Title: Modelling Nutrient Consumption Due to Turgor Maintenance in Fungal Networks

Presenter: Andrew Poelstra

Abstract: Filamentous fungi grow efficient nutrient transportation networks which are highly resilient to attacks by grazers. Understanding them can benefit the design of human-built networks, where such properties are sought after. During Frontiers in Biophysics 2012, we presented a mathematical model that improved previous 2-dimensional studies by representing the space in a 3-dimensional face-centered cubic lattice. While the model focused on structural aspects (hyphal orientation, branching, and fusion), these are closely tied to functional aspects, that is, the handling of nutrients. We refine our previous model by accounting for nutrient consumption—in particular, how nutrients are used for turgor maintenance at a particular network location. We calculate the exact local hyphal surface area by modelling the hyphal network as cylindrical tubes connecting spherical junction points. From this we derive the cost of turgor maintenance. This improves previous studies where the quantity was simplified, thus increasing the accuracy of fungal network models.

Title: Exploring feedbacks from phosphoinositides to Rho GTPasesin an actin-based 2D cell motility computation

Presenter: Leah Keshet

Abstract: The crosstalk and feedback f between phosphoinositides (PIs), Rho GTPases and F-actin is probed computationally. We identify both likely connectivity of these signaling networks and their functional roles in motility. We find that GTPases can account for most essential polarity-motility functions, but PIs sensitize the cells, and help to filter out conflicting spatial cues. My coauthors are: AFM (Stan) Marée, Veronica Grieneisen (John Innes Center, UK)

Title: Recent progress on the study of membrane protein structure, interaction and assembly using a range of biophysical techniques.

Presenter: Suzana Straus

Abstract: Membrane proteins are highly abundant in nature, but remain difficult to study because: 1) they are difficult to produce in large quantities; and 2) many methodologies are not easily amenable to the study of protein/lipid complexes. We have made a number of important contributions in both areas, leading to the elucidation of the mechanism of action of lipopeptide antibiotics, the interaction of U24 and binding partners such as Fyn-SH3 and WW domain proteins, the steps involved in the assembly of filamentous bacteriophage, and more. Findings from these different areas will be presented.

Title: THE INCHWORM: SIMULATING A NOVEL SYNTHETIC DNA NANO-MOTOR M. J.Zuckermann, Simon Fraser University

Presenter: Martin Zuckermann

Abstract: Biological molecular nano-motors are ENZYMES which function by transducing chemical energy (often from the hydrolysis of ATP) to mechanical energy. They are key components of cellular processes such as cell division, cell motility and intracellular transport. The main objective of our research is TO DESIGN, SYNTHESIZE AND MEASURE THE PERFORMANCE OF THE WORLD'S FIRST PROTEIN-BASED MOTOR. By applying this bottom-up approach, we test our understanding of structure-function relationships of actual biological nano-motors. Here we consider the modeling of synthetic molecular motors

fabricated from non-motor proteins, peptides and/or DNA. Such motors are conceptually able to move processively on a DNA or protein track with specific binding sites. An example of a motor in the process of construction by our international team is the TUMBLEWEED (TW) motor. In this poster we describe a second synthetic molecular motor fabricated from non-motor proteins and DNA, the INCHWORM (IW) motor. In particular, we report the results... (+45 more words)

Title: Proton modulation of voltage-gated sodium channels

Presenter: Peter Ruben

Abstract: Voltage-gated sodium channels (NaV) are critical determinants of membrane excitability in neurons, cardiac myocytes, and skeletal muscle cells. Activation and opening of these membrane-bound ion channels leads to the rising phase of the action potential, whereas inactivation contributes to the action potential shape and duration. Their position in the membrane makes NaVs vulnerable to a wide range of intracellular and extracellular modulatory factors. Protons are one such source of NaV modulation. Ischemia causes an increase in extracellular proton concentration through anaerobic metabolism. Here we report extracellular protons block Na+ conduction and shift the voltage-dependent gating and kinetic properties of NaV in an isoform-dependent manner. Low pH destabilizes fast inactivation, use-dependent inactivation, and gating charge immobilization in the cardiac isoform, NaV1.5. Protons bind to specific residues in the pore and turret regions of Domain II and III, respectively, and differentially affect conductance in wild-type and mutant NaV1.5.

