Modeling Intrinsically Disordered Proteins

A number of neurodegenerative disorders such as Alzheimer's disease and Parkinson's disease involve the formation of protein aggregates. The primary constituent of these aggregates belongs to a unique class of heteropolymers called intrinsically disordered proteins (IDPs). While many proteins fold to a unique conformation that is determined by their amino acid sequence, IDPs do not adopt a single well-defined conformation in solution. Instead they populate a heterogeneous set of conformers under physiological conditions. Nevertheless, despite this intrinsic propensity for disorder, a number of these proteins can form ordered aggregates both in vitro and in vivo. As the formation of these aggregates may play an important role in disease pathogenesis, a detailed structural characterization of these proteins and their mechanism of aggregation is of critical importance. One problematic issue is that the characterization of intrinsically disordered proteins is quite challenging because accurate models of these systems require a description of both their thermally accessible conformers and the associated relative stabilities or weights. These structures and weights are typically chosen such that calculated ensemble averages agree with some set of prespecified experimental measurements; however, the large number of degrees of freedom in these systems typically leads to multiple conformational ensembles that are degenerate with respect to any given set of experimental observables. In this talk I will discuss a method for modeling these systems that is based on Bayesian statistics. A unique and powerful feature of the approach is that it provides a built-in error measure that allows one to assess the accuracy of the resulting ensemble. We apply the method to the intrinsically disordered proteins, tau protein and alpha synuclein, which have been implicated in the pathogenesis of Alzheimer's disease and Parkinson's disease, respectively. The models reveal specific patterns of long-range contacts that may play a role in the aggregation process.