1530-Pos Board B374
Simulations of a Molecular Motor: Influence of Leg Number and Substrate Dimensionality on the "Molecular Spider"
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While many molecular motors such as kinesins and myosins take advantage of power strokes to produce meaningful work, others, such as collagenase, use substrate cleavage to rectify diffusive motion. A recent experimental report of a synthetic molecular machine, dubbed a ''molecular spider'', suggests that this cleavage-biasing mechanism may be a useful principle in motor design. In this work, we characterize the operational principles of such a machine by simulating model systems using both Monte Carlo (MC) and Langevin Dynamics (LD). In the MC simulations, the molecular spider is modeled by a ''point enzyme'' which can jump diffusively between neighbouring sites on a square lattice. Each lattice site represents the substrate to be cleaved and can be in one of two states: cleaved or uncleaved. Binding, unbinding and substrate cleavage by the enzyme are controlled by rate constants. The LD simulations are used to examine more complex motors such as spiders with multiple polymer ''legs'' with catalytic feet, but with binding and cleavage mechanisms similar to those used in the MC simulations. We focus on the following central issues: (a) the dimensionality of the substrate; (b) the number of heads that can engage the substrate; (c) the relative rates of substrate binding, cleavage, release and motor diffusion; and (d) the effect of a load on the dynamics of the spiders.

1531-Pos Board B375
Assessing the Driving Forces for Collapse of Archetypal Intrinsically Disordered Polypeptides
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Intrinsically disordered proteins (IDPs) are a class of proteins that do not adopt well defined structures in aqueous solutions. IDP sequences have low hydrophobicity and recent work has shown that polar tracts, which are archetypal IDPs, adopt collapsed conformations in aqueous solutions. Furthermore, polyglycine peptides, which are mimics of polypeptide backbones, also behave like chains in a poor solvent in water. Here, we ask why this should be true.
We modulated the strengths of dispersive and electrostatic chain-chain and chain-solvent interactions in a series of molecular simulations. In neat water and 8 M urea hydrophobic chains collapse to minimize the solute-solvent interface. Addition of dispersion interactions causes an accumulation of solvent around globules, with preferential solvation and enrichment of urea around the globule in 8 M urea. Accumulated solvent penetrates into the globule with increasing electrostatic interaction strength. While solvent penetration in neat water causes the formation of internally wet globules, there is a departure from globules in 8 M urea. We calculated the potential of mean force between short polyglycine chains in neat water and 8 M urea, and observed that the association between chains in water is always more favorable than in 8 M urea. Furthermore, chain electrostatic interactions in 8 M urea diminished preference for chain-chain association almost entirely. We conclude that the preference for collapsed states is encoded by driving forces which originate in the canonical hydrophobic effect. This preference is maintained in neat water because specific interactions between chain units are stronger in neat water than the effective interactions between chain units and solvent.

1532-Pos Board B376
Assessment of the Molecular Determinants Required for Dimerization of the Amyloid Precursor Protein Transmembrane Domain by a Combined Experimental and Computational Approach
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Removal of the ectodomain of the amyloid precursor protein (APP) by beta-secretase yields a carboxyl-terminal fragment (betaCTF) that is then degraded by the gamma-secretase to produce the neuropathogenic amyloid beta peptides (Abetas) involved in Alzheimer's disease (AD). Considerable evidence indicates that betaCTF is a transmembrane domain-mediated dimer and that dimer dissociation reduces the Abeta42/40 ratio, thus lowering the risk of AD. Little is known about the structural and thermodynamic features of betaCTF dimerization. Employing both coarse-grained and all-atom models coupled to metadynamics, we studied the free energy of dimerization of betaCTF transmembrane domain in an explicit dipalmitoyl phosphatidyl choline (DPPC) membrane bilayer. We show that the dimeric state consists of several stable configurations, featuring interfaces at different locations in the betaCTF transmembrane helix. The effect that point mutations along the transmembrane helix have on the stability of the dimer is assessed computationally and compared to experimental data. This information sets the stage to identify interface-derived small peptides as lead structures to guide the development of novel peptidomimetics that specifically target betaCTF dimerization and display therapeutic potential in AD.

