# Frontiers in Biophysics 2012

Simon Fraser University, Burnaby BC

Saturday February 11, 2012

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| 8:30-8:50 | Registration | Talk and Poster Setup | Breakfast |
| 8:50-9:00 | Welcome Address | | |
| 9:00 - 10:05 | Talk Session A | | |
| 10:05-10:35 | Surprise | | |
| 10:35-10:50 | Coffee Break | | |
| 10:50 - 12:05 | Keynote Talk | | |
| 12:05 - 13:05 | Lunch | | |
| 13:05 - 14:10 | Talk Session B | | |
| 14:10 - 15:10 | Poster Session A | Coffee Break | |
| 15:10 - 16:15 | Talk Session C | | |
| 16:15 - 17:15 | Poster Session B | Wine and Cheese | |
| 17:15 - 18:15 | Wine and Cheese | | |
| 18:15-18:30 | Poster Take Down | | |

## A MATHEMATICAL MODEL OF FUNGAL NETWORKS ACCOUNTING FOR HYPHAL ORIENTATION, BRANCHING AND FUSION

**Philippe J. Giabbanelli**[1], Laurens Bakker[2]

*1 MoCSSy Program and Dept. of Biomedical Physiology, Simon Fraser University*
*2 MoCSSy Program and School of Computing Science, Simon Fraser University*

A substantial research effort has been devoted to modelling filamentous fungi. However, only a few studies have explored the structure of fungal networks. These networks are very efficient at transporting materials and also highly resilient, as they survive after being attacked by grazers. Therefore, it has been suggested that they could serve as inspiration for the design of human-built networks. We report on the development of a new mathematical model accounting for three key mechanisms (hyphal orientation, branching, and fusion). This model involves a cellular automaton running on a (3D) hexagonal close packing arrangement, thereby improving on previous 2-dimensional studies.

## GENE EXPRESSION NOISE IN EMBRYONIC SPATIAL PATTERNING

**David Holloway**[1], Alexander Spirov[2]

*1 Mathematics, British Columbia Institute of Technology*
*2 Computer Science, Stony Brook University*

Fruit flies are model organisms for studying the genetic regulation specifying the body plan. We use stochastic modelling to study how the low DNA and mRNA copy numbers in early development affect the precision of early axis specification. The hunchback gene divides the embryo into head and tail regions; modelling its activation by the maternal protein Bicoid and inhibition by the Krppel protein identifies what dynamics (activation, self-regulation, inhibition) contribute to what noise components in hunchback expression, and what factors contribute to reliable expression. Model predictions have been corroborated in preliminary experiments with wild-type, mutant and transgenic flies.

## A DENSITY FUNCTIONAL THEORY OF TRANSFER FREE ENERGY IN PROTEINS

**Eric Mills**, Steven S. Plotkin

*Physics, University of British Columbia*

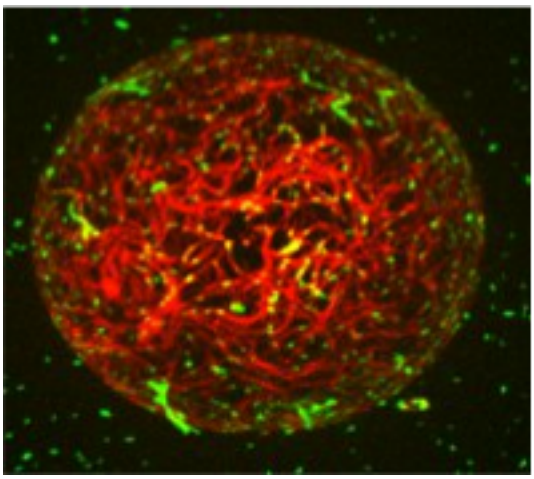
In cells, proteins fold and function in crowded environments. Existing approaches to model this scenario often neglect any changes in environmental entropy. I will be discussing a density functional theory we have developed for the osmolytes in the cell, which takes into account both the energy of the interactions and the entropy of the omsolytes as the protein folds. This formulation can address the transfer free energy in a more accurate way than surface area based approaches, with less computational power than explicit simulation approaches. I will demonstrate applications of our formalism to implicit solvent simulation methods and post-processing techniques.

