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2023-Pos
BIBEE: a Rigorous and Computationally Efficient Approximation to Continuum Electrostatics
Jaydeep P. Bardhan.
Rush University Medical Center, Chicago, IL, USA.
The computational costs associated with modeling biomolecular electrostatics using continuum theory have motivated numerous approximations, such as Generalized-Born (GB) models, that can be computed in much less time. Unfortunately, most of these approximate models abandon physics in favor of computational efficiency. On the other hand, a new approximation method for molecular electrostatics, called BIBEE (boundary-integral-based electrostatics estimation), retains the underlying physics of continuum theory, but is nearly as efficient as Generalized-Born models. The BIBEE approach derives from well-known results in potential theory and the theory of boundary-integral equations. Three main results demonstrate the value BIBEE may hold for biomolecular analysis and design. First, the integral-equation theory clarifies the origin of accuracy of the Coulomb-field approximation (CFA). Second, BIBEE models offer significantly better accuracy for individual pairwise interactions, relative to GB methods. Third, BIBEE readily provides provable upper and lower bounds to the electrostatic solvation free energy of the original (exact) continuum-theory problem.

2024-Pos
Evaluating Empirical Force Fields Through Combined QM/MM Computations of the Vibrational Stark Effect
Ashley L. Ringer, Alexander D. MacKerell, Jr.
University of Maryland Baltimore, School of Pharmacy, Baltimore, MD, USA.
The proper description of the electric environment of the interior of macromolecular structures is a critical challenge for force field methods. To test and validate the CHARMM force field's ability to describe this electric environment, combined QM/MM calculations have been used to calculate the vibrational Stark effect (VSE). The Stark effect refers to the characteristic shift of a specific vibrational frequency upon the introduction of an electric field. In this work, we calculate the Stark shift of several experimentally characterized Stark effect probes (5-cyanoindole, methyl thiocyanate, and fluorobenzene) in several solvents. The solvent environment around the probe is sampled through 20 ns molecular dynamics simulations of each molecule surrounded by several hundred explicit solvent molecules. From these simulations, two hundred snapshots of the solvent environment are collected for the QM/MM analysis. The QM/MM computation uses correlated electronic structure methods to calculate the vibrational spectrum of the VSE probe in the field created by the solvent molecules, which are treated as MM atoms with the CHARMM force field. From these computations, an average Stark shift is determined for each probe molecule and compared to experimental measurements. This information can be directly related to the electric field surrounding the probe molecule, and therefore may be used as a direct test of the ability of a force field to reproduce the electric field around those functional groups. Information from these calculations will act as the basis for additional optimization of the force field to more accurately represent the electric fields in macromolecules.

2025-Pos
Weighted Ensemble Path Sampling for Efficient Calculation of Steady State Properties
Divesh Bhatt, Andrew A. Petersen, Daniel M. Zuckerman.
University of Pittsburgh, Pittsburgh, PA, USA.
Steady states are common in biological processes, most famously in enzymatic catalysis. We present a rigorous path sampling procedure, generalizing the ''weighted ensemble'' (WE) method, to attain a steady state (SS) efficiently. We apply this procedure to several different systems, from toy models to the folding of the atomistic Trp cage mini-protein. For systems without significant intermediates, we find that the SS-WE procedure is able to attain steady state fairly efficiently. However, for systems with significant intermediates, we develop an enhanced version of SS-WE that shifts probability to speed-up the establishment of a steady state, without perturbing the system's natural dynamics. The enhanced SS-WE approach is able to attain a steady state in significantly less time for systems with significant intermediates, and gives correct results for the steady state rates and probability distribution. First-passage rates are also obtained simultaneously.