Title: Gene-Gene Interactions Controlling Reliable Formation of Fly Segments

Presenter: David Holloway

Abstract: In early fruit fly embryos, expression of the gap genes determines the future pattern of body segments. Building on experimental data and previous models, we show how the mutual interactions of two gap genes, hunchback (hb) and Krüppel (Kr; both activated by the spatially-graded maternal protein, Bicoid) create a stripe of hb expression responsible for the mid-body parasegment 4. hb-Kr interactions are modelled at the cis-regulatory level, with low binding site occupancy activating and high occupancy inhibitory. Using stochastic modelling, we predict that Kr stabilizes the precise location of the hb expression boundary. This has recently been corroborated experimentally.

Title: Modeling Cell Boundary Dynamics

Presenter: Mark Zajac

Abstract: Proper cell function often entails cell deformation. Modeling feedback between cell shape and intracellular dynamics requires the solution of reaction-advection-diffusion equations inside deforming regions. The Moving Boundary Node Method solves this problem. The method employs a "distance map" that is constructed by storing the shortest distance to the boundary at each node on a grid. The gradient of the distance map provides a vector that points from each node to the boundary, which is a known distance away. These vectors and corresponding distances give exactly the displacements that will move nodes onto the boundary, from points nearby. This yields a dynamic, structured, boundary-fitted grid that provides the basis for a finite-volume method. Applications include chemical gradient detection by migrating cells that change shape, with coupling between intracellular and membrane-bound reactants.

Title: A Facile Way to Tune Mechanical Properties of Artificial Elastomeric Proteins-Based Hydrogels

Presenter: Jie Fang

Abstract: Protein-based hydrogels have attracted considerable interests due to their potential applications in biomedical engineering and material sciences. Using a tandem modular protein (GB1)8 as building blocks, we have engineered chemically crosslinked hydrogels via a photochemical crosslinking strategy, which is based on the crosslinking of two adjacent tyrosine residues into dityrosine adducts. However, due to the relative low reactivity of tyrosine residues in GB1, (GB1)8-based hydrogels exhibit poor mechanical properties. Here we report a Bolton-Hunter reagent-based, facile method to improve and tune the mechanical properties of such protein-based hydrogels. Using this reagent, we can derivatize lysine residues with phenolic functional groups to modulate the phenolic (tyrosine-like) content of (GB1)8. We show that hydrogels made from derivatized (GB1)8 display significantly improved mechanical properties, including improved Young's modulus, breaking modulus and reduced swelling. These results demonstrate the great potential of this derivatization method in constructing protein-based biomaterials with desired macroscopic mechanical properties.

Title: A cell-level mechanobiological model of Drosophila dorsal closure

Presenter: Qiming Wang

Abstract: We report a model describing various stages of Drosophila dorsal closure. Inspired by experimental observations, we represent the amnioserosa by hexagonal cells that are coupled mechanically through the position of nodes and the elastic forces on the edges. Besides, each cell has radial spokes on which myosin motors can attach and exert contractile forces, the myosin dynamics itself being controlled by a signaling molecule. In early phase, amnioserosa cells oscillate as a result of coupling among the chemical signaling, myosin activity and mechanical deformation of neighboring cells. Cross correlation of area variation of neighboring cells calculated based on our model shows agreement with literature. In slow phase, our model predictions suggest internal ratchet as the main contributor to cell and tissue reduction, comparing to a supracellular ratchet proposed by previous studies. In fast phase, we gradually shrink the resting length of radial spokes to simulate the consistent tissue contraction.

Title: Imaging prion fibrils by atomic force microscopy to determine their bending rigidities and elastic moduli.

