Platform: Computational Methods

178-Plat
Modeling Proteins and Small Molecules with Inhomogeneous Dielectric Function: Implementation in Delphi
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Most implicit solvent models treat bio-molecules as homogeneous dielectric medium inside high dielectric water phase. However, the dielectric distribution inside biological macromolecules is non-homogeneous, which depends on various factors, such as amino acid composition, structure, packing and flexibility. Many approaches have been developed to model the inhomogeneous dielectric distribution in biomolecules, including amino acid specific dielectric constant, using non-typical probe radius in finite-difference algorithm or delivering the dielectric constant from Gaussian distribution of atomic densities. Here, in Delphi program, we developed an inhomogeneous dielectric method based on Gaussian smooth function. We tested this new method on calculating the solvation energies of 504 small molecules and the results show the method achieves better accuracy of the solvation energy calculation than homogeneous dielectric methods. Other tests on real proteins demonstrate that our inhomogeneous dielectric method is more reliable than homogeneous dielectric method for pKa and electrostatic potential calculations.

179-Plat
Introducing Charge Hydration Asymmetry in the Realm of Continuum Solvation
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Charge hydration asymmetry (CHA) manifests itself in the experimentally observed strong dependence of free energy of ion hydration on the sign of the ion charge. This asymmetry is not consistently accounted for by popular models of solvation; its magnitude varies greatly between the models. While it is clear that CHA is somehow related to charge distribution within a water molecule, the exact nature of this relationship is unknown. We propose a simple, yet general and rigorous criterion that relates rotational and charge inversion properties of a water molecule’s charge distribution with its ability to cause CHA. We show which electric multipole components of a water molecule are key to explaining its ability for asymmetric charge hydration. We then test several popular water models and explain why specific models show none, little, or strong CHA in simulations. We use the gained insight to derive an analogue of the Born equation that includes the missing physics necessary to account for CHA and does not rely on redefining the continuum dielectric boundary. The proposed formula is as simple as the original, does not contain any fitting parameters, and predicts hydration free energies and entropies of spherical cations and anions with high experimental uncertainty. We further incorporate CHA into the framework of Generalized Born continuum solvation model; our findings suggest that the gap between the practical continuum electrostatics framework and the more fundamental explicit solvent treatment can be reduced considerably by explicitly introducing CHA into the existing framework.

180-Plat
Enhanced Sampling Assisted Flexible Fitting of Atomic Structures into Electron Microscopy Maps
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For many problems in structural biology, flexible-fitting computational algorithms are often useful in interpreting low-resolution electron microscopy (EM) maps of macromolecular assemblies. A widely used ab initio simulation technique is molecular dynamics flexible fitting (MDFF), which has been applied to generate structural models of large complexes. All-atom explicit-solvent MDFF simulations are not only computationally demanding, but also can be sensitive to the resolution of the target EM map. Moreover, functional movements of many biomolecules require large-scale conformational reorganization elicited via domain translations/rotations, where methods such as MDFF may be limited in capturing the rotations of structural elements. To decrease the computational cost and alleviate the limitations stemming from domain orientations, one can combine MDFF with an enhanced sampling technique to accelerate the conformational search in a single atomistic simulation. In this work, we judiciously combine MDFF with temperature-accelerated molecular dynamics (TAMD), an enhanced sampling method, and carry out TAMD-assisted MDFF (TAMDFF) simulations of proteins and nucleic acids. We find that TAMDFF simulations can achieve target structures of similar quality as MDFF on short timescales. In some cases, only TAMDFF simulations are able to capture conformational changes likely because MDFF simulations are unable to overcome the underlying free-energy barriers. We suggest that TAMDFF may be a viable strategy for structural refinement of large ribonucleoprotein complexes such as the ribosome.

181-Plat
SAXS/WAXS Intensities and Pair-Distance Distribution Functions from Molecular Dynamics Simulations
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Solution scattering experiments on biological macromolecules measure one-dimensional intensity profiles that serve as signatures of the underlying three-dimensional atomistic structure. For X-rays, these intensities are Fourier transforms of the electron pair-distance distribution function (PDDF). The PDDFs contain the maximum amount of information accessible in such experiments, and they greatly aid in the interpretation of the scattering data. Because of this fundamental and practical importance of the PDDFs, inverse Fourier transform methods are commonly applied to obtain the PDDFs from the measured scattering data. However, these transforms are limited by the finite range of scattering angles probed in experiments and by statistical uncertainties. By contrast, in molecular dynamics simulation the real space information is directly accessible. We developed a method to calculate the PDDFs from atomistic structures, together with accurate scattering intensities in both SAXS and WAXS regimes. For a selection of proteins, we first show that the calculated scattering intensities are in excellent agreement with precise measurements. We then demonstrate that a q-range up to 2-3 Å⁻¹ in the WAXS regime is sufficient to resolve most of the features of the exact PDDFs, providing guidance for the design of scattering experiments.

