1236-Pos
Solution Structure and Backbone Dynamics of Human Liver Fatty Acid Binding Protein
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Liver Fatty Acid Binding Protein (L-FABP), a small (14 kDa) cytosolic protein most abundant in liver, performs several putative functions, including intracellular transport of fatty acids, nuclear signaling, and regulation of intracellular lipolysis. Among the various members of the intracellular lipid binding protein (iLBP) family, L-FABP is of particular interest, as it can bind more than one FA molecule at the same time and furthermore binds a large variety of other bulkier physiological ligands such as bilirubin and acyl CoA. To better understand these promiscuous binding and transport properties of L-FABP, we have applied multi-dimensional NMR spectroscopy for studies of its structure and backbone dynamics with and without the presence of ligands. The overall conformation of human L-FABP, as determined from NOE-derived distance restraints, shows a very typical b-clam motif comprised of 10 anti-parallel b-strands that are covered by 2 short nearly parallel a-helices. However, backbone dynamics of human L-FABP probed by hydrogen/deuterium exchange and ^{15}N relaxation measurements exhibit a conformational flexibility and backbone mobility that is remarkably different to that of other iLBPs. We hypothesize that the higher conformational flexibility of L-FABP helps to accommodate bulky ligands inside the binding cavity. Moreover, this structure and dynamic information of human L-FABP broadens our current understanding of the iLBP family and helps to explain its diversity and functional differences.

1237-Pos
Dynamic Predispositions of Protein-Protein Docking Orientation Revealed by Intrinsic Dynamic Domains
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Current study suggests that there exists an entropic restraint on protein-protein docking orientations. A physics-based, parameter-free approach has been developed to define intrinsic dynamic domains (IDDs) of proteins. Equilibrium dynamics of unbound protein pairs in 8 'difficult cases' are sampled by Gaussian Network Model (GNM) and dimension-reduced Elastic Network Model (dr-ENM). IDDs are defined for proteins in accord with the slowest motions projected onto reduced dimensions. Domain planes and axes are thereby determined using Linear Discriminant Analysis (LDA) and principal components (PCs) of the position covariance of the unbound partners. The unbound partners are then best-fitted onto themselves in the complexes and the relative orientations of domain axes/planes of the paired proteins are examined. Our results show that proteins dock into each other with clear dynamic preferences in their orientations such that the binding planes of proteins cut through their docking partners, and also the bending axes of the docking pairs tend to be perpendicular to each other, implying proteins in the complexes are dynamically silent in the direction of their docking pairs' vibrant movement. The dynamics-imposed restraints on protein docking orientations/locations shed light on entropic demands for proteins forming into complexes.

1238-Pos
Multiscale Modeling of Intra- and Inter-Molecular Communications Through Protein Structures
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Intra- and inter-molecular communications through protein structures often manifest as changes in the structure or flexibility of protein conformation due to ligand binding and solvent composition. They are also ubiquitous mechanisms by which the biological functions are regulated in the cell. As an attempt to elucidate how the architecture and molecular interactions encoded in protein structures facilitate the functional responses of intra- and inter-molecular communications, we analyze how the binding of a calcium ion affects the structure and flexibility of a serine protease subtilisin in solved and crowded environments. Calcium binding has been shown to play a determining role in the enzyme activity of subtilisin, even though the binding site is distant from the active site. A fluctuation matching method is applied to parameterize the force constants of a coarse-grained elastic network model from long trajectories of all-atom molecular dynamics simulations. This multiscale method allows the quantification of how intra-molecular and inter-molecular interactions in protein structures respond to different configurations of calcium binding and solvation environments. First, we will present the distribution of mechanical interactions throughout the structures of subtilisin. Loop motions that are sensitive to calcium binding and protein-protein interactions in a crowded environment will be described. We will also present the analysis of inter-residue interactions and how they drive the observed changes in protein conformation. Finally, the implications in connecting protein flexibility and enzyme activity will be addressed.

1239-Pos
Multiscale Modeling of Structural Dynamics in Actomyosin Complex
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To decrypt the mechanistic basis of myosin motor function, it is essential to probe the conformational changes in actomyosin with high spatial and temporal resolutions. In a computational effort to meet this challenge, we have performed a multiscale modeling of the allosteric couplings and transition pathway of actomyosin complex by combining coarse-grained modeling of the entire complex with all-atom molecular dynamics simulations of the active site. Our modeling of allosteric couplings at the pre-powerstroke state has pinpointed key actin-activated couplings to distant myosin parts which are critical to force generation and the sequential release of phosphate and ADP. At the post-powerstroke state, we have identified isoform-dependent couplings which underlie the reciprocal coupling between actin binding and nucleotide binding in fast myosin II, and load-dependent ADP release in myosin V. Our modeling of transition pathway during powerstroke has outlined a clear sequence of structural events triggered by actin binding, which lead to subsequent force generation, twisting of central β-sheet and the sequential release of phosphate and ADP. Finally we have performed atomistic simulations of active-site dynamics based on an on-path 'transition-state' myosin conformation, which have revealed significantly weakened coordination of phosphate by switch II, and a disrupted key salt bridge between switch I and switch II. Meanwhile the coordination of MgADP by switch I and P loop is less perturbed. As a result, the phosphate can be released prior to MgADP. This study has shed new lights on the controversy over the structural mechanism of actin-activated phosphate release and force generation in myosin motor.

1240-Pos
Diffusion and Alignment of Domain Repeats in Modular Proteins - A NMR Study
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Translational and rotational diffusion influences protein behavior in signaling cascades as well as other activities that involve protein-protein interactions. For modular proteins it is of interest to evaluate how the domains orient relative to each other within the single polypeptide chain. Often, the disposition of binding sites or motional properties are intimately linked to function and the relative orientation of and flexibility between domains are pivotal properties in that respect.
The present study concerned repeating domains that differ very little in sequence, and therefore allowed us to ask basic questions about the dependence of rotational diffusion and alignment with the magnetic field on linker lengths between the domains. Measuring residual dipolar couplings and relaxation properties by NMR as well as hydrodynamics provided insight into the diffusional behavior of such multi-domain proteins.

1241-Pos
Functional Motions of Immunoglobin Hypervariable Loops
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It is well known that the antibody structure IgG contains a Complimentary Determining Region (CDR) comprised of six hypervariable loops on each antigen binding fragment (Fab). Despite the great success of monoclonals in producing antibodies for a wide range of antigens we still do not fully understand the structure-function relationship between the entire IgG structure and the CDR. Here, we analyze flexibility and mobility in the hypervariable loops and build computational models supporting the hypothesis that the IgG structure has evolved to specifically facilitate coordinated movement of the CDR both in large-scale movements to bring the CDR to the antigen and in rearranging the atomic loop positions to intimately interact with its target. We find that low frequency normal modes predominantly act to move sequence variable regions of Fab domains and that such movements result in changes in mean squared internal distances within those regions; loops within a given variable domain move with respect to each other in the dominant modes. In the case of IgG, B-factors are heavily influenced by molecular interactions with other IgGs in the unit cell resulting in a thick lattice of tightly interconnected molecules. Some effects on functional motions of sequence deletions, insertions, and mutations are investigated.