Frontiers In Biophysics

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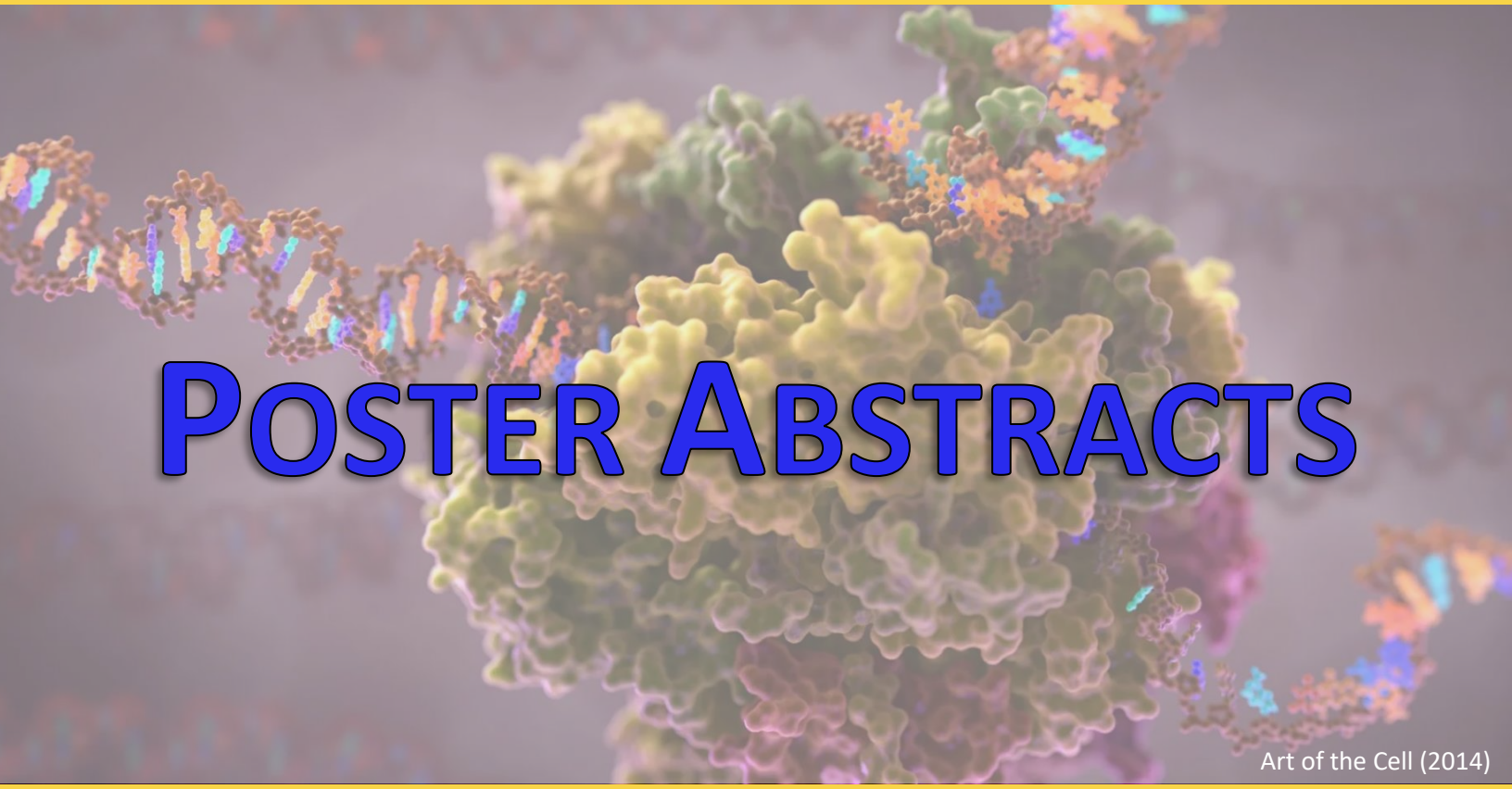

