standard Lennard-Jones, but is more than compensated for by the longer time step possible, so that overall simulation times are shorter when using the Morse potential. We suggest that the Morse potential form should be considered as an alternative for the Lennard-Jones form for coarse-grained molecular dynamics simulations. We are working on coarse-grained force fields for amphipathic molecules and for ions, and will provide a progress report on that work in this presentation.

2967-Pos

Optimizing the State Identities in Markov Models of Macroscopic Ion Channel Activity

Carrie A. Williams, Andrew Jenkins.
Emory University, Atlanta, GA, USA.

Ion channel kinetics are often modeled and simulated using Markov models, where rate constants provide the probability of transitioning between a defined connectivity of closed and open states. Usually, the connectivity and state identities (open versus closed) are set by the modeler and an optimization routine is used to search for the rate constants with which the model best matches the experimental activity. Here we present a novel approach for ion channel model specification where a genetic algorithm (GA) is used to optimize both the rate constants between state transitions as well as the identities of the states. Specifically, the GA chooses which states are open and which are closed. Including the state identities as free parameters improves efficiency by concomitantly searching multiple models within one optimization routine instead of individually fitting each model. Using this approach, we correctly identified models ranging from three to seven states that were used to simulate macroscopic concentration response relationships. We then fit experimental macroscopic $GABA_A$ receptor activity to seven models, ranging from three to eight states, where seven-state models with three open and four closed states provided the best fits. This approach may be particularly useful for fitting macroscopic data where the number of closed and open states is not delineated by dwell-time distributions, as with single-channel analysis, and provides an alternative where fewer constraints and assumptions are made of the ion channel models.

2968-Pos

Parameter Refinement, Optimization, and Extension of the Absinth Implicit Solvation Model

Nicholas J. Lyle, Rohit V. Pappu.
Washington University, St. Louis, MO, USA.

Computer simulations of biomolecules offer detailed insight into the molecular driving forces and mechanisms of fundamental biological processes such as protein folding and aggregation. Such studies present a challenge to biophysicists since most systems of interest possess a large number of degrees of freedom which must be rigorously sampled.

The ABSINTH model (Vitalis & Pappu, J. Comput. Chem.,30:673-700) attempts to address this challenge by coarse-graining the solvent degrees of freedom. This leads to considerable simulation speed-up and allows for the study of previously inaccessible length and timescales in silico. The unique aspect of the model lies in the parsing of biomolecules into solvation groups which have experimentally known free energies of solvation (FES). These reference FES are used directly to compute the mean-field interaction of the solvation group with the solvent milieu. This avoids decomposition of the FES into polar and nonpolar components, as is done in the Poisson-Boltzmann/Generalized Born formalism.

The ABSINTH model has been successfully used to describe polymeric properties and aggregation behavior of archetypal intrinsically disordered protein systems. Valuable insights into the aggregation mechanism of polyglutamine and the Huntingtin N-terminal domain along with the phase behavior of highly charged protamines were all made possible by this model, which gave readouts that were quantitatively comparable to experimental studies. The central assumption in the model is that the FES of the solvation groups is additive upon concatenation and this appears to be valid when sidechain behavior dominates the system, as is the case of those systems mentioned above. Polyglycine poses a particular challenge, as the additivity assumption makes the backbone appear overly hydrophilic. Here, we describe extensions and corrections made to the ABSINTH model to better describe backbone solvation equilibria.

This work was supported by NIH grant 5R01NS056114.

2969-Pos

Biomolecular Coarse-Grained Simulation Program CafeMol

Hiroo Kenzaki[1], Nobuyasu Koga[2], Shinji Fujiwara[1], Naoto Hori[1], Ryo Kanada[1], Kei-ichi Okazaki[2], Xin-Qiu Yao[1], Wenfei Li[1], Shoji Takada[1,3].
[1]Kyoto University, Kyoto, Japan, [2]Kobe University, Kobe, Japan, [3]JST-CREST, Tokyo, Japan.