## INFLUENCE OF PLANT STEROL STRUCTURAL DIFFERENCES ON THE CHAIN ORDERING OF AN UNSATURATED PHOSPHOLIPID; A 2H-NMR STUDY OF POPC/STEROL MEMBRANES

**Mehran Shaghaghi**[1], Jenifer Thewalt[1,2], Martin J. Zuckermann[1]

*1 Physics, Simon Fraser University*
*2 Molecular Biology and Biochemistry, Simon Fraser University*

Sterols are important regulators of the physical properties of biological membrane functions. By changing the membrane fluidity, sterols help to maintain the integrity of the cell. Cholesterol is also an important ingredient of lipid rafts where proteins are secured on the plasma membrane, and may aggregate to function efficiently. Using 2H-NMR spectroscopy, we have studied the effect of a series of different sterols on the chain ordering of POPC, an unsaturated phospholipid present in eukaryotic cell membranes. We have assigned specific roles to the sterol structural differences; these affect average lipid chain conformation.



## CELLULAR RECONSTITUTION: REBUILDING BIOLOGICAL SYSTEMS FROM THE BOTTOM-UP

Dan Fletcher

*Department of Bioengineering, University of California, Berkeley*

Understanding the molecular basis of cellular behavior is a central goal in biology and a critical guide for medical research. Increasing knowledge of the essential proteins in a complex process such as crawling motility raises the tantalizing question: Do we know enough to build it? In vitro reconstitution provides an import tool for identifying the roles of individual molecules, but defining components is not enough. Progress towards reconstitution of micron-scale cellular structures and processes has been limited by the challenges of generating in vitro reconstitutions that capture the spatial organization, physical constraints, and dynamics of living cells. This talk will describe on-going efforts to create functional reconstitutions of cytoskeletal and membrane processes involved in cellular protrusions and membrane transport. The lessons of what works and what doesn't are re helping to guide efforts to build biological systems from molecular parts.

## CHRONIC HIV INFECTION AND TREATMENT

**Alejandra Herrera**, Daniel Coombs, Jessica Conway, Berhard Konrad
*Mathematics, University of British Columbia*

The use of antiretroviral therapy has effectively decreased mortality for HIV-1 infected patients. However, there exists a persistent viral reservoir. It is believed that the primary viral reservoir consists of latently infected immune memory cells. The drug Auranofin has been shown recently to accelerate the activation rate of latent cells and to alter the kinetics of viral rebound when drug treatment is interrupted. I will present a mathematical model of HIV population dynamics and drug treatment, and Auranofin, with the goal of proposing new mechanisms to explain viral dynamics and the immune response to HIV in treated patients.

## A STOCHASTIC MULTISCALE MODEL OF ESOPHAGEAL ADENOCARCINOMA: FROM CLONAL EXPANSION TO DISEASE INCIDENCE

**Kit Curtius**[1], Georg Luebeck[2], Jihyoun Jeon[2], Bill Hazelton[2]
*1 Applied Mathematics, University of Washington*
*2 Fred Hutchinson Cancer Research Center*

The mathematical development of a cellular level stochastic model of EAC includes two hallmarks of cancer advancement: accumulation of mutations and clonal expansion of mutant cell populations on the pathway to cancer detection. Through stochastic birth/death processes of initiated and pre-clinical malignant cell populations, the model inherently provides realistic heterogeneity of tumor number and sizes in individuals. With maximum likelihood fitted parameters, we can also compute the US incidence rate of EAC by age and calendar year with the hazard function $h(t)$ and thus compare with SEER registry data to make future predictions of the disease.

## PATTERN FORMATION OF PROTEINS ON THE SURFACE OF A CELL DURING WOUND HEALING

**Cory Simon**[1], Leah Edelstein-Keshet[1], William Bement[2]
*1 Mathematics, University of British Columbia*
*2 Zoology, University of Wisconsin-Madison*

Upon the infliction of a small wound on the surface of an oocyte cell, two concentric, mutually exclusive rings of activity of the signaling proteins RhoA and Cdc42 form around the wound. The pattern of the two signaling proteins orchestrates the formation of dynamic cellular machinery that seals the wound. A key protein, Abr, was recently found to interact with both RhoA and Cdc42 and to play an essential role in the organization of the zones. We form a sequence of mathematical models to investigate how Cdc42, RhoA, and Abr form the spatiotemporal patterns observed.