182-Plat
Strategies for Model Reduction in DCA-Based Multibody Modeling of Biopolymers
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Numerical simulations of bio-polymeric systems are most often limited by their inherent size and complexity. As such, models with varying degree of fidelity, ranging from fully atomistic to continuum scale, are employed by researchers to study these systems. In reality, such complex molecular systems exhibits important physical phenomenon at multiple spatial and temporal scales. Moreover, characteristics of different sub-domains within a system are prone to change with time. In such systems, it is highly desirable that the hierarchy of reduced order (multiple scale) models be produced which can adaptively track and predict the behavior of the system while maintaining both accuracy and speed. Therefore, it is imperative that computationally intelligent and efficient numerical schemes are developed which can adaptively put effort where required. The divide and conquer (DCA) based family of multi-body dynamics algorithms has the potential to circumvent many problems associated with the simulations of complex molecular systems. This is achieved through modeling molecular systems as reduced order multi-rigid or multi-flexible body systems. Such approaches have shown to significantly lessen the model complexity while accurately capturing the overall conformational motion and important system behavior. Furthermore, the DCA based algorithms allow the transitions between different resolution models through removing or adding degrees of freedom (dofs), on-the-fly, during simulation with an overall low computational cost [O(log n)]. This work examines the challenges involved with the adaptive reduction in the model resolution within the DCA framework. The energy, momentum and temperature issues associated with removing single dof at a time are compared with instantaneous locking of multiple dofs. Numerical examples are presented that include both multi-rigid and multi-flexible body models and the results are compared for physically meaningful state of the system from both sequential and instantaneous transitions.

183-Plat
A Simple Coarse-Grained Model to Map the Transition Pathway Between Two Stable Conformations using the Anisotropic Elastic Network Model
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Conformational transitions in biomolecules, especially proteins, play an important role in signaling and regulation of various biological processes. Here we propose a fast and simple method for constructing a transition pathway between two stable conformations of a protein. The protein is represented as a simplified coarse-grained (CG) model with a single site located at the C-terminus of each residue. The energy function of the two-state CG model is approximated by the anisotropic network model (ANM) harmonic energy surfaces of the end-states. The simple two-state energy surface comprises two local minima centered on the positions of the stable states and the system resides in one of these minima. There is a cusp with discontinuous first derivative in the multi-dimensional configuration space of the system, which acts as the transition state surface for the two-state potential. Given this simple prescription, two structures constrained to remain similar to one another but each residing on the opposite sides of the cusp, are optimized using energy minimization. This virtual “dumbbell” of two structures is then used as a crude approximation to the transition state. The pathway in the multi-dimensional space is constructed by letting these two structures slide down on their ANM surface using steepest descent energy minimization until the stable end-points are reached. This simple two-state ANM model was applied to explore the multi-dimensional and collective character of the conformational transition pathways in several systems of biological significance, including adenylate kinase, leucine transporter, sarcoplasmic reticulum Ca-ATPase and the glutamate transporter.

184-Plat
Structure-Based Approaches to Amyloid Inhibitors
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More than 40 human pathologies, including Alzheimer disease, are associated with protein aggregates (both amyloid oligomers and fibers). Structure-based approaches were applied for seeking amyloid inhibitors in two scenarios. First, non-natural peptides were designed to block the fibrillation of an amyloid fiber formed by PAP248-286 (a proteolytic fragment of the protein prostate acid phosphatase), whose fiber forms enhance sexual transmission of HIV. We identified the fibril-forming segments of the PAP248-286 fiber and then determined their atomic structures. Using the structure of segments of the amyloid fiber as template, we have designed L-amino acid and non-natural L-amino acid inhibitors to bind to the end of the fibril-forming segment, blocking the addition of other segments. The 5 designed peptides and 3 non-natural peptides inhibit the PAP248-286 fibrillation and greatly inhibit the infectivity of HIV for human cells in culture.

Increasing evidence indicates soluble Aβ oligomers are the toxic species. We searched inhibitor of amyloid toxicity by characterizing binders of amyloid fiber (BAF), which stabilize amyloid fiber to reduce the toxic oligomers. The atomic structure of an amyloidogenic segment KLFF(Aβ(16-21)) binding with a BAF has been determined. Applying new modified RosettaLigand method for high-throughput docking, we identified candidate molecules from a vast space compound (~18 thousand) that interact favorably with the fiber structures. These BAF compounds bind to fibers and greatly inhibit amyloid toxicity. The derivatives of active BAF compounds were then included to expand the set. Out of 35 compounds and 24 compound derivatives tested, eight unique compounds and 4 compound derivatives showed the reduction of Aβ toxicity to mammalian cells in MITT cell assays. The success of our inhibitors demonstrated our powerful approach for structure-based inhibitor discovery, offering a new potential treatment for amyloid therapies.