Presenter: Guillaume Lamour

Abstract: Prion diseases such as Creutzfeldt-Jakob or mad cow diseases originate from the misfolding and aggregation of prion proteins, with invariably lethal outcome. In this study we generate mammalian prion fibrils with reproducible morphological properties and investigate their mechanical properties by atomic force microscopy. Fibril shapes are analyzed statistically using worm-like chain models that describe the bending of semi-flexible polymers under thermal fluctuations. This way we quantify the persistence lengths of several different types of prion fibrils (wild-type and mutants). Using fibrils heights we derive, for each fibril type, an estimated elastic modulus, which we check directly using recent AFM technology that monitors frequency changes in the second normal mode of the AFM cantilever. We find that both methods complement each other well and overall provide a system that could be used to correlate prion fibrils stability to their potential biological effects in cell lines or animal models.

Title: Polar localization of vital dye molecules within the periplasmic space of Escherichia coli.

Presenter: Mahdi Rezaei

Abstract: One of the important indicators in biology of metabolic activity is Tetrazolium salts, hence termed vital dyes. In a typical tetrazolium, often a single formazan granule generates at the one pole of Escherichia coli cells after reduction. Recent experimental evidence suggests that the aggregate localizes with a higher probability in the polar regions compared to the midcell. Computer simulations and minimal biophysical modeling shows that the probability of polar localization is dependent on the thickness of the periplasm as well as aggregate size. When the thickness is smaller than a critical size, localization happens at the pole in most of the cases but for larger thickness, polar and midcell regions have similar probabilities of aggregate localizations. It is also shown that for a large spatial ratio (>2) the aggregate has a higher tendency to localize in the midcell.

Title: Computational Models for Epigenetic Mechanisms - Overview

Presenter: Karthika Raghavan

Abstract: Definition and characterization of the role of Epigenetic mechanisms have gained immense momentum since the completion of the Human Genome Project. The human epigenetic layer, made of DNA methylation and multiple histone modifications, (the 2 key elements), is known to regulate the cellular events. Aberrations in DNA methylation supported by an abnormal landscape of histone modifications have been associated with Cancer initiation and development. The presentation here describes the framework of a theoretical micromodel (EpiGMP) that investigates the effect of histone modifications and gene expression for defined levels of DNA methylation. This micromodel has been applied to (i) test networks of genes involved in colon cancer and now currently (ii) being applied to an agent-based model to explore the chromatin remodelling inside the human genome. Ultimately, the goal is to provide coherence about these low level molecular changes that determine physical traits for normal and disease conditions in an organism.

Title: Modelling cotyledon growth in conifer tree embryos

Presenter: Ignacio Rozada

Abstract: Recent developments in experimental biology have provided insight in the early development of conifer tree embryos. We will discuss the features and early results of using a Turing-type model to describe cotyledon growth in conifer tree embryos (which can have up to 15, as opposed to the standard one or two on all other plants). A one-way coupled system of two Brusselator models is used, in connection to two biological processes that have been observed to occur in cotyledon development.

Title: A Stochastic Multiscale Model of Esophageal Adenocarcinoma

Presenter: Kit Curtius

Abstract: 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. These Luria-Delbrück distributions help analyze the efficacies of biopsy sampling techniques, screening strategies, optimal surveillance and ultimate survival rates.

Title: A Vector-Host Model for Coinfection by Barley Yellow Dwarf Virus

Presenter: Margaret-Rose Leung

Abstract: Barley and cereal yellow dwarf viruses (B/CYDV) are aphid-vectored pathogens that affect diverse host communities, including economically-important crops. Coinfection of a single host by multiple strains of B/CYDV can result in elevated virulence, incidence, and transmission rates. We develop a ODE model for a single host, two pathogen strains, and n vector species. A single parameter describes the degree of relatedness of the strains and of cross-protection between them. We compute the basic and type reproduction numbers of the model and demonstrate that, although the basic reproduction number describes stability of the disease-free equilibrium, the type reproduction numbers better describe the individual behavior of each strain and the dynamics of coinfection. We then conduct a sensitivity analysis on the components of the endemic equilibrium. Our results indicate that disease transmission rates and vector birth and mortality rates are the most influential parameters on the equilibrium prevalences of infection and coinfection.

