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Original Research

Multiscale simulation of microbe structure and dynamics

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ABSTRACT

A multiscale mathematical and computational approach is developed that captures the hierarchical organization of a microbe. It is found that a natural perspective for understanding a microbe is in terms of a hierarchy of variables at various levels of resolution. This hierarchy starts with the N -atom description and terminates with order parameters characterizing a whole microbe. This conceptual framework is used to guide the analysis of the Liouville equation for the probability density of the positions and momenta of the N atoms constituting the microbe and its environment. Using multiscale mathematical techniques, we derive equations for the co-evolution of the order parameters and the probability density of the N-atom state. This approach yields a rigorous way to transfer information between variables on different space-time scales. It elucidates the interplay between equilibrium and far-from-equilibrium processes underlying microbial behavior. It also provides framework for using coarse-grained nanocharacterization data to guide microbial simulation. It enables a methodical search for free-energy minimizing structures, many of which are typically supported by the set of macromolecules and membranes constituting a given microbe. This suite of capabilities provides a natural framework for arriving at a fundamental understanding of microbial behavior, the analysis of nanocharacterization data, and the computer-aided design of nanostructures for biotechnical and medical purposes. Selected features of the methodology are demonstrated using our multiscale bionanosystem simulator DeductiveMultiscaleSimulator. Systems used to demonstrate the approach are structural transitions in the cowpea chlorotic mosaic virus, RNA of satellite tobacco mosaic virus, virus-like particles related to human papillomavirus, and iron-binding protein lactoferrin.

1. Background

Microbes such as viruses and bacteria are organized hierarchically. For example, a virus is constituted of atoms assembled into macromolecules which, in turn, constitute several substructures. For a nonenveloped virus, the latter are genetic material and the capsid. For an enveloped system such as dengue virus, there is an outer protein net, a lipid zone, and an inner RNA-protein complex. Accompanying this hierarchical organization is a spectrum of time and length scales. The objective of this article is to present our strategy for developing a theory that parallels the hierarchical organization of microbes with a mathematical and computational framework for efficiently modeling microbial systems.

Modern nanocharacterization experimental methodologies make the development of microbial simulation approaches timely. For example, Atomic Force Microscopy (AFM) is employed to investigate a range of biological processes from unfolding of a single molecule to nano-indentation of viruses (Brown et al., 2007; Florin et al., 1994; Roos et al., 2010). A standard AFM can scan a sample more than 10 thousand times per second, yielding an ensemble measurement that parallels a statistical mechanical approach. Thus, to model such experiments computationally, a framework is needed that addresses structures in a range of sizes from single macromolecules to viruses and bacteria, without losing information at any time or length scale.

Nanotechnical methods for characterizing macromolecular assemblies include AFM (Hinterdorfer and Dufrene, 2006), Ion Mobility – Mass Spectrometry (Bernstein et al., 2009; Ruotolo et al., 2005; Uetrecht et al., 2010), chemical labeling (Beardsley et al., 2006), and nanopore measurements (Zhou et al., 2008). While these techniques provide information on structure, they are coarse-grained in that they do not resolve all-atom configurations. X-ray and electron microscopy provide detailed structure but do not provide information on dynamics (Barthel and Thust, 2008; Gaffney

Abbreviations: AFM, atomic force microscopy; CCMV, cowpea chlorotic mosaic virus; STMV, satellite tobacco mosaic virus; HPV, human papillomavirus; RMSD, root mean square deviation; CG, coarse-grained; MD, molecular dynamics; QM/MM, quantum mechanics/molecular mechanics; OP, order parameters; DMS, DeductiveMultiscaleSimulator.

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and Chapman, 2007). Solid-state NMR techniques do provide an ensemble of atom-resolved structures but cannot be used to give overall structure for a macromolecular assembly (Dvinskikh et al., 2006; McDermott, 2009; Svergun and Koch, 2003; Bauer et al., 2011). Thus, we suggest that a method which integrates multiple types of nano-characterization data with a predictive all-atom simulation approach would greatly advance the understanding of microbial systems; a preliminary approach of this type has been presented earlier (Pankavich et al., 2008).

The above and other (D'Alfonso et al., 2010; Florin et al., 1994; Goldstein et al., 2003; Lyon et al., 1998) experimental techniques can be performed under various microenvironmental conditions such as salinity and pH. These variations modulate interactions between solvent accessible parts of the microbe and host medium atoms, inducing structural and functional changes of the former. For example, viral RNA is found to be stable and facilitate encapsulation in a 2:1 electrolyte due to "tight" electrostatic binding with Mg^{2+} ions, but loses tertiary structure in a 1:1 electrolyte (Freddolino et al., 2006; Singharoy et al., 2010b). An all-atom model is often essential to correctly probe these interactions. Structural fluctuations and internal dynamics are a central feature of several biological processes. For example, in the presence of an energy barrier, the atomic fluctuations allow self-organization of lipids in membranes (Sung and Kim, 2005). Fluctuations are also important in expressing the conformational diversity of macromolecules that allows for large deformations upon drug binding (Rohs et al., 2005). Similarly, excessive fluctuations in viral epitopes appear to diminish immune response (Joshi et al., under review) and may explain the dependence of immunogenicity on their fluctuations (Nowak, 1996). Thus, an all-atom description is necessary to account for all sources of fluctuation in simulating aforementioned processes, and hence has been the basis of traditional molecular dynamics (MD) approaches (van Gunsteren and Berendsen, 1990).

