Title: Ensemble Predictions of beta-sheet Protein Structures

In this talk, I will describe my work in the area of protein structure prediction. I will introduce new ensemble modeling techniques which can analyze and predict an entire landscape of structural solutions, rather than simple single answer optimizations. This philosophy has a broad impact on our understanding of protein folding properties.

To describe our methods, I will start by illustrating how these techniques have been applied to transmembrane beta-barrel proteins. I will introduce a new family of algorithms for investigating this family proteins based only on sequence information, broad investigator knowledge, and a statistical-mechanical approach using the Boltzmann partition function. This provides predictions of all possible structural conformations that might arise in-vivo, along with their relative likelihood of occurrence. Using a parameterizable grammatical model, these algorithms incorporate high-level information, such as membrane thickness, with an energy function based on stacked amino-acid pair statistical potentials to predict ensemble properties, such as the likelihood of two residues pairing in a beta-sheet, or the per-residue X-ray crystal structure B-value.

In the second part of this talk, I will show how to generalize our methods for modeling ensembles of generic beta-sheet structures. From this ability to compute a realistic representation of the conformational landscape, we build a coarse-grained model of the energy landscape which is used to simulate folding processes. We illustrate our methods for dynamics prediction by applying it to the folding pathway of the well-studied Protein G. With relatively very little computation time, we show that our program tFolder is able to reveal critical features of the folding pathways which were only previously observed through time-consuming molecular dynamics simulations and experimental studies.