2002-Pos

A New, Fundamental Multiscale Modeling Framework Based on the Relative Entropy

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Our understanding of biology stems from models at many resolutions, as we seek from detailed atomic-scale interactions simpler emergent physical principles to support our understanding and to produce useful theoretical reductions and tractable simulations. In particular, multiscale methods coupling coarse-grained and atomic models are essential to modeling, predicting, and understanding the basic driving forces that operate across many biomolecular length and time scales. Yet, though coarse-graining strategies exist, it has been challenging to identify universal approaches to the multiscale problem that build systematic, quantitative connections between atomic interactions and reduced models.

We have created a powerful, rigorous theoretical framework that addresses this problem. Its focus is the relative entropy, an information-theoretic and statistical-thermodynamic quantity that measures the information lost when moving from a detailed to coarse-grained description of a system. We postulate that the most descriptive physical principles and simple models are those that minimize this quantity, hence minimizing the physical information lost when atomic detail is removed. Importantly, we show that this concept unifies and broadens a number of established statistical-mechanical principles. For the first time, the relative entropy provides a general, systematic framework for multiscale modeling.

A practical benefit is that the relative entropy suggests how to transform atomistic models into reduced ones that capture the same physics, enabling seamless integration of models spanning scales. We describe a family of algorithms that optimize coarse-grained molecular models by minimizing the relative entropy numerically. These coarse-graining algorithms are general to arbitrary models and the first to offer a universal metric for model quality. We describe the application of these algorithms to the development of simple models of water for modeling large-scale association processes driven by hydrophobic interactions, and to models of peptides for interrogating early steps in aggregation.

2003-Pos

Using Statistically Significant Correlated Motions of Residues in a MD Based Approach to Investigate Allostery in Ubiquitin Conjugating Protein

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Ubiquitin conjugating proteins (E2s) are an important component of the ubiquitin proteasome pathway. E2s interact with ubiquitin activating enzyme (E1) and ubiquitin ligases (E3s) to transfer ubiquitin to target proteins to mark them for degradation. In some E3s, RING domains act as scaffolds to bind E2s and target proteins so that the ubiquitin can be directly transferred from the E2 to the target protein. This ubiquitin transfer has been shown to be allosterically regulated: E3 RING domain binding to E2 at one site promotes ubiquitin release from the active site cysteine (~15Å distance) without substantial conformational change in E2. Previous studies used statistical coupling analysis (SCA) to identify clusters of residues that might transmit information. Here, we use a novel information-theory approach to identify residues with statistically significant correlated conformations in a set of equilibrium molecular dynamics simulations. From the matrix of correlations between residues, we observed substantial coupling between an E2's active site and its E3 RING domain binding site. However, in the I88A mutant, the pattern of correlations is disrupted, consistent with the experimental observation that this I88A mutation abrogates the allostery in the E2s. Thus, our approach is sensitive enough to identify effects of single point mutations in the protein. Unlike SCA, which infers couplings from many protein sequences, our approach identifies couplings between residues in individual proteins, some of which coincide with residues identified by SCA. As our approach is general and sensitive to small physical-chemical differences in sequence, structure, and dynamics, we can apply our approach to study similarities and differences in the allosteric networks of different E2s in order to better understand how protein degradation is regulated, also providing a mechanistic insight of the process.

2004-Pos

Toward Accurate Simulations of Cu+ - Protein Binding: Computational Studies of Model Systems with a Polarizable Force Field

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Cu+ binding and transport plays an important role in biological processes. It would be advantageous to have the ability to accurately determine their binding affinities via computational means. At the same time, simulation of ions presents a number of fundamental and practical difficulties. We have compared energetic and structural properties of the Cu+ ion complexes with small model molecules. While these simulations without explicit treatment of electrostatic polarization have in some cases lead to more than three-fold errors in the magnitudes of the binding energies, similar calculating with a polarizable force field produced results in good agreement with the available experimental and high-level quantum mechanical data. We believe that this work (a) demonstrates the importance of explicit treatment of the electrostatic polarization in ion-transport and binding simulations and (b) opens a road to accurate *in silico* determination of Cu+ and other ions binding affinities with proteins.

2005-Pos

Simulation Studies of a TRI-PEDAL, Protein-Based Artificial Molecular Motor

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Though the biological function of many natural molecular motors is fairly well established, many structure-function details responsible for motor performance remain vague or unknown completely. Recently, we have undertaken a new bottom-up approach to understanding biological molecular motors by designing and building an artificial, protein-based molecular motor dubbed the Tumbleweed (TW). The TW is a purely diffusive motor construct consisting of three DNA-binding proteins attached to a designed, protein-based central hub, where directional stepping along a DNA track is maintained by a temporally periodic external chemical supply. To better understand important design and performance characteristics of the TW, coarse-grained Langevin Dynamics (LD) simulations and numerical solutions to the Master Equation (ME) were carried out. The LD approach, which is a single motor simulation, is particularly suitable for exploring the diffusional behavior of the system, where the ME approach, which models an ensemble of motor states, is best suited for statistically exploring the parameter space of the system and the interaction of processes at different time scales. We present results from these two theoretical approaches that illuminate not only important design and experimental considerations, such as motor geometry and track spacing, but also produce unexpected diffusional behavior. Of particular interest is that the addition of certain internal symmetric potentials can increase motor performance. For example, the addition of a non-specific binding potential, symmetric about the DNA track, can double motor speed by replacing some of the 3D diffusional search by a relatively fast 1D diffusional slide along the DNA. This, and other symmetric potential inputs that increase motor performance by subtly amplifying asymmetries in the system, are not only fundamentally interesting but also may be applicable to any molecular motor that incorporates a diffusional search in its stepping cycle.

2006-Pos

Thermodynamic Efficiency Out of Equilibrium

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Equilibrium thermodynamics satisfactorily explains the efficiency of macroscopic machines, whose operation is posited as a quasi-static, infinite time, zero power process exemplified by the Carnot heat engine. Microscopic biomolecular motors differ markedly from their macroscopic counterparts, as they are subject to large fluctuations, operate far from equilibrium, and by necessity accomplish their tasks in finite time with non-zero power. They thus demand novel non-equilibrium frameworks. We explore thermodynamic length as an analytic framework for understanding the physical limits on biomolecular motors. Thermodynamic length defines the length of a non-equilibrium transformation as the root-mean squared fluctuations of the variables conjugate to the control parameters. It is a natural measure of distance between equilibrium thermodynamic states, but unlike the free energy change explicitly depends on the path taken through thermodynamic state space. Thermodynamic length equips thermodynamic state space with a Riemannian metric and thus facilitates the discovery of minimum thermodynamic length paths, which minimize the dissipation for slow, but finite time, transformations. We derive analytic expressions for Fisher information (related to the derivative of thermodynamic length) in simple bistable energy landscapes, finding that it can vary by several orders of magnitude across a given energy landscape. Our novel dynamic programming approach allows more detailed analysis of these model landscapes, establishing that thermodynamic length analysis accurately predicts the instantaneous dissipation of