C-alpha atoms_it is quite remarkable that they correlate so well with data from molecular dynamics simulations and experiment. There are, however, some limitations that can be improved: dependency of force constants, cutoffs, and problems in loop representation. Recent efforts have explored methods of improving the force constants in order to get a better representation of flexibility. Our method is based on deriving networks based on a Delauney tessellation of the protein space in order to represent protein flexibility. This method completely eliminates the need for arbitrary cutoff distances and gives a rational interpretation of forces to apply to the model. At the same time it maintains the small computational expense that characterizes these methods and has made them popular.

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Intrinsic Dynamics of the Regulatory Light Chain: Implications on Muscle Contraction

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The regulatory light chain (RLC) is part of the regulatory domain of myosin II, the most important contractile protein of the muscle. RLC resides in the neck region of myosin, which connects the coiled coil tail with the two globular heads. This region is essential in defining the mechanical properties of myosin. Indeed, it is part of the so-called lever arm, whose motion is the result of the propagation and amplification of conformational changes taking place in the motor domain during the contractile cycle.

Like other sarcomere components, RLC is implicated in the pathogenesis of the hypertrophic cardiomyopathy (HCM). Even if the mechanism of the disease pathogenesis is still unclear, particularly important is the effect of some mutations on RLC phosphorylation levels. The recent discovery of a cardiac-specific association of RLC with the Myosin Binding Protein C (MyBP-C) [1] further enforces the link between RLC and HCM.

Recent studies suggest a possible role of RLC phosphorylation in regulating the stiffness of the myosin lever arm and the propagation of forces through the myosin heavy chain [2]. We performed a preliminary study of the conformational variability of RLC in the regulatory domain by generating a simulated ensemble of structures. Essential Dynamics and Information Theory analyses based on a Structural Alphabet [3] were used to describe the collective motions of RLC and their coupling with the myosin heavy chain. The observed conformational changes were also compared with an ensemble of RLC experimental structures.

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The Structural Basis of Higher Activity of Truncated Cyclin E1-CDK2 Complexes in Tumor Cells

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Hyperactivation of the enzyme, Cyclin Dependent Kinase Type II (CDK2) on binding with low molecular weight isoforms of its activator protein, Cyclin E has been reported in vivo. Such isoforms of Cyclin E are primarily detected in the nucleus of cancer cells. Here, we study the conformational variations of CDK2 complexed with various isoforms of Cyclin E, via Molecular Dynamics simulations. Results show significant energetic and structural changes in various key regions of the complexes including the substrate binding pocket of CDK2-Cyclin interface, Our results correlate very well with the data from experiments. The study could help designing specific inhibitors to target abnormal kinases.

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Molecular Dynamics Study on Conformational Sampling of Triosephosphate Isomerase

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Triosephosphate Isomerase (TIM) is a glycolytic enzyme catalyzing the interconversion of Dihydroxyacetone phosphate (DHAP) to Glyceraldehyde-3-phosphate (GAP). TIM is a non-allosteric dimeric enzyme with three distinct loops (loop-6, 7 & loop-8) enveloping the active site. Loop-6 acts as a lid on the active site and residues from loop-7 and loop-8 stabilize the substrate in the active site. Depending on the orientation of loop-6 and loop-7, TIM can be classified into various conformational states. These different conformations of TIM suggest that for each task i.e. substrate binding, catalysis and product release, the protein adopts to a specific conformation suited for that particular task. Various NMR, X-ray and MM experiments have studied the conformational flexibility of loop-6 in presence or absence of natural substrates, various inhibitors and have suggested that the conformational exchange rate of loop-6 is similar to the catalytic rate of the enzyme (10^4/s). These studies have provided glimpses of individual events of what essentially is a dynamic process. We study the sequence of events from the binding of the ligand to the release of the product by molecular dynamics simulations. Our simulations revealed that loop-6 opens and closes in both apo and holo enzymes at microsecond time scale and also that N-termini (168P-169V-170W) and C-termini (176K-177V-178A) hinges of the loop-6 move independently which was also reported by Berlow et.al [Biochemistry **46** *2007* 6001]. Loop-7 on the other hand samples the closed state only when the active site is occupied by the ligand or an inhibitor. It was also observed that the conformational preference of loop-6 and loop-7 is independent of the conformation of the other.

2295-Pos Board B65

How does Water Boost the Protein Dynamics?

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Protein dynamics is crucial for its function and folding, and depends on various external parameters, among which, hydration is of particular importance. Enzymes lose their bio-activity when they are dry and the so-called dynamical transition, manifesting as an anharmonic onset in the mean squared atomic displacement around 180 ~ 230 K, occurs in proteins only when certain hydration level is achieved. Despite decades of study, the microscopic mechanism for how water boosts the protein dynamics and function is still lacking.

By combining the neutron scattering and molecular dynamics simulation, the present work decomposes the internal motions of lysozyme on the ps to ns time scales into three components: localized diffusion, methyl group rotation and random jumps. In terms of the energy landscape, the first component is ascribed to be intra-well motion, while the other two correspond to transitions among wells, i.e., barrier-crossing events. The analysis reveals that the major change of protein dynamics on these time scales induced by hydration arises mainly from the intra-well motion ''localized diffusion'', manifesting as increase of the diffusion size, via broadening the well. This result is contradictory to the traditional expectation that the hydration-boosted protein internal motions are barrier-crossing events through lowering the transition barriers, and will make a great impact on the future study of protein dynamics and function.

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Dimensionality Estimation of Disordered Protein Dynamics

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Recent studies have clearly demonstrated that proteins are best described in terms of structural ensembles, expanding our perception of the structure-function paradigm, one of the central tenets of molecular biology, beyond the traditional description of the lone native structure. Intrinsically disordered proteins (IDPs) push this emerging view to the extreme, begging the question of how the free-energy landscape of these proteins differs from proteins that fold to a native structure. In particular, the dimensionality of the motion exhibited by folding proteins should slowly decrease as the protein folds to its native structure, while dimensionality should stay relatively high for IDPs due to their persistent flexibility. We have performed molecular dynamics (MD) simulations of several natively folded and intrinsically disordered proteins in implicit and explicit solvent using various forcefields favored for modeling the disordered state. We then utilize dimensionality estimation techniques to analyze the MD simulations in order to probe the differences between the conformational landscape of the IDPs and natively folded proteins.

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Molecular Dynamics Simulations of Conformational Change in EPAC

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Recent work from the Bos group has shown that the exchange protein activated by cAMP (EPAC), binds a single cAMP to allosterically regulate an ionic lock inducing a large conformational change and opening a binding site for the GTPases Rap1 or Rap2. Their x-ray structures of EPAC consist of two large regions with five domains. An ionic lock is defined by R886 and D883 of CDC25-HD and E332, D307 and Q303 of the CNB. When this lock is released the hinge region swings closer to the CNB domain creating a 45-Angstrom shift in the structural region. Mutations in this ionic lock (R886A) in EPAC produce