Art of the Cell (2014)

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PRESENTER: ALAA AL-SHAER *(Simon Fraser University)*

Poster Number: 1

Sequence- and Temperature- Dependent Mechanics of Single Collagen Molecules

Collagen, the most abundant protein in mammalian organisms, has been selected via evolution as the preferred building block of extracellular structures. Our current understanding of collagen has evolved from a static building block to a highly dynamic and interactive component of the extracellular matrix. Amazingly, collagen proteins are thermally unstable at body temperature, implying that they are capable of assembling and mechanically supporting tissues while fighting their own structural instability.

In this study, we use atomic force microscopy to image different collagen types at different temperatures and analyze their mechanical properties. By analyzing their flexibility in a sequence-dependent manner, we have learned that interruptions in the triple-helix-defining sequence (Gly-X-Y) in collagen IV lead to a generally more flexible polymer with regions of enhanced flexibility correlating with the presence of interruptions. We compare these findings with collagen III – a continuously triple-helical collagen – and find that it also displays variable flexibility along its contour, most notably possessing a high flexibility region near the matrix metalloprotease (MMP) binding site. This result represents the first demonstration of a unique mechanical signature of the MMP site along collagen. We are currently exploring how temperature influences these mechanical properties, investigating the interplay between flexibility and structural stability as a function of protein sequence.

PRESENTER: ALBERT KONG *(University of British Columbia)*

Poster Number: 2

The Effects of ATP Depletion on Cell Contractile Energetics

The cell metabolism regulates and apportions cellular energy between various functions including motility, chemical synthesis, active transport, and morphogenesis. This energy is stockpiled as adenosine triphosphate (ATP) and is produced either through the breakdown of glucose (glycolysis) or oxidative phosphorylation. The latter is more efficient and is the preferred method of ATP production in healthy cells. Cancer cells however, produce ATP through glycolysis, in a phenomenon termed the Warburg effect. This in turn inspired nutritional approaches to cancer therapeutics, which remains an active field of research to this day. Nutritional studies however, have so far focused on biochemical or rate-of-mortality related changes in cells as a results of nutrient restriction. We propose that the consequences of nutrient restriction should instead be studied with more granularity, as it holds the potential to unraveling the limits and adaptations of the cell metabolism.

In this study, we report changes in the mechanochemical efficiency of contractile cells as a result of glucose deprivation. We employ a novel experimental platform, exploiting phototoxicity to induce a controlled contractile response in cells. The energetics of contraction were quantified from geometric cell data through a mathematical model considering the transduction of chemical energy from ATP hydrolysis in contractile stress fibres (SF) to work performed by the SFs against focal adhesions which anchor the cell to the external substrate.

Glucose deprived cells contained less than 50% of the ATP in our control cells. Furthermore they decrease in ATP after contraction whereas the control cells' ATP concentrations increased after contraction. This is accompanied by a 50% increase in contracted area from the glucose deprived to control cells. Through our model, we estimate that this corresponds to roughly a twofold increase in contractile efficiency from the control to glucose deprived cells - in agreement with existing reports of more efficient metabolisms in nutrient deprived cells. By interpolating between the control and glucose deprived contractile responses, our model suggests the existence of an optimal level of nutrition/glucose at which the contractile efficiency is maximal. Beyond this point, the contractile efficiency sharply drops with decreasing levels of nutrition.

