and numerical calculation of the dissipation and relaxation time, we verify that thermodynamic length analysis (though derived in a near-equilibrium limit) provides a strikingly good approximation even far from equilibrium, and thus provides a useful framework for further study of biomolecular motor efficiency.

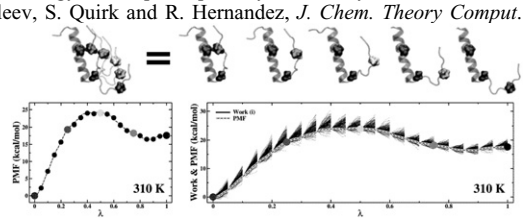
2851-MiniSymp

Adaptive Steered Molecular Dynamics: Unfolding of Neuropeptide Y and Decaalanine Stretching

Gungor Ozer[1], Stephen Quirk[2], **Rigoberto Hernandez**[1].
[1]Georgia Institute of Technology, Atlanta, GA, USA, [2]Kimberly-Clark Corporation, Atlanta, GA, USA.

The energetics of an unfolding event can be obtained using steered molecular dynamics (SMD) and Jarzynski's inequality with the cost of the calculation increasing dramatically with the length of the path. An adaptive algorithm has been introduced* that allows for the path to be nonlinear and staged while reducing the computational cost. The potential of mean force (PMF) obtained for neuropeptide Y (NPY) in water along an unfolding path confirmed that the monomeric form of NPY adopts the pancreatic-polypeptide (PP) fold. Adaptive SMD can also be used to reconstruct the PMF obtained earlier for stretching decaalanine in vacuum[#] at lower computational cost. The PMF for stretching decaalanine in water solvent (using the TIP3P water potential) at 300K has now been obtained using adaptive SMD. Not surprisingly, the stabilization from the water solvent reduces the overall work required to unfold it. However, the PMF remains structured suggesting that some regions of the energy landscape act partially as doorways.

*G. Ozer, E. Valeev, S. Quirk and R. Hernandez, *J. Chem. Theory Comput.* (2010), doi:10.1021/ct100320g.
[#]S. Park and K. Schulten, *J. Chem. Phys.***120**, 5946 (2004).



2852-MiniSymp

Non-Equilibrium Work Dissipation in Mechanical Unfolding of Large RNAS

Pan T.X. Li.
University at Albnay, SUNY, Albany, NY, USA.

Non-equilibrium thermodynamics is indispensible in studying mechanical unfolding of single RNA molecules. In a typical experiment, single RNA molecules are pulled and relaxed at fast loading/unloading rate that structure transitions occur under non-equilibrium. Work dissipation is reflected by hysteresis between forward and reverse trajectories in force-extension curve. Ligand and protein binding can stabilize a specific domain within a large RNA, which further complicates work dissipation in mechanical unfolding. Using experiment and simulation, we examined mechanical unfolding of large RNAs containing secondary and tertiary folding. The RNAs follow hierarchical folding pathways. Secondary structure forms before tertiary contacts, and tertiary interaction is disrupted before unfolding of secondary structure. Factors that selectively bind and stabilize tertiary structure lead to increased work dissipation by protecting secondary structure from unfolding. Furthermore, work dissipation is quantified as a function of pulling rate and factor binding.

2853-MiniSymp

Atomistic Simulations of the Force-Induced Dissociation of Retroviral RNA Kissing-Loops

Alan A. Chen, Angel E. Garcia.
Rensselaer Polytechnic Institute, Troy, NY, USA.

Retroviruses require two copies of their ssRNA genomes in order to form infectious virus particles. This is accomplished via a Dimerization Initiation Site (DIS), which forms a rivet-like ''kissing-loop'' that binds the two genomes together. Retroviral DIS kissing-loops have been shown to be unusually resistant to heat denaturation or mechanical pulling, given the small number (2-6) of Watson-Crick base-pairs involved. High mechanical stability is apparently required for retroviral fitness, as mutations that destabilize the DIS loop in-vitro also result in greatly reduced virus infectivity rates in-vivo. DIS kissing-loops are therefore attractive targets for antiretroviral therapeutic design; however, we must first understand the physical determinants that give rise to enhanced DIS kissing-loop stability.