Title: Single Molecule Force Spectroscopy Reveals Critical Roles of Hydrophobic Core Packing in Determining the Mechanical Stability of Protein GB1.

Presenter: Tianjia Bu

Abstract: Understanding how proteins are designed in nature to achieve desired mechanical stability not only is important for understanding biological processes but also holds the promise to design novel protein-based biomaterials. Here, we combine single molecule atomic force microscopy and protein engineering techniques to investigate the effect of side chain reduction and hydrophobic core packing on the mechanical stability of GB1. We found that three mutations, which are across the surfaces of two subdomains that are to be sheared by the applied stretching force, in the hydrophobic core (F30L, Y45L, and F52L) result in significant decrease in mechanical unfolding force of GB1. These results indicate that hydrophobic core packing plays an important role in determining the mechanical stability of GB1 and suggest that optimizing hydrophobic interactions across the surfaces that are to be sheared will likely be an efficient method to enhance the mechanical stability of GB1 and GB1 homologues.

Title: Solid state synthesis of fusion peptide mutant of the tick-borne encephalitis virus (TBEV)

Presenter: Jin Zhang

Abstract: The fusion peptide from the tick-borne encephalitis virus (TBEV), which is composed of 21 amino acid residues, plays a key role in membrane fusion. TBEV peptide, mutants and trimer peptide have been synthesized and their structures and fusion properties have been previously investigated[1]. TBEV is one of a number of flaviviruses. Looking at different flavivirus sequences, one can observe that TBEV is the only one that has a histidine at position 104 while the other family members have a glycine. In order to study the effect of this residue on activity and its binding ability with membranes， we have synthesized a histidine-to-glycine mutant (H104G) by solid state synthesis and purified the peptide using high performance liquid chromatography (HPLC). This data will be presented. Further research on the structures and fusiogenic activities will be done in the future.

Title: Exploring the binding properties of U24 protein

Presenter: Rui Zhang

Abstract: The binding properties of the protein U24 from Human Herpes Virus type 6 and 7 were

investigated. U24 is a tail anchored membrane protein with a proline-rich region at its N-terminus and is believed to potentially be implicated in diseases such as multiple sclerosis. As known proline-rich ligand scaffolds, SH3 and WW domains are crucial binding domains in different cellular signaling pathways. Therefore, studying the interactions associated between these domains and U24 could shed light into the role of U24 during infections. The interactions were characterized using pull-down assays and solution state NMR spectroscopy. Recent results will be presented.

Title: Attractive interaction between like-charge helical biomolecules

Presenter: Shahzad Ghanbarian

Abstract: We present the results of molecular dynamics simulations of electrostatic interaction between two parallel biomolecules, such as DNA. In particular we study a simple model for B-DNA with helical charge pattern in the presence of divalent mobile ions. The effective force on each molecule depends on the central distance and on the relative orientation of two DNAs. The force is almost always attractive over the entire range of the central distance. We investigate the role of charge distribution pattern of DNA model on the like-charge attraction phenomenon by analysing the mobile-ion cloud structure and calculating pair correlation functions.

Title: Density Functional Considerations in Transfer Free Energy

Presenter: Eric Mills

Abstract: The cell environment in which proteins fold and function is crowded with biological molecules, at densities of ~300g/L. Treating these molecules explicitly in a MD simulation introduces enormous computational cost, so accurate ways of modelling their contribution to protein behaviour is desirable. I will discuss existing models and propose a new approach, which uses classical density functional theory to calculate the effect of these solutes on protein folding. This approach yields a surprising result that redefines our concept of the transfer free energy.

Title: Modeling spatial interactions between breast cancer cells and macrophages

Presenter: Hildur Knutsdottir

Abstract: Experiments have shown that breast cancer cells invade into surrounding tissues and organs alongside macrophages. The two cell types communicate via a short ranged chemical signaling loop. We use reaction-diffusion partial differential equations to study the spatial interactions of these cells both analytically and numerically. We ask under what conditions aggregation of the two cell types is expected to occur. A linear stability analysis reveals that changes in chemical secretion, chemical degradation, chemotaxis coefficients and steady state concentrations in the model could eliminate the spontaneous aggregation of cells. Comparing the continuum results with simulations of a discrete cell-based model, we find good qualitative agreement.

