researchers, the diffusible beta sheet intermediates are in fact the most critical step in the prevention of Alzheimer's disease (AD) due to their high toxicity levels and function as precursors to amyloid betaproteins. Research has been focused on the amyloid beta (22-35) portion of the single point wild type mutation because of its high toxicity level during the progression of AD. Orthomolecular compounds, such as melatoninand curcumin, will be combined with the amyloid peptide in various concentrations and times to test their preventative effects on the amyloid fibrils due to their neurotoxicity. The hormone melatonin is naturally secreted by the body and can not only reduce AD patient symptoms of insomnia but it can also disrupt Aβ toxicity in the early stages of AD. Additionally, curcumin is the key component of the plant turmeric. Attenuated Total Reflectance Infrared Spectroscopy (ATR-IR) along with Ultraviolet visible spectroscopy (UV/Vis) and electron microscopy (EM) will be used in order to determine the structural confirmation and morphology on the pathway to fibril formation. This knowledge will help determine the specific mechanism used to destabilize the intermediate structures before they can form amyloid plaque and possibly lead to a cure and/or preventative.

2319-Pos Board B89

Diversity of Sequences Folding to Highly and Poorly Designable Structures

Sumudu P. Leelananda, Robert L. Jernigan.
Iowa State University, Ames, IA, USA.

Protein structures are evolutionarily more conserved than sequences, and sequences with very low sequence identity often share the same fold. This leads to the concept of protein designability. Elucidating the relationship between protein sequence and the three-dimensional structure that the sequence folds into is an important problem in computational structural biology.

45 protein chains (40-mer) from the PDB were analyzed. Hydrophobic-polar sequences were generated and contact energies calculated by threading each sequence onto Cα coarse-grained protein structures. The minimum energy structure for each sequence was identified and the number of sequences folding to each fold (designability) was obtained. Highly designable structures obtained were found to be popular structural motifs.

H/P mutational analysis of sequences folding to each conformation was performed. As designability increases, the total number of mutations was also found to increase. The sequences folding to the most designable structure (helix-turn-helix motif) were also analyzed. The degree of connectivity at each residue position correlates inversely with the degree of solvent exposure. The surface residues had fewer interactions compared to buried residues. Highly connected residues were also found to be more conserved than the other residue positions. i.e. the diversity of the sequences increases with designability; however, there are conserved positions.

Using tripeptide percentages of the most and least designable sequences, ten-fold cross-validation was performed and designable sequences were found to be distinguishable (accuracies $> 85\%$, AUC > 0.87). The same set of sequences was then used as a training set with a test set of real binary protein sequences. Designable sequences obtained mimic real protein sequences with accuracies of nearly 60%. Highly and poorly designable classes can be used to train machine learning algorithms to identify which real protein sequences are designable.

2320-Pos Board B90

Modeling CLIC2-RyR Interactions and the Effect of Disease Causing Mutation

Shawn Witham, Emil Alexov.
Clemson University, Clemson, SC, USA.

Our recent in silico studies have shown that chloride intracellular 2 (CLIC2) protein harbors a missense mutation in the H101Q position and gives significant changes in CLIC2's stability. In this work, we extend our investigation to include the plausible effects of the mutation on CLIC2-RyR (ryanodine receptor 1) interactions. For this purpose, we built a 3D model of the CLIC2-RyR complex by using ab-initio docking. The models are evaluated against electron microscopy data to assure that the binding interface of CLIC2-RyR is recovered. The models are then used to evaluate the role of electrostatics on CLIC2-RyR recognition by carrying out calculations with Delphi (compbio.clemson.edu/delphi.php). The results of electrostatics calculations indicate that charge complementarity plays an important role in the binding and that the disease-causing mutation affects the electrostatic component of the binding. By combining the outcome of electrostatic calculations with other in silico analyses, including solvent accessible surface area, docking predictions, and binding free energies, we were successfully able to gain insight into the effects of a missense mutation on the stability of CLIC2-RyR complex. The work is supported by NIH, NIGMS, grant number 1R01GM093937-01.