## RED BLOOD CELL CLUSTERS IN POISEUILLE FLOW

**Giovanni Ghigliotti**[1], Hassib Selmi[2], Lassaad El Asmi[2], Chaouqi Misbah[3]
*1 Chemical and Biological Engineering, University of British Columbia*
*2 Laboratoire dIngénierie Mathématique, Ecole Polytechnique de Tunisie*
*3 Laboratory of Interdisciplinary Physics, Université de Grenoble, France*

We present 2D numerical simulations of sets of vesicles in a parabolic flow, a setup that mimics red blood cells (RBCs) in the microvasculature. Vesicles, submitted to sole hydrodynamical interactions, are found to form aggregates (clusters) of finite size. The existence of a maximal cluster size is pointed out and characterized as a function of the flow intensity and the swelling ratio of the vesicles. An interpretation of the phenomenon is put forward based on the presence of boli (vortices) between vesicles. Both the results and the explanation can be transposed to the three-dimensional case.

## THE AMPHIPATHIC HELIX OF AN ENZYME THAT REGULATES PHOSPHATIDYLCHOLINE SYNTHESIS REMODELS MEMBRANES INTO HIGHLY CURVED NANOTUBULES

**Svetla G. Taneva**[1], Joseph M.C. Lee[2], Rosemary B. Cornell[1,3]

*1 Molecular Biology and Biochemistry, Simon Fraser University*
*2 Chemistry, University of British Columbia*
*3 Chemistry, Simon Fraser University*

CTP:phosphocholine cytidylyltransferase (CCT) is an amphitropic protein regulating phosphatidylcholine synthesis. Lipid-induced folding of its amphipathic helical (AH) membrane-binding domain activates the enzyme. We used electron microscopy to examine the property of CCT to deform vesicles into tubules in vitro. Tubulation was proportional to density of bound CCT and proceeded either as growth from a pre-formed surface bud, or as a global transformation of vesicles into tubules, depending on vesicle lipid composition. Tubules were protein-lipid structures with a limiting diameter of 12 nm and a high density of 1 CCT/50 lipids. The AH segment was necessary and sufficient for tubulation, which correlated with alpha-helical length. CCT binding to membranes may initiate deformations required for organelle morphogenesis and simultaneously stimulate synthesis of the PC required for membrane remodeling/expansion.

## CAN PHOSPHORYLATION ACT AS AN ELECTROSTATIC SWITCH TO TARGET AMPHIPATHIC HELICES TO CURVED OVER FLAT MEMBRANES?

**Sharon S.Y. Chong**, Joseph M.C. Lee, Svetla G. Taneva, Rosemary B. Cornell

*Molecular Biology and Biochemistry, Simon Fraser University*

Many peripheral proteins regulate their function through the reversible binding of amphipathic helices (AH) to cell membranes, a process often influenced by membrane curvature. Examining protein curvature sensitivity facilitates understanding of vesicular traffic and organelle remodelling. We are exploring the hypothesis that reduced electrostatic contribution to membrane binding of the AH of CCT, an enzyme regulating PC synthesis, is accompanied by an enhanced dependence on hydrophobic interactions with surface defects in curved vesicles. This curvature dependence appeared greater when glutamates were engineered adjacent to the AH motif to mimic phosphorylation. The electrostatic repulsion between the AH and anionic membranes could explain the requirement for highly curved vesicles for binding, which was relatively independent of ionic strength. These data imply that phosphorylation can sensitize AH motifs to curved vs. flat membranes.

## THE ADSORPTION OF A FACE-WISE AMPHIPATHIC ALPHA-HELICAL PEPTIDE ONTO HYDROPHOBIC AND HYDROPHILIC SURFACES

**Tsuki Naka**, Sandra Roy, Dennis Hore

*Chemistry, University of Victoria*

The change in secondary and tertiary structure accompanying the adsorption of proteins and peptides onto artificial surfaces is responsible for biofouling, incompatibility of medical implant materials,and the disruption of biosensor function. Some challenges associated with molecular-level characterization of the surface-biomolecule interactions are the complexity of biomolecular structures, the heterogeneity of the surface, and adequate control of the solution conditions. We have used all-atom molecular dynamics simulations to study the structure of a face-wise amphipathic alpha-helical Leu-Lys peptide when it is in contact with hydrophobic and hydrophilic surfaces. We have been able to examine the affinity of the side chains towards the surfaces and the extent to which the alpha-helicity is maintained when adsorbed.