Title: Evolutionary amplifiers.

Presenter: Alastair Jamieson-Lane

Abstract: Geometry matters- and in particular, it can have effects on evolution. This talk/post/whatever looks at an extremely simple model of evolution on a digraph, and examine how the arrangement of nodes effects the fixation probability of beneficial mutations.

Title: Mathematical Analysis of Actin Waves Model

Presenter: May Anne Mata

Abstract: In biological experiments, spatio-temporal patterns such as localized and propagating waves are observed. A recent example of these dynamic patterns is waves of actin and its regulators (nucleation promoting factors) that are seen in cells. We study this phenomenon by formulating a minimal model, based on reaction-diffusion equations (RDEs), depicting feedback between signaling proteins and filamentous actin. Aside from showing emergence of patterns, we used this model to highlight the properties of a nonlinear stability method known as Local Perturbation Analysis (LPA). The technique simplifies our analysis of the model as it allows us to delineate regimes of behavior and obtain stability information about the system. We found that LPA not only has wider applicability to RDEs with disparity in diffusion rates but also comparable to Turing analysis.

Title: MECHANICALLY UNTYING A PROTEIN SLIPKNOT BY SINGLE MOLECULE FORCE SPECTROSCOPY

Presenter: Chengzhi He

Abstract: Protein structure is highly diverse when considering a wide range of protein types, helping to give rise to the multitude of functions that proteins perform. In particular, certain proteins are known to adopt a knotted or slipknotted fold. How such proteins undergo mechanical unfolding was investigated utilizing a combination ofsingle molecule atomic force microscopy (AFM), protein engineering, and steered molecular dynamics (SMD) simulations to show the mechanical unfolding mechanism of the slipknotted protein AFV3-109. Our results reveal that the mechanical unfolding of AFV3-109 can proceed via multiple parallel unfolding pathways that all cause the protein slipknot to untie and the polypeptide chain to completely extend. These distinct unfolding pathways proceed via either a two- or three-state unfolding process involving the formation of a well-defined, stable intermediate state. SMD simulations predict the same contour length increments for different unfolding pathways as single molecule AFM results, thus providing a plausible molecular mechanism for... (+100 more words)

Title: Enhancing activity and decreasing toxicity of antimicrobial peptides using polyglycerol systems.

Presenter: Prashant Kumar

Abstract: Antibiotics have been used for decades to combat bacterial infection. However, there has been an increase in antibiotic resistance recently.Therefore, alternatives such antimicrobial peptides which have little or no antimicrobial resistance are ideal candidates for therapy. Two major problems faced when developing these peptides for therapeutics are host cell toxicity and decreased activity. Recently, there has been an increasing interest in polyglycerols (PGs) in biomedical applications due to their being highly biocompatible. Recent progress on methods to enhance activity and decrease toxicity of these peptides using polyglycerol systems will be presented.

Title: Occlusion of micro-capillaries by malaria-infected red blood cells

Presenter: Tenghu Wu

Abstract: Malaria-infected red blood cells (iRBCs) can easily occlude micro-capillaries because of their anomalous stiffness and stickiness compared with health red cells. Previous work suggested three factors in the loss of deformability of iRBCs: (i) the stiffening of the membrane, (ii) the reduction of the cell’s surface/volume (S/V) ratio, and (iii) the presence of solid parasites inside

the cell. These factors have been examined in experiments and simulations of the stretching of iRBCs by optical tweezers. In this work, we investigate the influence of the three factors on the blockage of micro-channels by using the smoothed particle hydrodynamic method. Three micro-fluidic channels with different constricting pore sizes (Thickness × Wide = 4.8 × 4.8, 4.0 and 3.2 \mum) are employed. Our results indicate the solid parasites as the main agent for micro-capillary occlusion. The decrease of cell's excess surface area causes blockage of the medium channel. Besides, the elevated membrane stiffness significantly... (+12 more words)

