ternary molecular complex formed upon binding of proNGF or NGF to their receptors.

1039-Plat
Local Temperature Evolution during Nanoparticle Hyperthermia Probed by Fluorescence Thermometry
Rahul Munshi, Idoia Castellanos-Rubio, **Arnd Pralle**.
Physics, University at Buffalo, Buffalo, NY, USA.
Here we investigate the spatial and temporal evolution of temperature around heating nanoparticles held in varies spatial geometries. We compare isolated nanoparticles to ones aligned along an axis inside magnetotactic bacteria, to cell-bound ones, whereby the density is varied to change the particle-particle interaction. The nanoparticles or the cell membrane are labeled with fluorophores whose fluorescence intensity and lifetime are reduced with increasing temperature (TAMRA or Dylight for the particles, GFP tagged proteins for the cell). We use superparamagnetic nanoparticles which were heated by radio-frequency magnetic fields in a custom built set-up permitting simultaneous fluorescence imaging. We studied the differences in the nature of heat dissipation between particles bound to cell membranes and particles in suspension, undergoing Brownian motion. A comparative study of the geometric effects arising from particle arrangement and placement within the cells have also been studied. We find local heating to be strongly dependent on geometric particle arrangement, as well as on the relaxation mechanism of the nanoparticles, Brownian or Néel relaxation. To aid the understanding of the theoretical aspects of nanoscale heat transfer we incorporate simulations of the nanoparticle heating mechanism and heat dissipation in our study. Together, these results provide insights on efficient experimental designs for biomedical application of nanoparticle heating in-vivo.

1040-Plat
Nanomechanical Characterization of Active Synapses in Live Hippocampal Neurons
Ju Yang[1], Roger Lefort[2], Ozgur Sahin[1,3].
[1]Department of Biological Sciences, Columbia University, New York, NY, USA, [2]Department of Pathology and Cell Biology, Columbia University, New York, NY, USA, [3]Department of Physics, Columbia University, New York, NY, USA.
Synapses are highly organized structures enriched with synapse-specific proteins and actin filaments. Dynamics of actin filaments is critical in both synapse formation and plasticity of mature synapses. Actin assembly also contributes membrane tension, which is capable of actively regulating membrane structure and cellular functions through mechanosensitive components. It remains challenging, however, to characterize the membrane mechanics at synapses. Here we combined torsional harmonic atomic force microscopy (AFM) with fluorescence microscopy to image synapses in live hippocampal neurons. The small indentation distances and piconewton scale forces employed by our AFM allowed us to measure mechanical properties with nanoscale resolution. We relied on post hoc immunostaining against synaptic markers to determine synapses and analyzed their mechanical properties from the cooresponding AFM data. Additionally, the activity of synapses was monitored with FM dyes. We found that synapses are substantially stiffer than other neuronal structures (e.g. somas, dendrites). The relatively high stiffness of synapses supports the notion that mechanical processes may be important in synapse formation and function.

Platform: Large-scale Molecular Simulations

1041-Plat
Computational Studies on the cAMP Modulation of the HCN2 Channel
Florentina Tofoleanu, Bernard Brooks.
NHLBI, NIH, Rockville, MD, USA.
Hyperpolarization-activated cyclic nucleotide-gated 2 (HCN2) ion channels play a fundamental role in electric signaling in nerves, muscles, and synapses; however, their ligand gating mechanism is not well understood. Through collaboration between experimental and computational methods, this study brings insight into the mechanism of cyclic adenosine monophosphate (cAMP) modulation of the HCN2 channel (residues 443-636) by exploring the monomer and tetramer dynamics in the apo and holo states. We applied all-atom and coarse-grained molecular dynamics on molecular systems containing HCN2 with and without cAMP. Starting from the holo structure resolved by X-ray crystallography, our simulations guide the protein into its apo state. Along this pathway, we observed unfolding of the C'-helix and loss of contact between A' and B' helices in the C-linker and the cyclic nucleotide binding domain (CNBD). In addition, by using tmFRET distances as restraints, we were able to capture structural changes in the CNBD. Our results corroborate recent experimental studies showing the outward movement of the C-helix in the absence of cAMP.

