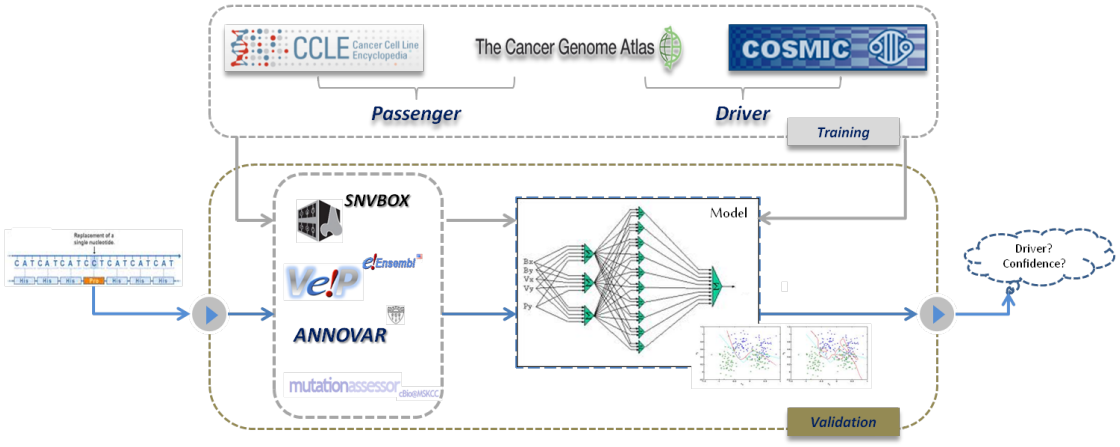

Figure 1. Flowchart of CanDrA System

P26

Mechanism of sporulation decision in B. subtilis

Jatin Narula[1], Seram N. Devi[2], Masaya Fujita[2] & Oleg A. Igoshin[3]
[1]Department of Bioengineering, Rice University, [2]Department of Biology and Biochemistry, University of Houston

Starving *B. subtilis* cells execute a gene-expression program resulting in formation of stress-resistant spores. Sporulation master regulator, Spo0A, is activated by a phosphorelay and controls the expression of a multitude of genes, including the forespore-specific sigma factor σ^F and the mother-cell specific sigma factor σ^E. Identification of the molecular mechanism underlying the sporulation decision is hindered by lack of direct control over the Spo0A activity, which can be overcome by using a synthetic system in which Spo0A activation is controlled by inducing expression of the phosphorelay kinase KinA. This induction results in a switch-like increase in the number of sporulating cells at a threshold level of KinA. Using a combination of mathematical modeling and single-cell microscopy we investigate the origin and physiological significance of this ultrasensitive threshold. The results indicate that the phosphorelay, despite its positive feedback architecture, displays only a graded rather than ultrasensitive response to KinA suggesting that the sporulation decision is made downstream. In contrast, activation of σ^F in the forespore and of σ^E in the mother-cell compartments which occur via a cascade of coherent post-translational feed-forward loops can produce fast and ultrasensitive responses as a result of KinA induction. While many cells activate σ^F even below the KinA threshold, σ^E activation in the mother-cell compartment only occurs above the KinA threshold. Since σ^E activation is essential for the completion of sporulation the ultrasensitive increase in σ^E activation explains the KinA threshold for sporulation induction. Time-lapse microscopy of starving wild-type cells showed that while many cells activate Spo0A and form asymmetric septa only cells that activate σ^E complete sporulation, thus confirming that σ^E activation is the cell-fate decision point. These results show that *B. subtilis* cells initiate morphological changes even before making a cell-fate decision. Thus the design of the sporulation network suggests that cells choose to defer their commitment but not the initiation of the sporulation program to minimize the effects of stochastic fluctuations by time-averaging but without compromising their response time.

P27

Predictive Control of an Engineered Optogenetic Signaling Pathway in *E. coli*

Evan J. Olson[1], Lucas Hartsough[2], Andrew Wu[2], Raghav Shroff[2] & Jeffrey J. Tabor[2]
[1]Applied Physics Graduate Program, [2]Department of Bioengineering,
Rice University, Houston, Texas (USA)

Signal transduction networks underlie many cellular decision making processes. Among the simplest of these networks are two component systems (TCSs), which comprise a signal-sensing histidine kinase protein and response regulator protein with which it interacts. When the sensor kinase detects signal it phosphorylates the response regulator which then typically binds to DNA. DNA binding modulates the transcription of one or more target genes, providing a means for the cell to respond to its surroundings. The relative simplicity of TCSs makes them ideal targets for synthetic control of cellular behavior. Previously, the EnvZ/OmpR and CcaS/CcaR TCSs have been engineered to reprogram E. coli to sense the color and intensity of light in the environment.