Title: Studying biomechanics at the single-molecule level with optical tweezers

Presenter: Naghmeh Rezaei

Abstract: Optical tweezers are a technique that use focused laser light to trap microscopic objects, which has provided unique insight into mechanical processes involved in protein and DNA kinetics, mechanics, structure, etc. We use optical tweezers to study the mechanical properties of short proteins that play a vital role in providing structural support for the body. Elastin and collagen are two important structural proteins: we study their mechanical response to an applied force, and try to understand how it relates to molecular structure and might impact their biological function. Our goal is to reveal how changes in chemical composition affect mechanical properties, to relate this to macroscopic defects that lead to disease, and to inform the design of new biomaterials.

Title: The Lawnmower: an autonomous synthetic protein motor

Presenter: Laleh Samii

Abstract: 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 bound to a quantum dot hub that interact with a one dimensional peptide substrate track via binding to and cleavages of the substrates. Cleavage of substrate by a protease releases a quencher molecule at one end of the peptide resulting in increased fluorescence of the DNA-bound product. Increased fluorescence thus acts as an indicator of the processivity of the lawnmower along the peptide track, which can be correlated to the motion of the lawnmower along the track. This correlation provides an assessment of the directionality and processivity of our molecular motor and insight into its mechanochemical coupling. Experimentally, we confirm with kinetic assays that our lawnmower is an active motor, also demonstrate the synthesis and characterization of a highly... (+12 more words)

Title: The curvature sensitivity of a membrane-binding amphipathic helix can be amplified by phosphorylation.

Presenter: Sharon Chong

Abstract: Many peripheral proteins regulate their function through the reversible binding of amphipathic helices (AH) to cell membranes, a property that can be influenced by membrane curvature. Examining protein curvature sensitivity facilitates understanding of vesicular traffic and organelle remodeling. CCT, an enzyme regulating PC synthesis, has a membrane-binding AH that induces curvature in vitro and in cells. We observed that CCT's AH can also be a curvature-sensing device. The binding of AH to membranes has electrostatic and hydrophobic components, and highly curved vesicles can enhance hydrophobic interactions due to their increased lipid packing defects. The wild-type AH and a phosphorylation-mimicking version

both show curvature dependence, but this dependence is accentuated for the phosphomimic when the vesicles have high surface charge. This is because the electrostatic contribution of the phosphomimic's binding is weaker, making it more reliant on hydrophobic interactions. Therefore, phosphorylation can increase sensitivity of AHs to curved vs. flat membranes.

Title: 2-H NMR Study of Functional Lipids in Membrane Structure for Therapeutic Drug Delivery

Presenter: Siyun Wang

Abstract: Cell membranes have been traditionally characterized as liquid crystalline bilayers. They help regulate permeability, serving as effective barriers to extracellular environment and impediments to drug delivery used in gene therapy and anti-cancer treatment. Recently developed lipid nanoparticles (LNPs) made of lipids complexed with small interfering RNA (siRNA) are promising in terms of transporting siRNA across the cell membrane. The LNPs shield and deliver the negatively charged siRNA into the cells via endocytosis. In order to improve our understanding of LNP association with endosomal membranes, we study the phase behavior of the anionic lipid phosphatidylserine (PS) in model membranes. The effects of temperature and pH on the bilayer to hexagonal phase transition are studied using chain-perdeuterated PS. Structural and motional information is obtained by measuring the 2-H NMR spectral width and lineshape. These measurements will be used for computational LNP simulations and for the design of in vivo animal model experiments.

