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Biomolecular Reconfigurable Signal Processing via Intrinsically Disordered Proteins: From Interaction Prediction to Genetic Variability, Disease Links, and Drug Design

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Abstract:

Signal processing is critical in both engineering and biological systems. In biomolecular systems, signal transduction pathways are of critical importance in disease and regulation of cellular functions. Just like reconfigurable networks in engineering, biomolecular systems are emerging with similar properties. Proteins that do not fold to a state of stable, ordered 3-D structure (i.e. disordered proteins) are highly represented in signaling pathways and protein interaction networks that communicate and process information. Specific regions within these disordered proteins, however, can take on an ordered structure upon binding to a partner. While predicting disordered regions and interacting segments within these regions can be done with fair accuracy, the nature of the resulting protein-protein interactions has not been established. Using a Bayesian network framework, we categorize and identify interactions between binding segments of disordered proteins and their ordered partners (AUC=93.6% on test set). This framework enables us to investigate the underlying biological processes involved, including the sequential and structural determinants of these interactions. The model can be used to identify potential binding partners of disordered proteins as well as predicting their class and the secondary structure of the disordered segments binding to them. Examining features underlying the model provides a plethora of new and potentially useful biological information. The results also lend themselves to a strategy for rational drug design whereby disordered regions can be targeted with a high degree of specificity and small molecule peptide mimetics of their binding regions can be utilized as drugs.