## STRUCTURE STUDY ON U24 FROM HHV-7

**Yurou Sang**, Andrew Tait, Suzana K. Straus
*Chemistry, University of British Columbia*

The structure study of membrane protein is always challenging due to the poor solubility. Through expressing the protein in E. Coli, we could get enough protein for NMR study. Also, a truncation form of U24, without transmembrane domain, was found during purification, which might simplify structure solving.

## MODELING AND SIMULATION OF DORSAL CLOSURE

**Qiming Wang**[1], James J. Feng[1,2], Len M. Pismen[3]
*1 Mathematics, University of British Columbia*
*2 Chemical and Biological Engineering, University of British Columbia*
*3 Chemical Engineering, Technion-Israel Institute of Technology, Israel*

Dorsal closure is a tissue-modeling process in the developing Drosophila embryo during which an epidermal opening is gradually closed. The amnioserosa cells that fill the opening exhibit oscillations during the whole process and even before dorsal closure. We model the cell network by a dissipative dynamical system to produce this behavior and to explore the mechanism behind.

## MODELING CLIMATE-DRIVEN RANGE SHIFTS

**Ying Zhou**, Mark Kot
*Applied Mathematics, University of Washington*

Many species are responding to climate change by shifting their ranges poleward in latitude or upward in elevation. We modeled species range shifts using an integrodifference equation that combines growth, dispersal, and a constant-speed shift in habitat. For our model, if the population's range shifts too rapidly, the population goes extinct. The critical speed for extinction depends on both growth parameters and on the shape of the dispersal kernel.

## DEVELOPMENT OF MICRO AND NANO-STRUCTURED NEURAL TISSUE ENGINEERING SCAFFOLDS

**Nima Khadem Mohtaram**[1], Darcy Ippolito[1], Junghyuk Ko[1], Martin Byung-Guk Jun[1], Stephanie Willerth[1,2]
*1 Mechanical Engineering, University of Victoria)*
*2 Division of Medical Sciences, University of Victoria*

This work focuses on developing micro and nano-structured biomaterial scaffolds to replicate the neural tissue found in the spinal cord. Poly ($\epsilon$-caprolactone) (PCL) microspheres and electrospun PCL nanofibers were fabricated to serve as biocompatible and biodegradable drug delivery systems and tissue engineered scaffolds respectively. PCL microspheres serve as a novel drug delivery system to control the release of protein molecules that promote neural tissue repair. The PCL nanofiber scaffolds can serve as substrates for stem cell cultures. We hypothesized that electrospun PCL fibers can promote induced pluripotent stem cell (iPS) differentiation into the desired neural phenotypes through their nanostructure.

## FIRST TEST TO DETERMINE PLATELET FUNCTION IN A DROP OF BLOOD

**Nathan Lee**[1], Gyasi Bourne[2], Audrey Labrie[2], Elisabeth Maurer-Spurej[3]

*1 Physics, University of British Columbia*
*2 LightIntegra Technology Inc.*
*3 Pathology and Laboratory Medicine, University of British Columbia*

ThromboLUX is a novel test that determines platelet function by measuring platelet morphology, platelet response to temperature stress, and microparticle content. Earlier data collected with ThromboLUX suggest that one in six platelet transfusions are ineffective, and that better platelet function leads to better transfusion outcomes.

Preliminary data suggest that ThromboLUX scores of donor samples can be predictive of the final transfusion outcome. ThromboLUX analysis of small whole blood samples would allow determination of the best platelet donors before collection, and would therefore eliminate unnecessary processing while improving transfusion outcomes and patient safety.

This study examined a novel protocol to perform ThromboLUX testing in whole blood.

