# Plenary Talk

**Tim Elston,** Department of Pharmacology, University of North Carolina, Chapel Hill
*Polarity establishment and chemotropic growth in budding yeast*

Saccharomyces cerevisiae (budding yeast) represents an ideal model system for studying cell polarization and gradient sensing. Here we combine mathematical modeling with various experimental approaches to investigate the molecular mechanism responsible for polarity establishment and the detection of spatial gradients of mating pheromone. Our analysis demonstrates how negative feedback in the signaling pathway responsible for polarization leads to oscillations of the polar cap and makes the system robust to variations in the abundance of pathway components. Additionally, we present a novel role for the protease Bar1, which degrades mating pheromone. In particular, we demonstrate how this secreted protein allows cells of similar mating type to avoid each other, thereby avoiding unproductive encounters.

# Talks

**Lisa M. Bishop**
Department of Applied Mathematics, University of Washington
*The Hidden Energy in the Noise as the Origin of Noise-Induced Phenomena in Biochemical Systems*

Stochastic bistability and stochastic focusing are two examples of noise-induced phenomena which can arise in cellular biochemical processes. These are examples of important cellular functions which are are non-equilibrium, driven phenomena. To quantify this fundamental aspect of cellular systems and their functions, we write completely reversible versions of each system and show that ultimately it is not the noise that gives rise to the phenomena, rather it is the hidden free energy in the non-equilibrium fluctuations that is responsible for the enhancement.

**Saeed Saberi** and Eldon Emberly
Department of Physics, Simon Fraser University
*CHROMOSOME DRIVEN SPATIAL PATTERNING OF PROTEINS IN BACTERIA*

The localization of proteins in bacteria plays an important role in many cell processes including cell division. Asymmetric division in C.Crescentus relies on differentially localizing certain proteins to the poles where they bind to the scaffolding protein PopZ that displays a bipolar pattern. Experiments on mutants and those where PopZ was expressed in E. Coli show that a variety of patterns are possible: from diffuse, to unipolar to bipolar. Interestingly, the aggregation of misfolded proteins in bacteria displays patterns that are nearly identical to that of PopZ. These experiments revealed that the presence of the chromosome plays an important role in the formation of patterns in these two systems. We have performed Monte-Carlo simulations to study how the volume exclusion effect of the chromosome generates entropic forces that drive the localization of aggregating proteins. The model shows a range of localization behavior as the concentrations of both the DNA and protein are varied, providing a quantitative explanation of the experimental observed patterns of PopZ and misfolded protein as well as suggestions for new experiments. As a result of our simulation we claim that the existing entropic forces cannot provide enough force to drag and anchor the origin to the pole, and indeed other mechanisms are utilized by the cell to localize the origin to the pole.

**William Carlquist**
Department of Mathematics, University of British Columbia
*Analysis of MinD and MinE Oscillation and Pattern Formation in E. coli*

An E. coli cell must divide symmetrically to produce viable daughter cells. Presence of the protein MinE inhibits the formation of the Z-ring, which contracts to separate the E. coli cell into two daughter cells. Throughout the cell cycle, MinD and MinE proteins oscillate from one cell pole to the other, resulting in higher MinD and MinE protein concentrations near poles than at midcell, allowing only midcell Z ring formation, thus resulting in symmetric cell division. Various mathematical models have accounted for experimentally observed behavior of MinD and MinE proteins, including traveling wave fronts, spiral wave formation, and stripe formation. However, no model accounts for all observable MinD and MinE behavior. I will briefly discuss present models and how their analysis can lead to a more comprehensive model of the MinD MinE system.

**S. Majid Hosseini**1 and James J. Feng1,2
*Effect of malaria merozoites on the deformability of infected RBC**
1 Department of Chemical and Biological Engineering, University of British Columbia
2 Department of Mathematics, University of British Columbia

This paper presents a three-dimensional (3D) particle-based model for the red blood cell (RBC), and uses it to explore the changes in the deformability of RBC due to presence of malaria parasite. The deformation of RBC by optical tweezers was simulated in both healthy and infected state. The cell membrane is represented by a set of discrete particles connected by nonlinear springs; the spring law enforces conservation of the membrane area to a high accuracy. The cytoplasm and the external liquid are modeled as homogeneous Newtonian fluids, and discretized by particles as in standard smoothed particle hydrodynamics (SPH) solution of the Navier–Stokes equations.