PRESENTER: ALIREZA MASHAYEKHI *(University of British Columbia)*

Poster Number: 3

Shear-Enhanced Coalescence in Oil-Water Emulsions

Emulsions, mixtures of two immiscible liquids, are present in various industries, from oil and gas to cosmetics, food, and pharmaceuticals. While in most applications such as food, cosmetics, and pharmaceuticals, a stable emulsion is required, breaking super-stable emulsions formed in the refining process is the main challenge in the oil and gas industry. Prior work with bitumen droplets showed that while they do not coalesce when pressed against each other, immediate coalescence happens when droplets are sheared against each other. Inspired by the phenomenon, we attempted to reproduce this effect in a more simplified system. We used a cantilevered-capillary force apparatus to precisely manipulate oil droplets in different aqueous solutions to produce steady, head-on collisions and continuously-oscillating shearing collisions. In this talk we present the results obtained when decane droplets are stabilized by different non-ionic surfactants or nanoparticles.

PRESENTER: CARIAD KNIGHT *(University of British Columbia)*

Poster Number: 4

Phosphorous Solid-State NMR of the Myelin Lipid Bilayer - a New Frontier for White Matter Characterization in Vivo

Myelin in white matter is integral to normal brain health and function, with its damage and degradation involved in many neurodegenerative diseases making it an important area of active research in magnetic resonance imaging (MRI). Conventional MRI is hindered in it's ability to directly detect myelin lipids due to their fast T2 relaxation. Solid-state phosphorous spectroscopy is expected to be an improved method for the study of myelin due to the high content and specificity of phosphorous in the phospholipids present in myelin lipid bilayers. We have used the solid-state nuclear magnetic resonance (NMR) technique of cross polarization (CP) to selectively filter and enhance the semi-solid component of the phosphorous NMR spectrum from both preserved and fresh white matter samples, and have demonstrated the feasibility of a two-stage magnetization transfer process with aqueous and membrane-bound hydrogen nuclei. This pairing of the solid-state NMR technique of CP with a two step polarization transfer process may provide a new frontier for the characterization and probing of myelin for in vivo MRI and opens new avenues for myelin lipid membrane investigation.

PRESENTER: DANE MARIJAN *(Simon Fraser University)*

Poster Number: 5

Intrinsic Protein Structural Properties Regulate Physiological Amyloid Aggregation

All cells must respond to changing conditions if they are to survive. One of the ways mammalian cells react to harsh stimuli is by forming physiological, RNA-seeded amyloid bodies (A-bodies) within their nuclei (Audas et al. 2016). Amyloids are highly organized, very degradation resistant protein structures commonly associated with debilitating diseases such as Alzheimer's and Parkinson's, earning a reputation of an irreversible, pathological protein state. Amyloid bodies, however, quickly disassemble upon stimulus termination, highlighting that amyloid aggregation does not always generate toxic structures. The proteomes of A-bodies induced by different stressors vary significantly, and their constituent proteins can be sequestered by one or more stressors (Marijan et al. 2019). This would suggest that cells use this pathway to selectively immobilize and inactivate only a particular subset of proteins under a given condition, thereby providing a tailored response. However, the molecular mechanisms that determine whether a protein is targeted to A-bodies during a particular stimulus have so far been largely unknown. Here, by using two highly related proteins as a model system, we have identified critical structural elements that regulate their heat shock specific amyloid aggregation. Our data shows that selectively modifying distinct, stabilizing structural pockets can either induce or restrict the A-body targeting of these proteins. We propose a model where A-body targeting during heat shock is regulated by the intrinsic structural stability of proteins, acting as thermal switches that expose or conceal their own A-body targeting motifs. Furthering understanding of the mechanisms of stimulus specific amyloid aggregation and its consequences on cell function will advance fundamental knowledge of how cells interact with their surroundings, both in physiological and pathological settings, and clue into how these pathways can be dysregulated.

PRESENTER: DANIEL SLOSERIS *(Simon Fraser University)*

Poster Number: 6

Investigating Age Related Changes to Molecular Collagen

Advanced Glycation End Products or AGEs are a group of potentially harmful crosslinks and adducts that are formed through non-enzymatic glycoxidation between sugars and proteins, lipids or nucleic acids known as the Maillard reaction. These non-reversible end products have been associated with increased levels of oxidative stress, inflammation and apoptosis (cell death). AGEs are consumed from cooked foods or formed in the body. However, AGEs are only removed by catabolism and therefore accumulate on proteins with slow turnover rates such as collagen. AGE accumulation on collagen has been associated with tissue stiffening and decreased turnover rate in collagen fibrils.

