accurate, yet computationally more efficient_and perhaps even better suited for supramolecular assembly dynamics modeling_than standard docking algorithms. Here, the relative efficacy, merits and demerits of RDIMs for estimating protein-protein interactions examined in the context of two key binding domains, namely myosin:actin and G-actin:G-actin.

2017-Pos

Automated Protein-Insertion into Membranes for Molecular Dynamics Simulation Set-Up Using Taragrid

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Given a known membrane protein structure, a crucial and non-trivial preparation step in order to perform simulations of the protein in a lipid bilayer is the creation of the equilibrated bilayer-protein system. TaraGrid links an implicit protein force field with standard MD packages to automate this process. In the initial steps TaraGrid places the protein into the membrane and carves any water molecules out of the protein volume. It also erases as many lipids as necessary to conserve the bilayer density. In the main optimization phase TaraGrid calculates intermolecular forces between the protein and the molecules of the bilayer-solution system. Molecules that are within the protein volume are assigned a force that pushes them out of that volume. Molecules outside of the protein surface are assigned a linear combination of electrostatic and van-der-Waals forces. These forces are passed to a subsequent MD step carried out with a standard MD package, to obtain new peptide and water positions. This procedure enables creation of realistic and reproducible starting conformations for membrane-protein simulations within a reasonable time and with minimal intervention. Presently TaraGrid is tested to interact with NAMD and GROMACS, but as a standalone tool it is designed to work with any existing MD package.

2018-Pos

Coarse-Graining Electrostatics in Multiscale Molecular Simulations of Proteins

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All-atom molecular dynamics (MD) simulations are a powerful tool to investigate the structure and function of biomolecular systems. Nonetheless, within the atomistic framework it remains computationally unaffordable to thoroughly sample size and time scales that are critical to most of the biological processes both in vitro and in vivo. Coarse-grained (CG) schemes have been introduced to overcome these limitations; nonetheless, many issues, such as the lack of universality and transferability, still afflict CG models and limit in turn their general applicability to a vast class of relevant biological problems.

We introduce a reliable and robust scheme to account for the intrinsic non-radial nature of backbone-backbone interactions in CG molecular dynamics simulations of proteins. Specifically, we define a new CG potential term, which, mimicking the backbone dipole-dipole interactions, is able to naturally stabilize elementary secondary structure motifs, such as α-helices and β-sheets, and to modulate basilar transitions to super-secondary structure assemblies. Moreover, the scheme can properly describe the long-range electrostatic contributions in a multiscale MD framework, contributing to an accurate description of protein-ligand and protein-protein recognition. Thus, this novel scheme represents a promising step towards the development of a CG force field able to take into account intrinsic anisotropy of protein structures, leading to an improved description of the structural and dynamic properties of protein assemblies and networks.

2019-Pos

Polymer Translocation Through a Nanopore in an Interacting Membrane

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The translocation of polymers through nanopores in membranes occurs in many biological processes, such as proteins transporting through membrane channels, DNA and RNA translocating across nuclear pores, and drug delivery. The mechanism of the translocations has attracted a lot of attention from experiments, analytical theories and computer simulations. In a recent simulation study, the influence of pore-polymer interaction on the polymer translocations was discussed. Some experiments implied that the interaction between polymers and membranes might play an important role in the polymer translocation through membranes. In the present work, we use dynamic Monte Carlo simulations to study the effects of interaction between polymer segments and the membrane on the translocation of polymer chains through an interacting membrane from *cis* side (high concentration of chains) to *trans* side (zero concentration). Results show that there is a critical adsorption point ϵ_c of the interaction strength ϵ . We find the translocation timeτ is almost independent from ϵ for$\epsilon < \epsilon_c$ and $\tau = f(exp(\epsilon), n)$ for $\epsilon > \epsilon_c$, where n is the length of polymer chains. We estimate the value of the critical adsorption point ϵ_c is about -0.3, which is in good agreement with previous results in many literatures studying the adsorptions of polymers on surfaces.