**Geoffrey Woollard**
Centre for High-Throughput Biology, University of British Columbia
*Computational redesign of the N-end rule protein ClpS*

The computational redesign of the N-end rule protein ClpS, which recognizes N-terminal amino acids with its hydrophobic binding pocket will be described. Several crystal structures of ClpS bound to various peptides have recently been reported and provide insight into its binding affinity and specificity. We have analyzed these structures and identified candidate residues involved in binding. We mutated the remaining functionally relevant residues and produced a library of mutants. Mutant ClpS candidates were ranked by the Rosetta energy function, which has empirically and physically derived potential terms. If their functionality is experimentally verified, these ClpS mutants could be used for high-throughput protein sequencing.

**Josh Zukewich**
Department of Mathematics, University of British Columbia
*Update rules for evolutionary dynamics on a graph*

The evolutionary dynamics of populations playing the Donation Game (a Prisoner's Dilemma) depend on population structure. In well-mixed populations defectors are favoured, but cooperation can be favoured when we let individuals occupy the nodes of a graph and limit interaction and reproduction to their neighbourhood. This holds for nite populations using a Moran-type stochastic update called Death-Birth. However, under Birth-Death cooperation is not favoured. Here, we study an update that uses DB with probability and BD with probability 1 using pair approximation. Provided DB is used in part ( > 0), cooperation can be favoured provided the cost-benefit ratio is high enough (b/c > k/ ). Results are confirmed with stochastic simulations.

**Sara Sadeghi**
Department of Physics, Simon Fraser University
*Using a coarse-grained atomistic model to study coiled-coils and their designability*

Coiled-coils are one of the most abundant protein structures among all the different possible protein folds. We have used a coarse-grained atomistic model to study coiled-coil formation and explore both their mechanical and thermodynamic properties. Our model is able to reproduce known coiled-coils structures using only a simple hydrophobic-polar (HP) representation of their sequence. To address how common coiled-coil formation is with respect to all possible helix packs, we have calculated the designability, defined as the number of sequences that can fold into a particular structure, of helical packs. We find that left-handed coils emerge as one of the most highly designable structures, and that right-handed coils are found to be less designable. From the designability calculation we can identify sequence patterns that design particular coiled-coil folds and mutations that lead to their instability.

**Lynn Kimlicka** and Filip Van Petegem
Department of Biochemistry and Molecular Biology, University of British Columbia
*Crystallographic investigation of several malignant hyperthermia mutations in Ryanodine Receptors*

Mutations in the Ryanodine Receptor (RYR) are known to underlie many genetic diseases. Despite an extensive analysis of disease mutations on the functional level, very little is known about the structural changes induced by them. Here we analyze the structures and stability of eight disease mutants and compare them to the wild type. The observed effects on structure and stability differ substantially among the mutants. Some cause a major destabilization of the overall fold; others mainly cause relative domain-domain movements. We discuss the likely implications of the disease mutations on the overall structure and gating properties of the intact RyR.

**Paolo Lobo**, Filip Van Petegem
Department of Biochemistry and Molecular Biology, University of British Columbia
*Plasticity in Cardiac Ryanodine Receptors: a Structural Rescue in Arrhythmias*

The contraction of cardiac muscle requires release of Ca2+ from the sarcoplasmic reticulum through the cardiac ryanodine receptor (RyR2). Among other mutations that cause triggered arrhythmias, one in particular, that causes a severe form of catecholaminergic polymorphic ventricular tachycardia (CPVT), is caused by removal of the third exon of RyR2. From a 2.3Å crystal structure, we highlight an almost paradoxical rescue of seemingly crucial structural elements encoded by exon 3. The rescue shows a novel mechanism by which RyR2 channels could adjust their Ca2+ release properties through altering the structure of an individual domain.

**Jetha, Nahid**1, C. Feehan1, V. Semenchenko2, N. Cashman3, and A. Marziali1
*Single molecule investigation of prion protein structural transitions important in disease*
1 Department of Physics & Astronomy, University of British Columbia
2 Department of Biological Sciences, University of Alberta
3 Faculty of Medicine, University of British Columbia

Prion diseases such as Bovine Spongiform Encephalopathy and Creutzfeldt-Jakob disease are caused by template-directed conversion of the prion protein (PrPC) into the infectious isoform (PrPSc). It has been hypothesized that unfolding of the - sheet located between the unstructured N-terminal domain of PrPC, and its structured C-terminal core represents the initial stages of the conversion process. We present results on the investigation of the kinetics of - sheet dissociation for wild-type PrPC and the D178N pathogenic mutant via single molecule nanopore force spectroscopy, which is a technique whereby single molecules can be electrostatically trapped in a nanometre-scale pore, and subjected to electrostatic forces which can unfold parts of the molecule.

