

Characterization of large scale motions in proteins in relation to their function

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The complete characterization at the atomic level of a representative set of large amplitude conformational changes of macromolecules, or of their complexes, is needed in order to determine those that might be involved in their function. This remains a challenging task for large systems in the field of molecular simulation. The exclusive use of molecular dynamics for such characterization might not be necessarily the best choice for many reasons. Indeed, in order to characterize a large variety of collective motions, extremely lengthy simulations are required, and moreover some motions may never occur due to the complexity of the system and high energy barriers. A convenient approach to circumvent this difficulty is to rely on the topology of the potential energy surface that gives useful information on the possible low energy pathways for the conformational changes to occur. I will present how normal mode analysis, which takes advantage of the curvature of the energy surface near a given conformation, may be used to identify the important large scale motions that might influence function, and how these motions may be explored by a combined use of normal modes with other simulation techniques such as energy minimization or molecular dynamics simulations. I will present a few applications to illustrate the techniques that we have developed in our laboratory to explain how collective motions are involved in the formation of cavities and tunnels in some proteins which are important for their activity. Such applications also open new areas for the discovery or design of inhibitors for a given protein exhibiting global conformational flexibility.