2012-Pos

Capturing the Roles of Attraction and Shape in Nonpolar Solvation

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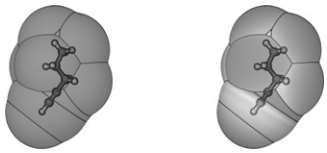
We present a new approach to computer modeling of solvation free energies of oil in water. Informed by the behavior of TIP3P waters around simple Lennard-Jones spheres, Semi-Explicit assembly is a fast implicit approach for computing the nonpolar solvation properties of arbitrary solutes. By summing 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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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