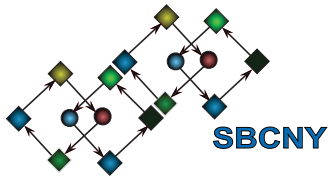


# SYSTEMS BIOLOGY CENTER NEW YORK



MOUNT SINAI  
SCHOOL OF  
MEDICINE

## 2009 SUMMER UNDERGRADUATE RESEARCH PROGRAM POSTER SESSION

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

**DATE: THURSDAY AUGUST 06 2009**  
**TIME: 3:00 - 5:00 PM**

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**Alisa Agafonova (Mentor: Azi Lipshtat)**  
City College of New York  
Major: Physics

## **Analysis of Stochastic Polymerization Dynamics**

**Alisa Agafonova<sup>1</sup>, Azi Lipshtat<sup>2</sup>**

<sup>1</sup>City College of New York, NY

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Mount Sinai School of Medicine, New York NY.

Polymerization of actin filaments is the underlying mechanism of various biological processes such as cell growth and motility. In order to analyze the dynamics of the polymerization process and to examine possible stochastic effects, we have constructed deterministic and stochastic models. The deterministic model is analytically solved, providing the average length of the polymer as function of time and kinetic parameters. The stochastic model was simulated using Kinetic Monte Carlo (Gillespie) algorithm, and steady state length distribution was calculated using the Master Equation.

Analysis of the results revealed three phases of dynamics. Initial phase is characterized by formation of a distribution with increasing width. In the main phase the width of the length distribution decreases as function of time, and can be approximated by a power law. The final phase is a steady state distribution that can be analytically calculated. The width of the distribution is a quantitative measure of the system's stochasticity. These simple models can be extended by additional reactions in order to make them more realistic and to analyze more complex systems.



**Johnson Ho (Mentor: Kevin Costa)**  
City College of New York  
Major: Biomedical Engineering

## **Post-Infarction Left Ventricular Remodeling using the Law of Laplace**

**Johnson S. Ho<sup>1</sup>, Kevin D. Costa<sup>2</sup>**

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The contractile function of a heart is determined by factors including cavity volume, wall thickness, internal pressure, intrinsic muscle property, and circumferential stress and strain. In this study, we used the Law of Laplace to investigate how left ventricular (LV) geometry and the heart's intrinsic properties impact chamber function during passive inflation. The geometric parameters were identified by means of image analysis of MRI scans of a healthy and failing mouse heart, while the end-diastolic pressure (EDP) and muscle property parameters were identified from literature. Changes in geometric configurations, pressure-volume relationships, and stress-strain relationships were studied across healthy and infarct geometries and three elastic modulus configurations. The results show that LV geometry and the muscle's intrinsic properties independently impact chamber function and together contribute to the changes in cardiac function.



**Kathleen McGovern (SBCNY Mentor: Eric Sobie)**  
Hunter College  
Major: Biophysics

## **Mathematical Approaches to Understand Changes in Cardiac Action Potential Morphology Caused by Non-Specific Drugs**

**Kathleen McGovern<sup>1</sup>, Eric A. Sobie<sup>2</sup>**

Hunter College<sup>1</sup>, New York, NY

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Changes to action potential duration and morphology are key factors in the development of cardiac arrhythmias. Torsades de pointes is a well-known arrhythmia that results from the prolongation of the QT interval. Prolongation of the QT interval is a direct result of extended action potential duration (APD) of cardiac myocytes. Action potential duration may be extended as a consequence of a congenital disorder, such as Long QT Syndrome, or it may be extended via pharmacological agents. Many drugs have been pulled off the market for causing toxic and sometimes lethal cardiac side effects. Terfenadine, an antihistamine, was removed from the market after exhibiting these types of lethal side effects. Prolongation of the action potential duration is not the only factor that can have potentially fatal consequences. Shortening of the action potential duration, when coupled with morphological changes, can lead directly to ventricular fibrillation. Unfortunately, some pharmacological agents are not shown to be lethal until the agent is exposed to a large enough population. Therefore, prediction of changes to action potential duration is of high importance for the development of safe drugs.

