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Using Dihedral Stabilities to Characterize Protein Folding Transitions

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Although molecular dynamics simulations have been shown to accurately refold some proteins, commonly used metrics to describe the refolding pathways created by simulation require the presence of a crystal structure for reference or clustering techniques. Furthermore, metrics which rely on combining multiple individual distances like RMSD make it difficult to distinguish the refolding of individual amino acids compared to their counterparts. To better resolve amino acid stabilization, we examined the dihedral stabilities of amino acids in a stable I91 module as well as in its perturbed state with the A strand separated from the I91 domain. In doing so we find we were able to resolve the time at which individual amino acids stabilized along the folding pathway thereby providing additional information about the potential refolding pathways of the perturbation. Furthermore, we found significant variation in the phi dihedral angle of proline residues which was more pronounced in the Charmm 22* force field than the Amber force fields. This suggests that examining dihedral stabilities may provide a useful tool for analyzing polypeptide chain refolding as well as for examining the effects of force fields on various proteins.

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Automatic Partition of Protein Molecular Dynamics using Coupled Hidden Markov-Ising Models

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Department of Chemistry, Georgia State University, Atlanta, GA, USA. A large number of Eukaryotic proteins have intrinsically disordered loops, which may form highly flexible binding regions that are not traditionally well-defined. Therefore, a deep understanding of the dynamics of the mechanism of proteins may lead to a new set of dynamic methods for designing drugs targeting intrinsically disordered proteins. Reductionist methods divide a complex system into simpler components with a tractable network of interactions. However, to our knowledge, no existing method automatically divides an MD simulation into explainable and coupled dynamics of simpler components, each containing multiple modes of internal dynamics. Free energy calculation, correlation network, and principal component analysis do not simultaneously partition a protein into groups of atoms and identify states of each group. Side-chain rotameric states combine to form an exponentially large number of conformational states. Therefore, the Markov state model of conformations cannot summarize the dynamics of side-chains without losing much of the details. Ad hoc mixture of multiple methods may require human interpretation to harmonize the different perspectives of the methods. Deep neural networks are not explainable because their parameters generally have no clear interpretation, contrary to statistical models. We fit an MD simulation to a unified statistical model containing hidden Markov models (HMM) coupled together to describe the dynamics between interacting components. The HMMs control the mixing of Ising models, which describe the modes of the network of interaction within each component. The model also automatically assigns each side-chain to one of the components. We expect this class of methods would provide a more transparent understanding of how perturbations at a small site can affect the whole protein through the perspective of coupled hierarchical dynamics.

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Force Field Error Diagnosis and Structure-Driven Correction for the ATP-Magnesium Complex

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The molecular recognition and catalytic processes that define the role of adenosine triphoshpate (ATP) are mediated largely by its magnesium chelate, ATP.Mg. Consequently, an accurate representation this complex is crucial to the theoretical study of a multitude of biochemical processes. In aqueous solution, two configurations can be distinguished, with Mg contacting either the terminal beta and gamma phosphate groups (bidentate; C2), or all three (tridentate; C3). C2 and C3 are approximately isoenergetic in solution, and are duly represented almost equally among known structures in the Protein Data Bank (PDB).

Building on molecular dynamics simulations showing prohibitively slow, microsecond-order interconversion between states in unbiased simulation, we calculate the free energy difference between C2 and C3 substates by means of an expanded ensemble incorporating rapidly converting states, using two widely employed parameter sets respectively compatible with the CHARMM and Amber force fields. Strikingly, we obtain estimates not only incompatible with experimental observations, but also emphatically contradictory in predicting opposite coordination modes as the more favourable.

Addressing these contradictory results, we recruit known ATP. Mg-protein complex structures from the PDB as additional experimental input. Building on the premise that perturbation of an experimentally determined structure away from its observed state should always yield a positive free energy value, we evaluate a panel of structures using both force fields. From the resulting distribution of values, we are able to identify a linear correction of the C2/C3 free energy difference for both force fields which restores consistency with experiment both for the panel of PDB structures and for the value in aqueous solution.

The approach described is of general interest as a diagnostic and optimisation tool applicable to otherwise intractable microscopic structural properties for which a sufficient variety of experimental structures are available.

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An Integrative Approach to Single-Molecule FRET Spectroscopy and Molecular Dynamics Simulations for the Study of Intrinsically Disordered Proteins

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Using Molecular Dynamics Simulations to Understand IR Spectroscopy Results in Green Fluorescent Protein

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The unnatural amino acid 4-cyano-L-phenylalanine (pCNF) can be used as an infrared (IR) spectroscopic reporter to probe local chemical environments