In this investigation we probe the mechanical properties of molecular collagen after inducing ageing in vitro. Using Atomic Force Microscopy (AFM) we quantify collagen molecule flexibility and find a decrease in flexibility without significant evidence for extensive cross linking, suggesting non-crosslinking AGE adducts play a role in changing collagen's flexibility. Further, we are currently investigating collagen's triple helical structure, stability and ability to form higher order structures (fibrils) using Circular Dichroism (CD) protease digestions by Trypsin and optical density measurements to analyze fibril growth with glycated collagen molecules.

PRESENTER: GUOJUN CHEN *(University of British Columbia)*

Poster Number: 7

Templated Folding of the RTX Domain of the Bacterial Toxin Adenylate Cyclase Revealed by Single Molecule Force Spectroscopy

The bacterial toxin adenylate cyclase (CyaA) is the key virulence factor of whooping cough. Upon secretion from the bacterial cytosol, CyaA binds extracellular Ca2+ and folds into a functional form that can invade host cells. The RTX domain, which is located at the C-terminus of CyaA and contains five blocks of tandemly arranged RTX repeats (RTX-i to RTX-v), plays important roles in ensuring the efficient secretion of CyaA toxin, and mediating CyaA toxin activity and pathogen virulence. It has been shown that the C-terminal capping structure of RTX-v is critical for the folding of the whole RTX domain. However, it remains unknown how the folding signal transmits within the RTX domain from RTX-v to RTX-i. Here we used single molecule optical tweezers to investigate the folding mechanism of RTX-iv and its influence by the folding of RTX-v. Our results revealed that RTX-iv alone is intrinsically disordered even in the presence of 10 mM Ca2+, but folds into a Ca2+-loaded β-roll structure in the presence of a folded RTX-v. By directly monitoring the folding trajectories of RTX-iv-v, we showed that the folding of RTX-iv is strictly conditional upon the folding of the whole RTX-v. Our results demonstrate that the folding of RTX-iv is templated by the folding of RTX-v. This templated folding effect not only allows RTX-iv to fold rapidly, but also leads to a significant mutual stabilization effect between RTX-iv and RTX-v. This templated folding provides a possible molecular mechanism allowing for the transmitting of the folding signal along the chain of the RTX domain.

PRESENTER: KOUSHIK BAR *(Simon Fraser University)*

Poster Number: 8

Incorporation of Temperature Control in a Centrifuge Force Microscope

Advancement in the field of single-molecule research has taken a huge leap over the past few decades. This has been aided by the development of instruments such as AFM (Atomic Force Microscopy) and optical tweezers. Such development has led to many remarkable findings, such as deep insight into receptor ligand interaction, DNA mechanics, and protein unfolding dynamics. Although the success of these instruments is indisputable, they come with a complex setup, high cost (~$100,000) and can usually probe only one molecule at a time, making statistical analysis of single-molecule biophysics notoriously tedious. Different instruments like multiplexed magnetic tweezer systems and centrifuge force microscopy (CFM) are put forward as cost-effective alternatives, which provide significantly higher throughput measurements. The proposed CFM is a further development of the work of Kirkness and Forde 2018, where a commercial benchtop centrifuge was used for applying forces. We plan to develop the first temperature-controlled cost effective (~$200) CFM for single-molecule force spectroscopy, with higher throughput, capable of measuring temperature-influenced force response of thousands of single molecules in parallel.

