2012-Pos
Capturing the Roles of Attraction and Shape in Nonpolar Solvation
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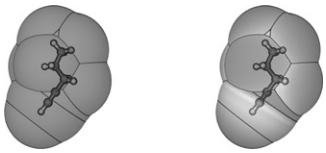
We present a new approach to computer modeling of solvation free energies of oil in water. Informed by the behavior of TIP3P waters around simple Lennard-Jones spheres, Semi-Explicit assembly is a fast implicit approach for computing the nonpolar solvation properties of arbitrary solutes. By summing interactions from whole regions of the solute molecule, this method solves problems that appear as nonadditivities in traditional γ A approaches. Semi-Explicit assembly involves little parameter fitting because the solute and water properties come from existing force fields. We test the predictions on alkanes, alkynes, linear and planar polyaromatic hydrocarbons, and on a general set of 504 molecules previously explored by explicit solvent simulations. We find that not all hydrocarbons are the same. Hydrocarbons have 'hot spots', places where first-shell waters interact more strongly with the molecule than at other locations. By accounting for these 'hot spots', Semi-Explicit assembly attains the physical accuracies of explicit solvent models, but because of the pre-computations and the regional additivities, it is nearly as fast to compute as γ A methods.



2013-Pos
Image Processing Techniques for Assessing Contractility in Isolated Adult and Neonatal Cardiac Myocytes
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We propose two computational frameworks for the assessment of contractile responses of enzymatically dissociated adult and neonatal cardiac myocytes. The proposed methodologies are variants of mathematically sound and computationally robust algorithms very well established in the image processing community. The computational pipeline for assessing contractility in adult cardiocytes comprises the following stages: digital video recording of the contracting cell, edge preserving total variation-based image smoothing, segmentation of the smoothed images, contour extraction from the segmented images, shape representation by Fourier descriptors, and contractility assessment. For assessing contractility of neonatal cardiocytes, the stages in the computational framework consist of digital video recording of the contracting cell, signal masking, representation by polar Fourier descriptors, and contractility assessment.
The physiologic applications of the methodologies are evaluated by assessing the contractions in isolated adult and neonatal rat cardiocytes. Our results demonstrate the effectiveness of the proposed approaches in characterizing the contraction process of the cardiocytes. The proposed methods provide a more comprehensive assessment of the myocyte contraction processes. Furthermore, adult contractility assessment method is suitable for determining myocyte contraction in cells that usually bend or move during contraction, e.g., atrial myocytes and isolated smooth muscle cells, or in cardiac myocytes which develop spatially nonuniform oscillatory contractile activity induced by intracellular calcium fluctuations. More importantly, the proposed methods can be utilized to evaluate changes in contractile behavior resulting from drug intervention, disease modeling, transgeneity, or other common applications to mammalian cardiocytes.

2014-Pos
Development of a High-Throughput Computational Protocol, AESOP, and its Application to the Electrostatic Analysis of the SUMO-1:SENP2 Complex
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Sumoylation of cellular proteins by the ubiquitin-like protein, SUMO, has been found to be one of the essential regulation mechanisms in signal transduction and genome integrity. SENP2, an endopeptidase, is responsible for both maturation of SUMO-1 into its conjugatable form, and the deconjugation of SUMO-1 containing species. Due to the excessive charge of SUMO-1 and SENP2, it has been proposed that electrostatics is important for the association of SUMO-1 and SENP2. In the current study we have used computational methods to investigate the possible role of electrostatics in the formation of the SUMO-1:SENP2 complex. Here we introduce a newly developed computational protocol, AESOP (Analysis of Electrostatic Similarities Of Proteins), which provides a systematic analysis of the contributions of each ionizable residue to the spatial distribution of electrostatic potential and their implied role in protein association. The AESOP protocol performs computational alanine scans, by mutating each ionizable residue within a protein or protein complex to alanine, one at a time. AESOP utilizes Poisson-Boltzmann electrostatic calculations to obtain the spatial distributions of electrostatic potential of proteins or protein mutants at atomic resolution. Electrostatic free energies of association, electrostatic similarity indices, and clustering methods then provide a quantitative comparison of the effects of each alanine mutation, leading to the prediction of key residues in protein association. The data of the current study provide a comprehensive comparison of several electrostatic clustering schemes that have been incorporated into the AESOP protocol. The data also depict important interactions for both SUMO1:SENP2 binding and the stability of the individual components of the complex. The produced predictions provide physicochemical insight into the mechanism of SUMO-1:SENP2 binding and will be used to guide mutagenesis experiments.

2015-Pos
Cardiomyopathy Mutations in Actomyosin: A Tertiary Structure Dynamics Approach within an in Silico Optical Trap Experiment
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Despite great success in simulating protein energetics, molecular dynamics approaches are currently too computationally intensive for use in studying supramolecular actomyosin assemblies. Here tertiary structure coarsegraining strategies are developed to create low-dimension potential functions (Tertiary Structure Models, or TSM) from MD-generated statistical potentials. The effect of domain selection is probed through comparison of successively finer coarsening, beginning with a 4-domain (lever-arm + converter, upper 50k, lower 50k, and n-terminal) TSM. In an attempt to discern and reproduce the basic characteristics of the power stroke the TSM is parameterized for the pre- and post-powerstroke states based on the scallop crystal structures 1qvi and 2ovk, respectively.
A first implementation of this approach to study the mechanical effect of mutations in the myosin actin-binding regions is presented in a rigid-body dynamics simulation of domain motion within an in silico optical trap experiment. Both the S532P and R403Q mutations to the myosin S1 are known to cause cardiomyopathy. It is known that the S532P mutation in the lower 50k domain decreases step size from wild-type while the R403Q mutation shows no difference with wild-type within the optical trap experiment. The differential effect of two mutations both occurring in the actin-binding regions is probed within simulation through alterations to the binding parameters of the upper 50k and lower 50k domains with actin. The ability of the TSM model to capture these fundamental results is used as a validation of the approach.

2016-Pos
Can a Reduced Dimension Interface Model be More Computationally Effective than a Docking Algorithm?
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Joel D. Marquez[1], Tess J. Moon[1,2].
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Actomyosin dynamics are central to elemental cellular processes, yet the precise molecular mechanisms by which actin and myosin transform ATP's chemical energy into mechanical work remain a mystery. Further advances in understanding the actomyosin machine require computational, molecular-level models of the structural dynamics of myosin and its actin complexes, which correlate multi-domain structural changes with force/movement measurements and biochemical kinetics, to serve as adjuncts to molecular-level experiments. Existing modeling approaches, e.g., molecular dynamics which provides atomic-scale simulations of crystal structures, statistical mechanics which provides molecule-size extrapolations of experimental results, lack either the computational speed or the structural resolution necessary to capture the details necessary to reveal critical dynamics of supramolecular assemblies like actomyosin. Novel modeling approaches using targeted coarse-graining of high-resolution crystal structures and interaction potential fields may offer unified, mechanically rigorous, yet computationally efficient method to model supramolecular assemblies, as well as to develop model adjuncts for experiments.
While a core component in any such model is adequately depicting protein-protein binding-domain dynamics, key structural transitions cannot be defined by static crystal structures, as they involve dynamically disordered states. As a result, development of reasonable, inter-molecular potential functions requires estimations of protein-protein interactions, which could be and typically are obtained from docking algorithms like ZDOCK/RDOCK or AutoDock that, depending on the specific proteins, can be computationally expensive. In this work, the conjecture that a Reduced Dimension Interface Model (RDIM), which is constructed using multipole potential expansions, is sufficiently

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.