Action potential duration and morphology are a result of a delicate system of ionic currents which bridge the intracellular space to the extracellular space of ventricular myocytes. These currents run through a network of channels that allow and restrict the flow of different ions at key instances. Blocking one or more of these channels can therefore have a dramatic effect on the action potential. One channel that has been shown to be of high importance to the action potential duration is the channel through which the rapid delayed rectifier current ( $I_{Kr}$ ) flows. This current is responsible for the repolarization of the cellular membrane, so a pharmacological agent which blocks the  $I_{Kr}$  channel will extend the duration of the action potential. Some drugs may not be specific for  $I_{Kr}$  only and as a result may block other channels in addition to  $I_{Kr}$ . How combinatorial blocks affect the action potential is difficult and expensive to test experimentally. Moreover, if a pharmacological agent is affecting action potential duration and/or morphology, how can a drug developer determine the channels responsible for the change? Computational simulations can be used to address these issues. Using a model of a ventricular myocyte, one can block different channels and observe the changes to the action potential. Mathematical analysis of the results can then lead to an understanding of how to discover probable channel blocks which lead to changes to action potential duration.



**Pamela Sanchez (SBCNY Mentor: Simon Hardy)**  
Queens College  
Major: Mathematics

## **A spatial model of ERK nuclear translocation**

**Pamela Sanchez<sup>1,2</sup>, Simon Hardy<sup>3</sup>**

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Mount Sinai School of Medicine, New York NY

The extracellular signal-regulated kinase (ERK) is involved in many important cellular processes such as gene expression, cell spreading and tumor growth. In the final steps of the ERK cascade, phosphorylated ERK dissociates from MEK and goes into the nucleus.

Various experiments have shown that MEK guides the localization of ERK. When ERK is overexpressed in a cell and it saturates MEK, the nuclear concentration of ERK increases and their diffusion coefficient decreases. Although this suggests that there is an agent which immobilizes ERK in the nucleus previous models of ERK nuclear translocation do not include this factor. In our simulations we tried to reproduce experiments of ERK nuclear translocation and we did not have a sustained nuclear accumulation until we added an anchor molecule.

We constructed a spatial PDE-based model from a previous ODE model made by Fujioka et al. with the VirtualCell software. Our goal was explore two different theories explaining MEK's control over ERK localization in the MAP kinase pathway and to reproduce ERK nuclear translocation experiments done by Costa et al. We found that Raf concentration is cell-type specific and that in order to reproduce the Costa experiments we had to add an anchor molecule in the nucleus, increase the nucleus-to-cytoplasm ratio, and increase the cRaf concentration.



**Mariola Szenk (SBCNY Mentor: Avi Ma'ayan)**  
Hunter College  
Major: Bioinformatics & Economics

## **Signaling Pathway Visualization with Flash and BioPAX 3.0 Pathway Exchange Format**

**Mariola K. Szenk<sup>1</sup>, Avi Ma'ayan<sup>2</sup>**

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Cell signaling pathways transduce a stimulus from the extracellular environment through cascades of biochemical reactions to induce biological responses. Details about components and interactions making up pathways is emerging at a fast pace, and therefore, systematic approaches to representing such information are required. Dynamic and automated presentation of signaling pathways on the web is of necessity to the scientific community. While there are several web-based pathways viewers, there is still room for improvement. To this end, we have developed a Flash-based cell signaling pathway viewer. The viewer accepts XML input files to display pathways on any web-page. To demonstrate the usability of this viewer we have implemented it for the representation of the "Neuro2A Differentiation by G alpha i/o Pathway" [Ma'ayan et al., *Sci. Signal* 2:54 (2009)]. Furthermore, we converted this pathway into the BioPAX (Biological Pathway Exchange) level 3.0, a newly develop exchange format developed by the BioPAX community.