PRESENTER: LAURENT MACKAU *(University of British Columbia)*

Poster Number: 9

Viscoelasticity and Topological Transitions: How to Produce Fluidity in the Developing Salivary Gland

Drosophila salivary glands develop from a roughly flat sheet of cells into a narrow invaginating tube, serving as a relatively simple model system for studying the mechanical requirements of developmental tube formation. A recent biophysical model of the salivary gland succesfully reproduced many key experimental findings and elucidated the contributions of the various myosin pools to the invagination process. This model treated cell-cell interfaces as a network of elastic springs, deforming due to a combination of local myosin forces and other tissue-scale forces. However, the rigidity of the elastic springs prevented the occurence of many topological transitions in the network, termed intercalations, which are though to be a main driver of the tissue's flow into the duct. We have modified the model to incorporate viscoelastic effects, demonstrating where, when, and how these viscoelastic effects can enhance intercalations and general tissue fluidity to influence the moprhology of the resulting ductal tube.

PRESENTER: LIONEL PEREIRA *(Simon Fraser University)*

Poster Number: 10

Identifying Cellular Factors Regulating Amyloid Body Disaggregation

Cellular proteostasis is essential for the proper function of eukaryotic cells. Harmful stressors, such as high temperature, result in misfolded polypeptides that can form reversible protein aggregates termed amyloid bodies (A-bodies). These protective physiological structures form upon expression of long non-coding RNAs from the ribosomal DNA cassette, which act as a scaffold for A-body constituents. A-bodies are biophysically similar to pathological amyloids found in debilitating human neuropathies. While much has been done to understand the process of amyloid aggregation, the systemic view of A-body disaggregation in a biological context is not well understood. This disaggregation is thought to require heat shock proteins (Hsps) (e.g., Hsp70 and Hsp90), as well as other regulatory molecules. Therefore, we hypothesize that cellular factors that associate with A-body proteins mediate the disassembly of A-bodies, and the dysregulation of these factors may be associated with pathological amyloid formation. To identify these cellular factors, a biotin-dependent proximity labeling system fused to different A-body constituents will biotinylate interacting or nearby proteins, mapping out potential protein-protein interactions (PPIs). Then, mass spectrometry of the biotinylated proteins may reveal candidates that are necessary to disassemble A-bodies. Further, these identified protein candidates will be characterized through overexpression or inhibition to observe their effect on amyloid disaggregation. Subsequently, any identified factors will be cross-referenced with mutations which have been implicated in pathological amyloid formation. This largely depends on the nature of the factors identified by the PPI screen. Generally, this would involve expressing the disease-linked form of any identified factor and examining its effect on A-body disassembly. Identifying these factors involved in the disaggregation process of A-bodies would provide valuable insight for our current understanding of cell biology. Furthermore, knowing which pathways and factors are responsible for A-body disaggregation may provide new avenues in developing targeted therapeutics for amyloid-associated diseases.

PRESENTER: LUKE REYNOLDS *(University of British Columbia)*

Poster Number: 11

Understanding T1 Relaxation in Heterogeneous Systems: Fractional Order Modeling in White Matter and Beyond

Reliably quantifying longitudinal relaxation in heterogenous systems like white matter is challenging because measured parameters are sensitive to details of the measurement technique. In particular, cross-relaxation/magnetization exchange between aqueous and non-aqueous tissue components may lead to multi-exponential relaxation during inversion recovery, depending on the difference in the pools' initial magnetizations. We use a generalization of the Bloch equations to fractional order to show that the additional component stemming from this exchange is better described by a stretched Mittag-Leffler function than a standard exponential in solid-state NMR experiments with multiple heterogenous systems including ex vivo bovine and porcine white matter as well as in vivo human white matter MRI. This approach provides an additional metric reflecting the material's structure at a small scale through the stretching parameter, beta. This shows preliminary use as a biomarker potentially sensitive to morphological complexity in lipid membranes.

