1230-Pos
Integration of Computer Simulation and Neutron Scattering in the Characterization of Protein Dynamics
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Protein function often requires large-scale motion of functionally-important domains. Few techniques are available that can directly probe protein motions. Among the most direct is molecular dynamics simulation in which, using an empirical potential energy function, the equations of motion of a system of atoms are solved numerically. In this way detailed descriptions of protein dynamics can be built up for timescales up to about 100 ns. Integration of molecular dynamics simulations and neutron scattering provide insights of process in the proteins in the atomic details. An exciting new development in the experimental detection of functionally-important domain motions in proteins is the application of neutron spin-echo spectroscopy (NSE). Spin echo directly probes coherent (i.e., pair correlated) scattering on the 10-100 ns timescale. Recent work has demonstrated that domain motions in the tetrameric protein Alcohol Dehydrogenase (yADH) can be positively identified and characterized with this technique. Inspired by these results, we conducted theoretical calculations of the coherent time correlated neutron scattering from all-atomic molecular dynamics simulations data of the same protein. NSE allows the direct measurement of the intermediate scattering function and this way allows the direct comparison between simulation and experiment. The global translational and rotational diffusional components were decomposed and the internal dynamics of these functional domains characterized. The translational, rotational, and the internal effective diffusion constants were determined from the intermediate scattering function and the results compared with the NSE data.

1231-Pos
Pisqrd: A Novel Variational Scheme to Identify Dinamical Domains in Proteins
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A key biophysical problem is how to describe accurately the internal dynamics of proteins in terms of movements of few approximately-rigid subparts. This issue has important implications ranging from the analysis and interpretation of data from experiments or numerical simulations to the design of optimal coarse-graining schemes for multiscale description of the kinetics of interacting biomolecules.
We report on a novel variational clustering scheme that can be used to decompose proteins into rigid moduli (dynamical domains) by using internal dynamics data from atomistic molecular dynamics simulations or coarse-grained elastic network models. The method not only has a physically appealing and transparent formulation, but is also apt for efficient computational implementation.
By applying the decomposition scheme to several biomolecules of high biological interest, such as Adenylate Kinase or HIV-1 protease and other members of the hydrolase superfamily, we demonstrate that the identification of dynamical domains can provide valuable insight into the functionality of proteins and especially enzymes.
The decomposition algorithm is made freely available to the academic community in the form of a web server at the address http://pisqrd.escience-lab.org/.

1232-Pos
Enzyme Millisecond Conformational Dynamics Do Not Catalyze the Chemical Step
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In recent years, the idea that dynamical coupling between the conformational motions and the chemical coordinate in an enzymatic reaction can be a key to understanding enzyme catalysis has attracted major experimental and theoretical interest. However, experimental studies have not to date been able to directly and conclusively establish that the conformational motions do in fact transfer energy to the chemical coordinate, and simulating enzyme catalysis on the relevant timescales has been impractical. Here, we have introduced a renormalization approach, which transfers the energetics and dynamics of the enzyme to an equivalent low-dimensional system, allowing us to simulate the dynamical coupling on a millisecond timescale. The resulting simulations establish (by means of several independent approaches) that the conformational dynamics is not remembered during the chemical step, and thus does not make a significant contribution to catalysis. Nevertheless, understanding the precise nature of this coupling is a question of great importance.

1233-Pos
Jamming Proteins with Slipknots and Their Free Energy Landscape
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Theoretical studies of stretching proteins with slipknots reveal a surprising growth of their lifetimes when a stretching force is increased to an intermediate range.
We explain this behavior as arising from different unfolding routes at small and large forces.
Responsible for longer lifetimes at higher forces is the existence of an intermediate, metastable configuration with the slipknot jammed. Our studies are based on simulations performed within a coarsed grained model and quantified using a refined description of the geometry of the slipknots.
This allows us to determine the free energy landscape (FEL) of the protein, which supports recent analytical predictions.

1234-Pos
A Study Of Unfolding and the Beta Sheet-To-Alpha Helix Conformational Switch in Beta-Lactoglobulin
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The enigma of protein folding stems from the seeming deficit of guidance for the folding process. Of tandem interest is the process of conformational switching from beta sheet to alpha helical structure. Consideration of these two processes brings to mind several questions such as, ''Are the local domains involved in events like hydrophobic collapse also involved in conformational switching? Is the protein largely unfolded during the conformational switch, or is unfolding limited to localized domains? Is the conformational refolding concerted or do domains refold in parallel? Indeed the answers to these questions may be protein-specific. One tried-and-true technique for studying the protein un/re/folding processes is Fourier transform infrared (FTIR) spectroscopy because the amide I band frequency (ca.1600 - 1700 cm^{-1}) tracks secondary structure changes. This study applies FTIR spectroscopy to the unfolding and beta sheet-to-alpha helix refolding of beta-lactoglobulin with analytical focus on the sequence of transitional domains leading to each final state. The appearance of transitional domains is indicated by transient absorption bands. We will examine the transitional bands for each process with the goal of identifying correlated domain changes.

1235-Pos
The Relative Significance of External and Internal Friction in Protein Conformational Changes
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One of the fundamental questions in enzyme reaction mechanisms is how the dynamical properties of the protein and the solvent affect the rate constant of an enzymatic reaction step. This intricate relationship between protein dynamics and enzyme kinetics is most clearly manifested by the temperature and viscosity dependence of the kinetic rate constants. It is, however, not at all obvious how to separate the effect of the internal friction of a protein (resulting from intrachain interactions) from that of external friction (due to the displacement of the solvent molecules) on the rates of conformational changes. By studying the activation of two trypsin mutants at different temperatures and different viscogenic cosolvent concentrations, we demonstrate that the introduction of small changes in the amino acid sequence of a protein (with little effect on the pre- and post-transition structures but allowing the conformational transition to advance along different pathways) can be a valuable tool in determining the magnitude and relevance of internal friction.
In particular, we show that a power law dependence of the rate constants of enzymatic reactions on the solvent viscosity provides the best and physically most sensible description of these processes. The fact that the exponent is strongly affected both by the substitution of a single amino acid and also by a change in the temperature indicates that (i) a considerable and pathway dependent fraction of the energy dissipation takes place internally in the protein; and (ii) the pathway of the reaction can be altered by changing either the amino acid sequence of the protein or the ambient temperature. The exponent can thus be used as a sensitive sensor for detecting pathway changes of conformational transitions.