Kinetics and a Landscape Survey of Realistic Protein Folding Models

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Over the last 10-15 years a general understanding of the chemical process corresponding to protein folding has emerged from statistical mechanics. The principle of minimal frustration states that native contacts must be more favorable, in a strict statistical sense, than non-native contacts, in order for proteins to fold on physiological time scales. This result may seem quite natural, but the near isoenergetic character of productive native-like interactions, and non-productive non-native interactions inferred from the molecular force fields usually used in computer simulations, makes this a difficult task when trying to model folding realistically. The goal of this work was to create methods that would efficiently be able to characterize the global potential energy minima, and calculate their kinetic behavior.

We combined a minimal protein model that does well in predicting protein structure from sequence from the Wolynes Group of the University of California, San Diego, within the basin-hopping method of the Wales group of Cambridge University. In a basin-hopping search, random Monte Carlo Cartesian coordinate steps are followed with a numerical quasi-Newton minimization at constant temperature. By combining Monte Carlo and minimization the basin-hopping method has proven to be effective in identifying global energy minima of many different inorganic materials. For several different systems, we have found that

basin-hopping does find lower minima than previous simulated annealing protocols, but these still substantially agree with experimental structures. We see better minimization of local excluded volume, and Ramachandran energy terms, which sum to about $20\,kT$ on average. The configurational space search is rapid, and does not sample many different structures during a simulation. One method of improving the configuational search characteristics of the folding simulation would be to take internal coordinate moves around the phi and psi bonds of the protein backbone.

We have also combined the Wolynes group's reduced protein model and energy functions into the Wales group's software for locating saddle points on potential energy surfaces, thereby allowing the calculation reaction pathways. Recent results have produced transition states between folding minima. This result will facilitate the calculation of folding rates with energy functions that are transferable, but structurally realistic. We hope to identify the kinetic effects of non-additive terms, and also investigate the effects of persistence length and secondary structure formation.

References

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