2041-Pos Board B60
Small Protein Folding using Weighted Ensemble Simulation: A Case Study of Trp-Cage
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The 20-residue protein Trp-cage is a rapidly folding protein ideal for testing different strategies in folding simulations. The system was studied via the weighted ensemble (WE) approach where trajectories evolved according to Langevin dynamics in implicit solvent. In the WE method [Huber and Kim, Biophys. J., 1996], the configuration space is divided into arbitrary regions called bins. Trajectories arriving to new bins are replicated into identical daughter trajectories that inherit the history and a corresponding fraction of the parent’s weight. In general, WE is a parallel method that forces a system to explore timescales and regions of configuration space typically inaccessible in regular simulations. Unbiased estimates of rates and other properties are produced. Appropriate selection of bins remains a challenging aspect of WE, however, especially in non-trivial systems such as proteins. For Trpcage, different binning strategies are explored using 1D and 2D binning coordinates with the goal of improving efficiency. Rate constants calculated in both the high and low friction regimes are compared with independent estimates.

2042-Pos Board B61
Quantifying the Drive-Response Relationships between Residues in Protein Folding
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In protein folding processes, mutual correlation and cooperativity are commonly used to describe the interactions between different residues in a protein. However, these metrics do not provide any information on the causality relationships between these residues. The drive-response relationships in protein folding processes are still poorly studied and, due to technical limitations, are difficult to measure experimentally. The information theory transfer entropy (TE) provides a direct measurement of causality between two times series. We have used this method to quantify the causality between residues in the folding process of a rapidly folding protein generated from molecular dynamics simulations for six small proteins, i.e., Trp-cage, BBA, Villin, WW domain, NTL9 and BBL (Lindorff-Larsen K. et al. 2011). Instead of using one single TE value, we calculated the time-dependent TE using the residue-based Q-scores along the folding/unfolding processes. Preliminary analysis reveals that the residues in the hydrophobic cores are frequently involved in drive-response relationships, indicating the critical roles of these residues. The time-dependent TE also allows us to identify key events during the folding and evaluate the contributions from non-native contacts. We expect further studies may disclose more details on the causality relationships of the residues and the folding mechanisms of these proteins.

2043-Pos Board B62
Deciphering the Protein Folding Code through Zipping Steps
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Earlier experiments suggest that the evolutionary information (conservation of amino acids and coevolution between amino acids) encoded in protein sequences is necessary and sufficient to specify the fold of a protein family. However, there is no computational work to quantify the effect of such evolutionary information on the folding process. Here we simulate a repertoire of native and artificial WW domain sequences using a physics-based protein structure search method called ZAM (Zipping and Assembly method), which samples conformational space effectively towards native-like conformations through zipping and assembly search mechanism. We explore the sequence-structure relationship for WW domains and find that the coevolution information has a remarkable influence on local contacts of N-terminal β-turn of WW domains. This turn would not form correctly in the absence of such information. Moreover, through maximum likelihood approach, we identify five local contacts that play a critical role in folding. Using the contact probability of those five local contacts at the early stage of folding, we built a classification model. This enables us to predict the foldability of a WW sequence with 81% accuracy. Based on this classification model, we re-design the unfoldable WW domain sequences and make them foldable by introducing a few mutations that lead to stabilization of these critical contacts.

2044-Pos Board B63
Analyzing Protein Folding by High-throughput Simulations
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Molecular Dynamics allows investigating the dynamical properties of biomolecules. Protein folding simulations are computationally challenging when simulating all involved (solvent) atoms considering timescales of ms or slower. Native structure based models (SBM, Go-models) reduce computational complexity and have been proven to be a robust and efficient way for exploring the folding landscapes (Schug and Onuchic 2010; Thirumalai, O’Brien et al. 2010). They are based on energy landscape theory and the principle of minimal frustration. Using this framework, we simulate protein folding for a large set (~200) of non-homologous monomeric proteins sized from 50-150 amino acids in coarse-grained simulations, representing each amino acid by a single bead. A fully automated workflow implemented with the help of eSBM (Lutz et al.) guides these simulations. From the simulations, we extract typical folding properties like phi-values, folding free energy landscape and transition state ensembles. We repeat the simulations for a variant SBM with flavored contact strengths pending on amino acids composition. The resulting database estimates the robustness of folding parameters, quantifies the folding behavior, compares the behavior to existing experimental data and can serve as a baseline for comparison to future experiments or simulations of protein folding.


2045-Pos Board B64
Simulations of the Thermodynamics and Structural Properties of the TC10b Trp-Cage Protein
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The Trp-cage is an extensively studied miniprotein. Most of the literature, however, studies the TC5b variant of this protein. Andersen et al., showed that by mutating the first four residues to a high alanine content, it is thought that the alpha helix is further stabilized, resulting in a higher folding temperature for the TC10b variant than for the original, TC5b, sequence. In this study, we computationally investigate the higher folding temperature and its causes using Replica Exchange Molecular Dynamics (REMD). First, we show that indeed the TC10b variant has a higher folding temperature in our simulations than TC5b. We also find that the helical fraction is higher as well. Computing the structural ensemble, we further found differences in the lack of a prevalent secondary substrate, as is the case for TC5b. We finally compute thermodynamics parameters that define the stability diagram, Delta G(P,T), and show that while many other parameters are identical, such as the compressibility, linear expansion coefficient etc., we find that the free energy of folding is more than twice that of TC5b. We conclude that our results support the contention that in most ways, the sequence yields an almost crystalline nature of Aβ1-39 (Japanese) Mutant, a Molecular Dynamics Study
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Alzheimer’s disease (AD) has been identified as a progressive, neurodegenerative disorder associated with protein misfolding due to the aggregation of monomeric β-amyloid proteins (Aβ) to form fibrillar plaques. Experimental attempts to purify and chemically analyze the structure of Aβ protofibrils and to elucidate the mechanism of fibril formation have yet to reveal much about the molecular etiology of AD, due to the low solubility and non-crystalline nature of Aβ. It has been shown experimentally that the ΔE22-Aβ1-39 (Japanese) mutation of the β-amyloid leads to production of typical