1533-Pos Board B377
Computational Model to Predict Folding Stability of FKBP
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The folded structure of a protein is stabilized by a variety of interactions including hydrophobic and electrostatic interactions. A computational method to predict the effects of mutations on folding stability of FKBP is presented here, and the predictions are compared with experimental data from our lab. The method improves upon our previous studies [1-3] and incorporates conformational sampling, generated by a molecular dynamic simulation of the wild-type protein, in the calculations. We apply a clustering method to remove apparent outliers in the sampled conformations, thereby increasing the robustness of the calculation results. For 16 point mutations involving charged or polar side chains, the root-mean-squared deviation between electrostatics-only prediction and experiment is 0.9 kcal/mol. Further improvement is sought by including contributions of van der Waals and hydrophobic interactions. Our combined computational and experimental study will provide insight on the physical basis of protein folding stability.
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1534-Pos Board B378
Molecular Dynamic Simulation of Dihydrofolate Reductase Unfolding Pathways
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Dihydrofolate reductase (DHFR; 5,6,7,8-tetrahydrofolate:NADPC oxidoreductase, EC 1.5.1.3) catalyzes the reduction of 7,8-dihydrofolate (DHF) to 5,6,7,8-tetrahydrofolate (THF) by hydride transferring from the NADPH cofactor. DHFR plays a central role in cell growth and proliferation because it is the sole means of production of THF that is essential for purine and thymidylate synthesis.
We present here using the molecular dynamic (MD) simulation to study the unfolding mechanism of DHFR and its Circular Permutation (CP) in mitochondrial import (one way pulling) and AFM (two way pulling). We found that in the equilibration stage, DHFR, DHFR-CP25P, and DHFR-CP38K fluctuated for about 4 Å, and this lacking of mechanically stable structure could be the reason for different AFM experimental results observed in previous studies. In both one way pulling and two way pulling simulations, DHFRs form core structures that stabilize the protein from further denaturation. The formation of core structure gives us information about the ''stiffness'' of the secondary structures. We showed that the factors that affect one way pulling is not only the secondary structure adjacent to pulling point as proposed before, but a more complex composition of interaction between secondary structures. The force required for AFM denaturation covers a wide range for all DHFRs and we see different pathways with different core intermediates. Also, the binding of substrate/coenzyme stabilizes DHFR against both AFM pulling, and mitochondrial import.

1535-Pos Board B379
Predicting Protein Mutant Stability With A Combined Experimental/ theoretical Approach
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A complete understanding of the relationships between protein structure, stability and dynamics remains an open biophysics problem. Much of our insight comes from laborious experimental analyses that perturb structure via directed mutation. The glycolytic enzyme lysozyme is among the most well characterized proteins under this paradigm, due to its abundance and ease of manipulation. To speed up such analysis, efficient computational models that can accurately predict mutation effects are needed. We employ a minimal Distance Constraint Model (mDCM)[1] to predict the stability of mutant lysozyme structures. The mDCM has 3 fitting parameters: v_{dha} and δ_{nat}, respectively, describe the energy and entropy of native-like residue conformations, whereas

u_{sol} describes the energy of H-bonds to solvent. These three model parameters are obtained by fitting to experimental C_p curves. Best fits on 19 different lysozyme mutants under the same thermodynamic conditions (pH, ionic strength, etc.) reveals that u_{sol} can be treated as constant. Moreover, u_{sol} can be robustly parameterized with as few as five experimental mutants (the standard error of 100 random quintets is $<12\%$). It was observed that a second degree of freedom could be removed due to a linear relationship (R=0.86) between the remaining two parameters (δ_{nat} and v_{dha}) indicating that a global balance in enthalpy-entropy compensation must be maintained. Consequently, over a fairly wide range of δ_{nat} values {0.4, 1.6}, the correlation between the experimental and theoretical T_m's is nearly constant (ranging from 0.68 to 0.72). Using the best parameter set, T_m can be predicted for new lysozyme mutants. Results on a validation set of an additional 81 lysozyme point mutations will be presented. This work is supported by NIH R01 GM073082.

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1536-Pos Board B380

Computational Studies of Nucleosome and Chromatin Folding

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Understanding the packaging of nucleosomes on DNA, including how various proteins interact with DNA, is important for understanding the dynamics of the cell. With this goal in mind, we have developed a shape-based model to map histone-DNA recognition quantitatively in terms of atomic contacts and DNA deformability. This method reduces the complexity of nucleosome structure from 3D visualization to a 2D mapping. Comparison of 32 available nucleosome crystal structures with this approach shows promise in deciphering the sequence-dependent binding mechanism of nucleosomes on DNA. We have also developed a novel Monte-Carlo method, involving multi-scale dinucleotide and dinucleosome modeling, to simulate the communication of proteins over long stretches of chromatin-compacted DNA. We compare our predictions of chromatin looping with recent experimental measurements of enhancer-promoter interactions, focusing on (i) the role of the histone tails in enhancing chromatin looping and (ii) the internal folding structures of chromatin under different ionic conditions.

1537-Pos Board B381

In Silico Examination Of The Influence Of Nucleotide Modifications And Magnesium Ions On tRNA Structure And Dynamics

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In our work the influence of chemical modificatons and ions on RNA structure and dynamics has been tested. The effect of nucleotide modifications on E. coli and yeast tRNA in solution has been examined with a molecular dynamics approach. Simulations show a decrease of helical content in RNA secondary structure due to those modifications. In another step magnesium ion binding effects on the same tRNA were looked at by performing simulations with and without ions bound to tRNA. Ions coordinating nucleotides in those simulations show them highly affecting local secondary structure motifs. Thus the simulations performed give new hints on the function of nulceotide modifications and ion binding to RNA.