## NONLINEAR ANALYSIS FOR SIMPLE MODELS IN QUORUM SENSING

W. Y. Chiang[1], Yue-Xian Li[2] **Pik-Yin Lai**[1]

*1 Physics, National Central University, Taiwan*
*2 Mathematics, University of British Columbia*

Quorum sensing refers to the change in the cooperative behavior of a collection of elements in response to the change in their population size or density. This behavior can be observed in chemical and biological systems. These elements/cells are coupled via chemicals in the surrounding environment. Here we focus on the change of dynamical behavior, in particular from quiescent to oscillatory, as the cell population changes. For instance, the silent behavior of the elements can become oscillatory as the system concentration/ population increases. In this work, two simple models (phase model and amplitude model) are constructed that can produce the essential representative properties in quorum sensing[1]. Using the mean-field approximation, the parameter regime for quorum sensing behavior can be identified, analytical results for the detailed dynamical properties, including the phase diagrams, are obtained and verified numerically. We further consider the effect of diffusion of the signaling chemicals with a spatial concentration profile, and analyze the bifurcation due to the onset of quorum sensing.

[1] Phys. Rev. E 84, 041921 (2011).

## CHARACTERIZING THE PROLIFERATION AND MORPHOLOGY OF HUMAN DERMAL FIBROBLASTS (HDFS) FOR THE PURPOSE OF GENERATING INDUCIBLE PLURIPOTENT STEM CELLS (IPSCS)

**Sanam Shafaat Talab**, Janine Roller, Pauline Dan, Glen Tibbits

*Biomedical Physiology and Kinesiology, Simon Fraser University*

Our aim is to better understand congenital heart disease including familial hypertrophic cardiomyopathy (FHC) and channelopathies both of which are arrhythmogenic and can result in Sudden Cardiac Death (SCD). Events surrounding any arrhythmia are influenced by many patient-specific factors, such as age, sex, and systemic health. We hypothesize that the use of patient-specific iPSCs will better model the abnormal phenotype in the context of mutations associated with these arrhythmias. iPSCs can be generated by genetically reprogramming patient-specific dermal fibroblast through viral-based methods, and subsequently be induced to differentiate into cardiomyocytes. In this study, we characterized HDFs by examining their proliferation, morphology and response to injury, in preparation for the transformation process.

## CHARACTERIZING THE VISCOELASTICITY OF COLLAGEN SOLUTIONS

**Marjan Shayegan**[1], Nancy R. Forde[2]

*1 Chemistry, Simon Fraser University*
*2 Physics, Simon Fraser University*

We investigate microscale mechanical properties of collagen, the major structural protein of connective tissues. The presence of non-helical ends of collagen (so-called telopeptides) contributes significantly to the mechanism of fibril formation, a critical physiological step in the formation of the extracellular matrix and many connective tissues. However, it is not known whether this small difference in molecular structure alters mechanical properties at the micron scale. Using optical tweezers to probe the viscoelastic response of collagen solutions, we find that their high-frequency response is altered by the presence of telopeptides, and determine concentration regime at which elasticity becomes comparable to viscosity.

## HIGH THROUGHPUT FUNCTIONAL PROTEOMICS FOR SURFACE PROTEINS ON MOUSE EMBRYONIC STEM CELLS

Bingyun Sun[1], **Wilson Chim**[1], **Dmitri Oleinikov**[2], Jessica Kovatch[1], Albert Badiong[3]

*1 Chemistry, Simon Fraser University*
*2 Molecular Biology and Biochemistry, Simon Fraser University*
*3 Biology, Simon Fraser University*

The dense layer of glycans on cell surface plays important roles in molecular and cellular recognition. A lectin array can characterize the structure of cell-surface glycans in high throughput, but this assay is challenging to perform as the binding affinity of lectins to glycans is weak. The non-bound cells are difficult to remove without disrupting the bound cells. We are optimizing the assay conditions to overcome these difficulties for the reproducible and quantitative lectin-array assay. We will report the differences before and after applying our optimization, and validate our assay with cells carrying known lectin binding properties.

## HYBRID APPROACH TO UNDERSTAND THE ORGANIZATION OF THE MYCOBACTERIAL PARTITION FILAMENT

**Barnali N. Chaudhuri**[1,2], Sayan Gupta[3], Volker S. Urban[4], Shuo Qian[4], Mark R. Chance[3], Rhijuta D'Mello[3], Rebecca Dean[1]

*1 Hauptman Woodward Institute, Buffalo NY*
*2 University of Buffalo*
*3 Center for Proteomics and Bioinformatics, Case Western Reserve University*
*4 Center for Structural Molecular Biology, Oak Ridge National Lab*

The bacterial chromosome partitioning cassette (ParABS) is a DNA trafficking device, which is composed of two proteins (ParB and ParA) and a set of centromere-like DNA sequences (parS). The ParBs assemble on the parS proximal chromosome to form the partition assembly, which recruits cytoskeletal ParA for the condensation and segregation of chromosome. The organization of partition assembly will be described using a combination of solution X-ray and neutron scattering with H/D contrast variation, X-ray footprinting and electron microscopy. Our result provides a basis for understanding how ParBs condense parS-proximal chromosome, thus setting the stage for the further condensation and segregation.