The Moloney Murine Leukemia Virus (MMLV) serves as a particularly tractable model system due to its simplicity, as it composed of two GACG tetraloops held together by just two intermolecular base-pairs. Single-molecule pulling experiments (by Pan Li at SUNY Albany) have shown that it requires as much force to break these two loop-loop base pairs as is required to unfold an entire 11-bp hairpin. Using a combination of equilibrium and non-equilibrium all-atom molecular dynamics simulations, we have developed a detailed model for the kinetic intermediates of the force-induced dissociation of the MMLV DIS kissing-loop. We find that the transition state geometry allows for an equal distribution of the applied force among all of the intermolecular hydrogen-bonds, which is intrinsically more stable that the sequential h-bond breaking exhibited by simple RNA hairpins. In addition, we observe that stacking interactions with adjacent, unpaired loop adenines are able to further stabilize the complex, and that the breaking of these stacking interactions are the rate-limiting step for force-induced dissociation of the MMLV DIS complex.

2854-MiniSymp

An Intrusive Entropic Barrier Induced by Force

Ronen Berkovich[1], Sergi Garcia-Manyes[1], Joseph Klafter[2], Michael Urbakh[2], Julio M. Fernandez[1].
[1]Columbia University, New-York, NY, USA, [2]Tel Aviv University, Tel Aviv, Israel.

Single-molecule force spectroscopy has opened up new approaches to the study of protein dynamics. For example, an extended protein folding after an abrupt quench in the pulling force was shown to follow variable collapse trajectories marked by well-defined stages that departed from the expected two-state folding behavior that is commonly observed in bulk. Here, we explain these observations by developing a simple approach that models the free energy of a mechanically extended protein as a combination of an entropic elasticity term and a short-range potential representing enthalpic hydrophobic interactions. The resulting free energy of the molecule shows a force-dependent energy barrier of magnitude, $\Delta E = \epsilon(F - Fc)^{3/2}$, separating the collapsed state of the molecule from a force-driven extended conformation, that vanishes at a critical force Fc. By solving the Langevin equation under force quench conditions, we generate folding trajectories corresponding to the diffusional collapse of an extended polypeptide that mimics those observed experimentally. Further we apply this model to force extension conditions in order to investigate the role played by the force-induced energy barrier on the two-state hopping phenomena that has been observed in single protein molecules placed under a stretching force. Langevin dynamics across such force induced barrier readily demonstrates the hopping behavior observed for a variety of single molecules placed under force. Our model interprets AFM force-clamp data and accounts as well for force-extension and hopping observed in optical tweezers, thus unifying the field of protein force spectroscopy. Moreover, given that this barrier does not exist at zero force, extrapolating hopping trajectories to zero force could not be compared to bulk measurements.

2855-MiniSymp

Building Stochastic Feedback Models from Limited Data; A Maximum Entropy-Based Solution

Steve Presse.
University of California, San Francisco, South San Francisco, CA, USA.

We present a general, maximum entropy-based method for modeling stochastic feedback dynamics of small chemical and biochemical systems. Our method, Maximum Caliber, uses experimental data in the form of dynamical averages and correlations to construct ensembles of system trajectories. These theoretical ensembles are used to infer long-time dynamics from short-time trajectories. In particular, the method does not have to invoke complex reaction schemes to predict dynamical features such as multistability. On the other hand, traditional stochastic modeling methods often require knowledge of rates and reaction networks. Such parameters are rarely validated independently of the experimental curve-fitting. Maximum Caliber requires both fewer assumptions regarding the reaction network and fewer parameters to capture the effects of feedback. We demonstrate the principle on the genetic toggle switch and the circadian clock.

Platform BC: Interfacial Protein-Lipid Interactions

2856-Plat

Lung Surfactant Peptide-Mimic KL4 Improves Reversibility of Synthetic Model Lung Surfactant Collapse Behavior

Niels Holten-Andersen[1], Phillip W. Miller[1], Alan J. Waring[2], Frans J. Walther[3], **Ka Yee C. Lee**[1].
[1]The University of Chicago, Chicago, IL, USA, [2]UCLA and UC Irvine, Los Angeles and Irvine, CA, USA, [3]LA Biomedical Research Institute, Harbor-UCLA, Torrance, CA, USA.

We have investigated the origin of the effect of the peptide KL4 on lung surfactant lipid monolayers containing DPPC and POPG. Using surface balance techniques, fluorescence microscopy and atomic force microscopy we