secondary structure were found at the MDM2 binding site that are very similar to estimates based directly on experimental observations. Structures were identified in the random assembly of unbound segments that are highly similar to short p53 peptides bound to MDM2, even though the ensembles were re-weighted using unbound experimental data. Ensembles were generated using chemical shift data (alpha carbon only, or in combination with other chemical shifts) and cross-validated by predicting residual dipolar couplings.

1143-Pos Board B94
IDPs that Fold Upon Binding: What is the Role of the Partner Protein? Sarah L. Shammas, Joseph Rogers, Michael Crabtree, Jane Clarke. Chemistry, University of Cambridge, Cambridge, United Kingdom.

Many intrinsically disordered proteins perform their functions within the cell by binding to a partner protein, often forming a defined structure (such as a helix or an extended strand) when they bind. To date most studies of coupled folding and binding have centred on the disordered protein or peptide, giving little consideration to the folded partner protein. Our recent work with 'model' IDP systems reveals that the folded partner protein can play an unexpectedly important role in the binding process.

1144-Pos Board B95

Conformational states of proteins and peptides are not solely determined by their sequence, but are also strongly dependent on the environmental conditions. In addition to factors like salt concentration or pH, the environment presented by the surrounding molecules also play a major role on the conformational behavior of proteins and peptides. In this study, by using molecular dynamics simulations, we perform a comparative study on the conformational behavior of LKalp-a-14 peptides in bulk water vs. macroscopic and molecular interfaces. The molecule under study is designed to have an alpha-helical conformation with the sequence (LKKLLLKL).2. Our replica exchange simulations show that, similar to intrinsically disordered proteins, this molecule lacks a unique conformation when isolated in bulk water. However, in the presence of an air/water interface the molecule uniquely adopts the alpha-helix conformation. Further more, such a stabilizing effect is not limited to macroscopic interfaces, but can also be seen in the presence of molecular interfaces presented by surrounding molecules. Even when they are in a disordered state, molecules in solution display temporary molecular interfaces as a result of segregation of their hydrophobic and hydrophilic residues. Our simulations show that, these temporary molecular interfaces act as molecular chaperons in both accelerating the folding of peptides and also stabilize the alpha helical conformation when it forms. In light of these results, LK peptide can be identified as a classic example for conformational selection model.

1145-Pos Board B96
An Evolutionary Algorithm for the Design of Different Degrees of Secondary Structure in Intrinsically Disordered Proteins (IDPs) Tyler S. Harmon1, Rohit V. Pappu2,3.

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In recent experimental studies of coupled folding and binding of IDPs investigators have adapted methods from the protein folding literature whereby point mutations are used to identify the degree to which different regions are pre-folded prior to the rate limiting step in binding and folding. These approaches assume a one-to-one correspondence between coarse-grained readouts of structure such as alpha helicity and the degree of foldness. Our previous work demonstrated a lack of correlation between alpha-helicity and the degree of disorder within unbound IDPs. Therefore, an important first step toward mutagenesis based approaches for dissecting the mechanisms of coupled folding and binding is the design of sequences that (a) have a target alpha helicity (b) have a prescribed degree of disorder and (c) retain the residues corresponding to the binding interface. We report results from an evolution algorithm (EA) that designs sequences to meet the specified criteria. We coupled this sequence design algorithm to atomistic simulations based on the ABSINTH model to quantify individually specific helicities for each sequence. We demonstrate our approach using the sequence of PUMA, which folds upon binding to its target protein MCL-1. In the unbound ensemble, PUMA forms two uncorrelated helical segments that partition the sequence into two halves. In the bound complex, PUMA forms a single long helix. Our design strategy successfully generates sequences that span the spectrum of conformational options for the unbound PUMA that includes sequences with uncorrelated helical segments N- and C-terminal and sequences with a single helix that spans the entire sequence length. Our approach is well suited to the design of sequences for use in experiments geared toward dissecting the mechanisms of coupled folding and binding of IDPs.

1146-Pos Board B97
CIDER: Classification of Intrinsically Disordered Ensemble Regions Alex S. Holehouse, James Ahad, Rahul K. Das, Rohit V. Pappu. Biomedical Engineering, Washington University in Saint Louis, St Louis, MO, USA.

Intrinsically disordered proteins (IDPs) and intrinsically disordered regions (IDRs) of proteins fail to fold into well-defined three-dimensional structures as autonomous entities. These sequences play important functional roles in signaling pathways, transcriptional regulation, and RNA metabolism. Recent studies have uncovered the physical principles underlying the relationships between IDP / IDR sequences and the range of conformations they adopt. IDP / IDR sequences can be classified into distinct conformational classes based on their amino acid compositions. These classes reflect the sequence-encoded balance between solvent-mediated intrachain electrostatic repulsions and attractions. Specifically, the number and linear sequence distribution of oppositely charged residues partitions the space of IDP / IDR sequences into globules, chimeras of globules and coils, designable random coils, and semi-flexible rod-like conformations. Here, we present CIDER (Classification of Intrinsically Disordered Ensemble Regions) [http://pappulab.wustl.edu/CIDER]. The CIDER webserver provides a rapid and intuitive computational route for designating the appropriate conformational class to a sequence and calculating a number of key parameters that enable inferences regarding conformational properties of IDPs / IDRs. CIDER and a freely available web version can be used online via a web server to achieve rapid annotation of sequence-disorder relationships for IDPs / IDRs. We also present a freely available non-web version (localCIDER), which we use to perform a high throughput prototolic state sequence analysis to uncover patterns that govern known phosphorylation sites within IDP sequences. The correlation between known phosphorytes and the distribution and fraction of charged residues suggests that phosphorylation is used to modulate the underlying charge patterning to engender an expansion of the disordered sequence. This hints at the use of phosphorylation as a reversible switch to toggle IDPs between distinct conformational classes.

1147-Pos Board B98
Intrinsically Disordered Protein: A Thermodynamic Perspective Jing Li1, James O. Wrabl2, Vincent J. Hilser1.
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Protein intrinsic disorder is commonly viewed as a binary attribute. This paradigm has been exploited for development and interpretation of prediction algorithms, which often classify positions as either "structured" or "disordered" based on sequence information. This work proposes a different perspective, based on the free energy difference between the disordered and structured thermodynamic states of the protein. Although requiring the assumption that intrinsically disordered protein is simply destabilized structured protein, several puzzling aspects of disorder can be subsequently rationalized. Most important of these is the fundamental insight that a small stability difference results in a large change in population of conformational states, meaning that only a few kcal/mol of energy (obtainable from ligand binding or pH change) could transform a disordered protein to a structured one. Thus, intrinsically disordered proteins may actually be energetically "poised to respond" to facilitate biological function. Several lines of computational evidence, generated using the eScape algorithm, support such a view. First, residues experimentally annotated as disordered exhibited distributions of lower predicted stability than structured residues. Second, the relative magnitudes of the average stability differences were small and thus consistent with possible population shifts between "structured" and "disordered" upon stability perturbation. Third, these stability differences were significantly correlated with disorder propensity, side chain volume, and experimental hydrophobicity scales. Finally, the thermodynamic information was used to train moderately effective support vector machine predictors of disorder. Although these novel predictors would benefit from technical refinement, their initial effectiveness suggests that progress in identification and classification of intrinsic disorder could be achieved by viewing disorder as part of a free energy continuum. In this new framework, the binary description would be replaced by a physical picture: a context-dependent estimate of conformational population.