can be time-ordered according to the DIMS trajectory and this ordering is essentially the same for forward and backward transitions. These results suggest that DIMS is capable of simulating realistic macromolecular transitions. From the simulated trajectories we can present a molecular detailed picture of a macromolecular transition. We discuss the conformational change of AdK with respect to the presence or absence of ligands, the relevance of salt bridges, and the motions of rigid domains.

[1] C. Vonrhein, G. J. Schlauderer, and G. E. Schulz. Movie of the structural changes during a catalytic cycle of nucleoside monophosphate kinases. Structure 3 (1995),483–490.

**363-Pos Board B242**

**Conserved Protein Flexibility And Pathways Of Energy Flow In Enzyme Catalysis**

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Conformational fluctuations in enzymes have significant affect on catalysis. Several enzymes show the presence of a network of coupled motions associated with the catalytic step. Here, we describe our recent studies to identify and characterize coupled motions in members of a diverse family of enzymes namely the dinucleotide binding Rossmann fold proteins (DBRP), sharing a common sub-step of hydride transfer from the dinucleotide cofactor to the substrate.

Results show that in spite of low sequence/structural homology, the overall intrinsic dynamical flexibility during the course of the enzyme reaction is conserved. These dynamical fluctuations span from the exterior surface regions to the active site of the protein and form pathways. These pathways are connected via hydrogen bonds/hydrophobic interactions, which are conserved across prokaryotes and eukaryotes alike.

In order to characterize the energy flow within these pathways, we use an integrated information theoretic and biophysical approach to study how energy may propagate within the DBRP super-family. The studies reveal for the first time how energy is propagated from the exterior flexible surface regions of the protein to the active site of the protein.

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**Accelerated Target Selection By Repair Enzymes Through Charge Transport**

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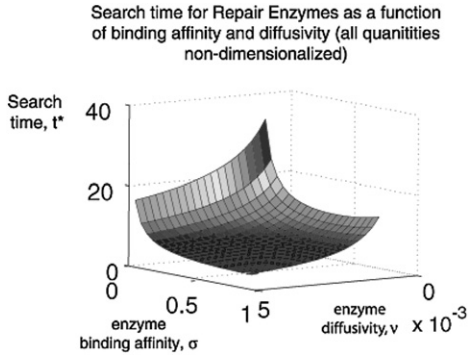
A Charge Transport (CT) mechanism has been proposed in several papers (for example see Yavin *et al.* PNAS **102**, 3546 (2005)) to explain the co-localization of Base Excision Repair (BER) enzymes to lesions (damaged bases) on DNA. The CT mechanism relies on the presence of iron-sulfur clusters on the enzymes; these clusters can undergo redox reactions to modify the enzymes' binding affinity. The redox reactions are mediated by the DNA strand and involve the exchange of electrons between individual BER enzymes. This process effectively increases the desorption rate of enzymes to promote their redistribution and co-localization to lesions.

We study the search times of BER enzymes to lesions by using a mass action model of enzyme dynamics and electron transport. We show that when the enzyme copy number is small, the CT mechanism reduces the search time of otherwise ''passive'' enzymes that simply attach to the DNA without desorbing. Other physical effects in our enzyme model include an explicit treatment of their dynamics in solution, diffusion along the DNA and facilitated adsorption by guanine radicals.




**365-Pos Board B244**

**Reference-Free Identification of Dynamic Structural Domains in Proteins: Comparison of Numeric Predictions with NMR Measurements**

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Understanding proteins' functionalities, which are intimately related with their structural conformations, require a robust characterization of conformational changes which occur in proteins in response to external impacts, as well as spontaneously. This presentation introduces a novel numeric methodology to identify dynamic structural domains in proteins, which is based on the recent theoretic invention [M. Stepanova, Phys. Rev. E76 (2007) 051918]. The methodology employs a fundamental, reference-free approach including identification of essential collective coordinates by the covariance analysis of molecular dynamics trajectories, construction of the Mori projection operator with these collective coordinates, and analysis of the corresponding generalized Langevin equations (GLE). The dynamic domains are identified as groups of atoms that show a dynamic coupling in the GLE. Since the methodology is based on a rigorous theory, the outcomes are physically transparent: the dynamic domains are associated with regions of relative rigidity, whereas off-domain regions are relatively soft. In the presentation, applications of the new structural analysis are demonstrated for the examples of protein G and prion proteins. Experimental NMR-based model-free S2 profiles, random coil indexes, and amplitude correlation data are compared with the numeric analysis, which includes (i) robust systems of dynamic structural domains and (ii) dynamically consistent local flexibility descriptors. It is shown that these numerical results agree well with the available NMR experiments. It is also demonstrated that the dynamic domains and the corresponding flexibility descriptors represent highly sensitive scores for characterization and comparison of proteins' conformations. Even very subtle changes in collective behaviors in macromolecules can be easily detected, visualized, and interpreted. The introduced methodology provides the community with a novel powerful tool for interpretation of NMR experiments, as well as for characterization, comparison, and dynamic analysis of proteins' conformational behaviors.

**366-Pos Board B245**

**Spontaneous Substrate Binding and Formation of the Bound State in Glycerol-3-Phosphate Transporter (GlpT)**

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GlpT is an antiporter mediating the uptake of glycerol-3-phosphate (G3P) across the membrane using preexisting gradient of inorganic phosphate (Pi). GlpT is believed to function through an alternating access mechanism, in which the two functional states inter-convert through rocker-switch type of conformational changes. However, the crystal structure of GlpT is only available in its cytosol-open state. Furthermore, the location of the binding site and residues involved in substrate binding are largely unknown. We have carried out an exhaustive set of long (50 ns or longer) molecular dynamics simulations of GlpT in the presence of all physiologically relevant substrates, i.e., monovalent and divalent Pi and G3P, as well as in the apo state as control. The substrate is placed at the opening of the lumen in the beginning of each simulation. In all of the simulations, we observe rapid, spontaneous binding of the substrate in less than 10 ns. All trajectories consistently yield a common binding pathway, composed of several conserved residues: K80 acting as a ''fishing hook'', one of the symmetrically positioned arginines (R45), and H165. The phosphate moiety of the substrate first binds to K80, which brings the substrate to a close contact with R45 and H165. Despite its symmetrical position to R45, no direct contact with conserved R269 is observed in any of the simulations. Neutralizing any one of the above residues impairs binding as revealed by additional simulations. Moreover, substrate binding results in appreciable closure of the helices in the cytoplasmic side illuminating initial steps of the rocker-switch mechanism. Our MD simulations reveal a common pathway involved in binding of the substrate, a detailed view of the binding site, and initial protein conformational changes induced by substrate binding.

**367-Pos Board B246**

**Single Molecule Fret Reveals Novel Dynamic Structure And Stoichiometry Of L27 Domain-mediated Polarity Complexes Formed By Drosophila Sdt/DPatj/DLin-7**

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Cellular differentiation is frequently regulated by multi-protein complexes where the spatial proximity of the components facilitates biological function. There is immense interest in isolating the individual components involved as