Our group are developing biomolecular coarse-grained (CG) simulation program, which we call CafeMol. CG molecular dynamics (MD) simulation is able to reach much larger time- and spatial- resolution than conventional all-atom MD simulation. Thus, CG model have been used for long time simulation of biomolecular system, such as protein folding, DNA duplex melting, and self-assembly of lipid bilayer. CafeMol includes CG- protein, nucleotide, lipid models. We are developing to applicable protein-nucleotide and protein-lipid system.

For protein model, we use off-lattice Go model and multi-basin model. Go model is minimal model for representing funnel-like energy landscape of protein folding, and multi-basin model, is extension of Go model, can treat large conformational change. CG DNA chain is repeat of three bead, which are represent base, sugar, and phosphate, respectively. This model distinguishes major- and minor- groove of DNA duplex. CG lipid molecules are composed of several beads. These lipid molecules self-assemble into bilayer vesicle. Now, CafeMol beta-version is released at http://www.cafemol.org/, which includes only CG protein model and attaches source code, manual, and some examples.

2970-Pos

Multi-Scale, Integrative Model Development using High-Performance Computer Architectures

Laura A. Doyle, Joseph L. Greenstein, Raimond L. Winslow.
Johns Hopkins University, Baltimore, MD, USA.

In the field of biophysical modeling, it has often been desirable to build models that can run in real-time on a standard desktop workstation, but this is becoming more difficult to achieve. The complexity of molecular model components is increasing. Models of protein kinetics are evolving into large Markov chains where there were once a handful of Hodgekin-Huxley gating variables or algebraic equations. Additionally, models are integrating more modules for many aspects of cellular regulation, greatly increasing the number of states and expanding the range of relevant timescales. These models achieve mechanistic accuracy at the cost of greatly increased computation. Approximations may be made to decrease simulation time, but with some sacrifice of simulation accuracy. A simplified model of cardiac excitation-contraction (EC) coupling such as the coupled L-type Ca2+ channel-Ryanodine Receptor (LCC-RyR) model can provide a reasonable facsimile of EC coupling gain by modeling only a single LCC-RyR pair per cardiac dyad, far less than what is observed experimentally. To produce more detailed output the number of channels modeled per dyad can be increased, leading to an exponential growth in the number of states and compute time.

Increased computing power is becoming more readily available in the form of multi-core processors, cluster computing, and general purpose graphics processing units (GPUs.) As the cost of such advanced computation decreases, the added benefit of including the fully detailed biophysical mechanisms in these models outweighs the computational cost of maintaining the model's complexity. The methods used here show how implementation of the coupled LCC-RyR model on the parallel GPU architecture can lead to significant speedup in simulation time. Use of the GPU also provides a beneficial scaleup in performance as models comprised of more states can be simulated on a larger machine in less time.

2971-Pos

Finite Element Modeling of Cell-Matrix Adhesive Interaction

Martin Y. Chiang.
National Institute of Standards and Technology, Gaithersburg, MD, USA.

Finite Element Modeling of Cell-Matrix Adhesive Interaction

When cells adhere to extracellular matrix (ECM) or other bioactive surfaces (substrates), the bond formation is mediated by the bindings of cell receptors, which can diffuse along the cell membrane surface, to immobilized ligands in ECM. Cells spread and the adhesion zone grows as bond formation at the adhesion front increases to a critical level. This process consists of multiple physical and chemical mechanisms and involves the coupling of reaction-diffusion and mechanical contact between cells and ECM. In this study, we have developed a finite element code to incorporate the kinetics of receptor-ligand interaction into the mass diffusion of cell receptor. For the mechanical interactions attributed to the cell adhesion development and spreading, this code is implemented in a commercial finite element program, through features of user subroutine provided, using its coupled diffusion-displacement solver. This can take into account the fully coupling of reaction-diffusion with mechanics of cell/substrate contact and deformation. In the finite element model, interaction forces between cell and substrate include the specific attraction due to the receptor-ligand binding and the nonspecific repulsion due to glycocalyx proteins associated with cell surface. Parametric studies are also performed to

investigate effect of various system parameters, such as ligand density and mechanical properties of the receptor-ligand interaction, on the kinetics and mechanics of cell adhesion process. More importantly, this study provides a computational framework, with multi-scales and multi-physics, that can be extended for better controlling of cell interactions at the cell-biomaterial interface and for modeling the cell motility.

