2011 SUMMER RESEARCH PROGRAM IN SYSTEMS BIOLOGY

POSTER SESSION

DATE:
MONDAY AUGUST 15 2011

LOCATION:
ANNENBERG BUILDING, ROOM 19-79
1468 MADISON AVE, NEW YORK, NY 10029
MOUNT SINAI SCHOOL OF MEDICINE

TIME:
1:00 PM - 3:00 PM

For more information about the program, please visit www.sbcny.org/2011_program.htm

SBCNY is supported by Grant Number P50GM071558 from the National Institute of General Medical Sciences
Principal Investigator: Ravi Iyengar, PhD

The Systems Biology Center New York (www.sbcny.org) is one of the National Centers for Systems Biology funded by the National Institute of General Medical Sciences (NIGMS). Researchers and educators from Mount Sinai School of Medicine, Courant Institute of Mathematical Sciences NYU, Stony Brook University (SUNY), City University of New York (CUNY), National Centre for Biological Sciences (India), and the IBM T.J. Watson Research Center, form the Systems Biology Center New York. The Center is organized as three major sections: 1) Education and Outreach Core (EOC); 2) Experimental and Computational Core (ECC) and 3) Research Projects. All of the research projects have opportunities for interdisciplinary collaboration. The research activities of the Center form a continuum with our education and outreach activities that include pre- and postdoctoral training, a summer undergraduate research program focused on recruiting underrepresented minority groups and training for educators.

SBCNY investigators want to understand how the effects of molecular interactions are propagated across scales of organization from cells to tissues and organs affecting physiology and pathophysiology. We posit that the dynamic organization of motifs (regulatory loops) within multi-scale networks provides the basis for propagation of effects across scales from molecules to cells to tissues. We study drug action at a genomic scale to understand and predict adverse events. We are actively engaged in the development of the new discipline of Systems Pharmacology.

The goals of the Systems Biology Center New York are to develop and disseminate approaches that provide a mechanistic understanding of how molecular interactions within regulatory networks in cells lead to the physiological function of tissues and organs, and how therapeutic agents affect cellular networks to alter pathophysiological states i.e. “the therapeutic implications of the design logic of scalability in mammalian systems”.

The research focus of SBCNY is on the development and analysis of scalable models to identify regulatory patterns and how they are reconfigured by drugs. Such reconfiguration may result in therapy for a targeted pathophysiology while producing unanticipated adverse events. One of the goals of Systems Pharmacology is to develop algorithms to predict adverse events in a personalized and reliable manner. Our computational models originate from experimentally measured interactions and parameters, and the predictions of models are used to develop experiments that shed light on the design logic of the system to better understand how organ level physiology arises from cellular organization and genomic variations. We anticipate that such understanding will enable the development of network based polypharmacology and the prediction of adverse event risk on an individual basis.
2011 Summer Research Program

Program Description: The Systems Biology Center New York offers summer research fellowships to undergraduates who are planning to pursue PhD or MD/PhD degree programs and are interested in incorporating systems biology approaches into the research that they pursue. The SBCNY Summer Research Program is a full-time 10-week research-intensive systems biology training program within laboratories of the Center. The fellowship includes a stipend for the research training period from June 6, 2011 to August 12, 2011.

Participated in Activities of the Center

Che, Abonghatou  
Rutgers University  
Undergraduate

Komosinski, Michael  
Colgate University  
Undergraduate

Luo, Yan Fei  
Brooklyn College  
Undergraduate

Rahman, Fatema  
York College  
Undergraduate

Song, Roy  
The City College of New York  
Undergraduate

Zaringhalam, Matthew  
Colgate University  
Undergraduate

Gordonov, Simon  
University of Cambridge  
Graduate Student

Dalal, Pavan  
Mount Sinai School of Medicine  
Medical Student

SBCNY Summer Fellows and Research Projects

http://sbcny.org/2011_program.htm
**Poster Session Participants**

**Independent Research Projects:** All SBCNY Fellows conduct an individual research project under the mentorship of a SBCNY Investigator. In addition to the independent research projects, Fellows attend a weekly research seminar aimed at introducing projects which integrate experimental and computational components and incorporate a systems biology approach.