Here, we have exploited the millisecond-time scale red/green photoreversbility of the CcaS phytochrome to dramatically reduce the gene expression response time, and to achieve precise, quantitative control of gene expression levels in real-time. First, we have constructed a programmable array of light emitting diodes (LEDs) that allows calibrated dosing of different colors of light in any desired temporal pattern in up to 64 standard tubes of growing cells. We demonstrate that the application of different activating to inactivating light ratios allows us to set a desired analog gene expression level. By shining light ratios in a time-varying sequence, we can then drive cells to move between desired analog expression levels without adjusting the growth media. Gene expression is reported by GFP fluorescence and single-cell data is acquired from each culture via flow cytometry.

Our observations of cells grown in a variety of time-varying light sequences are well described by a model incorporating two variables: the gene production rate, whose kinetics are determined by the red and green illumination intensities, and the measureable gene expression level which follows the production rate with kinetics determined by the growth rate of the cells. By calibrating the parameters of this model with an array of gene expression time-courses under a variety of illumination patterns, we have successfully predicted light control sequences that will generate desired gene expression time-courses.

This level of quantitative, temporal control of gene expression would be extremely difficult to achieve with traditional modes of gene regulation. As it has in neurobiology, the precise perturbative nature of optogenetic tools therefore stands to contribute significantly to systems and synthetic biology.

P28

Context-dependent estimates of substitution rates in human, chimpanzee and gorilla indicate acceleration in the human lineage.

Navin Rustagi[1], Ivan Gorlov[2], Sharon Plon[3,4], Marek Kimmel[1], William Amos[5]

[1] Department of Statistics, Rice University, Houston, Texas; [2] The University of Texas MD Anderson Cancer Center, Houston, Texas; [3]Genome Sequencing Center; [4]Texas Children's Cancer Center, Department of Pediatrics, Baylor College
of Medicine, Houston, Texas; [5] Department of Zoology, University of Cambridge, Cambridge, UK

Motivation: The 'molecular clock' remains the basic null model for how mutations accumulate. Among mounting numbers of exceptions is the suggestion that substitution rates decline in the hominoid lineage.

Similarly, sequence context seems important, with many species showing highly significant deviations for the expected occurrences of dinucleotide motifs relative to random expectations.
Aims and methods: To explore these issues in detail, we use a form of relative rate test using the exon and intron sequences of Human (H), Chimpanzee (C) and Gorilla (G), with Orangutan (O) as the out-group. Context was analyzed by considering each base in terms of its immediately flanking bases, giving 64 possible combinations (4 bases x 16 flanking dinucleotides). Relative mutation rates were determined using three way alignments >100bp in length (obtained using http://galaxy.psu.edu/) of HCO, HGO, and CGO. To reduce the influence of poorer alignments only triplets where the flanking bases are identical in all three species are used. Regression-based techniques were developed to reconcile the substitution frequencies from the pairwise comparisons. For comparison, also four-way HCGO alignments were used to generate estimates.
Results and conclusions: Predictably, the estimates depend on the assumptions underlying the evolutionary model, particularly on the mutation rate assumed in the phylogeny branch leading from the HCG ancestor to the HC ancestor sequence. The length of this branch is similar in both models and when used jointly with the HCGO alignments it produces qualitatively similar estimates to those based on regression methods. Introns exhibit higher substitution rates and more consistent species-specific rate differences than exons. Humans have the lowest rates and gorillas the highest, supporting the hominoid slowdown. All mutation rates are strongly context-dependent, with CpG triplet much higher than others, but also a four-fold rate difference between different XAY triplets. There is some evidence that the hominoid slowdown is more apparent for some subsets of triplets than for others.

P29

IRF3 and NF-_B: Transcription factors acting in a coordinated way under double stranded RNA stimulation

Roberto Bertolusso[1], Bing Tian[2], Aqeeb Sabree[3], David Wallace-Bradley[1], Allan Brasier[2], Tomasz Lipniacki[4], Marek Kimmel[1]

[1] Rice University, Houston, TX, USA, [2] University of Texas Medical Branch, Galveston, TX, USA [3] Texas Southern University, Houston, TX, USA [4] IPPT, Warszawa, Poland

Dynamics of innate immunity system under viral attack is still not understood in detail. However, new insights are emerging based both on novel experiments and on system modeling approach. We report a model of coordinated response of IRF3 and NF-κB transcription factors pathways in A549 lung cancer cells, under double stranded RNA (dsRNA) stimulation, itself a model for viral RNA. Viral infection leads to multiplication of viral RNA which is sensed by the innate immune system at a later stage. dsRNA, instead, rapidly activates the IRF3 and NF-κB pathways, leading to responses which are stronger and better localized in time. dsRNA is sensed both by RIG-like family of helicases (RIG-I) and toll-like receptor 3 (TLR3). Activation of RIG-I leads, via multistep pathway, to the nuclear translocation of IRF3. In turn activation of TLR3 leads to phosphorylation and degradation of primary NF-κB inhibitor IκBα, freeing NF-κB which also translocates to the nucleus. IRF3 and NF-κB are independently and cooperatively responsible of the activation of a number of genes involved in innate immune and inflammatory responses, in particular both IRF3 and NF-κB are needed for the activation of the interferon β. In addition NF-κB also activates a number of inhibitors, among them IκBα and A20, inhibiting both pathways or selectively one pathway. Four kind of experiments were performed:

- Time series (0, 0.5, 1, 2, 4 and 6 hours) of key mRNAs induced by NF-κB and IRF3transcription factors.
- Time series of key phosphorylated proteins at same time points as above.
- Knock-down experiments using small interfering RNA (siRNA) on NF-κB, IRF3, RIG-I, and IKK with and without dsRNA stimulation.
- Single-cell imaging time series (18 hours at 6 min intervals) of IRF3 and NF-κB targeted by fluorescent proteins (GFP and cherry).

The emerging mathematical model of differential equations with extrinsic stochasticity considers 93 species and 165 reactions. It seems to be the first aggregate model of dynamics of NF-κB and IRF3, and shows agreement with experimental data.

P30

A branching process model of hematopoiesis with applications to Chronic Myeloid Leukemia

Thomas McDonald[1] and Marek Kimmel[1]

Acknowledgements: Thomas McDonald was supported by an NCI T32 training grant CA096520.

[1]Department of Statistics, Rice University, Houston, TX 77005. E-mail: tom2@rice.edu, kimmel@rice.edu

Short Abstract — An age-dependent reducible branching process model is proposed to model hematopoiesis and the genesis and relapse of chronic myeloid leukemia stem cell populations. The model attempts to determine the probability of nonextinction of a population and the amount of time until a population reaches a specific size. The model is motivated by a pseudo-stochastic model that introduces within-tissue plasticity although it does not account for cell death, removing part of the variability due to stochasticity in small populations.

Keywords — reducible branching processes, hematopoiesis, stem cell plasticity, chronic myeloid leukemia.

I. Introduction

Roeder and Loeffler propose a pseudo-stochastic model of hematopoietic stem cell organization and proliferation accounting for plasticity within functionally similar stem cells prior to differentiation [6, 7]. The model relies on an amended definition of tissue stem cells formulated to account for plasticity within the tissue while relying on the functionality of stem cells. A stem cell is defined by its capabilities rather than properties of the cell, including the ability to self-maintain, self-renew, and the residence in a growth or quiescent environment [3, 5].

According to the model, as cells remain in the growth environment, they divide at every time step into 2 daughter cells with a propensity to differentiate. However, with some probability the cells can enter a quiescent environment and lose the propensity for differentiation, bringing them back toward an earlier state. Once differentiated, a cell exits this cycle and can enter the peripheral system, preparing it for maturity and eventual cell death [6]. The authors show the application of their model and simulation to the study of chronic myeloid leukemia, its treatment and the potential for relapse [2].

Simulations of CML treatment include the effect of cytostatics such as imatinib or hydroxurea which reduce the number of leukemic stem cells (and normal stem cells with treatment of HU). However after the treatment period is finished, there is a potential for CML stem cells to self-renew their population count and relapse to occur, which is a common situation. The model does not account for cell death, and at low population counts, the associated stochasticity is not considered which could lead to extinction of the CML population of cells instead of a relapse. Variability of the time until relapse may also vary due to the stochasticity of cell fates. Both should be considered after treatment [2, 6].

II. Branching process model and its predictions

We propose an age-dependent multitype branching process model as a stochastic model of hematopoiesis with within-tissue plasticity. Such a model will allow us to account for variability during the genesis of CML and after therapy. We can determine the probability of nonextinction of leukemic cells and the time until a sizable population has been achieved (as in a relapse event). Our model assumes stem cells exist in a growth or quiescent environment proliferating until exiting a final state to become fully differentiated. Once differentiated, cells are no longer stem cells and continue into maturity before death, so the process is reducible. Since we are dealing with a potentially large population of cells, asymptotics and large number approximations of the process are determined [1, 4].

At the present stage, the results include determination of feasible range of parameters and a sensitivity study of the model. This will be followed by calibration to existing experimental and clinical setups.

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Mathematical methods in researches over the origins of life

Dariusz Myszor
Institute of Informatics, Silesian University of Technology
44-100 Gliwice, Poland
dmyszor@polsl.pl

RNA world hypothesis postulates a central role of RNA molecules in the early living organisms. Life based on RNA is widely considered as one of the first possible stages in the early evolution of this process. It is assumed that during this period, RNA molecules played a dual role, they were carriers of genetic information and catalysts of chemical reactions. Simulation of RNA world usually is a complex process and requires high computational power and sufficient amount of time. Therefore there is a constant search for methods which are able to improve this process and reduce time and resources needed to achieve results.

Poster will described utilization of branching processes in the model of Monte Carlo simulation of the early phase of RNA world. Introduced modifications allows for sufficient reduction of time of computation and help to rule out artificial limitations.