All-atom MD simulations of macromolecular assemblies involving more than a million atoms (such as a virus in an explicit solvation environment) require large computational capabilities and have been accomplished using more than 1000 processors for a single time-course. To simulate viruses over microseconds on such a platform would require engaging this many processors for months (assuming the usual femto-second MD timestep). This restricts traditional MD to less than 50 nm structures and hundred nano-second timescales. Hence, incorporating information about atomic processes into microbe modeling has been a challenge. Billion-atom MD simulations have been accomplished (Abraham et al., 2002; Ahmed et al., 2010; Sanbonmatsu and Tung, 2006, 2007; Schulz et al., 2009; Germann et al., 2005). However, these simulations neglect Coulomb interactions, bonded forces, or the rapidly fluctuating proton. All the latter are central to biomolecular structure and dynamics. Thus, such billion-atom simulations should not be viewed as the standard for microbial modeling.

Multiscale approaches have been developed to address the above computational challenges. These methods yield insights into the dynamics of a system as it simultaneously evolves across multiple scales in space and time. By the definition adopted here, a multiscale method simultaneously accounts for processes on a range of scales. This scale bridging requires development of models for various scales which are thermodynamically and structurally consistent with each other (Noid et al., 2008a). For example, the deductive multiscale methodology (Section 1.1) maintains the effect of all degrees of freedom while greatly accelerating simulations. The advantages and shortcomings of this and other methods are compared in Section 1.3.

1.1. Deductive multiscale analysis

Deductive multiscale analysis is a collection of concepts and mathematical techniques for understanding the dynamics of a complex system as derived from a primitive model cast at the finest scale of interest. In essence, it adheres to the basic program of statistical physics that started, for example, with Gibbs (Gibbs, 1981) and Liouville (McQuarrie, 1976). A goal of our studies is to retain information on all scales simultaneously and capture the dynamic cross-talk between processes on the relevant spectrum of space-time scales. For example, overall viral structure affects atomistic fluctuations. These fluctuations mediate the stability of entire structure through the free-energy driving forces, illustrating an interscale feedback underlying microbial processes.

The main steps in deductive multiscale analysis can be summarized as follows:

1. The starting point is a primitive model that is cast in terms of variables describing the systems at the shortest space-time scale. For the present case, the fine-scale description is cast in terms of the positions and momenta of all the atoms in the system. This description is a viable starting point as it contains much of the physics of biological systems and, through deductive multiscaling, results in coarser-grained model which needs minimal recalibration given an interatomic force filed (e.g., CHARMM (MacKerell et al., 2001) or AMBER (Ponder and Case, 2003)).
2. Deductive multiscaling then facilitates the identification of coarse-grained variables (order parameters) that describe the salient features of a system on longer space-time scales. For microbial simulations, these order parameters (OPs) capture overall structural information, e.g., the position, shape, size, and orientation of major components of the microbe.
3. Deductive multiscaling provides criteria for determining the completeness of the set of OPs (Section 2.4).
4. Rigorous Smoluchowski/Langevin equations for evolving the OPs are then derived. These equations are stochastic because the behavior of matter at the nanoscale is strongly influenced by the fluctuating states of the atomic configurations. To address this, deductive multiscaling yields the co-evolving quasi-equilibrium ensemble for fine scale (atomistic) states consistent with the instantaneous values of OPs. Thus, the all-atom description of the system is retained.

In summary, deductive multiscaling is a method for deriving equations capturing the two-way flow of information between fine- and coarse-scale variables. With this, it probes the interplay of far-from-equilibrium and equilibrium processes that underlies many microbial behaviors. For example, much of the structure of membranes and DNA or RNA corresponds to a free-energy minimizing state. In contrast, the self-assembly of proteins and genetic material into a virus, and the diffusion of molecules across a membrane or within a cell, are far-from-equilibrium processes. Deductive multiscaling provides a way to obtain the free-energy gradients that drive the afore-mentioned processes.

1.2. Multiscale analysis

As the OPs evolve slowly in time, they change the conditions determining the ensemble of all-atom configurations. Since atomistic variables change rapidly, the associated probability takes an equilibrium-like form as suggested by the Gibbs-hypothesized equivalence of long-time and thermal averages. This probability then influences the factors in the equations of OP dynamics. The resulting transfer of information from the OPs to the atomistic configurations (characterized by the quasi-equilibrium probabilities) and, in turn, back to the OPs, is summarized in Fig. 1. This provides a natural way to transfer information between descriptions at various scales that are rigorously derived from the