a multiproperty reaction coordinate and conformational clustering. In this way, structures along the pathways are assigned native, intermediate and denatured states and the properties of these states are calculated and compared. The unfolding of the CTPRs is initiated by the loss of contacts between two repeat motifs which leads to the destabilization and subsequent unfolding of those repeat domains as intra-helix contacts are lost. The unfolding of individual repeats leads to partially unfolded species in agreement with experiment.

3310-Pos

An Fft-Based Method for Modeling Crowding Effects when Both Test Proteins and Crowders are Represented at the Atomic Level

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Macromolecular crowding affects protein folding, binding, and aggregation, and such effects have been studied by computer simulations. In direct simulations of test proteins mixed with crowders, the proteins have been represented at a coarse-grained level and the crowders modeled as spheres; protein-crowder interactions are assumed to be repulsive. Our recently developed postprocessing approach has allowed test proteins to be represented at the atomic level [1]. In this approach, the motions of a test protein and those of the crowders are followed in two separate simulations. The effects of crowding are then modeled by calculating $\Delta\mu$, the crowding-induced change in the chemical potential of the test protein. For a repulsive type of protein-crowder interactions, $\Delta\mu$ is related to the fraction, f, of allowed placements of the test protein into a box of crowders. An algorithm has been developed to calculate f for spherical crowders. Here we present a new algorithm that enables the calculation of f for atomistic crowders. We express f as the correlation function of two spatial functions, one defined for the crowders and one for the test protein. The correlation function was calculated by fast Fourier transform. As the first application, we studied the effects of ellipsoidal crowders on the folding and binding free energies of atomistic proteins, and found that the nonspherical shapes of the crowders lead to greater stabilization effects than spherical crowders of the same volume. This finding has significant physiological implications since the macromolecules inside cells have many different shapes. Additional applications to proteins as crowders and other *in vitro* crowding agents are underway, marking a major step toward realistic modeling of intracellular environments.

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3311-Pos

Negative and Positive Design in Protein Folding and Thermodynamic Stability: Insights from Computational Mutagenesis and Simulations

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Negative and positive components of protein design are crucial for stability and uniqueness of native proteins. The main goal of this work is to investigate mutual work of positive and negative components of design via the effects of non-specific single and multiple mutations on protein thermodynamic stability and folding dynamics. Proteins representing all four major fold types are under consideration. All mutations are done according to single-nucleotide polymorphism, and coarse-grained protein models with Cα representation are constructed based on native-centric approach and are used in Molecular Dynamic (MD) simulations with Langevin dynamics. Inclusion of non-native interactions to the protein dynamics increases the folding/unfolding transition temperatures compared to the model without non-native interactions regardless of protein type. Depending on mutation types and where they are located, changes in thermodynamic stability consistent with experiments are observed. Mutations can also affect the population of transition-state conformations and folding/unfolding dynamics. Positive and negative components are indispensible parts of protein design, and they should be considered in all experimental and computational studies of protein structure and folding. In particular, specific roles of non-native repulsive interactions illuminated in this work calls for in-depth exploration of the role of unfolded conformations in thermodynamic stability and kinetics of protein folding.

3312-Pos

Towards Comprehensive Analysis of Protein Family Quantitative Stability/flexibility Relationships

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The Distance Constraint Model (DCM) is a computational modeling scheme that uniquely integrates thermodynamic and mechanical descriptions of protein structure. As such, quantitative stability/flexibility relationships (QSFR) can be computed. Using comparative QSFR analyses, we have previously investigated the give-and-take between thermodynamics and mechanics across a small number of protein orthologs, ranging from 2 to 9 [1-3]. However, a comprehensive protein family analysis requires consideration of hundreds of proteins. Consequently, homology models are necessary to fill in the structural gaps. As a first step towards such comprehensive analyses, herein we assess the differences within QSFR quantities calculated from the human c-type lysozyme x-ray crystal structure and homology models constructed from various orthologs. We parameterize our current minimal DCM (mDCM) by fitting to experimental C_p curves. All models are able to reproduce the experimental C_p curve. Interestingly, the least squares fitting error is not correlated to homology model accuracy. We present quantitative differences within various QSFR metrics between the x-ray and model structures, and establish thresholds on model accuracy based on their ability to reproduce the QSFR metrics of the x-ray structure.

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[3] Mottonen et al. (2009). *Proteins*, 75:610-627.

3313-Pos

Huntingtin: Stability and Interaction with Molecular Partner from Computational Biophysics Studies

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Huntington disease is a neurodegenerative disorder producing motor, cognitive and psychiatric symptoms. It is caused by a trinucleotide CAG repeat gene mutations, encoding an expanded polyglutamine (polyQ) tract in the respective protein. Proteolytic processing of mut-Htt lead to the formation of short N-terminal polyQ-containing fragments that have the propensity to aggregate and cause neurodegeneration. These fragments form insoluble β-sheet aggregates that are the hallmark of the disease. Here we shall present a simulation study aimed at pinpointing key factors for the structural stability of polyQ aggregates based on classical molecular dynamics simulations and first-principles calculations. Such study is complemented by a structural prediction of a complex between F-actin and the N-terminal part of mut-Htt, which it is proposed to bind F-actin and to trigger cell apoptosis. This may play an important role in determining the aggregation potential of mut-Htt in cells.

3314-Pos

Analysis of Site-Specific Folding of Helix-Turn-Helix Proteins with Statistical-Mechanical Models

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Isotopically-edited IR spectroscopy can provide detailed site-specific information about the protein folding mechanism. Our equilibrium unfolding studies of two simple helix-turn-helix (*hth*) proteins revealed complex, heterogeneous processes, which involve structurally diverse ensembles of partially folded intermediates. In order to obtain a consistent picture of the folding mechanism, and insights into its physical origins, it is necessary to connect the sets of site-specific experimental data within a framework of a model, which can explain the observations in terms of the structural and energetic properties of the protein. We have analyzed the experimental data, circular dichroism (CD) and infrared (IR) which included spectra of multiple ^{13}C isotopically labeled variants, for both model *hth* proteins using Ising-like statistical-mechanical models. We implemented the Muñoz-Eaton (ME) model, which can be enumerated exactly using efficient transfer matrix methods, and Galzitskaya-Finkelstein (GF) model in double- and triple-sequence approximation. Model parameters were optimized by simultaneously fitting the complete set of data for each protein. With a single parameter for the contact energy, neither variant was capable of simultaneously fitting all the experimental data. However, with Miyazawa-Jernigan residue-specific potentials the GF models closely reproduced the site-specific unfolding, as well as the CD. The ME model, on the other hand, did not improve. For both model proteins, the results are consistent with the proposed folding mechanism and demonstrate that simple, Ising-like statistical mechanical model for protein folding is capable of correctly reproducing multiple site-specific sets of folding experimental data.

3315-Pos

A Physics-Based Approach for Understanding Foldability

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Statistical coupling analysis (SCA) indicates that in addition to the conservation of amino acid composition at individual site, the coupling information between sites is necessary and sufficient to specify a protein fold.[1] To