**Undergraduate**

**Komasinski, Michael**  
Colgate University, B.A., Major: Mathematics/Computer Science  
Project Title: Integrating, Predicting, and Visualizing Mammalian Protein-Protein Interaction Networks  
*SBCNY Mentor: Avi Ma’ayan PhD*

**Luo, Yan Fei**  
Brooklyn College, Major: Physics  
Project Title: Finding Potential Drug Targets to Stimulate Calorie Restriction Benefit  
*SBCNY Mentor: Avi Ma’ayan PhD*

**Song, Roy**  
The City College of New York, Major: Biology  
Project Title: Regulation cAMP-specific Phosphodiesterase PDE4D3 by Brain-derived Neurotrophic Factor and Dopamine  
*SBCNY Mentor: Susana Neves PhD*

**Zaringhalam, Matthew**  
Colgate University, Major: Molecular Biology/Applied Mathematics  
Project Title: Parameter Interactions in Electrophysiological Models of Cardiac Cells  
*SBCNY Mentor: Eric Sobie PhD*

**Graduate**

**Gordonov, Simon**  
Rutgers University, B.S., Major: Biomedical Engineering and University of Cambridge, M.Phil., Major: Computational Biology  
Project Title: Uncovering Upstream Regulatory Mechanisms from Gene Expression Profiles of Breast Cancer Tumors from Patients  
*SBCNY Mentor: Avi Ma’ayan PhD*
The inherent biological inter-patient heterogeneity of breast cancer motivates the identification of unique, clinically relevant, global molecular signatures of the disease. Indeed, the ability to correlate phenotypic similarities and differences with mutations, other genetic aberrations, and whole genome transcriptomic signatures enables clinicians to stratify individual patients to predict survival outcomes and risk of recurrence. However, gene signatures established by various studies to prognose the same clinical outcome differ significantly across literature and current methods often fail to identify the cell signaling pathways and networks that are altered in subtypes of the disease. Consequently, understanding the cell signaling mechanisms in different subtypes of cancer may improve prognostic disparities, which is critical for the development of reliable patient-tailored, personalized therapeutics. To this end, we utilized Expression2Kinases (X2K), a software tool that uses prior knowledge from ChIP-seq/chip profiling of transcription factors, protein-protein interaction databases, and kinase-substrate databases, to connect changes in gene expression to cell signaling pathways. We applied X2K to analyze a cohort of breast cancer tumors by developing the following computational workflow: a) identify co-expressed gene modules whose levels vary across tumor samples; b) infer transcription factors that potentially regulate the differentially expressed modules using ChIP-seq/chip data; c) build a transcription factor-centered complex using data from databases of protein-protein interactions; d) score protein kinases based on identified kinase substrates in the transcription factor-centered complexes. Using this workflow, we discovered intra-subtype similarities and inter-subtype differences in cell signaling networks that regulate the function of tumor cells from the cohort of patients. We visualized the results of the inferred pseudo-activity contribution scores of upstream transcription factors and protein kinases that regulate the differentially expressed genes using a variety of clustering techniques. The unsupervised grouping of patients based on inferred cell signaling mechanisms revealed visually-discernable clusters of patients by breast cancer subtype and risk of distant recurrence that was assessed from a clinical prognosis gene signature. Moreover, using a subset of co-expressed genes that are up-regulated in metastatic tumors, we identified modulators that are preferentially activated in patients with distant recurrence. The notable subset of transcription factors are: SUZ12, JARID2, SMAD2/3, P53, TBX3, and PPARG/D, and the protein kinases: MAPK1, HIPK2, CDK1, TGFBR2, and MAPK14. These upstream regulators are potential targets for oncological therapeutic development.
An important goal of Systems Biology research is the elucidation of the human “interactome”, namely the myriad protein-protein interactions largely responsible for cellular structure, regulation and homeostasis. While there are large-scale protein-protein interaction databases readily available online, efforts to integrate, evaluate, and filter such resources still need to be developed. To this end, we first integrated content from the following databases: BioGrid, IntAct, the Human Protein Reference Database (HPRD), BIND, the Molecular Interactions Database (MINT), Kinase Enrichment Analysis (KEA), InnateDB, the Protein-Protein Interaction Database (PPID), Vidal et al (Nature, 2005), Stelzl et al (Cell, 2005), Figeys et al (Molecular Systems Biology, 2007), the Kyoto Encyclopedia of Genes and Genomes (KEGG), the Database of Interacting Proteins (DIP), Vidal et al (Nature Methods, 2011), MIPS, BioCarta, and PDZBase; the result was an aggregate network which comprised of 495,283 protein-protein interactions between 24,147 proteins. All the interactions in this consolidated database were extracted from publications that reported interactions identified experimentally.

