4ap Customized Bioengineering in Inhomogeneous Environments

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Biological molecules, such as proteins and DNA, interact and perform their respective functions in a variety of inhomogeneous environments such as surfaces and cellular cytoplasm. The ability to control and manipulate these interactions is increasingly valuable in science and technology. For example, directing the adsorption or tethering of biomolecules is in important in medical implants, protein arrays, DNA microarrays, biosensors, and chromatography. Due to the diverse behavior of proteins and nucleic acids, and the myriad of different environments in which they are found, modeling and prediction of these interactions aids in the advancement of such technologies.

The techniques and devices mentioned above demonstrate that we have entered a new era in bioengineering where the aim is to manipulate or control a small number of molecules or even a single molecule. Since such systems do not concern ensembles or populations, the one-size-fits-all strategies of correlation, scaling, and continuum theory cannot provide the predictive modeling capabilities. Molecular simulations provide a valuable tool to understand the biophysics involved at the atomic scale, but due to the complex energy landscape characteristic to biological molecules, and the long time scales associated with biological processes, the traditional brute force methods such as molecular dynamics and Metropolis Monte Carlo face significant limitations. To overcome some of these challenges, we have developed a novel class of Monte Carlo formalisms, termed Density-of-States based methods, that facilitate considerably the study of these macromolecules.

The power of these methods is two-fold. First, they allow effective sampling of the relevant phase space despite location on the energy landscape. This is accomplished through sophisticated Monte Carlo moves and techniques as well as artificially eliminating the energetic barriers associated with biological systems. Second, they connect the simulation results to “real world” thermodynamic quantities, such as entropies, free energies, heat capacities, and potentials of mean force, as a continuous function of temperature or reaction coordinate. Following a brief introduction to these methods, results for several systems of interest will be presented. These include proteins on surfaces, where different surface chemistries and topographies are examined, proteins in confined spaces, and DNA microarrays. The last includes a look into a new, united-atom model for DNA which reduces a nucleotide to three beads. This representation accounts for sequence and base stacking interactions while still allowing molecules of several hundreds of nanometers to be investigated, thus filling a length-scale gap in the multi-scale modeling of DNA.