2972-Pos

A Search for Energy Minimized Sequences of Proteins

Anupam Nath Jha, G.K. Ananthasuresh, Saraswathi Vishveshwara.
Indian Institute of Science, Bangalore, India.

Computational design of sequences for a given structure is generally studied by exhaustively enumerating the sequence space, which is prohibitively expensive. However, we point out that the protein topology has a wealth of information, which can be exploited to design sequences for a chosen structure. We design a computationally efficient method for ranking the residue sites in a given native-state structure, which enables us to design sequences for a chosen structure. The premise for the method is that the topology of the graph representing the energetically interacting neighbors in a protein plays an important role in the inverse-folding problem. We use edge-weighted connectivity graph for ranking the residue sites with reduced amino acid alphabet and then use continuous optimization to obtain the energy-minimizing sequences. Our methods enable the computation of a lower bound as well as a tight upper bound for the energy of a given conformation. We validate our results by using three different inter-residue energy matrices for five proteins from protein data bank (PDB), and by comparing our energy-minimizing sequences with 80 million diverse sequences that are generated based on different considerations in each case. Some of our chosen energy-minimizing sequences are similar to the sequences from non-redundant protein sequence database with an E-value of the order of 10^{-7}. In summary, we conclude that proteins show a trend towards minimizing energy in the sequence space but do not seem to adopt the global energy-minimizing sequence. The reason for this could be either that the existing energy matrices are not able to accurately represent the inter-residue interactions in the context of the protein environment or that Nature does not push the optimization in the sequence space, once it is able to perform the function.

2973-Pos

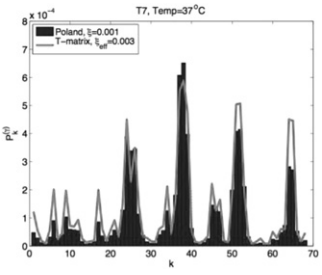
Simplified Theory for DNA Melting Maps

Tobias Ambjörnsson[1], Bo Söderberg[1], **Jonas O. Tegenfeldt[2,1]**.
[1]Lund University, Lund, Sweden, [2]University of Gothenburg, Gothenburg, Sweden.

DNA melting maps on DNA stretched on surfaces or in nanochannels give a coarse grained picture of the underlying sequence with potential applications in studies of structural variations and for identification of (micro)organisms. The underlying mechanism is based on the difference in free energies associated with breaking AT and GC basepairs so that DNA melts first in AT-rich regions and only at higher temperature in GC-rich regions. With a suitable choice of dye the melted regions and the unmelted regions can readily be distinguished.

The Poland-Scheraga (PS)model is an Ising model with a long-range term due to the entropy associated with the single-stranded regions and, although computationally slow (~ square of the number of basepairs), has proven to well reproduce melting data. However, by adapting our algorithms to the resolution of the experimental melting mapping (1kbp) we can make them computationally more efficient.

We combine a transfer matrix approach and an exact Poland-type algorithm to study opening probabilities along DNA. We systematically explore different degrees of simplifications such as capping the long-range interactions or using a coarse-grained effective-medium approach. We evaluate our simplifications against exact solutions to the PS model for known sequences (figure).



2974-Pos

Testing a Hybrid Solvation Model with a Transition Layer Via Molecular Dynamics Simulation

Wei Song[1], Peihua Qin[2], Yuchun Lin[3], Andriy Baumketner[3], Wei Cai[4], Donald Jacobs[3].
[1]Bioinformatics Department, UNC Charlotte, Charlotte, NC, USA, [2]Institute of Computational Mathematics, Chinese Academy of Sciences, Beijing, China, [3]Department of Physics and Optical Science, University of North Carolina at Charlotte, Charlotte, NC, USA, [4]Department of Mathematics and Statistics, University of North Carolina at Charlotte, Charlotte, NC, USA.