## MODELING RETINAL WAVES IN STARBURST AMACRINE CELLS

**Benjamin Lansdell**, J. Nathan Kutz, Eli Shlizerman

*Applied Mathematics, University of Washington*

Retinal waves are an example of spontaneous activation in the developing central nervous system. This activity occurs in developing neural circuits prior to visual stimulus. The waves are the result of neighboring retinal cells spiking in a coordinated fashion which spreads across the whole retina. We develop a continuous spatial and temporal model of this phenomenon in order to understand how the wave properties depends on underlying parameters. We use the Fitzhugh-Nagumo model of neuron dynamics and include spatial coupling via a neurotransmitter field representing a novel mechanism for generating spatiotemporal patterns in the developing central nervous system.

## MOLECULAR DETERMINANTS OF U-TYPE INACTIVATION IN KV2.1 CHANNELS

**Samrat Thouta**, Y. M. Cheng, J. Azer, C. M. Niven, P. Mafi, C. R. Allard, J. Qi, T. W. Claydon

*Biomedical Physiology and Kinesiology, Simon Fraser University*

Kv2.1 voltage-gated potassium channels are expressed in a variety of cells, including neurons and cardiac muscle. In the heart Kv2.1 channels provide a role in repolarization of the action potential. A characteristic feature of Kv2.1 channels is inactivation that is rapid at moderate voltages and reduced at more positive voltages. That is manifest as a U-shaped voltage-dependence of inactivation and enhanced inactivation during repetitive membrane depolarization. Little is known regarding the molecular mechanisms underlying U-type inactivation. Here, we have identified specific residues in the S3-S4 and S5-P-loop linkers that are responsible for U-type inactivation in Kv2.1 channels.

## MOLECULAR MECHANISMS RESPONSIBLE FOR SLOW GATING IN HERG CARDIAC POTASSIUM CHANNELS

**Christina M. Hull**, Y. May Cheng, John Azer, Christine M. Niven, Charlene R. Allard, Thomas W. Claydon

*Biomedical Physiology and Kinesiology, Simon Fraser University*

The hERG potassium channel is an important contributor to cardiac repolarization and loss of function is associated with the life-threatening arrhythmia, long QT syndrome. The activation (opening) and deactivation (closing) kinetics of hERG channels are unusually slow compared to other voltage-gated potassium (Kv) channels, where counter-charge interactions within the voltage sensing region stabilize the open or closed state. Here we identify primary sequence differences between hERG and other Kv channels. We show that charge-conserving amino acid differences in the voltage sensing unit of hERG channels are critical determinants of the channel's unusual gating kinetics.

## RANOLAZINE EFFECTS ON BRAIN SODIUM CHANNELS AND MODULATION BY PH

**Colin Peters**, Peter Ruben

*Physiology, Simon Fraser University*

Ranolazine is an anti-anginal drug previously shown to block persistent currents of the cardiac voltage gated sodium channel, NaV1.5. We studied the effects of Ranolazine on neuronal sodium channels, NaV1.2, and its modulation by extracellular protons to mimic conditions during ischemic stroke. The addition of Ranolazine at both pH 7.4 and pH 6.0 led to a faster rate of open state inactivation, slower recovery from inactivation and an increase in use-dependent block of current. These effects were decreased at low pH. Our results suggest Ranolazine stabilizes fast inactivation and interacts with protons to decrease the efficacy of Ranolazine.