Title: Substrate Binding Modes of UDP-N-acetylgalactopyranose Mutase Revealed by Molecular Dynamics Simulations and Saturation Transfer Difference NMR Spectroscopy

Presenter: Yun Shi

Abstract: UDP-N-acetylgalactopyranose mutase (UNGM) is a bifunctional enzyme as it recognizes both UDP-galactopyranose (UDP-Galp) and UDP-2-acetamido-2-deoxy-galactopyranose (UDP-GalpNAc) as substrates. However, only UDP-Galp is recognized by UDP-galactopyranose mutase (UGM), an enzyme highly homologous with UNGM. To study the binding modes of UDP-Galp and UDP-GalpNAc with UNGM, a protocol that combines molecular dynamics (MD) simulations and saturation transfer difference (STD) NMR spectroscopy was applied to the investigation of four enzyme-substrate complexes, namely UNGM:UDP-Galp, UGM:UDP-Galp, UNGM:UDP-GalpNAc, and UGM:UDP-GalpNAc. Binding models from MD simulations demonstrated significant agreement with mutagenesis studies and limited crystallographic data. Moreover, theoretical STD effects calculated from MD simulations showed excellent correlations with experimental values, further validating the binding models. The binding modes thus revealed have been used to explain the lack of catalytic activity of UGM for UDP-GalpNAc, and more importantly, the bifunctionality of UNGM.

Title: Measurement of Drug Accumulation in Single Acute Myeloid Leukemia (AML) Patient Cell Using the Microfluidic DEP chip and the Clinical Implications

Presenter: Avid Khamenehfar

Abstract: The reversal effect of MDR inhibitors on single cell drug accumulations has been measured in order to improve drug sensitivity on the cancer cell. The measurement is achieved using a new microfluidic chip designed to combine dielectrophoresis with the same-single-cell analysis (SASCA). A MDR cell has low initial drug accumulation and an obvious reversal effect in terms of substantial fold increase in drug accumulation. We have applied the method to measure acute myeloid leukemia (AML) patient cells. We have found 78% correlation between our SASCA measurement results and patient clinical outcomes, and we envision such

a method may provide useful information for clinical monitoring of patients undergoing chemotherapy in the future.

Title: Probing interactions between collagen proteins via microrheology

Presenter: Marjan Shayegan

Abstract: Collagen is the major structural protein of the extracellular matrix and many connective tissues. It provides integrity and mechanical strength through its hierarchical organization. Defects in collagen can lead to serious connective tissue diseases. Collagen is also widely used as a biomaterial. Given that mechanical properties are related to the structure of materials, the main goal of our research is to understand how molecular structure correlates with microscale mechanical properties of collagen solutions and networks. We use optical tweezers to trap and monitor thermal fluctuations of an embedded probe particle, from which viscoelastic properties of the solution are extracted. We find that their overall response is altered by concentration and particularly high-frequency response is affected by the chemical modifications (presence of non-helical ends of collagen). We, then, evaluate possible models for viscoelastic behavior of collagen solutions.

Title: Nanofluidic flow enhances both sensitivity and specificity of DNA hybridization in the nanobioarray chip

Presenter: abootaleb sedighi

Abstract: The potential of DNA microarrays to create huge amount of information put them among the most powerful biological tools. However DNA microarray suffers from the long analysis time usually required in its diffusion limited process. Nanobioarray (NBA) chip utilizes nanofluidic flow to deliver the target molecules and render the hybridization process reaction limited. Both the sensitivity and the specificity of DNA hybridization are enhanced as a result of the conversion in the rate-limiting step. Here we aim to model DNA hybridization inside a nanofluidic channel and find out how the flow help achieve more sensitive and specific signals in shorter analysis time. The hybridization kinetic constants were measured using Surface Plasmon Resonance (SPR) spectroscopy. Convection-diffusion equation and Langmuir kinetics were used to simulate target mass transfer and hybridization reaction, respectively. The signals predicted by the model were verified by experimental data from nanobioarray chips.

