Platform: Protein Dynamics II

1085-Plat
Atomic Stress Propagation Reveals Allosteric Pathways in Proteins
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Long-range information transfer within proteins, specifically from the substrate binding site to a distant surface site, plays a vital role in regulation of its activity. Understanding this allosteric modulation of protein activity is expected to aid in designing drugs that can achieve high specificity to the target protein. Exactly how the information is transferred from the allosteric site to the substrate-binding site is not well understood. We present a novel computational method based on atomic stresses and molecular dynamics simulation for identifying allosteric sites and the respective pathways. We demonstrate the method here using the PDZ domain. Tracing the path with highest stiffness from the substrate binding site through the protein core revealed a pathway that shows significant overlap with that previously inferred from evolutionarily conserved residues, and other computational methods. The method presented here has an additional advantage of visualizing stress transfer through the protein during a molecular dynamics simulation, which is likely to provide more insight into protein allostery.

1086-Plat
Investigating the Role of Interfacial Residues in Mediating the Interdomain Allosteric of Hsp70
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The heat shock protein 70 (Hsp70) family serves as molecular chaperones that play several critical roles in the cell, such as quality control of protein folding and regulation of intracellular trafficking. The versatile functions of Hsp70 rely on the allosteric interaction between its two domains: nucleotide binding domain (NBD) and substrate binding domain (SBD). They undergo very large conformational changes as the systems performs its functions, going through open/closed conformations of the SBD upon unbinding/bind- ing of a substrate, and coupling/uncoupling of the two domains upon ATP hydrolysis.

Understanding the interdomain allosteric of Hsp70 is key to rational design of inhibitors, yet the mechanism of allosterism remains a challenging problem. The Perturbation Response Scanning, PRS, method provides a graph theoretical approach to investigate the dynamical basis of signal transduction in proteins. This method involves the study of the response of each aminoacid to a perturbation on a given aminoacid of the system. In the present study we build upon our previous examination of the system1 and discuss the application of PRS, via elastic network models, to investigate allosteric interactions between the two domains of Hsp70. Here we analyze the covariance in the movements of different structural elements, to show how the perturbation of the interfacial interactions propagates across the two domains. The analysis sheds light on pathways that dynamically mediate the allosteric communication between the highly conserved or co-evolving sites. An all-atom molecular dynamics simulation shows the differences between the αA and ADP-bound structures of Hsp70, and provides insight into the physical forces that underlie those pathways, thus reconciling the predictions based on network connectivity considerations and the simulations performed with full atomic potentials.


1087-Plat
Investigation on Structure and Dynamics of Heterodimeric SAM:SAM Complexes using Micro-Second Molecular Dynamics Simulations
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The sterile alpha motif (SAM) for protein-protein interactions is encountered in over 200 structures and binding dynamics. But the structure and binding dynamics are just becoming clear. We analyzed the structure and dynamics of the EphA2-SH2P2: SAM heterodimeric complexes using micro-second molecular dynamics simulations. Starting from three different initial configurations that had been suggested by experimental NMR restraints for the complex by our group, several mutants were built to stabilize specific conformations. Compared to the original SAM:SAM complexes, the mutated complexes showed a preference for alternate structures in the simulations. Analyzing the binding behavior of the protein complex, we found that both the mutant residues and the initial structure of the complex can influence the stability of the protein complex. Mutations also frequently cause protein complex separation. During the separating process of two SAM proteins, the contacting surfaces first experienced a conformational change, which led to unfavorable electrostatic interactions between proteins. We are investigating the role of water molecules in the separation process. To our knowledge this is the first time protein-protein dissociation has been simulated extensively at the all-atom level.

1088-Plat
Multi-Resolution Simulation in Biochemistry: Methodological Issues and Exploration of Peptide Folding and the Origins of Differential Catalysis Observed between Two Structurally Similar Enzymes
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Theoretical-computational modelling with an eye to explaining experimental observations in regard to a particular chemical phenomenon or process requires choices concerning essential degrees of freedom and types of interactions and the generation of a Boltzmann ensemble or trajectories of configurations. Dependent on the degree of freedom that are essential to the process of interest, e.g. electronic or nuclear versus atomic, molecular or supra-molecular, quantum or classical-mechanical equations of motion are to be used. In multi-resolution simulation, various levels of resolution, e.g. electronic, atomic, supra-atomic or supra-molecular, are combined in one model. This allows an enhancement of the computational efficiency, while maintaining sufficient detail with respect to particular degrees of freedom. The basic challenges and choices with respect to multi-resolution modelling are reviewed and as illustrations the reversible folding of polypeptides and the differential catalytic properties of two enzymes with similar folds but different substrates with respect to these substrates are explored using multi-resolution simulation at the electronic, atomic and supra-molecular level of resolution.

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1089-Plat
Structural Basis of How Ferric Binding Proteins Utilize pH Differences for Controlled Release of Iron
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Human transferrin (hTF) binds and delivers Fe⁺ to cells; lowered pH within the endosome (5.6) is implicated in the controlled release of bound ions [1]. Although the kinetics of the process is well studied, detailed molecular mechanisms at work are unknown. Bacterial transferrin, also known as ferric binding protein(FBP), is involved in scavenging iron from hTF[2]. These host/pathogen iron uptake proteins are thought to be distantly related through divergent evolution from an anion binding function; FBP displays similarity to one of the iron binding lobes of hTF in structural fold and highly conserved set of iron-coordinating residues.

Perturbation response scanning (PRS) takes advantage of the differences between ligand-bound/unbound conformations to decipher residues having a direct effect on binding mechanisms [3]. PRS on apo and holo forms of FBP implicates D52, a charged residue located ca. 30 Å from the bound ion, as playing a crucial role in ion release. Using pKa calculations [4] we find D52 is the most sensitive to subtle pH variations in the physiological range. The effect of protonation and D52A mutation in both the apo and holo forms was investigated via a series of molecular dynamics simulations. Only in the protonated and D52A holo FBP is an hinge motion triggering opening of the iron binding site observed. Our results lend clues as to how a single residue may be utilized for pH regulation of protein binding modes in iron transport proteins such as FBP and hTF.


1090-Plat
Integrating Genomic Information with Molecular Simulation for Protein Dynamics
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Protein function often requires a protein to form a complex or adopt multiple conformations during its function cycle. Structural characterization of these states is experimentally difficult as they are typically stabilized by transient interactions. Here, we demonstrate how a mixed theory approach can predict such structures on the example of two-component signal transduction systems (TCS), a ubiquitous signal response system. We predicted the TCS complex structure in high agreement (3.5 RMSD) with concurrent experimental work [1] by combining molecular dynamics [2] and statistical genomic analysis [3]. Similarly, we were able to predict the active conformation occurring during