One of the uses of experimentally identified protein-protein interaction databases is their utility as a benchmark dataset for algorithms that predict protein-protein interactions from indirect evidence. We implemented such an algorithm to predict protein-protein interactions from a high-throughput immune-precipitation followed by mass-spectrometry (HT-IP/MS) publication by Malovannaya et al. (Cell, 2011). Given sets of proteins identified in the related HT-IP/MS experiment, our algorithm scores to the likelihood that any two proteins directly interact based on their frequency to appear in pull-downs; from this scoring scheme, a putative network can be constructed and evaluated with the known consolidated protein-protein interaction database we aggregated from multiple online sources. The algorithm was found to assign high confidence scores to known interactions at a rate far greater than random.

To visualize the resultant networks as ball-and-stick diagrams, a program called Text2Graph was developed using Python. This program overcomes the difficulty for novice users of uploading medium to large-size networks into network visualization software. Text2Graph takes as input simple formatted text files and outputs an interaction network in file formats native to the graph viewers and editors: yEd and Cytoscape. The consolidated protein-protein interactions database, the algorithm to infer protein-protein interactions from indirect evidence, and the tool to visualize interaction networks can all become useful resources for the Systems Biology research community.
Studies have shown that caloric restriction (CR) diet, a diet with limited calorie intake but without malnutrition, has an anti-aging effect in yeast, worm, fly, rodent and primate [1-5] while several genes have been implicated in their involvement in this process. Particularly, the studies of CR in rodents and primates showed that several indicators of aging were lessened, including greater insulin sensitivity, lowered blood pressure, and reduction in arterial stiffness [3]. Although there is no conclusive experimental evidence for CR benefits for humans, in the Comprehensive Assessment of Long-term Effects of Reducing Intake of Energy (CALERIE) Phase 1 study reported some positive indicators [6]. These observations support the notion that programmed organism death (phenoptosis) in humans, similarly to the programmed cell death (apoptosis), can be manipulated. This provides hope that we could therapeutically extend life span significantly while delaying the onset of diseases that correlate with age by properly targeting the pathways that promote aging.

To further identify genes that may be relevant to aging, we implemented the following approach: We assumed that if we find a gene expression signature that is a result of CR in yeast, we could find additional evolutionary conserved genes that may be involved in aging pathways. We identified two yeast genome-wide gene expression microarray datasets that restricted glucose intake: Brauer et al. who limited glucose levels over a time course [7] and Tirosch et al. who switched the media conditions from glucose to glycerol [8]. We mapped the yeast gene names to human gene names, and then used Grid Analysis of Time Series Expression (GATE) [9] to create time-series animated movies of expression from both datasets and extracted the top differentially expressed genes. After this analysis, we obtained four lists of genes: one with up-regulated genes, and one with down-regulated genes, for each associated dataset.

We then compared the four lists with other lists of genes from the following resources: Two lists from the Mouse Genome Informatics Molecular Phenotype (MGI-MP) browser [10] labeled as Aging-Mortality and Extend-Life-Span. These lists were created from observing the phenotype of knockout mice. Five Lists of genes from GenAge [11]: two lists of DNA repair genes, one associated with aging and the other not associated with aging, a list of genes labeled as human longevity genes, and two lists of differentially expressed genes from microarrays collected from studies that compared aged and young tissues from mammalian organisms. Finally, 18 lists of differentially expressed genes after treatment of cancer cell lines with Resveratrol, a supplement that was shown to extend life-span in yeast, from the Connectivity Map database (C-MAP) [12].