2020-Pos

Conservative Algorithm for an Adaptive Change of Resolution in Mixed Atomistic / Coarse-Grained Multiscale Simulations

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Understanding complex materials often requires investigating multiple, tightly coupled time and length scales. Neither atomistic nor coarse-grained simulations are often able to adequately capture all the relevant scales. To combine the efficiency of coarse-grained models with the accuracy of atomistic models for systems that require atomistic resolution only locally, for example at an interface, mixed-resolution models have been developed. These models use a coarse-grained description for the part of the system distant from an active site and atomistic description for the active site and its direct environment. Since the active zone may diffuse during a simulation, the simulation algorithm needs to permit an on-the-fly reclassication of atoms as they transition between the high- and low-resolution regimes. In this paper, we derive a conservative Hamiltonian and present an explicit symplectic integrator for mixed-resolution systems that allows for such a change in resolution of selected groups of atoms during a MD simulation.

2021-Pos

Hydrogen-Bonding Strengths in Pyrrolidinyl Peptide Nucleic Acid and DNA Base Pairs: A Density Functional Theory (DFT) Study

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The H-bond strengths of the single base pair formed from Pyrrolidinyl Peptide Nucleic Acid (PNA) and charged as well as neutral Deoxyribonucleic Acid (DNA) were studied using the density functional theory. The B3LYP/6-31+G(d,p) level of theory was employed for evaluating the binding energies and structural parameters of heterogeneous and homogeneous base pairs. The strongest H-bond strengths were obtained from the heterogeneous base pairs, yielding the binding energies of -29.9 and -18.9 kcal/mol for the PNA-GC-DNA and PNA-AT-DNA base pairs, respectively. In contrast, a dramatic change on the H-bond strengths was observed from the charged homogenous base pairs with the binding energies of -6.2 and $+10.2$ kcal/mol for the DNA-GC-DNA and DNA-AT-DNA base pairs, respectively. With the neutralization of negative charges in the DNA backbone, the corresponding values of -29.1 and -11.7 kcal/mol were elucidated from the Na-DNA-GC-DNA-Na and Na-DNA-AT-DNA-Na base pairs, respectively, proving that the repulsion between two negative charges in the phosphate backbone plays a significant role to the H-bond interactions in base pairs. In addition, a high specificity and preferential binding between the pyrrolidinyl PNA and DNA base pairs were also observed.

2022-Pos

Protein Classification Based on Physicochemical Descriptors

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ystematic and efficient analysis of proteins on the proteome scale requires their classification into meaningful sub groups. Approaches to the problem are either top-down, following the evolutionary pathways (SCOP, CATH) and bottom-up, where structures are compared pairwise and aggregated to clusters (DALI). Here we present a novel way of protein classification based on physicochemical descriptors. Atomistic structures are for classification purpose overly rich in information and we distilled biologically relevant features by projecting from the structure space into a lower dimensional descriptor space. Chosen descriptors fall into three groups, sequence dependent, topology, and overall structure and consist of amino acid distribution, charge, hydrophobicity, average path length, cluster coefficient, helix content, sheet content, solvent accessible surface area, radius of gyration, besides others. All descriptors were corrected for chain length and normalized by the standard deviation.

Over 3000 representative and non-redundant structures from the pdb Cluster90 were mapped to descriptor space and clustered. The identified clusters coincide to large extend with those from existing classification methods. Our method provides, unlike others, a direct measure for the distance between any two proteins and is easily expandable by for instance descriptors for molecular dynamics.

Nothing about protein structure classification makes sense except in the light of evolution.
Valas, R.B., Yang S., and Bourne P.E. Curr Opin Struct Biol 2009 19:329-34 Multipolar representation of protein structure.
Gramada, A. Bourne P.E. BMC Bioinformatics 2006 7:242

2023-Pos
BIBEE: a Rigorous and Computationally Efficient Approximation to Continuum Electrostatics
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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
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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
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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
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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
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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
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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