1538-Pos Board B382

Estimating Orientational Entropies At Protein Interfaces

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Entropy effects of the surrounding water layer at the protein interface have been studied for a long time, and their relevance e.g. for protein folding is well recognized. In molecular dynamics simulations entropy estimates for surrounding explicit water molecules are difficult to calculate with established methods such as thermodynamic integration. Here we present a new method to calculate the orientational contribution to the solvent entropy near the protein interface. We exploit the permutation symmetry of the Hamiltonian such that we get trajectories of ''localized'' water molecules. Orientational correlations are unaffected by this transformation, which therefore enables us to obtain spatially resolved entropy estimates for the protein water shell.

1539-Pos Board B383

Hydration Dynamics As Revealed By The Fluorescence Stokes Shift: The Origin Of Slow Hydration Dynamics And Breakdown Of Linear Response

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Hydration dynamics in the immediate vicinity of a protein, probed by time-dependent fluorescence Stokes shift experiments, is critical to understand its biological function. Protein Stokes shifts typically exhibit biphasic relaxation following photo-excitation: fast relaxation occurs on a time scale of several picoseconds while slower components indicate additional hydration dynamics on a time scale of tens of picoseconds, or longer. Theoretical studies using both linear response and non-equilibrium molecular dynamics (MD) calculation qualitatively reproduce the observed biphasic behavior of time dependent Stokes shift for Trp-7 (W7) in myoglobin. Comparison with constrained MD simulations with protein frozen at the instant of photo-excitation reveals the molecular mechanism of slow hydration process and establishes the critical role of protein flexibility. Coupled protein-water motion is shown to be necessary for the observation of the slow component of hydration dynamics. Qualitatively similar results are found for a series of additional cases, such as monellin and staph. nuclease. We illustrate why tracking the separate contributions to the Stokes shift without constrained MD studies may not yield an accurate interpretation of protein hydration dynamics. Additionally, we examine the extent to which protein fluctuations obey Gaussian statistics and the linear response approximation to the Stokes shift is valid. Equilibrium fluctuations of the ground-excited energy difference, which control the absorption and fluorescence line shapes, in the ground and excited electronic states are not independent of each other. We illustrate how small differences from Gaussian statistics in one electronic state can be a signature of very significant deviations from linear response theory, such as isomerization, in the other electronic state.

1540-Pos Board B384

Effect of Temperature on the Structural and Hydrational Properties of Human Islet Amyloid Polypeptide in Water

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Structural and hydrational properties of full-length human islet amyloid polypeptide 1-37 (hIAPP) were studied in relation to the hydration water properties in a temperature range from 250 to 450 K by MD computer simulations. At all temperatures studied, hIAPP does not adopt a well-defined conformation. The alpha-helical content and the number of intrapeptide H-bonds of hIAPP decrease with temperature. The distribution of residues showing dihedral angles characteristic of beta-sheets and poly(L-proline) II helices along the peptide chain is close to random, whereas a clear trend towards cooperative ''condensation'' is seen for residues showing alpha-helical dihedral angles. This cooperativity is suppressed by heating or by introducing the native intramolecular disulfide bond. Intrinsic volumetric properties of hIAPP were estimated by taking into account the difference in the volumetric properties of hydration and bulk water. The temperature dependence of the density of hydration water indicates that the effective hydrophobicity of the hIAPP surface is close to that of carbon-like surfaces. Similarly to the case of the Aβ(1-42) peptide, the thermal expansion coefficient of hIAPP is negative: upon heating, it continuously decreases from $\sim -3\cdot10^{-4}$ to $\sim -2\cdot10^{-3}$ K^{-1}. A spanning H-bonded network of hydration water, which covers hIAPP homogeneously at low temperatures, breaks via a quasi-2D percolation transition, whose midpoint is at about 320 K. Approximately at this temperature, the experimentally measured lag time of hIAPP aggregation drops in a drastic way. We discuss the possible role of the temperature-induced percolation transition of hydration water on the conformational changes and aggregation propensity of amyloidogenic peptides.

1541-Pos Board B385

A Modified Primary Hydration Shell (PHS) Method Allows Up To Two Orders Of Magnitude Time Saving In Molecular Dynamics Simulations: Application To Large Systems And Lipid Bilayers

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A realistic representation of water molecules is essential in molecular dynamics simulation of proteins. However, the standard method of solvating biomolecules, i.e. immersing them in a box of water with periodic boundary conditions, is computationally very expensive. The primary hydration shell (PHS) method, developed more than a decade ago [1], uses only a thin shell of water around the system of interest, and so greatly reduces the computational power needed for simulations [2]. The method, however, was not perfect especially when large proteins are concerned. We have modified the PHS method in several ways to improve its performance when large systems are simulated [3]. The model is applied to several systems with different sizes, and both water and protein behaviors are compared with those obtained from standard simulations with periodic boundary conditions and with experimental data. Specifically, Lipari-Szabo order parameters for the proteins of interest are shown to be in good agreement with those derived from standard simulations and NMR relaxation