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Special Issue Preface

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Macromolecular Systems Understood through Multiscale and Enhanced Sampling Techniques

Complex systems of contemporary interest simultaneously evolve on multiple spatiotemporal scales—they are fundamentally multiscale in nature. This volume focuses on multiscale systems constituted of N atoms evolving via classical mechanics and interatomic force fields. Given the many atoms involved in these complex systems, the question arises as to the possibility of introducing "coarse-grained" (CG) variables natural for characterizing their overall features. Since changes in the CG variables may involve the coordinated motion of many individual atoms, CG variables often evolve on time scales much greater than that of individual atomic fluctuations. In this sense, CG variables are special functions of the atomic positions and momenta that experience slower dynamics by filtering out high frequency fluctuations. The object of this volume is to present contemporary multiscale and ensemble methods that enable us to understand and model these systems.

Assemblies of thousands of atoms can readily be simulated via traditional molecular dynamics (MD). Larger systems, e.g., $>10^9$ atoms, can be modeled via continuum methods, while systems with lattice periodicity can be modeled using solid state techniques. However, biological and other macromolecular systems which exhibit complex dynamics across both micro- and mesoscales present challenges for chemical theory and computation. Examples of these systems include

- intelligent nanoparticles that respond to their micro-environment by performing selected chemical functions
- nanocapsules for drug delivery or medical imaging
- viruses and virus-like particles
- ribosomes, mitochondria, and other subcellular structures
- ultramicro bacteria
- fiber bundles for solar energy harvesting

These systems are constituted of many atoms which interact strongly via bonded, Coulomb, van der Waals, and other forces. These forces underlie direct interactions between atoms, as well as indirect effects such as hydrophobic/hydrophilic interactions. Through these forces, the atoms form molecules, which, in turn, constitute higher-level assemblies. As larger assemblies tend to evolve much more slowly than individual atoms, these systems simultaneously change on a spectrum of time scales. This is just one way by which their behavior takes on multiscale character. The occurrence of rare events associated with large energy barriers or entropic effects can also underlie dynamics involving the coupling of processes across multiple scales in space and time. For example, a macromolecular assembly may experience occasional peptide bond cleavage followed by long periods of quasi-equilibrium fluctuating behavior.

Since complex systems involve the fluctuating dynamics of many atoms, underlying a CG theory is ultimately a microscopic stochastic model. This suggests that multiscale theory should not only provide governing equations for the coarse-grained state but also a probabilistic accounting of the fine-grained states consistent with the slowly evolving coarse-grained one. While the CG variables are slowly evolving, the microscopic ones are simultaneously rapidly visiting an ensemble of configurations. The Gibb's hypothesized equivalence of long-time and ensemble averaging indicates the close relationship between multiscale dynamical theory and ensemble methods.

A traditional starting point for understanding the statistical state of an N-atom system is the Liouville equation (LE). This equation is the conservation law of the probability ρ of the microscopic state. Most multiscale analyses ultimately yields governing equations for the CG state and the coevolving probability density of the microstate from the LE. The advantage of adopting this deductive perspective is that calibration of continuum equations with experimental or MD data can be avoided. The deductive approach, starting with the LE equation, yields governing CG equations, all factors within which are determined by interatomic force fields based on ensemble methods.

The concepts underlying multiscaling also arise in the design of simulation algorithms. Conventional Monte Carlo and MD proceed through configuration space via atomic-scale moves. This provides a procedure for generating an ensemble of microscopic states for relatively small systems. With increasing complexity of macromolecular and other assemblies, an algorithm must sample configurations which vary over a large ensemble of CG states, e.g., those belonging to free energy basins characterized by different values of an order parameter. In this case, enhanced sampling may greatly accelerate the discovery of multiple free energy basins. To arrive at a fuller perspective of the free energy landscape, a sampling calculation must avoid being trapped in a single basin.

A wide variety of enhanced sampling methods have been set forth; these include introducing basic moves on larger scales, replica exchange which brings the system from one macroscopic state to another, and methods where free energy barriers are artificially reduced. Several are presented in this volume.

The rare event problem is a manifestation of the inherent roughness of the underlying potential energy surface that describes complex molecular systems. Rough potential surfaces consist of a vast number of local minima separated by barriers of sufficient height to prevent frequent crossing between minima. This roughness renders extremely difficult the problem of sampling conformational equilibria in order to generate potentials of mean force from which free energy differences and CG models are derived because these potentials require extensive sampling. The development of robust algorithms capable of producing this level of sampling remains one of the outstanding computational challenges in molecular science. Algorithms such as replica-exchange, hyperdynamics, metadynamics, temperature-accelerated molecular dynamics, adiabatic

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free energy dynamics, transition path sampling, and numerous others all attempt to address this problem with their own sets of assumptions and limitations. At present, it is not clear whether it is more fruitful to pursue universally applicable techniques or to focus on the development of approaches more tailored to specific classes of rare-event problems.

This volume contains three types of articles:

- identification of CG variables
- derivation and implementation of equations of coupled CG variables and *N*-atom state probability coevolution
- construction of ensembles

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