2321-Pos Board B91

Sampling of Random Amino Acid Mutations: Folding and Binding Stability of Coat Proteins in a Simple Virus

Kuo Hao Lee, F. Marty Ytreberg.
University of Idaho, Moscow, ID, USA.

It is recognized that protein-protein interactions are a vital component of protein evolution since it is thought that well over half of proteins exist as protein complexes. Previous studies have shown that most random amino acid substitutions destabilize protein folding (i.e., increase the folding free energy), however, no such study has been carried out for protein-protein binding. Thus, we used FoldX to estimate the free energy of folding and binding for coat proteins in a simple virus. Our results suggest that most random mutations destabilize protein folding, consistent with previous findings. However, by contrast, most random mutations stabilize protein-protein binding. In addition, natural selection appears to favor stabilizing folding rather than stabilizing binding for this virus. Finally, the temperature of the virus affects binding stability more strongly than folding stability.

2322-Pos Board B92

Hamiltonian Replica Exchange Simulations to Enhance Sampling for Protein Folding

Abhinav Verma, Alexander Schug.
Karlsruhe Institute of Technology, Karlsruhe, Germany.

In order to enhance sampling in biomolecular simulation many efforts have focused on reducing the effective degrees of freedom and employing coarse-grained models. Structure-based or Go-models for protein folding are based on the energy landscape theory and the principle of minimal frustration have demonstrated good agreement with experimental measurements and are computationally sufficiently tractable to allow simulating large-scale structural transitions and provide sufficient sampling even of large-scale conformational transitions. Linking these minimal or coarse-grained models to physically motivated empirical force fields would enhance understanding of the underlying physical/chemical interactions.

Here, we present a novel approach combining an efficient coarse-grained native structure-based model with a physics based all-atom model. This approach targets the sampling problem that has plagued traditional simulation methods for decades while providing an energetically accurate description of conformational transitions. Our approach is based on Hamiltonian exchange, a variant of the Replica-exchange concept, by coupling the Hamiltonians that operate not on different temperatures, but on different levels of representation. Each level is occupied by a combination of the two mixed Hamiltonians $H\text{total}=\lambda H1+(1-\lambda)H2$. During simulation, one permits exchanges between neighboring levels. We observe frequent transitions between neighboring levels and an enhanced sampling efficiency for model proteins.

2323-Pos Board B93

Analysis of Amino Acid Specific Energy Contributions to Native Conformations in High-Resolution Protein Structures

Timo Strunk, Moritz Wolf, Wolfgang Wenzel.
Karlsruhe Institute of Technology, Eggenstein-Leopoldshafen, Germany.

Because most proteins are marginally stable, each amino acid must contribute a near-optimal stabilization energy to the overall protein-structure. In this study we have analysed the specific energy contribution of each amino acid found in the native conformation of globular proteins. Using our free-energy forcefield PFF02 we devise a local energy measure on a per-amino acid basis and relax a population of 50 high resolution experimental globular protein structures on POEM@HOME with an evolutionary Monte Carlo energy minimization algorithm. The obtained set of relaxed structures is screened for locally stable segments, ruling out intrinsical disorder, and datasets of the energy ranges are assembled correlated with the position of the amino acid (interior, exterior, solvent-exposed).

POEM (Protein Optimization using Energy Methods) identifies the native conformation of the protein as the global minimum of the protein free-energy forcefield PFF02, which stabilized the native conformation of all 32 monomeric proteins (without cofactors) against all decoys in the Rosetta decoy set. In addition we could fold a set of 13 proteins with helical, sheet and mixed secondary structure from completely unfolded conformations to near-native conformations, to an average 2.87 Å resolution.

The simulations we have conducted, were run on the POEM@HOME (http://boinc.fzk.de) volunteer computing architecture using a multiple population evolutionary strategy, which explores the free-energy surface in many parallel Monte-Carlo random walks. Various distinct temperature populations are evolved to the global free-energy minimum by balancing energy improvement and population diversity.