1042-Plat
From Small to Large to Very Large: Modeling of Biomolecular Structures in Implicit Solvent
Alexey V. Onufriev.
Computer Science and Physics, Virginia Tech, Blacksburg, VA, USA.
Water is as important to biomolecular simulations as it is to biology. However, accurate treatment of solvation effects explicitly, by representing solvent as discrete particles, can be computationally expensive. A popular alternative that can speed-up practical simulations is based on representing solvent as a continuum: solvent effects on the biomolecule in question are accounted for implicitly, at various levels of approximation. Molecular simulations within this so-called implicit solvent framework can speed up conformational search dramatically, but the expected acceleration depends strongly on system details. Her I will discuss applications of the methodology across many length scales: from atomistic simulations of the folding of small proteins to studies aimed at understanding chromatin compaction and dynamics at the level of the entire cell nucleus.

1043-Plat
Acute Modulation of Sodium Channel Biophysical Properties using High-Frequency Stimulation
Steven Poelzing[1], Michael Entz[1], Seth H. Weinberg[2].
[1]Virginia Tech, Roanoke, VA, USA, [2]Old Dominion University, Suffolk, VA, USA.
Voltage-gated ion channels are typically characterized by families of voltage-dependent curves, in particular, steady-state activation/inactivation (SSA/SSI) and peak current-voltage (IV) curves, which are often shifted or altered during disease. Previous studies have demonstrated that high-frequency stimulation (HFS) can be used to block electrical conduction in nerve axons, and more recently, in cardiac tissue. However, the use of HFS to acutely modulate ion channels has not been explored. We demonstrate that HFS can acutely and reversibly modulate sodium channel biophysical properties using a combined theoretical, computational, and experimental approach. Using the sodium channel kinetic description from the LR1 myocyte model and a multi-scale method based on a separation of time scales, HFS is predicted to shift and reduce the steepness of the SSA and SSI curves, and shift and reduce the peak IV curve. Myocyte simulations demonstrate HFS depolarizes the resting membrane potential, such that the steady-state inactivation is increased. In agreement with theoretical and computational predictions, whole-cell patch clamp of isolated guinea pig ventricular myocytes show that 25-kHz HFS significantly reduces peak sodium current and suggest a shift in the peak to more depolarized potentials. Importantly, upon HFS cessation, peak current returns to control levels, demonstrating that HFS is acutely reversible. Further, in whole-heart optical mapping experiments, 25-kHz HFS reversibly decreased lateral and transverse conduction velocities in a graded manner, consistent with increased sodium channel inactivation. We demonstrate a novel method for the acute modulation of sodium channel biophysics using HFS. Further, our theoretical work predicts that HFS may be a general approach to modulate all voltage-dependent ion channels, suggesting a multitude of potential applications.

1044-Plat
Analysis of Domain Movement and Dynamics of Norwalk Virus Capsid by Molecular Dynamics (All-Atom and Coarse Grained) Simulations and Normal Mode Analysis
Mahendra B. Thapa[1], Mark Rance[2], Jarek Meller[3].
[1]Physics Department, University of Cincinnati, Cincinnati, OH, USA, [2]Department OF Molecular Genetics, Biochemistry and Microbiology, University of Cincinnati, Cincinnati, OH, USA, [3]Department of Environmental Health, University of Cincinnati, Cincinnati, OH, USA.
Norwalk virus is the major cause of epidemic gastroenteritis in humans. The capsid of the virus consists of 180 copies of a single protein which has a protruding (P) domain and a shell (S) domain. In this work, the mechanism of domain movements of the protein is investigated by Gaussian network model(GNM) and anisotropic elastic network model(ANM). The dynamics of various residues and C-terminus are examined by Molecular Dynamics Simulations (MD):Coarse-grained and all-atom. Preliminary results are as follows:(i) slow coordinated motions are identified in the hinge regions, (ii) the C-terminus residue interacts with specific residues within P domain only and (iii) normal mode analysis, coarse-grained MD and all-atom simulation generate largely consistent results.