## PROTON MODULATION OF CARDIAC VOLTAGE-GATED SODIUM CHANNEL GATING CURRENTS

**David K. Jones**, Tom W. Claydon, Peter C. Ruben

*Biomedical Physiology, Simon Fraser University*

Protons destabilize cardiac voltage-gated sodium channel (NaV1.5) fast inactivation, thereby contributing to cardiac arrhythmogenesis. The molecular underpinnings by which protons modulate NaV1.5 gating remain uncharacterized. To determine whether protons affect charge movement, we recorded NaV1.5 gating currents with solutions titrated to pH 7.4 or pH 6.0. Low pH significantly depolarized the voltage-dependence of NaV1.5 gating currents. Additionally, the slow component of "off" gating current decay was significantly reduced at voltages greater than -40 mV. These results represent the first recordings of NaV1.5 channel gating currents at low pH and suggest a molecular basis by which protons destabilize the fast-inactivated state.

## FLUORESCENT MEASUREMENT OF DRUG ACCUMULATION IN SINGLE ACUTE MYELOID LEUKEMIA (AML) CELLS ON A MICROFLUIDIC CHIP

**Avid Khamenehfar**[1], Donna E. Hogge[2], Paul C. H. Li[1]

*1 Chemistry, Simon Fraser University*
*2 Terry Fox Lab, BC Cancer Agency*

The same single cell analysis (SASCA) is used in order to measure drug accumulation in multidrug resistance cancer AML cells. The drug accumulation is the combined effect of passive drug uptake and active drug efflux. Single cells obtained from AML cell culture as well as cryopreserved AML patient blood samples were measured when they are retained in a microfluidic chamber. We also design an upstream microfluidic element to be interfaced to the microfluidic chamber for isolation of cancer cells among a large blood cell population prior to SASCA measurement to provide reliable information for clinical monitoring of patients undergoing chemotherapy.

## GYPSY MOTH PHEROMONE BINDING PROTEINS DISPLAY ENDOGENOUS LIGAND BINDING TRIGGERING CONFORMATIONAL CHANGES

**Jason Nardella**[1], Nicolette Honson[2] Erika Plettner[1]

*1 Chemistry, Simon Fraser University*
*2 The Centre for Drug Research And Development*

Insect olfaction is not fully understood. While much is known about organization of olfactory components on a cellular level, it is in large part the dynamics of binding proteins and receptors which remain elusive. The gypsy moth carries at least two pheromone binding proteins in its sensory organs which have been shown to bind endogenous ligands as well as pheromone. These ligands, which were identified as C16 and C18 fatty acids, are present in high concentrations in the environment of the proteins. Finally ligand binding has been shown to trigger conformational changes in secondary structure of the proteins.

## BINDING DYNAMICS OF HAPTENS TO A MONOCLONAL ANTIBODY: INSIGHTS FROM MOLECULAR DYNAMICS SIMULATIONS

**Yun Shi**, B. Mario Pinto

*Chemistry, Simon Fraser University*

In order to obtain improved binding affinity towards a monoclonal antibody SYA/J6, two haptens ($\alpha$-glycopeptide and $\beta$-glycopeptide) were designed based on the structures of a pentasaccharide and an octapeptide, both of which are known haptens to SYA/J6 with moderate binding affinities. However, $\alpha$-glycopeptide showed no inhibition towards SYA/J6 in "wet" experiments. Herein we conducted molecular dynamics simulations of SYA/J6 Fab in complex with four related haptens, revealing the dynamics of the pentasaccharide and the octapeptide bindings. More significantly, we offered a reasonable explanation for the lack of inhibition in $\alpha$-glycopeptide and a prediction that $\beta$-glycopeptide is also inactive.

## PARACRINE SIGNALING BETWEEN MACROPHAGES AND BREAST TUMOR CELLS CONTRIBUTES TO METASTASIS, CORROBORATED WITH A 3-D MODEL

**Hildur Knutsdottir**

*Physics, Simon Fraser University*

It has recently been demonstrated experimentally that breast tumor cell invasion into blood vessels and surrounding tissues is directly associated with macrophages. The breast tumor cells secrete colony-stimulating factors, CSF-1, that bind to macrophages, who in response secrete epidermal growth factors, EGF, which bind to the macrophages. This results in a so called paracrine loop. I have written a 3D stochastic model to simulate this process. The objective of the model is to gain better understanding of how this EGF-CSF-1 paracrine loop works and understand the underlying mechanisms of the observed motility patterns.