Using the software Lists2Networks[13] we found several genes that statistically significantly overlapped with the genes we identified to be differentially expressed in yeast due to CR: for example, MLST8 and MTOR (Fisher test, p-value < 0.04, with the MGI-MP Extend-Life-Span and the genes increased in expression in the Brauer et al study), and AKR1B1, AP2S1, CRAT, DNAJB1, FDXR, FZR1, GFPT2, HSPH1, IKBP1, RAB11B, RBKS, SLC25A16 (Fisher test, p-value < 0.005, genes increased in expression in the Brauer et al study and are up in one of the Resveratrol studies from C-MAP). These genes potentially play a role in aging and their role is conserved from yeast to mammal and is identified through independent approaches. Two genes that we found, namely MLST8 and MTOR, physically interact and are members of the same pathway. Interestingly, Rapamycin, a drug that targets the MTOR pathway, was recently shown to extend life of older mice [14].
Mitogen-activated protein kinase (MAPK) and protein kinase A (PKA) pathways are two important cascades in neuronal signaling. In the nucleus accumbens (NAc), a region in the ventral striatum central in reward-related learning, the MAPK pathway is activated by the binding of brain-derived neurotrophic factor (BDNF) to extracellular Trk family of receptors, primarily TrkB receptor. The PKA pathway can be stimulated by the binding of dopamine (DA) to its dopamine D1 receptor (D1R). BDNF, through a series of signaling events, leads to the rapid phosphorylation of MAPK. DA, a key neurotransmitter involved in the reward pathway in striatal neurons, activates adenylate cyclase (AC5) through its activation of the heterotrimeric G-protein Gs by D1R, and increases the synthesis of cyclic adenosine monophosphate (cAMP), that leads to the activation of PKA. α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) are ionotropic Glutamate receptors that mediate rapid excitatory synaptic transmission that is necessary for plasticity. AMPAR are composed of 4 subunits: GluR1-4. The phosphorylation of the GluR1 subunit by PKA is required for the delivery and recycling of AMPARs to the synapse. The strength of neuronal transmission by AMPAR is thus, regulated by PKA. cAMP-specific phosphodiesterase (PDE4D3) is an enzyme that modulates PKA activity by degrading cAMP. PDE4D3 catalytic activity is dynamically regulated by MAPK and PKA phosphorylation; MAPK phosphorylation inhibits the activity of PDE4D3, while PKA phosphorylation increases the activity of PDE4D3 over basal. Psychostimulant drugs, such as cocaine, augment dopamine receptor signaling and BDNF TrkB-mediated signaling in NAc neurons leading to an increase in PKA and MAPK activity. BDNF stimulation has been shown to lead to increases in AMPAR membrane insertion, but the mechanism remains elusive. In this study we address how the opposing regulation of PDE4D3 activity by MAPK and PKA can lead to the integration of DA and BDNF signaling and may result in AMPAR insertion. We have constructed a computational model on VCell, a computational program used for modeling and simulation of intracellular signaling. Our model recapitulates the experimental data, with a decrease in PDE4D3 activity to ~55% of the original activity at 6 minutes due to BDNF-activated MAPK. As expected, cAMP levels and PKA activity increase with BDNF or DA stimulation. We have predicted an enhancement of AMPAR insertion by DA and BDNF. However, the effect of BDNF on AMPAR insertion was significantly greater at basal DA concentration than at high DA concentration. We predict PDE4D3 regulation as a key integrator of BDNF and DA signaling, and neuronal excitability.
Parameter interactions in electrophysiological models of cardiac cells

Matthew Zaringhalam\textsuperscript{1,2}, Eric Sobie\textsuperscript{2}

\textsuperscript{1}Colgate University, Hamilton, NY  \textsuperscript{2}Department of Pharmacology and Systems Therapeutics, Systems Biology Center New York, Mount Sinai School of Medicine, New York, NY

Traditional methods of parameter sensitivity analysis focus on the effects of variation in a single parameter on the outputs. These methods, although they can offer valuable information pertaining to a parameter’s importance, assume parameter independence, neglecting parameter interactions and its possible effects on model outputs. Here, we describe a universal method that is able to identify and distinguish between parameter independence and dependence. Randomly varying parameter sets were created for the Luo Rudy Phase 1 (LR1) and ten Tusscher (TNNP) cardiac myocyte models and from those sets, model outputs – action potential characteristics – were calculated. The parameter sets were then log-transformed, mean-centered and normalized by a set standard deviation ($\sigma$). Each normalized parameter set was augmented to include every combination of parameter pairs, which was done by multiplying the normalized parameter values. The addition of the “quadratic” pairs was aimed at identifying parameter interactions. A Non-linear Iterative Partial Least Squares (NIPALS) algorithm was employed to compute regression coefficients – parameter sensitivity values – for both individual parameters and the parameter pairs. Compared to the individual regression coefficients alone, the addition of the quadratic pairs in each model proved to better predict the model outputs from the randomized parameter sets (LR1: $R^2 = 0.907$ vs 0.975, Action potential duration (APD)). To identify parameter interactions, separate versions of each model were created in order to determine the model outputs for parameter pairs that increased iteratively, both separately and simultaneously. The computed model outputs were compared to the predicted model outputs, which were computed using the individual and quadratic parameter sensitivity coefficients. The addition of the quadratic parameter sensitivity coefficients offered more robust predictions for individual parameters along with parameter pairs. Interactions were observed when the predictions using the individual and quadratic parameter sensitivity interactions significantly differed from the predictions using only the individual parameter sensitivity coefficients. When the two predictions did not differ significantly, the two parameters were determined to act independently. For the Luo Rudy model, interactions between $G_{si}$ and $G_{k}$ were observed because the quadratic sensitivity predictions closely fit the actual output change and were different than the individual sensitivity predictions. $G_{si}$ and $G_{b}$ did not display any interactions because the two predictions were similar to each other and the actual output change. The quadratic parameter sensitivity analysis was applied to the Bernus cardiac myocyte model in order to determine whether the computed interactions could provide insight into dramatically prolonged, potentially arrhythmogenic action potentials. The analysis not only identified interactions between $G_{Ca}$ and $G_{k}$, but it was able to more closely predict prolonged APDs than the analysis using linear sensitivity coefficients. The use of quadratic parameter sensitivities in addition to the traditional individual – linear – sensitivities offers a more robust model analysis by offering insight into parameter interactions. This method along with parameter interactions can be applied to any model and can provide more biologically relevant analysis for complex model behavior that a traditional analysis could not provide.
What is the SBDT training area? This program trains students to integrate approaches in **systems biology**, **genomics** and **pharmacology** in order to elucidate the pathophysiology of complex human diseases and develop novel therapeutic strategies.