**Bernhard Konrad**, Jessica M. Conway, Alejandra Herrera and Daniel Coombs
Department of Mathematics, University of British Columbia
*Stochastic-model predictions on the emergence of drug-resistance against anti-retroviral treatments for HIV*

Anti-retroviral drug treatments (ARTs) significantly lowers HIV viral load in chronically infected HIV individuals and thus improves quality and length of life. However, ARTs may fail if a drug-resistant virus strain emerges. We employ a continuous-time branching process model to investigate mechanisms of emergent drug-resistance (DR). In particular, we compare two hypotheses: (i) the drug-resistant strain is developed during treatment, despite the low viral load, or (ii) the drug resistant strain is released by an activated latently infected cell, i.e. an infected cell that only produces virus upon activation, and may have been infected years before the initiation of treatment. We show some preliminary results and discuss how they can guide public health decisions.

# Posters

**Yana Nec** and Michael Ward
Department of Mathematics, University of British Columbia
*Existence and stability of spike-type solutions to one dimensional Gierer-Meinhardt model with sub-diffusion*

Spike-type solutions are shown to exist for a reaction – sub-diffusion system with Gierer-Meinhardt kinetics. Sub-diffusion induces an asymmetry in the algebraic-differential system governing the evolution of an n-spike pattern, and causes a loss of in exion invariance in the spike motion. The system depends on the anomaly index and is stable, conforming to o(1) eigenvalues of the original system. Full stability analysis, conforming to O(1) eigenvalues, yields a fractional non-local eigenvalue problem. For a pattern of n identical spikes the system is decoupled, and the stability onset threshold and eigenvalue locations are shown to change in a non-intuitive way.

**Shirin Hadizadeh**
Brain Research Centre, University of British Columbia
*The effect of osmolytes on protein folding*

The fraction of the cellular interior volume that is taken by biomolecules is about 30%, leading to a highly crowded environment. Biomolecules present in an extremely dense environment inside a cell have a completely different set of kinetic and thermodynamic behavior than in a test tube. Therefore comprehending the effect of crowding conditions on biological molecules is crucial to broad research fields such as biochemical, medical and pharmaceutical sciences. The purpose of our work is to investigate analytically the effects of crowding agents on protein folding and stability.

**Laleh Samii**
Department of Physics, Simon Fraser University
*Time-dependent molecular motor properties of molecular spiders*

Molecular spiders are synthetic molecular motors featuring multiple legs that each can interact with a substrate through binding and cleavage. Experimental studies of molecular spiders suggest the motion of the on a track is biased towards uncleaved substrates. By using Monte Carlo simulations, we investigated how experimental parameters, such as number of legs, leg length and substrate cleavage rate, can be tuned to optimize motor properties. We find that these each affect properties such as binding time on the track, processivity and speed in different ways. We then study the thermodynamic efficiencies of multipedal molecular spiders, and find that these are force- and time-dependent.

**Ben Vanderlei**
Department of Mathematics, University of British Columbia
*A computational model of cell polarization and motility coupling mechanics and biochemistry*

The motion of a eukaryotic cell presents a variety of interesting and challenging problems from both a modeling and a computational perspective. The processes span many spatial scales (from molecular to tissue) as well as disparate time scales, with reaction kinetics on the order of seconds, and the deformation and motion of the cell occurring on the order of minutes. The computational difficulty , even in 2D, resides in the fact that the problem is inherently one of deforming, non-stationary domains, bounded by an elastic perimeter, inside

of which there is redistribution of biochemical signaling substances. We present a computational scheme using the immersed boundary method to track an elastic cell perimeter. We adopt a reaction-diffusion system that represents the internal regulatory mechanism controlling the polarization of a cell, and determining the strength of protrusion forces at its front. Using this computational scheme we are able to study the effect of protrusive and elastic forces on cell shape on their own, the distribution of the reaction-diffusion system in irregular domains on its own, and the coupled mechano-chemical system. We find that this representation of cell crawling can already recover important aspects of the spontaneous polarization and motion of certain types of crawling cells.

