Multi-Scale Modeling from Multi-Resolution Data: Unveiling Functional Motions of Macromolecular Machines

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Large-scale structural rearrangements in proteins and nucleic acids are important for a variety of functions including catalysis and regulation of activity. The recent developments in experimental methods such as cryo-electron microscopy (cryo-EM) have revealed structures and structural transitions of large-molecular assemblies at low-resolution. While most of the information on these dynamical transitions is based on experiment, computational methods must be employed to complement experimental observations. Indeed, by using theory to explore functionally important rearrangements observed in such low-resolution experiments, it is possible to gain insights into the mechanism of these transformations that are presently inaccessible to the experiments.

Normal mode analysis (NMA) can be used to gain biological insights. Recent developments in this field, such as elastic normal mode theory, allow calculations for molecular assemblies as large as viruses and ribosome. Using different levels of structure description, ranging from all-atom calculations to pseudo-atomic representations one can confirm or predict functional motions. In addition, NMA can be used to bridge the resolution gap between high-resolution X-ray structure and low-resolution structural data as obtained from cryo-EM experiments. Applications of these methods to study biologically important conformational change in systems such as the ribosome, viruses and the protein-conducting channel will be presented.