Monday, April 26, 2010

The Sackler Biophysics Symposium on *physics of biomolecular interactions*

Nonlinear elastic materials to direct cell growth

Paul Janmey
University of Pennsylvania

Many cell types are sensitive to mechanical signals, modulating their proliferation, morphology, motility, and protein expression in response to substrate stiffness. Studies of stiffness sensing typically employ linear elastic materials whose stiffness is independent of the applied strain. Biological materials, however, often stiffen in response to increasing strain, and this stiffness change alters the response of cells attached to the material. For example, fibroblasts and mesenchymal stem cells, adherent to linearly elastic gels typically display a small, round phenotype on soft substrates and increase spread area as the elastic modulus of their substrate increases. On strain-stiffening fibrin or collagen gels, the same cell types are maximally spread even when the gel's low strain elastic modulus would predict a round morphology. Traction microscopy reveals that cells apply active displacements of several microns up to five cell lengths away, and atomic force microscopy shows that these displacements locally stiffen the gel by deforming it beyond its linear range. Non linear elasticity of both intracellular and extracellular biomaterials allows cells to alter their own stiffness as well as that of the extracellular matrix by applying tensions that locally strain the networks and cells appear to exploit local stiffness chances for long range mechanical communication.

The virtues of promiscuity: How a molecular motor contacts its substrate

Ariel Kaplan
University of California, Berkeley

Many essential processes in biology involve the translocation of DNA or RNA by ring-shaped molecular motors that use the energy from ATP hydrolysis as a fuel. While the mechano-chemistry of these motors is relatively well understood, little is known about how they interact with their substrates, and how these interactions in turn regulate these conformational changes. With the DNA packaging motor of bacteriophage Φ29 as a model, we addressed these questions by following in an optical tweezers the dynamics of translocation as a single motor encounters regions of chemically and structurally modified DNA. In contrast to the prevailing picture that these motors make simple, sole, ionic contacts with the phosphate charges, we found a much more complicated and intricate interaction between the motor and DNA.

"Smart" Bio-Gel within Neurons Forces, Interactions and Elasticity of Neurofilaments

Roy Beck
University of California, Santa Barbara

Understanding biological systems poses huge theoretical and experimental challenges, attributable to their complexity, dynamics and many different elementary lengths scales involved in their interactions. These interactions scale from specific atomic-scale covalent bonds through non-specific long-ranged electrostatics. The complexity of biological systems is multi-scaled as well, as even a single cell is composed from many different, very complicated building-blocks.
In this talk, I will introduce our recent results about neurofilament hydrogel, a very basic component of the neurons' cytoskeleton. After we purify the three different subunit proteins from bovine spinal-cord, they self-assemble to form supra-macromolecules filaments with a 'bottlebrush'-like geometry. When assembled at high density, these neurofilaments form a liquid-crystalline hydrogels and serve as the matrix for the neuron's long processes (axons and dendrites). They impart mechanical stability and act as structural scaffolds. Using synchrotron small angle x-ray scattering under osmotic pressure coupled with various microscopy techniques, we directly measure the interfilament forces responsible for the mechanical properties of neurofilament hydrogels.

Decoding the ubiquitin signal

Gali Prag
Tel Aviv University

The signal of ubiquitin (Ub), a small protein modifier that changes the molecular landscape of numerous cellular proteins, is decoded by a large set of Ub-receptors. Each Ub-receptor comprises a Ub-binding domain (UBD) tethered to a functional domain *F(x)* that links *in trans* the ubiquitylated-target to a specific function. Ub-receptors are regulated by self-ubiquitylation, a modification that confers a closed conformation (*cis*) incapable of binding its ubiquitylated-target protein. However, deubiquitylating enzymes reverse this inhibition. Thus, Ub-receptors can exist in three forms: free (*apo),* bound to ubiquitylated-target (*trans*) and inactive (*cis*). The transient nature of the *cis* form has impeded the analysis of its structure-function relationships until recently. We bypassed this difficulty by developing a novel bacterial ubiquitylation system that captures the *cis* structure. Our biophysical studies including X-ray crystallography, analytical ultra-centrifugation

Water in protein function: from nanopores to proton pumps

Gerhard Hummer
National Institutes of Health, USA

Water plays an important role in the function of many proteins. In my talk I will explore how proteins exploit the unusual properties of water at the nanoscale. Computer simulations of water in nanpores and proteins show that weakly polar cavities can be filled by water at equilibrium, but such filling is highly sensitive to small variations in the polarity of the cavity. In the filled state, water forms wires and clusters held together by tight hydrogen bonds. Simulations on quantum energy surfaces also show that one-dimensional water wires in hydrophobic environments facilitate rapid proton motion. These unique properties of water in weakly polar environments help explain the rapid flow of water through molecular pores, the controlled proton delivery in enzymes, the gating of ion transport through membrane channels, and the function of mitochondrial proton pumps.

Mechanisms of programmed cell death through structural biology

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Programmed cell death, also known as apoptosis, is central to the development and homeostasis of metazoans. Dysregulation of apoptosis leads to a variety of human pathologies, including cancer, autoimmune diseases, and neurodegenerative disorders. Since the concept of apoptosis was established in 1972, research efforts have led to the identification of hundreds of genes that govern the initiation, execution, and regulation of apoptosis primarily in three model organisms: *Caenorhabditis elegans*, *Drosophila melanogaster*, and mammals. The central pathway of apoptosis is conserved among the three organisms and involves the activation of cell-killing proteases known as caspases. In this lecture, I describe systematic characterization of the molecular mechanisms of programmed cell death by an integrated approach of structural biochemistry and biophysics.

Effect of confinement on self assembly: granular materials to viruses

Daniel Harries
The Hebrew University, Jerusalem

Systems under strong confinement exhibit unique assembling properties. Two examples are presented for particles that preferentially order in the bulk at large enough densities. When packaged in small volumes not much larger than the assembling particles themselves, vibrated granular rods on the one hand, and viral chromatin on the other, are shown to follow predictions of simple equilibrium models. The analysis shows that packaging and patterning are determined by the competition of particle-particle and wall-particle interactions.