We previously developed a three dielectric layer hybrid solvation model for the electrostatic interactions of biomolecules in solvents using the linearized Poisson-Boltzmann equation. In this model, the interior spherical cavity contains the solute and explicit solvent molecules. Rather than employing the commonly invoked classical Kirkwood model that assumes a discontinuous change in dielectric constant from inside to outside the sphere, we introduced an intermediate buffer layer. Outside the spherical shell defines the exterior layer, where bulk solvent is modeled implicitly and characterized by a dielectric constant. Within the buffer layer, a special dielectric permittivity profile is constructed to give a continuous transition from the interior cavity to the exterior region. The purpose of the buffer layer is to remove unphysical divergence in electrostatic force at the cavity boundary. The electrostatic force within the cavity due to the reaction field of solvents with various ionic strengths is calculated using discrete image charges. Molecular dynamics simulation is performed using a recently developed simulation protocol to benchmark the effectiveness of the buffer layer, for various thickness, h, and different ionic concentration. Monitoring response functions and distributions of force and torque on molecular water facilitates relative comparisons. This work is supported by NIH 1R01 GM083600-03.

2975-Pos

Data-Driven Analysis of Cell Motility on Nanostructured Surfaces

Cristian Gradinaru, Joanna M. Lopacinska, Kristian Molhave, Henrik Flyvbjerg.
DTU, Kgs Lyngby, Denmark.

Experimental time series for trajectories of motile cells contains so much information that a systematic analysis yields cell-type-specific motility models. Using a range of cell types on various nanostructured surfaces we have explored how the surface type and cell type result in different motility models. This reflects the cells' different roles in the organism by showing that a cell has a memory of past velocities. They also suggest how the nanopatterns imprinted on the various surfaces affect cell motility.

2976-Pos

Development and Application of Non-Additive Force Fields for Molecular Simulations of Lipid Bilayers and Integral Membrane Proteins

Sandeep Patel.
Univ. of Delaware, Newark, DE, USA.

Molecular simulations today are applied across many scientific disciplines. Complementing experiment, these tools afford a molecular-level understanding and interpretation of physico-chemical processes at resolutions and timescales difficult or practically inaccessible to experiment. At the heart of such methods is the description of interactions between atoms and molecules, the force field. Traditionally, non-reactive force fields have treated electrostatic interactions using an additive, Coulomb model between fixed partial charges on atomic sites. Though quite successful, there has been conjecture as to the effects of incorporating non-additivity in classical force fields, particularly in biological systems. Over the last several decades, attempts to incorporate electrostatic non-additivity in the form of inducible dipole interactions or dynamically varying partial charges have provided a vast body of knowledge that has aided in the development of a new class of force fields attempting to explicitly account for non-additive effects. We will present our recent work in developing one such class of models, charge equilibration force fields, and applications of such models to aqueous solution interfaces, membrane bilayers and simple integral membrane peptides such as the gramicidin A bacterial channel, and recent work on modeling of protein-ligand interaction free energetics.

Imaging & Optical Microscopy III

2977-Pos

In Situ Measurements of Oligomerization State of NBCe1-A in Rat Kidneys Via Spatial Fluorescence Intensity Fluctuation Analysis

Mikhail Sergeev[1], Antoine G. Godin[1], Liyo Kao[2], Natalia Abuladze[2], Ira Kurtz[2], Paul W. Wiseman[1].
[1]McGill University, Montreal, QC, Canada, [2]UCLA, Los Angeles, CA, USA.

NBCe1-A plays an important role in absorbing sodium bicarbonate across the basolateral membrane of the proximal tubule. We have previously showed that minimal functional unit of NBCe1-A is a monomer, and based on in-vitro biochemical studies in HEK293 cells, the oligomeric state of the cotransporter was shown to be predominantly dimeric with monomeric and higher oligomeric forms also present. We developed an in situ measurement methodology to determine the oligomeric state of NBCe1-A without requiring tissue disruption