investigate the significance of coupling information, we simulate a repertoire of artificial WW domain sequences using a physics-based search method called ZAM (Zipping and Assembly method).[2] Our result shows that coupling information has a remarkable influence on the local contacts of N-terminal β-turn of WW domains. This turn would not form correctly if lack of such information. Interestingly, the formation of N-terminal β-turn has been determined as the nucleator and rate-limiting step experimentally.[3] We also identify specific crucial contacts at the beginning of folding process, and accomplish to predict the foldability of a WW sequence, based on its favor of these crucial contacts. 1. Soccolich M, Lockless SW, Russ WP, Lee H, Gardner KH, Ranganathan R. 2005. Evolutionary information for specifying a protein fold. Nature 437: 512 2. Ozkan SB, Wu GA, Chodera JD, Dill KA. 2007. Protein folding by zipping and assembly. Proceedings of the National Academy of Sciences of the United States of America 104: 11987 3. Jager M, Nguyen H, Crane JC, Kelly JW, Gruebele M. 2001. The folding mechanism of a beta-sheet: The WW domain. Journal of Molecular Biology 311: 373

3316-Pos Prediction of H Exchange from Perfectly Funneled Structure Based Models Patricio O. Craig1,2, Joachim Lätzer1, Patrick Weinkam4, Ryan Hoffman1,2, Elizabeth Konnives1, Peter Wolyne1,2, 1University of California San Diego, La Jolla, CA, USA, 2Center of Theoretical Biophysics, La Jolla, CA, USA, 3Rutgers University, Piscataway, NJ, USA, 4University of California at San Francisco, San Francisco, CA, USA.

Simulations based on perfectly funneled landscapes have been able to capture many of the fundamental aspects of protein folding. When frustration is low enough the topology becomes the main factor determining the folding process. In the most fundamental implementation of the minimal frustration principle only native interactions significantly contribute to the stabilization of the protein. Using these ideas and coarse grain models an extensive sampling of the energy landscape could be achieved. We explored the use of such models to interpret subtle dynamic motions near the native state and whether they are able to give a quantitative description of the native protein ensembles. For this aim we developed a method for the quantitative comparison of the local stability of proteins simulated using perfectly funneled structure based models, and detailed experimental measurements of single residue hydrogen/deuterium exchange of backbone amides (HDX) which depends on structural and dynamic properties. The method was applied to ubiquitin, cysteocyte-C, HEWL, S6, and IkBalpha-70-206. The predicted exchange patterns agree with the experimentally determined HDX protection factors under native conditions. A variety of simulation models with homogeneous, heterogeneous, additive as well as non additive contact potentials were evaluated for their agreement with experiment. We also compare the results obtained using different criteria for structurally defining the open and closed states based on the number of native contacts of each residue, the dynamics of hydrogen bonded residues or a combination of both criteria.

3317-Pos Computational Prediction of Hotspots in Protein Misfolding for Rational Immunotherapy Steven Plotkin, Neil Cashman, Will Guest.
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Physics-based algorithms can predict the misfolding mechanisms of proteins involved in aggregation-related diseases, including SOD1 whose misfolding template-directed conversion is involved in Amyotrophic lateral sclerosis and PrPc, wherein propagation of the misfolded protein is central to the prion diseases. We have recently developed an algorithm capable of predicting thermodynamically likely regions for misfolding, by employing modeling which involves both atomistic interactions and surface-area based coarse-graining, along with a heterogeneous dielectric function inside the protein. Predictions based upon the algorithm are consistent with recent immunological assays that have uncovered disease-specific epitopes in SOD1 and prion protein, and point to diagnostic and therapeutic applications. This research was performed in collaboration with Dr. Neil Cashman at the Brain Research Centre, University of British Columbia, and involved joint supervision of M.D./Ph.D. student Will Guest.