**Mariola Szenk (SBCNY Mentor: Avi Ma'ayan)**  
Hunter College  
Major: Bioinformatics & Economics

## **Construction and Analysis of a Mammalian Kinase-Kinase Regulatory Network**

**Mariola K. Szenk<sup>1</sup>, Avi Ma'ayan<sup>2</sup>**

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Kinases are enzymes that transfer phosphate groups to their substrates. They phosphorylate linear motifs on Serine, Threonine, or Tyrosine amino-acid residues. Phosphorylation regulates protein-protein interactions, protein translocation, protein degradation and protein enzymatic activity of kinase substrates. These events play vital roles in all cellular regulatory processes. The sequencing of the human genome identified 518 kinase genes. Since many protein kinases are substrates for other kinases and such relationships are known, we constructed a kinase-kinase mammalian regulatory network from data reporting kinase-substrate relationships from the literature. This network contains 385 kinases interconnected through 2156 links. Using the Markov Clustering and the Molecular Complex Detection Algorithms, we detected clusters of protein kinases in this network. Such clusters are subgraphs of densely interconnected kinases which may have specific functional regulatory roles. To associate function to clusters we performed statistical enrichment analysis of the kinase clusters against background datasets of lists of genes with a common associated function. We compared the kinase clusters against OMIM (Online Mendelian Inheritance in Man), GO (Gene Ontology), and protein domains from InterPro and PFAM to yield a better perspective of the kinome network by understanding the relationships between and within the kinase clusters.



**Sara Wildstein (SBCNY Mentor: Eric Sobie)**  
Queens College, Macaulay Honors College  
Major: Art History  
Minors: Biology & Chemistry

## **Computational modeling of “leaky” ryanodine receptors and triggered arrhythmias in heart cells**

**Sara Wildstein<sup>1,2</sup>, Eric A. Sobie<sup>3</sup>**

<sup>1</sup>Queens College, <sup>2</sup>Macaulay Honors College, New York, NY

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Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT) is a rare inherited disorder caused primarily by mutations in the gene encoding for the ryanodine receptor (RyR), the key intracellular calcium release channel in the heart. Patients with CPVT have structurally normal hearts; however, lethal arrhythmias may transpire during exercise or emotional stress linked to increased levels of circulating catecholamines. Arrhythmias in CPVT are thought to be triggered by spontaneous sarcoplasmic reticulum (SR) calcium release leading to inappropriate depolarization of the cell membrane.

The current accepted understanding is that “leaky” RyRs are responsible for the arrhythmias in CPVT. However, increasing the RyR open probability decreases the  $[Ca^{2+}]_{SR}$ , and this change makes spontaneous  $Ca^{2+}$  release and arrhythmias less likely. Instantaneously increasing the RyR “leakiness” causes the  $Ca^{2+}$  transient amplitude to increase for the first few beats, but this quickly returns to the original levels as the  $[Ca^{2+}]_{SR}$  decreases. Hence, there is no reason to assume that “leaky” RyRs will increase the risk of the arrhythmia. We implemented an integrative computer model that simulates  $Ca^{2+}$  movements between the extracellular space, cytosol, and SR. The model considers both the normal, physiological triggering of SR  $Ca^{2+}$  release and the risk of spontaneous, pathological  $Ca^{2+}$  release. With this model we evaluated how changes in RyR “leakiness” and  $Ca^{2+}$  movements across the cell membrane may increase or decrease arrhythmia risk under different conditions.

Our simulations produced several novel, counterintuitive, and testable predictions. First, RyR leakiness may either increase or decrease the risk of arrhythmia, depending on the experimental conditions. Second, altering the  $Ca^{2+}$  entry into the myocyte with each beat qualitatively changes the relationship between leakiness and arrhythmia risk. Third, and perhaps most surprisingly, decreasing extracellular  $Ca^{2+}$  can increase rather than decrease the risk of arrhythmia due to altered triggering of physiological  $Ca^{2+}$  release. These results demonstrate the value of computational modeling for the analysis of the multiple interacting components of complex biological systems and may be of use in determining the best course of treatment for patients with CPVT.