Modeling the Conformational Flexibility of Proteins

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Proteins are involved either directly or indirectly in all biological processes in living organisms. It is now widely accepted that conformational changes of proteins can critically affect their ability to bind other molecules and that any progress in modeling protein motion and flexibility will contribute to the understanding of key biological functions. However, modeling protein flexibility has proven a very difficult task. Experimental laboratory methods such as X-ray crystallography produce rather few structures, while computational methods such as Molecular Dynamics are too slow for routine use with large systems. We will discuss how we can use dimensionality reduction techniques to transform the original high-dimensional representation of protein motion into a lower dimensional representation that captures the dominant modes of motions of proteins. For a medium-sized protein this corresponds to reducing a problem with a few thousand degrees of freedom to one with less than fifty. Although there is inevitably some loss in accuracy, we show that we can obtain conformations that have been observed in laboratory experiments, starting from different initial conformations and working in a drastically reduced search space. We will also discuss geometric problems that arise in the above context as well as the application of robotics-based probabilistic methods for exploring the conformational space of proteins.