PRESENTER: MARK REMPEL *(Simon Fraser University)*

Poster Number: 12

Optimizing Efficiency and Motility of a Polyvalent Molecular Motor

Molecular motors play a vital role in the transport of material within the cell. A family of motors of growing interest are burnt bridge ratchets (BBRs). BBRs rectify spatial fluctuations into directed motion by creating and destroying motor-substrate bonds. It has been shown that the motility of a BBR can be optimized as a function of the system parameters. However, the amount of energy input required to generate such motion and the resulting efficiency has been less well characterized. Here, using a deterministic model, we calculate the efficiency of a particular type of BBR, namely a polyvalent hub interacting with a surface of substrate. We find that there is an optimal burn rate and substrate concentration that leads to optimal efficiency. Additionally, the substrate turnover rate has important implications on motor efficiency. We also consider the effects of force-dependent unbinding on the efficiency and find that under certain conditions the motor works more efficiently when bond breaking is included. Our results provide guidance for how to optimize the efficiency of BBRs.

PRESENTER: MATHIS GRELIER *(Simon Fraser University)*

Poster Number: 13

Discrete Work Transducers

Molecular motors are essential to any living beings. Operating in physiological environments, they are submitted to strong fluctuations. Although stochasticity is omnipresent for these nanoscale motors, they succeed to transduce energy from one form to another. Here we focus on the well-known biomolecular motor F_0F_1-ATP synthase. Researchers have been focused developing continuous model for this engine, however discrete models remain sparsely advanced. The following discrete model permits to explore the thermodynamic characteristics of such bipartite systems without loss of generality. We show that the output power is maximized when there is no information flow between the subcomponents of the motor for one heat reservoir at stake. This maximization implies also an equality between the entropy productions of each subsystem which is in agreement with the results found in continuous model. Then, information flow comes into play when different heat reservoirs are added for each subsystem, alternating between conventional and information engine.

PRESENTER: SABRINA LESLIE *(University of British Columbia)*

Poster Number: 14

Non-Equilibrium Structural Dynamics of Supercoiled DNA Plasmids Exhibits Asymmetrical Relaxation

Cells are dynamic systems, existing out-of-equilibrium to perform the reactions that support life. For instance, DNA is constantly replicated, transcribed, or otherwise accessed by proteins and other cellular machinery. DNA is supercoiled inside cells, which can drive structural transitions away from B-DNA that may play important roles in gene regulation. In this work, we use Convex Lens-induced Confinement (CLiC) microscopy to study such structural transitions with high throughput and without artificially constraining molecular structure. We used a model plasmid system containing an AT-rich region susceptible to melting at low temperatures when supercoiled to study the dynamics of structural transitions after a perturbation away from equilibrium. We found that structural transitions can be slow, leading to long lived states whose kinetics depend on the direction of perturbation. We hypothesize that such slow transitions are caused by competitions among several secondary structures. Our findings highlight the importance of out-of-equilibrium studies of structural transitions in supercoiled DNA.

PRESENTER: SABRINA LESLIE *(University of British Columbia)*

Poster Number: 15

Simultaneous, Single-Particle Measurements of Size and Loading Give New Insights Into the Structure of Drug-Delivery Nanoparticles

Nanoparticles are a promising solution for delivery of a wide range of medicines and vaccines. Optimizing their design depends on being able to resolve, understand, and predict biophysical and therapeutic properties, as a function of design parameters. While existing tools have made great progress, gaps in understanding remain because of the inability to make detailed measurements of multiple correlated properties. Typically, an average measurement is made across a heterogeneous population, obscuring potentially important information. In this work, we develop and apply a method for characterizing nanoparticles with single-particle resolution. We use convex lens-induced confinement (CLiC) microscopy to isolate and quantify the diffusive trajectories and fluorescent intensities of individual nanoparticles trapped in microwells for long times. First, we benchmark detailed measurements of fluorescent polystyrene nanoparticles against prior data to validate our approach. Second, we apply our method to investigate the size and loading properties of lipid nanoparticle (LNP) vehicles containing silencing RNA (siRNA), as a function of lipid formulation, solution pH, and drug-loading. By taking a comprehensive look at the correlation between the intensity and size measurements, we gain insights into LNP structure and how the siRNA is distributed in the LNP. Beyond introducing an analytic for size and loading, this work allows for future studies of dynamics with single-particle resolution, such as LNP fusion and drug-release kinetics. The prime contribution of this work is to better understand the connections between microscopic and macroscopic properties of drug-delivery vehicles, enabling and accelerating their discovery and development.

