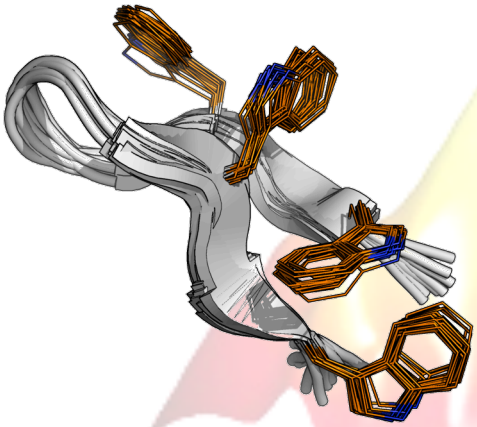

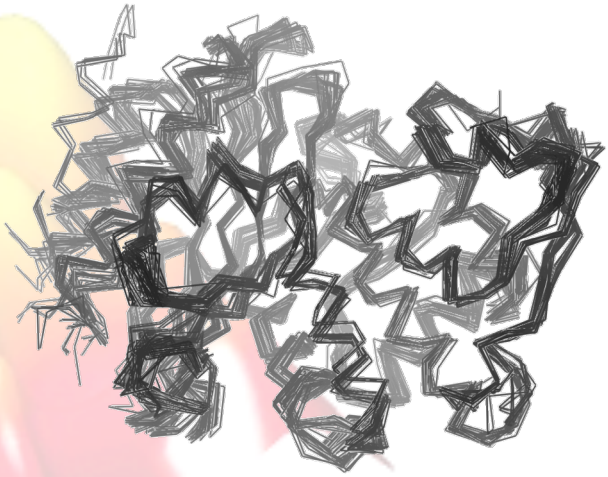

Applications for Physical Models of Proteins: Folding, Structure Prediction, and Crystallographic Structure Determination

Dr. Christopher D. Snow
Chemical and Biological Engineering
Colorado State University

Physical models play myriad roles in the understanding and engineering of proteins. One key bottleneck for structural biologists and protein engineers is the difficulty of routinely determining protein structural models via crystallographic x-ray diffraction or NMR. Computational structural biologists deploy physical models to attack the problem of protein structure prediction on multiple fronts.

For small, model proteins, we seek to determine not only the protein's structure, but also the kinetics and mechanism through which that structure is adopted. This is one interpretation of the protein-folding problem. For small model proteins, it is possible to understand the microsecond conformational dynamics using many thousands of relatively short simulations.

Larger proteins of high interest for biomedical or bioengineering applications are less tractable for characterization with detailed simulations. However, the need remains to predict the structure of these proteins, and to understand how the structure relates to the function of the molecules. Physical models can also be applied to these questions. We simple require a sampling algorithm for generating candidate protein conformations and an energy function that can effectively score/rank the potential energy of the different shapes. However, the current state of the art is insufficient to reliably improve upon mediocre initial models – current methods fail to move models into closer agreement with experimental data.

We are developing a new strategy for improved protein sampling that breaks the protein into pieces, provides these pieces with alternative positions, and relies on combinatorial optimization methods to search for the best combination of the fragments. To efficiently search the space of fragment combinations, we approximate the energy associated with a combination in terms of low-order contributions (i.e. one-body, two-body, three-body fragment interactions). The resulting search is analogous to optimization of a spin glass. We will discuss the pros and cons of the resulting graph-based models compared to traditional molecular dynamics simulations. Time permitting, I will compare the in silico recombination of protein fragments with a similar experimental project in which we have crystallized and determined the structure of proteins composed of recombined sequence blocks.