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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[2] Dong, F. and H.-X. Zhou (2002) Electrostatic contributions to T4 lysozyme stability: solvent-exposed charges versus semi-buried salt bridges. *Biophys. J.* **83**: 1341-1347.
[3] Zhou, H.-X. (2002) A Gaussian-chain model for treating residual charge-charge interactions in the unfolded state of proteins. *Proc. Natl. Acad. Sci. USA* **99**: 3569-3574.

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