PRESENTER: SHAWN HSUEH *(University of British Columbia)*

Poster Number: 16

First Principles Calculation of Protein–Protein Dimer Affinities of ALS-Associated SOD1 Mutants

Cu,Zn superoxide dismutase (SOD1) is a 32 kDa homodimer that converts toxic oxygen radicals in neurons to less harmful species. The dimerization of SOD1 is essential to the stability of the protein. Monomerization increases the likelihood of SOD1 misfolding into conformations associated with aggregation, cellular toxicity, and neuronal death in familial amyotrophic lateral sclerosis (fALS). The ubiquity of disease-associated mutations throughout the primary sequence of SOD1 suggests an important role of physicochemical processes, including monomerization of SOD1, in the pathology of the disease. Herein, we use a first-principles statistical mechanics method to systematically calculate the free energy of dimer binding for SOD1 using molecular dynamics, which involves sequentially computing conformational, orientational, and separation distance contributions to the binding free energy. We consider the effects of two ALS-associated mutations in SOD1 protein on dimer stability, A4V and D101N, as well as the role of metal binding and disulfide bond formation. We find that the penalty for dimer formation arising from the conformational entropy of disordered loops in SOD1 is significantly larger than that for other protein–protein interactions previously considered. In the case of the disulfide-reduced protein, this leads to a bound complex whose formation is energetically disfavored. Somewhat surprisingly, the loop free energy penalty upon dimerization is still significant for the holoprotein, despite the increased structural order induced by the bound metal cations. This resulted in a surprisingly modest increase in dimer binding free energy of only about 1.5 kcal/mol upon metalation of the protein, suggesting that the most significant stabilizing effects of metalation are on folding stability rather than dimer binding stability. The mutant A4V has an unstable dimer due to weakened monomer-monomer interactions, which are manifested in the calculation by a separation free energy surface with a lower barrier. The mutant D101N has a stable dimer partially due to an unusually rigid β-barrel in the free monomer. D101N also exhibits anticooperativity in loop folding upon dimerization. These computational calculations are, to our knowledge, the most quantitatively accurate calculations of dimer binding stability in SOD1 to date.

PRESENTER: SINA FALAKIAN *(Simon Fraser University)*

Poster Number: 17

Inference of the DNA Replication Kinetics in Human Genomes

In almost all organisms, genetic information is stored in DNA molecules. Replication of DNA is nature's way of copying information and is an essential part of life. In the human genome, this process occurs at a rate of roughly 100,000 bases per second inside a nucleus having a diameter of about 1 µm, which is remarkable. To understand this process, experimental techniques have been developed since the 1980s, and they are still developing. The kinetics of the replication process in bacteria and yeast have been fairly well understood using the experiments. But the widely used experimental techniques have not been able to provide enough data to understand the kinetics of this process in humans. In this talk, I will briefly review how the replication process works and how experimental techniques have been used to infer this process. Then we will see how a new experimental technique called Optical Replication Mapping (ORM) might be a good candidate for understanding the replication process in the human genome, and I will discuss how we are going to use stochastic modelling of experimental data to shed light on this phenomenon.