2026-Pos
Simulations of Binding Free Energy of Targeted Nanocarriers to Cell Surfaces: the Effects of Antigen Flexural Rigidity, Glycocalyx Resistance, and Shear Flow
Jin Liu, Neeraj J. Agrawal, Portonovo S. Ayyaswamy, David M. Eckmann, Ravi Radhakrishnan.
University of Pennsylvania, Philadelphia, PA, USA.
We develop an equilibrium mesoscale model to study the binding free energy of functionalized nanocarriers (NC) to cell surfaces, which plays a central role in targeted drug delivery. Our model is parametrized to mimic interactions between intercellular adhesion molecule 1 (ICAM-1) on cell surface and anti-ICAM (antibody) on NCs and accounts for ICAM-1 diffusion and flexure, bond stiffness, effect of glycocalyx, and shear flow; parameters are chosen from several independent literature experiments. Using umbrella sampling in conjunction with Monte Carlo simulations, we compute the potential of mean force (PMF) as a function of distance between the NC and the cell surface. Our results show that the PMF landscape is rugged along the distance of the NC from the cell surface with multiple equilibrium points separated by free energy barriers of comparable magnitudes. Calculations reveal: (1) a significant effect of the antigen flexural rigidity, namely with decreasing flexural rigidity, even though the multivalency of binding increases, we record decrease in the binding free energy due to increasing entropic penalty; (2) The presence of glycocalyx does not alter multivalency, but significantly reduces the binding free energy; (3) Hydrodynamic shear stress plays a central role in mediating the binding conformations and alters the PMF landscape. Our results provide quantitative assessments of the effects of tunable/controllable properties on the binding of NCs to cell surfaces. Our model provides a rational and unique approach to bridge single molecule and biophysical measurements at the molecular scale with microscopy and flow experiments at the micro and macroscales. This integrative step will enhance optimization of delivery vehicles for use in targeted therapeutics.
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2027-Pos
Multi-Body Knowledge-Based Potentials for Protein Structure Prediction Evaluation
Yaping Feng, Robert L. Jernigan, **Andrzej Kloczkowski**.
Iowa State University, Ames, IA, USA.
Knowledge-based potentials have been widely used in the last 20 years for fold recognition, evaluation of protein structure predictions from amino acid sequences, ligand binding, protein design, and many other purposes. The most commonly known are two-body residue-level contact potentials, especially those first introduced by Miyazawa and Jernigan in 1985, and then rederived using an updated, larger protein dataset in 1996. Dense packing of residues in globular proteins is one of their characteristic features. Because of such dense packing cooperative multi-body interactions, especially in protein cores are important. The four-body contact potentials and short-range interaction potentials have been derived by considering different aspects of protein structures than those used to derive pair-contact potentials. The four-body contact potentials are appropriate for representing the cooperative parts of the protein folding process, and we have shown that they are quite successful for recognizing the native structures among hundreds or even thousands of decoys from the Decoys'R'Us database. Short-range interaction energies allow us to estimate free energies from the statistical distribution of local conformational descriptors. We developed two types of four-body potentials: sequential and non-sequential ones. We have found that combining the former ones with short-range interactions yields excellent results for threadings, that significantly outperforms all other methods for coarse-grained models of proteins. We have developed also our knowledge-based potential server http://gor.bb.iastate.edu/potential for coarse-grained protein energy estimations that uses two types of four-body potentials, short-range potentials, and 23 different two-body potentials.

2028-Pos
Prediction of Calcium Binding Site in the RCK1 Domain of BK_{Ca} Channel Using Multisite Cation Model
Akansha Saxena[1], David Sept[2].
[1]Washington University, St Louis, MO, USA, [2]University of Michigan, Ann Arbor, MI, USA.
Calcium plays a major role in controlling the opening and closing of the large conductance BK_{Ca} channels. Two high affinity binding sites have been identified in the channel structure and one of these sites is the DRDD loop in the N-terminus of the RCK1 domain. Mutation of the first aspartate in this conserved DRDD motif significantly reduces Ca^{2+} sensitivity and hence this residue has been implicated as a coordinating group in the binding site. Here we present results on the prediction of the Ca^{2+} binding site based on a series of detailed computational studies. We use a novel multisite cation model for calcium ion to accurately simulate the ion-coordination. The basic protocol involves multiple