3318-Pos Protonation/deprotonation Effects on the Stability of Trp-cage Mini-protein Camilo A. Jimenez-Cruz, Angel E. Garcia.
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The effect on the folding/unfolding equilbrium of protonating the aspartic acid on the Trp-cage miniprotein is studied by explicit solvent molecular dynamics simulations. Replica exchange molecular dynamics (REMD) simulations spanning the temperature range from 280K to 358K were carried out to the micro second scale using the AMBER99SB forcefield in explicit TIP3P water. The root mean square distance from the backbone of the NMR structure shows two highly populated basins close to the native state with peaks at 0.6 A and 1.6 A which are consistent with previous simulations using the same forcefield. The fraction of folded replicas shows a drastic decrease because of the breaking of the salt bridge. However, significant populations of conformations with the arginine sidechain completely exposed to the solvent, but within the folded basin. This shows the possibility to reach the folded state without formation of the ion pair contrary to the expected.

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All-atom implicit solvent molecular dynamics simulations of the tryptophan zipper trpzip2 were carried out with a fast multiple time stepping integrator and a replica exchange method to improve sampling. Two modifications of the backbone dihedral angle potential energies in the AMBER (99) parameter set were compared. Individual trajectories were run for over 375 ns, and aggregate simulation times were over 7.5 microseconds. Several measures of folding behavior in simulations began from both folded and unfolded ensembles showed convergence to near-equilibrium values, allowing thermal phase behavior to be inferred and compared with experiment.

3320-Pos The Mechanism of Geometrical Frustration in SH3 Heiko Lammart, Jose N. Onuchic.
University of California San Diego, La Jolla, CA, USA.

Structure-based protein models build a minimally frustrated energy landscape to focus on the influence of geometrical factors on their dynamics, and they have demonstrated that the native structure is often sufficient to determine the folding mechanism. We customize structure-based models with a flexible interaction potential to investigate this geometrical control of the folding pathway. In the case of SH3 a polarized transition state results from the delayed formation of the N-terminal beta sheet. We isolate the contributions of the native contact map, of chain connectivity and of excluded volume interactions to identify their roles in the creation of this specific mechanism. While the native contacts are a direct expression of the native structure we find that the unspecific repulsion is essential to understand how geometrical frustration guides the folding process.

Heme Proteins

3321-Pos A Biophysical-Biochemical Comparison of Hemoglobins from Mammoth, Asian Elephant, and Human Priyamvada Gupta1, Nancy T. Ho1, Tong-Jian Shen1, Virgil Simplescau1, Michael Hofreiter2, Alan Cooper3, Kevin L. Campbell4, Chien Ho1, 1Carnegie Mellon University, Pittsburgh, PA, USA, 2University of York, York, United Kingdom, 3University of Adelaide, Adelaide, Australia, 4University of Manitoba, Winnipeg, MB, Canada.

This study is aimed at investigating the molecular basis of environmental adaptation of hemoglobin from tropical climate to low temperature in the Arctic region. We have carried out a biochemical-biophysical characterization of the structural and functional properties of hemoglobins from woolly mammoth (Hb WM) and Asian elephant (Hb AE) and compared those to human hemoglobins (Hb A and Hb A2) in 0.1 M phosphate buffer. Hb A consists of two α and two β subunits. Hb AE was found to contain two α subunits and two β/β fusion subunits. Hb WM was expressed by inserting Asian elephant α/β chains and a mammoth-specific residue differences (IHP), is the most prominent on Hb A2 as compared to Hb A, Hb AE, and Hb WM. Hb AE has the higher O2 affinity as compared to Hb WM, and a replica exchange method to improve sampling. Two modifications of the backbone dihedral angle potential energies in the AMBER (99) parameter set were compared. Individual trajectories were run for over 375 ns, and aggregate simulation times were over 7.5 microseconds. Several measures of folding behavior in simulations began from both folded and unfolded ensembles showed convergence to near-equilibrium values, allowing thermal phase behavior to be inferred and compared with experiment.

The Mechanism of Geometrical Frustration in SH3