**Resources on the web:**
Integrated Predoctoral Training Program in Pharmacological Sciences is supported by grant number T32 GM062754 from the National Institute of General Medical Sciences. www.mssm.edu/pharmacology/predoc/training_grant.shtml

The Systems Biology Center New York (SBCNY) is supported by grant number P50 GM071558 from the National Institute of General Medical Sciences. www.sbcny.org
Fall 2011 Course BSR1800 (G301)
SYSTEMS BIOMEDICINE: MOLECULES, CELLS AND NETWORKS

Core Course for the Systems Biology of Disease and Therapeutics (SBDT) Training Area

Department of Pharmacology and Systems Therapeutics
Mount Sinai School of Medicine

COURSE DIRECTOR:
Jeanne P. Hirsch, PhD, Associate Professor

6 CREDIT COURSE
Course Dates:
August 22, 2011 to December 19, 2011

Location:
Annenberg Building, 19th Floor, Room 19-50, Department of Pharmacology and Systems Therapeutics

Lecture Topics
Module 1: Introduction
- Responsible Conduct of Research
- Protein Structure
- Membrane Transport
- Physiological Homeostasis
- Enzyme Kinetics
- Receptor Binding
- Introduction to MatLab
- MatLab Workshop: Simulation of Enzyme Kinetics
- Transcription
- Epigenetics
- Protein Translation
- Analysis of Large Datasets
- Classical Genetics
- Advanced Genetic Techniques

Module 2: Diabetes
- Overview of Diabetes
- Glucose Metabolism
- Glucose/Fatty Acid Metabolism and OXPHOS
- Genetics of Diabetes
- Insulin Secretion
- Drug Discovery
- MatLab Workshop: Modeling Metabolism
- RTK Signaling
- Organ Cross-talk in Pathogenesis of Diabetes
- Drug Strategies

Module 3: Cancer
- Growth Control: Cell Cycle and Apoptosis
- MatLab Workshop: Modeling the Cell Cycle
- Oncogenes and Tumor Suppressors
- Use of Model Organisms in Studying Cancer
- Signaling Pathways in Cancer
- Cancer Genetics
- Metastasis
- Cancer Pathology
- Cancer Biology
- Chemotherapeutics
- Cancer Epidemiology
- MatLab Skill Enhancement
- MatLab Workshop: Chemotherapeutics

Module 4: Renal
- Renal Physiology
- Cytoskeleton in Polarized Epithelium
- Disease of Renal Podocytes, Cytoskeleton Disorders, Cytoskeleton and Cell Shape
- Actin Regulation in Podocyte Disease
- Introduction to Channelopathies
- Channel Disorders: Barter and Liddle’s Syndromes
- Modeling Signaling Pathways, Cytoskeleton and Cell Shape
- Implication of Network Analysis in Disease
- Personalized Medicine in Kidney Disease

Module 5: Drug Abuse
- Receptors, Transporters and Signaling
- Synaptic and Structural Plasticity
- Channels and Transporters in Addiction
- Introduction to Animal Models of Addiction
- Modeling in Addiction Signaling
- Neurocircuitry in Addiction
- Neuroadaptive Mechanisms in Addiction
- Neuroimaging of Receptors and Transporters
- Clinical Perspective on Drug Addiction Disorders
- Systems Modeling of Addiction Signaling Networks

The Systems Biology Center New York (SBCNY) is supported by grant number P50 GM071558 from the National Institute of General Medical Sciences. Integrated Predoctoral Training Program in Pharmacological Sciences is supported by grant number T32 GM062754 from the National Institute of General Medical Sciences.

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