185-Plat
Interactive Chromatin Folding, Nucleosome (Mis)Positioning and Chromatin Structure
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In the absence of the myriad influences that exist in a cell nucleus, the positioning and stability of nucleosomes on a short segment of DNA are governed by the material properties of the DNA. In the simplest view sequences of DNA that are intrinsically flexible or that are intrinsically curved lead to nucleosome positioning. Nucleosome positioning is thus an intra-nucleosomal effect depending on the context of nucleosome interactions and extra-nucleosomal (e.g. chromatin remodeling factors) interactions must also be considered. In case of inter-nucleosomal based positioning, DNA material defects (defined as variations in flexibility or conformation) are hidden because the histones force the DNA to assume a well defined super helical fold. Except for specifically constructed sequences of DNA, chromatin structures determined by intra-nucleosomal interactions are irregular because the nucleosome positions will be irregular.

In case inter- or extra-nucleosomal interactions determine the nucleosome positions some DNA defects will be exposed in linker DNA regions. Exposure of the defects impacts the global structure of chromatin, e.g. a bent linker yields bent chromatin.

We propose that chromatin structure is biased toward one method of positioning or the other depending on environmental conditions. Thus for a given sequence of DNA both regular and regular structures can be obtained. Our Interactive Chromatin Modeling Web Server http://www.latech.edu/~bship captures these ideas. Here we present a case study of how ICM Web can be used to study the folding of the mouse mammary tumor virus promoter complex (MMTV). ICM properly predicts the locations of six positioned nucleosomes in the MMTV and shows how mispositioning reveals sequence specific material defects that bend chromatin.

Platform: Muscle: Fiber and Molecular Mechanics & Structure

186-Plat
Determinants of Transversal Stiffness of Single Muscle Sarcomeres by AFM
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The thin slips of muscle sarcomeres largely determine tensile muscle stress. However, thin is incorporated into sarcomeric I-bands not strictly in parallel with the sarcomere axis, being anchored to actin at Z-disks and myosin at A-bands. On tensile sarcomere strain, which stretches the thin slips, a force component arises longitudinally, but somewhat also laterally. The latter component may contribute to increased sarcomeric transversal stiffness, decreased lateral myofilament spacing, and length-dependent activation of stretched muscle. We attempted to directly test by atomic force microscopy (AFM) force mapping whether the thin slips contribute to sarcomeric transversal stiffness and how a thin-based lateral force component would compare with other possible sources of lateral stiffness, such as osmotic forces. Single myofibrils were isolated from rabbit psoas (stiff titin-titin isoform) or diaphragm (compliant titin-titin isoform) muscles and placed in physiological buffer under the MFP-3D-BIO AFM (Asylum Research). Force curves (50x50) were performed over a region-of-interest encompassing a whole sarcomere. Force mapping revealed distinct transversal stiffness patterns along psoas and diaphragm sarcomeres, reflecting different Z-disk, I-, A-, and M-band stiffness. A-band transversal stiffness at 25nm indentation was higher in rigor (4.2nN/um) than in relaxed sarcomeres (0.4nN/um). Titin digestion by low-dose trypsin decreased rigor but not relaxed stiffness. A-band lateral stiffness did not differ between relaxed psoas and diaphragm sarcomeres at slack length (~2.2um) but increased significantly after stretch to ~3.2um, albeit more highly in psoas than in diaphragm. Following osmotic compression by 5% dextran, A-band lateral stiffness rose 5-fold, similarly in psoas and diaphragm. We conclude that stiff titin contributes more to transversal stiffness than compliant titin, confirming a role for titin in lateral force generation. However, osmotic forces alike those present in vivo may laterally compress the sarcomeric lattice to a degree that the titin contribution becomes negligible.

187-Plat
Contractile Properties of Half-Sarcomeres Mechanically Isolated from Skeletal Muscle Myofibrils
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The goal of this study was to develop a system to experiment with half-sarcomeres mechanically isolated from skeletal muscle. Single myofibrils from rabbit psoas were transferred into a temperature-controlled (10°C) bath. Half-sarcomeres were isolated using two pre-calibrated glass microneedles; the first pierced externally adjacent to the Z-line, and the second internally, adjacent to the M-line. The force produced during activation of the half-sarcomere was measured by tracking the displacement of the microneedles. The half-sarcomere length (HSL) was obtained by interpolating the displacement of the needles from the initial to the final distances measured from the Z-line to the center of the sarcomere. Half-sarcomeres (n=12) produced a stress of 24±3.7 nN/um2 at HSL between 1.0 and 1.4um. The result was comparable to that observed in isolated sarcomeres (25.5±3.1 nN/um2), at SL between 1.8 and 3.0um. Preliminary trials in which we imposed stretches (ranging from 12 to 33% of the initial HSL/SL, at a speeds of