## A EUKARYOTIC EXPRESSION SYSTEM FOR PRODUCTION OF COLLAGEN WITH NATIVE STRUCTURAL FIDELITY

**Andrew Wieczorek**[1], Clara Chan[2], Cindy Li[3], Nancy R. Forde[1]

*1 Physics, Simon Fraser University*
*2 Biomedical Engineering, University of California, Los Angeles*
*3 Molecular Biology and Biochemistry, Simon Fraser University*

Collagen is the most abundant protein in vertebrates. Modifications to collagen by mutation (e.g. Ehler-Danlos syndrome), nutrition (scurvy or diabetes), enzymatic remodelling (cancer), or during aging (arthritis) all have detrimental effects. We have developed a eukaryotic cell-based expression system that allows us to mimic these conditions. Our goal is to determine their effect(s) on collagen mechanics at the microscale and single-molecule levels using optical tweezers and transmission electron microscopy. Here, we show that we have successfully expressed and purified type II collagen (wild-type and mutants), and present evidence that these collagens exhibit structural characteristics of tissue-derived collagen.

## THE INCHWORM MOTOR: SIMULATING A SYNTHETIC DNA-PROTEIN BASED MOTOR WHICH WALKS ON A 'BED' OF REPRESSOR PROTEINS IN A NANO-CHANNEL

**Martin J. Zuckermann**[1], Laleh Samii[1], Gerhard Blab[2], Nancy Forde[1], James Walsh[3], Heiner Linke[4]

*1 Physics, Simon Fraser University*
*2 Biophysics, Utrecht University, Netherlands*
*3 Physics, University of New South Wales, Australia*
*4 Physics, Lund University, Sweden*

The Inchworm Motor, at present under construction, is composed of a charged DNA strand moving directionally in a nano-channel 80nm in diameter via temporally periodic ligand and salt pulses, the latter causing the motor to contact and then stretch. The DNA ends are engineered to bind to different repressor proteins on the nano-channel walls in the presence of the appropriate ligands. We examine the directionality and processivity of the Inchworm Motor under different conditions using several simulation techniques: Langevin Dynamics, Gillespie algorithm calculations, Master equation methods and a model based on stretching forces.

## THE LAWNMOWER: AN AUTONOMOUS SYNTHETIC PROTEIN MOTOR

Suzana Kovacic[1], **Laleh Samii**[1], Gerhard A. Blab[2], Heiner Linke[3], Paul M.G. Curmi[4] Martin J. Zuckerman[1], Nancy R. Forde[1]

*1 Physics, Simon Fraser University*
*2 Molecular Biophysics, Utrecht University, Netherlands*
*3 The Nanometer Structure Consortium and Division of Solid State Physics, Lund University, Sweden*
*4 Physics, University of New South Wales, Australia*

Here, we describe the design and construction of a novel protein-based synthetic motor, the "lawnmower", which uses a burnt-bridges mechanism to autonomously and diffusively move forward. The blades of the lawnmower are proteases covalently linked to a quantum dot hub that interact with a one dimensional peptide substrate track via binding to and cleavage of the substrates. The protease motor diffuses to the substrate track where productive binding between the protease and substrate facilitates proteolytic cleavage of the substrate. Once cleaved, the decreased binding affinity between the protease and resulting product allows the motor to diffuse along the track and form new interactions with uncleaved substrate molecules.

## PROBING MECHANICAL PROPERTIES OF COLLAGEN II USING OPTICAL TWEEZERS

**Naghmeh Rezaei**, Andrew Wieczorek, Nancy R. Forde

*Physics, Simon Fraser University*

Studying mechanical response of biological molecules at microscopic level is crucial for better understanding of their function. Optical tweezers create a trap for dielectric objects that enable scientist to study microscopic mechanical properties. Dielectric spheres attached to molecules, can be trapped and manipulated by applying forces in the pN-range. We use optical tweezers to study mechanical properties of structural proteins such as collagen, an important structural protein in development, tissue regeneration and repair. In this work, we discuss the challenges of linking the molecule to microspheres for optical tweezers analysis. Mechanical properties of Collagen II are studied with optical tweezers.

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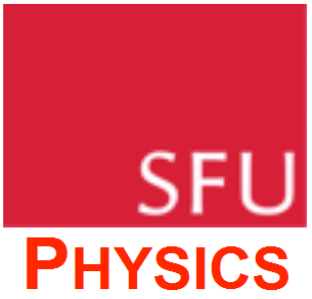


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