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1265-Plat
Predicting Charged-Ligand Binding from Molecular Simulations
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We seek to use molecular simulations to predict and understand protein-ligand interactions. Our approach uses so-called "alchemical" free energy calculations to quantitatively predict binding affinities. Here, we will discuss recent work on blind predictions of protein-ligand binding in a model binding site in cytochrome C peroxidase, as well as related work in other binding sites. We discuss the outcome of our predictions, what we learned, and the challenges facing computational methods in predicting biomolecular interactions. We also discuss ongoing related work in other binding sites, and implications of our work for binding studies more broadly.

1266-Plat
Ribosomal Kinetics and Concerted Motions from Nanoseconds to Seconds
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During the elongation cycle, after peptide-bonds are formed in the ribosome, transfer RNAs translocate to their new binding sites. Combining high-resolution crystal structures, cryo-EM data of multiple translocation intermediates of factorless retro-translocation, and atomistic molecular dynamics simulations, we have analysed collective motions, intrinsic time scales, and overall transition rates of ribosomal motions promoting tRNA translocation. From a Marcus-Theory type transition state analysis of fast molecular fluctuations, unexpectedly fast sub-microsecond intrinsic rates were resolved for body and head rotations as well as swiveling motions. The tRNA transitions between A,P, and E site are seen to be clearly slower than microseconds and seem to determine the overall transition rate between the intermediates. Remarkably, our kinetic analysis recovers the sequence of intermediates proposed in Fischer et al. that was purely based on structural similarity, thereby adding time information to these data. Together with the millisecond dynamics revealed from single molecule studies and the slow dynamics between pre and post states, a Frauenfelder-type hierarchy of time scales and corresponding free energy barriers emerges, underscoring the notion of the ribosome as a stochastic molecular machine.

1267-Plat
Accelerate Sampling in Atomistic Energy Landscapes using Topology-Based Coarse-Grained Models
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Successful simulations of biomolecules require sufficient sampling of the relevant conformational space. This has remained a major challenge due to large conformational space and significant energy barriers, especially with atomistic force fields. Temperature replica exchange (REX) has emerged as a powerful and popular technique for enhanced sampling. Yet, efficiency of temperature REX can be severely limited by the presence of sharp cooperative conformational transitions as well as due to large entropic barriers frequently associated with folding transitions. A coarse-grained representation is often necessary to significantly reduce the conformational space and allows faster sampling of reversible conformational transitions, albeit at the expense of reduced detail and accuracy. Here, we describe a multi-scale enhanced sampling (MSES) method that directly couples topology-based coarse-grained protein models with atomistic ones to accelerate the sampling of complex and rough atomistic energy landscapes. The bias from the coupling potential is completely removed by performing Hamiltonian/temperature REX, allowing one to benefit simultaneously from faster transitions of the coarse-grained model and the accuracy of the atomistic force field. The method has been applied to implicit solvent simulations of several peptides and small proteins including protein GB1, protein A and villin headpiece. The results demonstrate that MSES dramatically increases the number of folding/unfolding transitions sampled and improve the convergence of various thermodynamic properties of interest in all cases. Importantly, this method is simple and fully scalable to larger and more complex systems.

1268-Plat
Analysis of Size and Compositional Distributions of Pleomorphic Ensembles Arising from Clustering of Multivalent Biological Molecules
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Pleomorphic ensembles are aggregates of molecules linked through multivalent low affinity binding sites. Several examples serve to illustrate the diversity and ubiquity of such systems in cells: Nephrin-Nck-NWasp, P-granules, mRNA granules, focal adhesions, postsynaptic density regions and the aggregation of receptor signaling platforms. The classical polymer physical chemistry theory developed by Flory and Stockmayer provides an analytical framework for treating multivalent interactions in systems with up to two types of molecules and binding sites. We describe and validate a numerical algorithm that extends the theory to accommodate systems more often encountered in biology, such as interactions among many types of molecule and binding sites, and involving cooperativity. The algorithm breaks each molecule into its smallest representative unit in order to deterministically predict the probability of bonds, or fraction of molecules in each state. The pairing of molecules is computed stochastically, followed by sorting of the resulting bonds into clusters of connected molecules. This hybrid treatment is more computationally efficient compared to fully stochastic methods. The method can be used to describe kinetic or equilibrium systems. We show that the occurrence of rings (intramolecular interactions) in the largest cluster is a robust numerical predictor for gelation (when the molecules in the system form macroscopic aggregates). We use published experimental data on the nephrin-Nck-NWasp system to illustrate how the method can be used to help characterize the type of interactions between molecules in biological systems of interest. This work was supported by the National Institutes of Health grants TRO1DK087650, R01HL097431, R01GM095485 and P41GM103313.

1269-Plat
Dynamic Re-Discretization Allows Simulation of Biopolymers Across Length-Scales
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The dynamic behavior of polymers like DNA and proteins, such as actin filaments, plays a key role in many cellular functions from gene regulation to cell mobility. A major challenge to gaining better physical insight into the role of these polymers inside a cell lies in accessing all the relevant time and length scales within a simulation. Recent published work by Koslover and Spakowitz has highlighted a new technique that correctly captures the behavior of stretchable, shearable Wormlike chains (ssWLC) across length-scales, allowing simulations that were previously too large or complex to be run much faster on a single machine. We have extended this work to look at the complex nature of polymer-polymer interactions, which are a hallmark of cellular processes. Our first application is on the timescales for DNA looping, and we discuss simulation results that can capture the looping time for DNA segments regardless of the initial discretization of the DNA chain. A second example focuses on the interactions of actin, where our simulation methodology makes it possible to capture the behavior of many interacting polymers in solution. Our work is closely matched to recent experimental results that would have been computationally impossible to simulate previously. These results highlight the power of this technique to address the interactions that play a key role in the dynamic behavior of DNA and proteins within a crowded cellular environment.

Awards and National Lecture

1270-Natl
A Journey Through Cellular Processes: One Molecule at a Time
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Forces and torques play an important role in many biological phenomena, from molecular binding and catalysis to the segregation of chromosomes and muscle contraction. How do forces and torques affect molecular behavior and how do these arise from the interactions between molecules? The answers to these questions have only begun to emerge during the last two decades through the advent and development of methods of single molecule manipulation. With these methods it has been possible to follow in real time the behavior of individual molecules subjected to the effects of force or torque and to measure the forces and torques generated in the course of their reactions. I will survey several systems that we have been studying in our laboratory from the initial characterization, more than two decades ago, of the DNA elasticity both extensional and torsional, to the mechanical unfolding and refolding of proteins and RNA and the study of the inner workings of various complex molecular machines. I will show how our studies have benefited from parallel developments in our understanding of the statistical physics of irreversible processes in microscopic systems and how to use these fundamental results to learn about the energetics of complex molecular processes.