**Clara Chan**, Andrew Wieczorek and Nancy R. Forde
Department of Physics, Simon Fraser University
*Investigating in Vitro Fibril Formation of Recombinant Collagen Type II*

Collagens are a large family of triple helical proteins that are found throughout the body and provide supportive functions in structural tissues such as bone, tendons, skin, and cartilage. In these tissues, collagen fibril formation is a multistep process which involves molecular packing into an ordered structure. Therefore, identification of fibrillogenesis kinetics is required to understand, at the molecular level, the principles governing collagen fibril formation. Here we explore the in vitro assembly of collagen type II into fibrils by enzymatic cleavage of its purified soluble precursor under physiological conditions. We furthermore use transmission electron microscopy (TEM) imaging to examine the collagen fibrils.

**Christine Lind Cole**
Department of Applied Mathematics, University of Washington
*The Brownian Ratchet Revisited: Multiple Filamentous Bundle Growth*

We present a mathematical model based on a diffusion formalism for the Brownian Ratchet (BR), which we extend to incorporate a bundle of N identical filaments. In the absence of a load, the bundle growth rate is similar to that of a single filament. However, under the stalling condition, the bundle can oppose N times the external force. We derive a set of relationships describing the velocity of the BR movement (Vz) and its apparent diffusivity (Dz) as functions of the resistant force (F) and the number of filaments in a bundle (N).

**Hildur Knutsdottir**
Department of Physics, Simon Fraser University
*A 3D model of interactions between macrophages and tumor cells during metastasis*

The presence of macrophages in tumors has been correlated with poor prognosis for years. Recent experiments by J. Wyckoff et al. have shown that gradients of either epidermal growth factor, EGF, or colony-stimulating factor, CSF-1, stimulated invasion of both macrophages and tumor cells into blood vessels. This was the first evidence that the two interact during cell migration. I have written a 3D model to simulate this process. The goal is to gain better understanding of how the EGF / CSF-1 paracrine loop works and what the underlying mechanism for the fixed ratio of 1 macrophage to 3 tumor cells that is observed.

**Marjan Shayegan**1 and Nancy R. Forde 1,2
1 Simon Fraser University, Department of Chemistry
2 Simon Fraser University, Department of Physics
*Probing the viscoelasticity of collagen solutions with optical-tweezers-based microrheology*

Collagen as the major fibrillar protein of connective tissues has been studied in this work. Determining mechanical behavior of collagen from a single molecule to a network of entangled chains will contribute to understanding the correlation between molecular structure and mechanical properties. We probe the concentration dependence of viscoelastic response using optical tweezers and find that elasticity becomes comparable to viscous behavior at collagen concentrations of 5mg/ml. We attribute this increased elasticity to chemical and/or physical interactions between molecules. By varying these interactions in the system, we will demonstrate the role they play in conferring elasticity to collagen solutions.

**Sherry S.W. Leung**, Luis Bagatolli, Jenifer Thewalt
Simon Fraser University
*Effects of fluorescent probes on lipid membranes*

It is usually assumed that the trace amounts of probe used in fluorescence studies do not alter the behaviour of the systems being observed. Our previous work suggests otherwise: even a minuscule amount (0.1 – 0.5%) of the fluorescent probe DiIC12 can significantly change the liquid ordered/liquid disordered miscibility transition temperature (Tmix) of lipid membranes by up to 6°C. DiIC12 preferentially partitions into the liquid disordered phase and it is suspected that this played a role in altering the lipid membranes. We now turn to a different probe Laurdan, which does not exhibit preferential partitioning, for further examination.

**Naghmeh Rezaei**, Andrew Wieczorek, and Nancy R. Forde
Department of Physics, Simon Fraser University
*Using optical tweezers to study mechanical properties of structural proteins*

Studying mechanical response of biological molecules at microscopic level is crucial for better understanding of their function. Optical tweezers are instruments that enable scientists to study mechanical properties at microscopic level. It is based on a highly focused laser beam that creates a trap for microscopic objects. Dielectric spheres attached to molecules, viruses, bacteria, living cells and organelles can be trapped and manipulated by applying forces in the pN-range. Our group uses optical tweezers to study mechanical properties of structural proteins such as collagen and elastin. In this work, mechanical properties of procollagen are studied with single beam optical tweezers.

