electron donating properties that would optimize photoinduced electron transfer (PET) from the ligand to the protein and prompt charge-induced conformational changes.
Our study focuses on the interaction of four 3,9-substituted perylenes with Human Serum Albumin (HSA), which is the prime protein model for the binding of PAH. We present docking simulation results for possible sites for the perylenes within HSA with the lowest free energy of binding and correlate the docking simulations with fluorescence result. Docking simulations reveal that all the peylen derivatives bind at the core of HSA and that the dimethoxy derivative has larger affinity than the other perylenes. Docking seems to be stabilized by aromatic interactions with Tyr and Trp groups.

**313-Pos Board B99**
**Calmodulin Conformational Binding Entropy Is Driven by Transient Salt Bridges**
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Calmodulin (CaM) is a calcium-binding protein that mediates signal transduction through an ability to differentially bind to highly variable binding sequences in target proteins. Experimental measurements show a linear correlation between conformational entropy and overall binding entropy, suggesting that a predictive ability to calculate conformational entropy is critical to the identification of binding partners and their relative affinities. To identify how binding affects low- and high-frequency motions, and their relationships to conformational entropy, we have employed fully atomistic molecular dynamics simulations with explicit solvent. The calculated quasiharmonic entropies of CaM bound to the targets relative to unbound CaM are in agreement with experimentally derived conformational entropies, where extrapolation to infinite simulation time showed that at least 92% of the backbone entropy is captured over the course of the 100 ns simulation. Enhanced side chain entropy results from conformational disruption of the protein backbone within loop regions between sub-domain elements, acting to facilitate the formation of transient salt bridges between Lys148 at the C-terminus and GLU sidechains both in CaM helix A and GLU side-chains present in selected binding sequences (i.e., endothelial and neuronal nitric oxide synthases). Comparison of Cα root-mean-squared fluctuations and MET sidechain dihedral distributions of CaM bound to each of the targets revealed that MET sidechains have more torsional freedom when the backbone is more flexible, showing that MET sidechain rotation mirrors the overall conformational binding entropy. Taken together, these results help to illuminate the interplay between electrostatic, hydrophobic, backbone and sidechain properties in the ability of CaM to recognize and discriminate against targets by tuning its conformational entropy.

**314-Pos Board B100**
**Substrate Binding in Lactate Dehydrogenase: A Story Told by Conformational Sampling and Energy Landscape Analysis**
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Lactate Dehydrogenase (LDH) catalyzes the interconversion of pyruvate and lactate with concomitant interconversion of NADH and NAD+. Due to the widespread presence in a variety of organisms, LDH has been served as a general model for studying the catalytic mechanism of enzymes. Extensive IR spectroscopic studies by Callender et al. have revealed complex conformational sub-states for different substrate binding to LDH in mesophilic and thermophilic organisms. To facilitate the elucidation of the underling mechanism of LDH enzyme reaction, molecular dynamics simulation approaches were applied to study the conformational dynamics of mesophilic LDH in complex with substrate or its mimics. The functionally important motions were characterized by conformational sampling. To determine the relationship between protein stability, flexibility, and catalytic activity, thermophilic LDH enzyme will be further investigated. The energy landscape within the Michaelis complex will be explored. The computational study in connection with the experimental findings will shed new light on the mechanism of enzyme dynamics and function.

**315-Pos Board B101**
**Understanding Allosteric Inhibition in Ligand AG6 Bound to NS5B using Molecular Dynamic Simulations**
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Abstract: Hepatitis C Virus (HCV) is a major health concern; the virus infects 270-300 million people worldwide. The large number of people infected has spurred efforts to identify small molecules that may be effective in treating HCV infection. One of the targeted viral enzymes in these efforts is the viral RNA Dependent RNA polymerase (NS5B) that plays a vital role in replicating the HCV genome. Several allosteric inhibitors are known to bind to NS5B in the thumb, fingers and palm domains of the enzyme. Our goal is to understand the mechanism of allosteric inhibition in NS5B using molecular dynamic simulations. We are particularly interested in ligand AG6 that has been shown to bind to the fingers domain. Relatively few allosteric inhibitors are known to bind to this region of the protein. Studying allosteric inhibiton involving this uncommon binding site has led to new insights into the mechanisms of allostery in NS5B. Moreover, crystallographic data indicate that NS5B can bind simultaneously to AG6 and another allosteric inhibitor in the thumb domain. This has given us an opportunity to learn what mechanisms underlie synergistic binding of multiple allosteric inhibitors to the enzyme. We used molecular dynamic simulations to understand how changes in the free energy landscape of NS5B mediate the allosteric effects of inhibitor binding.

**316-Pos Board B102**
**Computational and Experimental Analysis of the Interactions Between C3 and Compstatin Family Peptides**
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We present the physicochemical basis of binding for several active peptides from the compstatin family against the immune system protein C3. The peptide sequences are tailored to promote enhancement of the structural and physicochemical properties that contribute to binding, including consideration of the dynamic character of the protein/ligand system. The peptide sequences are designed using: (i) computational sequence selection and approximate binding affinity calculations, (ii) molecular dynamics simulations, and (iii) rational optimization [1–3]. A subset of the new peptides has been tested in ELISA inhibition assays using human serum, and produced comparable IC50 values to those of known peptides. The most promising new designs acquire an advantage in that they combine a more optimal balance between hydrophobicity, which is important for binding, and polarity, which is important for solubility, compared to the most potent known peptides. Thus, the new peptides are good candidates to become therapeutics, upon further optimization. Given the species specificity of known compstatin family peptides for primate but not for non-primate mammals, some of the new designs aim at binding to both human and rat C3. The dual specificity design was conducted using molecular dynamics simulations based on our recent atomic detail model for compstatin-human/rat binding [3]; however, the efficacy of the new peptides for rat C3 binding and inhibition remains to be seen in experimental assays using rat serum.
[1] Bellows et al. 2010. New compstatin variants through two de novo protein design frameworks, Biophysical Journal 98:2337–2346.
[2] López de Victoria et al. 2011. A new generation of potent complement inhibitors of the compstatin family, Chemical Biology & Drug Design 77:431–440.
[3] Tamamis et al. 2010. Species specificity of the complement inhibitor compstatin investigated by all-atom molecular dynamics simulations, Proteins 78:2655–2667.

**317-Pos Board B103**
**Crossing the Entropic Barrier to Coupled Folding and Binding**
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Intrinsically disordered proteins (IDPs) function in many important cellular pathways, and their disruption contributes to many human diseases. IDPs display minimal if any secondary or tertiary structure in their unbound forms, but will often fold into ordered structures upon binding. It is believed that the coupling of folding and binding is important in balancing the affinity and specificity of the interaction due to the reduction in conformational entropy of the residues at the binding interface. Potential mechanisms include induced folding and conformational selection, which are not mutually exclusive and the predominant method utilized may be biased by the entropic barrier in coupled folding and binding. A model system using the transactivation domain of the tumor suppressor p53 (p53TAD) and its binding partners, the ubiquitin ligases MDM2 and its homologue MDMX, was designed. p53TAD is an IDP that folds when binding with MDM2/X. The conformational entropy of p53TAD is systematically varied using mutagenesis and these mutations result in significant and predictable changes in the binding affinity. This is the first attempt to quantify how