Intrinsically Disordered Proteins (IDP) and Aggregates II

1137-Pos Board B88
Optimized Force Fields for Simulations of Intrinsically Disordered Proteins
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Some frequently encountered deficiencies in all-atom molecular simulations, such as nonspecific protein-protein interactions being too strong, and unfolded or disordered states being too collapsed, suggest that proteins are insufficiently well solvated in simulations using current state-of-the-art force fields. In order to address these issues, we make the simplest possible change, by modifying the short-range protein-water pair interactions, and leaving all the water-water and protein-protein parameters unchanged. We find that a modest strengthening of protein-water interactions is sufficient to recover the correct dimensions of intrinsically disordered or unfolded proteins, as determined by direct comparison with small-angle X-ray scattering (SAXS) and Förster resonance energy transfer (FRET) data. The modification also results in more realistic protein:protein affinities, and average solvation free energies of model compounds which are more consistent with experiment. Most importantly, we show that this scaling is small enough not to affect adversely the stability of the folded state, with only a modest effect on the stability of model peptides forming alpha-helix and beta-sheet structures. The proposed adjustment opens the way to more accurate atomistic simulations of proteins, particularly for intrinsically disordered proteins, protein:protein association, and crowded cellular environments.

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Adaptive Particle Simulations of Alpha-Synuclein Fibril Formation
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A number of intrinsically disordered proteins, including alpha-synuclein and beta-amyloid, are known to form amyloids in neurodegenerative diseases such as Parkison's and Alzheimer's diseases, respectively, indicating generic behaviour of this class of proteins. The accompanying large conformational transition, from disordered to a beta-sheet, makes it difficult and extremely time-consuming to study the aggregation process by standard simulation methods. We have developed a Lambda Dynamics technique in which the coarse-grained particles, representing sequences of consecutive amino acids, respond to their environment by changing shape and interaction properties [1]. The evolving states of the particles are determined by internal and external interactions. The translational and rotational motion of the anisotropic particles are simulated with a newly developed concise Brownian Dynamics algorithm [2,3]. We present results on the aggregation of solvated spherical, disordered proteins into fibrils of elongated, beta-sheet forming proteins.
[1] I.M. Ilie, W.K. den Otter and W.J. Briels, in preparation
[2] I.M. Ilie, W.J. Briels and W.K. den Otter, in preparation
[3] I.M. Ilie, W.K. den Otter and W.J. Briels, J. Chem. Phys. 141, 065101 (2014)

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What does Evolution Tell us about the Structure of a Functional Amyloid Protein?
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Amyloids are insoluble fibrillar protein aggregates. While they are commonly found in human diseases, it is becoming increasingly clear that this type of structure is essential for a range of biological functions, with prominent examples in organisms ranging from bacteria to human. Functional amyloid and pathogenic amyloid share similar physical and chemical properties. Unlike pathological amyloids, however, the structures of functional amyloids are formed by polypeptide sequences whose amyloid structure has been under a positive evolutionary selection pressure. This important distinction provides us with an opportunity to obtain structural insights from an unexpected source: the covariation of amino acids among sequences within the same family of a functional amyloid protein. There is a long history for the idea of using coevolution for molecular structure prediction, but recent growth in sequence databases and new, efficient algorithms to disentangle indirect couplings in a network, have dramatically improved our ability to predict residue-residue contacts. We used recently developed sequence analysis methods (EVcoupling, PSICOV and GREMLIN) to extract distance restraints from a multiple sequence alignment of a functional amyloid protein. Together with an efficient force field, these restraints allow us to determine atomic resolution structural models. We find that the protein forms a beta-helical structure, where each turn corresponds to previously identified repeat sequences. The proposed structure is validated by previously published solid-state NMR, electron microscopy and X-ray diffraction data, and confirms an earlier proposed model derived by complementary means. To our knowledge, this is the first time the analysis of correlated mutations and computer simulations have been used together to study the structure of a functional amyloid. The current study therefore serves as a probe into the potential applicability of the approach in this domain.

1140-Pos Board B91
Enabling Biophysical Characterization of Intrinsically Disordered Protein Ensembles
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Elucidating structural details of protein conformations and its relation to protein function is a forefront area in structural biology. In this project, we will investigate nuclear co- activator binding domain (NCBD), an intrinsically disordered protein (IDP) implicated in acute myeloid/lymphatic leukemia (AML/ALL), which has the propensity to adopt extended conformations in unbound form and undergoes synergistic folding with substrate specific conformations when bound. Since IDPs like NCBD are highly flexible, their full conformational range is not observable by any one structure determination technique. We have developed a novel, integrated experimental and computational technique to elicit high-resolution structural details of such IDP ensembles. Specifically, we have (1) developed methods to prepare amino-acid-type selectively deuterated NCBD and utilize SANS contrast variation techniques to refine high-resolution conformational ensembles; (2) constructed parallel ensemble simulation strategies on heterogeneous computer architectures to generate millisecond timescale atomistic simulations; and (3) designed Bayesian inference techniques for statistical characterization of IDP conformational ensembles. The integrated approach enables accurate understanding, simulation and prediction of recognition mechanisms of NCBD under physiological condition.

1141-Pos Board B92
Developing a Protocol for Ensemble and Vibrational Probe-Containing Molecular Dynamics Simulations of the Nipah Ntail-XD Complex
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Intrinsically disordered proteins (IDPs) prove difficult to characterize using typical protein secondary structure indicators, such as CD and NMR spectroscopy, because of their dynamic nature. Molecular Dynamics (MD) simulations can be adapted for use in highly dynamic systems such as IDPs through enhanced sampling techniques. This project involves the characterization of the "fuzzy" Nipah Virus nucleo- and phosphoprotein bound complex by using MD simulations and vibrational probes. In order to run MD simulations on IDPs, a viable structural ensemble must be generated; this can be done by varying the simulation temperature to overcome energy boundaries and exchanging high-energy structures with those generated at low temperature ("replica exchange"). Once an ensemble of structures is generated, shorter simulations can be run in which a site-specific thiocyanate probe is incorporated into each structure. Eventually, an infrared (IR) lineshape can be simulated from the conformational ensemble for each label site and directly compared to experimental data. Progress towards each step of this multi-step simulation protocol will be discussed, as well as the prospects for a hybrid spectroscopic-theoretical determination of the conformational distribution of "fuzzy" bound complexes.

1142-Pos Board B93
Using Chemical Shifts to Generate Structural Ensembles for Intrinsically Disordered Proteins with Converged Distributions of Secondary Structure
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A short segment of the disordered p53 transactivation domain (p53TAD) forms an amphipathic helix when bound to the E3 ubiquitin ligase, MDM2. In the unbound p53TAD, this short segment has transient helical secondary structure. Using a method that combines broad sampling of conformational space with re-weighting, it is shown that it is possible to generate multiple, independent structural ensembles that have highly similar secondary structure distributions for both p53TAD and a P27A mutant. Fractional amounts of transient helical