**Chang Min Kim**
Department of Physics, Simon Fraser University
*Probing Electronic Transport Mechanisms at Single-molecular Junctions using Conductive Atomic Force Microscopy*

We investigated charge transport mechanisms at the interface between a 1,8 ocanedithiol (ODT) and gold and platinum electrodes by repeatedly breaking the bond between a molecule and an electrode using conductive probe atomic force microscopy (C-AFM). The interaction between thiol-metal electrode is essential property of applications for Self-assembled monolayers (SAMs). We compared conductance of ODT binding with gold and platinum and behaviours as a function of bias voltage to find out effects on charge transport due to geometric and electronic binding mechanism of thiol-Au and thiol-Pt.

**Jessica Conway**
Department of Mathematics, University of British Columbia
*A stochastic model of and viral load and viral blips in HIV patients on ART*

While on anti-retroviral treatment (ART) for HIV, an infected individual's viral load remains non-zero, though it is undetectable by routine testing. However, blood tests show occasional viral blips: very short periods of detectable viral load. We present a stochastic model that shows that this residual viral load can be explained principally by the activation of cells in the latent reservoir, seeded before the initiation of treatment, and that viral blips represent large deviations from the mean. The model is validated through direct numerical computation and allows us to estimate blip probabilities and magnitudes.

**Nessy Tania**
Department of Mathematics, University of British Columbia
*Dynamics of Cofilin Regulation and the Early Peak of Actin Barbed Ends in Invasive Tumor Cells*

Cofilin is an important regulator of actin polymerization, cell migration and chemotaxis. Recent experimental data on mammary carcinoma cells reveal that stimulation by epidermal growth factor (EGF) generates a pool of active cofilin that results in a peak of actin filament barbed-ends on the timescale of 1 min. We present results of a mathematical model for the dynamics of cofilin and its transition between several pools in response to EGF stimulation. We demonstrate that a high basal level of active cofilin stored by binding to membrane lipids PIP2, and the localized region of high F-actin at the cell edge is essential in capturing the barbed-end amplification observed experimentally.

**Babak Sanii**
Lawrence Berkeley Lab
*Producing Peptoid Nanosheets*

Peptoids are analogs of proteins whose side group is bonded to the Nitrogen instead of the - Carbon. This design change removes hydrogen bonding and chirality, but enables greater robustness and access to more diverse chemistry. Our community endeavors to mimic and expand on protein function and structure with synthetic Peptoids. We have designed - sheet-like structures that assemble into free-floating nanosheets, millimeters long yet 2.7nm thick. These sheets survive high temperatures, vacuums, and pH extremes, and are attractive platforms for biosensing. Here I focus on the unusual physical mechanism for producing peptoid nanosheets, which is analogous to a thermodynamic pump.

**Bill Holmes**
Department of Mathematics, University of British Columbia
*Modeling and Analysis of Rho Protein Mechanics in Cell Polarization*

We discuss the autonomous symmetry breaking process responsible for cellular reorganization/polarization and motility in a 1D setting. A new model of rho protein mechanics with lipid feedback based on a wave pinning instability is presented. It is shown that this model accounts for observed characteristics not found in related models. A local perturbation technique is used to analytically determine the presence of both Turing and wave pinning instabilities and provide a qualitative understanding the model system's dependence on parameters. Additionally, the role of signal detection/gradient sensing as a pre-processor to the polarization mechanism is discussed.

**Mehran Shaghaghi**
Simon Fraser University
*2H-NMR STUDY OF POPC/STEROL MEMBRANES: ROLE OF STEROL'S ALKYL TAIL STRUCTURE IN CHAIN ORDERING OF POPC*

Sterols are well known to dramatically enhance chain order of saturated lipid membranes, but their effect on unsaturated lipid membrane is relatively less well-explored. Y-W Hsueh et al. showed that the 2H-NMR spectral width (M1) of POPC/cholesterol multilamellar bilayers increased linearly to at least 60 mol% cholesterol. In contrast, M1 for POPC/ergosterol increased linearly to 25 mol% sterol, but leveled off for higher concentrations [1; Y-W Hsueh et al., (2007) Biophys. J. 92:1606-1615]. To study this behavior in more detail we investigated the effect of increasing the sterol concentration of POPC/sterol membranes on M1 for a series of different sterols differing only in their alkyl tail structure: campesterol, brassicasterol, stigmasterol,  - sitosterol.We found that the sterols with bulky substituents and/or double bonds are least able to organize POPC's chains.