arising from the central hydrophobic core, and precipitated by the residues belonging to the N-terminal region. Adaptive biasing force based potential of mean force (PMF) calculations estimating the free energy changes as the peptide strands collapse towards each other demonstrate that the SWCNT causes the 'open' and the 'collapsed' states to be in near equilibrium, by bringing down the energetic cost of 'loop opening'. The observed phenomena of peptide localization and decreased propensity for loop collapse could have important implications for site-directed drug delivery and for altering the kinetics of the peptide's self assembly.

3716-Pos Board B577

Multiscale Simulation of Polyglutamine and the Effect of Neighboring Amino Acids on Oligomerization

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Several proteins possess a segment of amino acids composed of successive glutamines. In many, this segment affects the native folding when expanded above 35 to 40 glutamines. Such effect is associated to neurodegenerative diseases such as Huntington's in which the huntingtin protein misfold. As the huntingtin protein has over 3000 amino acids, it is easier to focus on the glutamine sequence alone as well as part of the neighboring amino acids to this segment. Several experiments characterized the folding of polyglutamine with various amino acid lengths, yielding sometimes contradictory structural and dynamical information. It is safe to say that, at the moment, the early oligomerization is still not clearly understood at an atomic level. To address this question, we present molecular dynamical simulations on various polyglutamine segments from 30 to 40 glutamines with and without neighboring amino acids to assess their importance on folding and fold stability. To reach relevant time-scales, we combine simulations using a coarse-grained model as well an all-atom model with explicit solvent.

3717-Pos Board B578

Monitoring the Mechanism of Fiber Assembly of AB Peptides in Alzheimer's Disease (AD) by Two-Dimensional Ultraviolet (2DUV) Spectroscopy

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Understanding the aggregation mechanism of amyloid fibrils is a critical step in the investigation of several neurodegenerative disorders associated with the misfolding of proteins. In a previous study (Rojas *et al.*, JMB 2010 404, 537–552), the growth mechanism of β-amyloid peptide fibrils which is associated with Alzheimer's disease (AD), was successfully modeled by using a physics-based coarse-grained united-residue model and molecular dynamics (MD) simulations. We report a simulation study of coherent two-dimensional chiral signals based on the trajectories obtained by Rojas *et al*. to monitor this growth mechanism at different simulation times. Far ultraviolet signals (FUV)(λ = 190–250 nm) originated from the backbone $n\pi^*$ and $\pi\pi^*$ transitions, and near ultraviolet signals (NUV) ($\lambda >= 250$ nm) are associated with aromatic side-chains (Phe and Tyr). These signals display distinct cross peak patterns in the two-dimensional spectra that can be used, in combination with MD, to monitor local dynamics and conformational changes in the secondary structure of Aβ peptides during the aggregation process. 2DUV total chiral signals in the aggregation process are combinations of subset of chiral signals from a monomer Aβ peptide, an amyloid fibril and the interactions between them.

3718-Pos Board B579

Conformational Transition Pathways of Adenylate Kinase Explored by the String Method

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Large-scale conformational changes in proteins involve barrier-crossing transitions on the complex free energy surfaces of high-dimensional space. Here we show that, by combining the on-the-fly string method and the multi-state Bennett acceptance ratio (MBAR) method, the free energy profile of a conformational transition pathway in Escherichia coli adenylate kinase can be accurately determined. The minimum free energy paths (MFEPs) of adenylate kinase were searched by the on-the-fly string method in 20-dimensional space spanned by the 20 largest-amplitude principal modes, and the free energy and various kinds of average physical quantities along the MFEPs were successfully evaluated by the MBAR method. The influence of ligand binding on the MFEPs was characterized in terms of rigid-body motions of the LID and AMPbd domains. It was found that the LID domain was able to partially close without the ligand, while the closure of the AMPbd domain required the ligand binding. The transition state ensemble of the ligand bound form was identified as those structures characterized by highly specific binding of the ligand to the AMPbd domain, and was validated by unrestrained MD simulations. It was also found that complete closure of the LID domain required the dehydration of solvents around the P-loop. These findings suggest that the interplay of the two different types of domain motion is an feature in the conformational transition of the enzyme.

3719-Pos Board B580

Conventional and Accelerated Molecular Dynamics Simulations of *Staphylococcus Aureus* Sortase A

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The targeting of surface proteins to the cell wall, necessary for the full virulence of Gram positive bacteria, can be traced back to the actions of sortase enzymes. These enzymes recognize a specific sorting sequence in proteins destined to be displayed on the surface of the bacteria, and catalyze the transpeptidation reaction that results in the attachment of the protein to a cell wall precursor molecule. With the rise of antibiotic resistant strains of bacteria, sortase enzymes are promising new drug targets. Specifically, in light of the growing emergence of methicillin resistant *Staphylococcus aureus* (MRSA), we are looking at *Staphylococcus aureus* Sortase A (SrtA). SrtA cleaves proteins at the LPXTG sorting signal and attaches them to lipid II. Here, we have used both conventional and accelerated molecular dynamics simulations to simulate the enzyme in its apo and holo (bound to the LPATG sorting signal) states. Results reveal the importance of loop motions of which are situated proximal to the active site, specifically the β6/β7 and β7/β8 loops, and suggest dual functionality of the catalytic arginine residue. Additionally, in a subset of the holo simulations we observe movement of the sorting signal away from the active site to distinct metastable states and find that motions of the enzyme in the accelerated molecular dynamics simulations suggest an induced fit binding mechanism. These results improve our understanding of the functioning of SrtA and will ultimately aid in the development of new drugs to combat MRSA infections.

3720-Pos Board B581

Classical Force Field Development and Molecular Dynamics of [Nife] Hydrogenase

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An understanding of the force-field parameters necessary to describe metal clusters in [Ni-Fe]-hydrogenase enzymes currently limits an ability to use classical molecular dynamics (MD) simulations to understand how changes in the coordination geometry around the metal centers promote catalysis. Using density functional theory (DFT), we have developed force-field parameters for three catalytic states of the [Ni-Fe] active site as well as the reduced and oxidized states of the three Fe/S clusters. Calculations were made using small model clusters that approximate the protein environment, respectively replacing cysteinate and histidine coordinating side-chains with thiolates and imidazole. Parameters were tested using 25 ns MD simulations of gas-phase model clusters and classical harmonic frequency analysis. Matching of DFT and MD normal modes verified that the derived force field parameters reproduce the DFT modes and frequencies, even the low-frequency torsion modes that couple with protein backbone motion. The utility of the determined force-field parameters was further established in situ using explicit-solvent, all-atom, 25 ns MD simulations of [Ni-Fe] hydrogenase in three catalytic states (Ni-A, Ni-B, and Ni-C). These results establish the utility of the derived force-field parameters, and provide the basis for testing current models that suggest changes in the coordination geometry of the active site metals promotes catalysis.

3721-Pos Board B582

Nano-Scale Mechanics of Nacre: Forces at Protein-Crystal Linkages and Flaws

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The major constituent of nacre, calcium carbonate (CaCO3) in form of aragonite, is intricately embedded into a soft matrix of protein and chitin, resulting in a highly mechanically robust hierarchical structure. (1) A novel forcefield for aragonite has been developed in this study, which well captures the shear and elastic moduli of the aragonite. Most importantly, the new set of parameters features a calcium ion charge of +1.668, reflecting the partial charge transfer effect in condensed matter. The newly developed CaCO3-water interaction parameters also yield accurate descriptions of water coordination. (2) Our