PRESENTER: STEVEN BLABER *(Simon Fraser University)*

Poster Number: 18

Efficient Two-Dimensional Control of Barrier Crossing

Modern advances in single-molecule biophysics make possible the precise spatial and temporal control of biological systems. Despite the relative freedom of control, experiments and simulations rarely exploit the possibility of optimized control protocols, and the ones that do are generally limited to optimization of a single control parameter. We design minimum-dissipation protocols for harmonic trapping potentials under two-dimensional control (of both trap center and stiffness), for driven barrier crossing. This greater control allows specification of both the time-dependent mean and variance of the position distribution, and results in qualitatively distinct designed protocols. For any duration, the designed protocols significantly improve performance in terms of both dissipation and flux compared to naive and one-dimensional control.

PRESENTER: SULIAT YAKUBU *(University of British Columbia)*

Poster Number: 19

Position Specific Context-Enriched Automated Activity Classification in Collegiate Women's Soccer Using Trunk-Mounted Inertial Measurement Units

Soccer is a popular sport, but also has a high risk of injury. Evidence-based injury prevention routines have poor uptake. Additionally, injury incidence rate is reported in terms of total athlete time, however not all activities carry the same level of risk. Real time activity classification could provide a detailed history of exposure to high-risk activities. This would provide coaches with additional information, to use in choosing from existing injury prevention routines. We aim to improve existing Inertial Measurement Unit (IMU) -based activity classification methods by incorporating contextual information, regarding player position using a Hidden Markov Model (HMM). IMU-based classifiers have successfully been used to identify activities in exercise and sport-based contexts. HMMs are a popular tool for pattern recognition in time serial data. 11 collegiate varsity female soccer players will be instrumented with a single IMU, placed on the lower back, to capture on-field activity data. Ground truth activity labels will be determined using video footage. The collected sensor and video data will be used to train a Random Forest (RF) algorithm, and to develop an HMM to incorporate context. To assess the proposed framework, the accuracy of the generic RF classifier, the RF classifier combined with a general HMM, and the RF classifier combined with a position-specific HMM will be compared. Developing systems capable of collecting, analyzing, and delivering this information on a personalized level could allow non-professional sports teams to have access to elite level physiological analytics, protecting athletes at all levels and stages of their careers, and enabling them to reach their full on-field potential.

PRESENTER: YUN-HAN HUANG *(University of British Columbia)*

Poster Number: 20

Rheological Characterization of Neurospheres and the Effects of Oxidative Stress

Mechanical characterization of brain tissue is important, but limited by the unavailability of representative live tissue models and deficient measurement techniques that can precisely measure the mechanical response of tissues. In this work, we treated progenitor-derived neurospheres with non-cytotoxic levels of hydrogen peroxide and studied their rheological properties along with their cellular composition and structure. The rheological characterization was carried out using a cantilevered-capillary force apparatus (CCFA). We also performed fluorescence staining to understand the cellular structure of the neurosphere. Our results confirm that neurospheres exhibit viscoelasticity and show for the first time that the elasticity of the neurospheres has a clear dependence on the size of the neurosphere. However, our work also demonstrates some of the challenges inherent with testing microparticles of biological tissue. Finally, we see a clear correlation between oxidative stress, the chemical state of the tissues, and their biophysical properties.

PRESENTER: ZELAI XU *(University of British Columbia)*

Poster Number: 21

Poroelastic Modeling and Simulation Supports Gel-Compression Hypothesis for Albuminuria

The etiology of albuminuria has been controversial. A recently revived hypothesis attributes the barrier function for the glomerular capillary to compression of the glomerular basement membrane (GBM) as a gel layer. The loss of podocytic foot processes is believed to allow the gel layer to stretch circumferentially, thereby enlarging its pores so albumin and other proteins can pass into the urine. We present a mechanical model based on a poroelastic representation of the GBM, and use numerical computation to demonstrate that (a) the filtration pressure in healthy glomerulus compresses the GBM to increase the density of the solid network and reduce the permeability to solutes; (b) loss of the pedicels allows the GBM to stretch circumferentially under filtration pressure to increase its permeability; (c) the model predicts the right amount of increase in permeability using physiologic parameters. Thus, this mechanical model supports the gel-compression hypothesis.