Title: MD-generated volume profiles for study of the folding of macromolecules

Presenter: Heather Wiebe

Abstract: Understanding the mechanism by which conformational changes, particularly folding and unfolding, occur in proteins and other biopolymers is a central question in theoretical biophysics. Molecular dynamics (MD) simulations of protein folding/unfolding present a formidable challenge since these conformational changes occur on a time scale longer than what can be afforded at the current level of computational technology. Transition state (TS) theory offers a significantly more economic description of kinetic properties of reaction system by relating them to the properties of the TS. Its application to protein folding is significantly restricted by ambiguity in the definition of the TS of for this process. We propose to identify the TS by comparison of its experimentally determined volumetric properties, known as volume of activation, to the structure-specific volume profile of the process calculated using MD. We illustrate this approach by its successful application to unfolding of a model chain system.

Title: Using deuterium nuclear magnetic resonance spectroscopy to study the effects of fluorescent probes on lipid membranes

Presenter: Sherry Leung

Abstract: The lipid raft hypothesis postulates that nano-scale lateral compositional heterogeneity in cell membranes plays functional roles. Fluorescence techniques are routinely used to study membranes and fluorescent probes are widely available, but only recently have systematic studies on probe behaviour emerged. It was found that probe behaviour can be altered by membrane composition, for example. Using 2H NMR, we showed that trace amounts of the carbocyanine probe DiIC12 are enough to alter phase coexistence behaviour of membranes, while the equipartitioning probes, Laurdan and another carbocyanine probe DiOC18, had little effect. Complicating the picture is the fact that non-equipartitioning probe, naphthopyrene, also did not affect membrane phase coexistence. Most biological molecules are only present in the cell in small amounts. In addition to shedding light on why micron-scale phase separation is observed in model membranes, but not in living cells, our work can elucidate the mechanism by which minor cellular components function.

Title: Single-Molecule Stretching of Type II Collagen using Optical Tweezers

Presenter: Thomas Brouwer

Abstract: Collagen represents approximately 25% of total protein in the human body. It is a prime component of connective tissues such as bone, cartilage and skin. Three pro-α chains coil into a triple helix to form 300nm monomers of collagen, which assemble into fibrils and other higher order structures. Despite collagen being the most abundant protein in our bodies, a molecular level understanding of collagen's mechanics the influence of its chemical composition remain surprisingly untested. Here we describe the construction of an optical tweezers apparatus adept at stretching human type II collagen. We implement a microfluidic system to improve the resolution of higher stretching forces, necessary to test models of how collagen responds to applied force. To assess the performance of this instrument, we initially characterize DNA molecules. Future directions will extend this work to study force-dependent structural changes in collagen and how these are influenced by proteolytic cleavage and aging.

Title: Identifying the network of interactions between insulator proteins by analyzing HI-C data

Presenter: saeed saberi

Abstract: The packing of DNA inside a cell into chromatin is a highly regulated process. Chromatin is organized into domains by the formation of loops, and domains are distinguished by different sets of chemical marks along the DNA. Using Drosophila Melanogaster HI-C data which measures the frequency of chromatin looping in 3D space at every position along the DNA, we study the nature of the interactions between different domains of chromatin. Using principal component analysis (PCA), we first identify the dominant free energy interaction profiles within chromatin. We then use a physical model from statistical physics that takes into account the underlying domain structure to fit the free-energies of interaction between chromosomal territories. This study reveals the nature of the interactions between different domains and how they structure the chromosome.

Title: Frequency Mapping of Rat Spinal Cord at 7T

Presenter: Evan Chen

Abstract: The spinal cord is an integral part of the nervous system responsible for sensory, motor, and reflex control. Due to its non-invasive nature, magnetic resonance imaging (MRI) is well matched for characterizing and imaging of the spinal cord, and is used extensively for clinical applications. Recent developments in MRI at high field (7T) using phase represents a new approach of characterizing spinal cord myelin. Theory suggests that microstructure differences in myelinated white matter (WM) and non-myelinated gray matter (GM) affect MR phase, converted to frequency shifts. Our results show that frequency shifts are measured between not only between WM and GM, but also between specific WM tracts of the dorsal column. Comparisons to traditional MR methods (diffusion tensor imaging, myelin water imaging) and histology provide insight into new information that frequency mapping can reveal about spinal cord tissue microstructure, and lays important groundwork for future in-vivo and human studies.