Molecular Dynamics III

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Coarse-Grained MD Simulations of Pegylated Coiled Coils and their Self-Assembled Micelles
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Coarse-grained (CG) molecular dynamics simulations were performed to understand the conformation and dynamics of trimeric α-helical coiled coils grafted with poly(ethylene glycol) (PEG) of different sizes and conjugate positions and the self-assembled micelle of amphiphilic trimers. The CG model for the trimeric coiled coil is verified by comparing the α-helical structure and interhelical distance with those calculated from all-atom simulations. In CG simulations of PEGylated trimers, the end-to-end distances and radii of gyration of PEGs grafted to the sides of peptides become shorter than those of free PEGs in water, which agrees with experiments. This shorter size of the grafted PEGs is also confirmed by calculating the thickness of the PEG layer, which is less than the size of the mushroom. These indicate the adsorption of PEG chains onto coiled coils since hydrophobic residues in the exterior sites of coiled coils tend to be less exposed to water and thus interact with PEGs, leading to the compact conformation of adsorbed PEGs. Simulations of the self-assembly of amphiphilic trimers show that the randomly distributed trimers self-assemble to micelles. The outer radius and hydrodynamic radius of the micelle, which were calculated respectively from radial densities and diffusion coefficients, are ~7 nm, in agreement with the experimental value of ~7.5 nm, while the aggregation number of amphiphilic molecules per micelle is lower than the experimentally proposed value. These simulations successfully reproduce the experimentally measured size of PEGs grafted to the trimeric coiled coils and their self-assembled amphiphilic micelles and suggest the lower aggregation number of the micelle.

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Molecular Dynamics Simulations on the Periplasmic-Open State Lactose Permease
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Lactose Permease (LacY) is a secondary active transporter (SAT) that belongs to major facilitator superfamily (MFS). LacY structures of the cytoplasmic-open and more recently occluded-like structure have been determined. The structure of periplasmic-open LacY is important for understanding complete proton/sugar transport of LacY as well as other similar transporters. Though the exact structure of periplasmic-open LacY has not been obtained experimentally, a few molecular models have been determined. Previously, Pendse et al. (JMB, 404: 506-521) obtained a periplasmic-open LacY model through a two-step hybrid implicit-explicit (IM-EX) simulation method. Radestock et al. (JMB, 407: 698-715) proposed two new periplasmic-open LacY models by swapping inverted-topology repeats and adopting the outward L-fucose-proton symporter (fucP) crystal structure. The accuracy of these three periplasmic-open state models are tested by performing MD simulations on LacY-apo and LacY-ββ-(Galp)2. The comparison of the calculated pore radii to the data of the crystal structure indicates that the IM-EX model of LacY remains in periplasmic-open state. However, Radestock et al.'s models close on the periplasmic side and partially close on the cytoplasmic side, which indicates these two outward LacY models are unstable. Compared to the DEER experimental data, the selected residue pair distance changes demonstrates that the repeat-swapped LacY seems to be in the occluded state by 100ns. We will run MD simulations with labeled residues to directly compare with DEER for the IM-EX model to verify the effects of the spin label size and orientation on the accuracy of the distance measurement.

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Elastic Property of Dynein Motor Domain Obtained from All-Atom Molecular Dynamics Simulations in Explicit Water
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Dyneins are large microtubule motor proteins that play important roles in various biological processes. Cytoplasmic dynein is responsible for cell division, cell migration and other basic cellular functions. The motor domain of dynein consists of a ring-shaped ATPase hexamer called the AAA+ modules. Recently, ADP-bound high-resolution structures of cytoplasmic dynein have revealed the organization of the motor domain that comprises the AAA+ ring, the linker, stalk/strut and C-sequence (PDB IDs: 3vkh and 3vkg). However, the high-resolution structure of an ATP-bound dynein remains unclear. Here, we built the ATP model from the ADP model, and carried out a molecular dynamics (MD) simulation of both models to investigate the effect of ATP on the structures and dynamics by comparing their trajectories. The higher resolution structure (3vkg), which is a truncation mutant, was chosen. Then, we modeled the missing residues and added the truncated domain from the wild type structure (3vkh). Four ADP molecules were placed at their original positions in the ADP model. The nucleotide in the AAA1 module, which is important for the dynein's function, was replaced from ADP to ATP in the ATP model. A rectangular water box was placed around dynein. We used our new MD program, psygene-G, which utilizes GPGPU for the acceleration of the non-bonded computation. Electrostatic interactions were treated with our zero-dipole summation method. A 200-ns MD simulation for both models revealed that the stalk of the ATP model was more flexible than that of the ADP model. Additional 100-ns simulations starting from the ADP model with ATP ligand and from the ATP model with ADP ligand reproduced this flexibility. The rigidness of both obtained trajectories qualitatively agrees with experimental results.

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Membrane Binding of the Osh4 Curvature-Sensing Peptide
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This work presents the study of the binding mechanism and function of peripheral membrane protein Osh4 curvature sensing peptide (ALPS-like motif). Osh4 is a lipid transport protein, member of a family of seven homologue oxysterol binding proteins in yeast. It was previously shown, using molecular dynamics simulations, that Osh4 has six membrane binding regions (*JMB* 2012, **423**:847-862). Non-specific interactions with anionic lipids are an important driving force for the Osh4 attraction to yeast membranes. The ALPS-like motif of Osh4, a 29 amino acid peptide which also forms the lid to protect sterols, has also been identified as a membrane curvature sensor (*Nature SMB* 2007, **14(2)**:138-146). This work examines the binding mechanism of the peptide with bilayers containing different lipid types. A previous study showed ALPS peptides bind to membranes with surface-packing defects (*BJ* 2013, **104**:575-584). Unsaturated lipids and increasing values of surface tension were implemented to increase the surface packing defects of our membranes. The simplest model had only phosphatidylcholine (PC) lipids; phosphatidylserine (PS) and ergosterol (ERG) were added to model yeast membranes more closely. Simulations using pure 1,2-Dioleoyl-sn-glycero-3-phosphocholine (DOPC) bilayers, a lipid with one double bond per tail, were carried out at different values of surface tension (γ). Additional systems exploring the role of charged lipids and ERG in binding of the peptide were DOPC-DOPS (60:40) and DOPC-ERG (50:50) mixtures. Molecular dynamics were carried out for 200ns using the CHARMM36 force field and the NPT ensemble. Binding events were characterized through hydrogen bonding and binding free energy calculations. Since binding events are stochastic, replicate simulations were carried out for each system. Time in the Anton machine allowed us to run longer simulations for the DOPC-DOPS (60-40) bilayers to study trajectories of 2μs.

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Combined QM/MM Study of the Translocation of Chloride Ions through Escherichia Coli Chloride Ion Transporters
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Chloride ion transporters (ClC) move Cl- across cellular membranes and are associated with numerous physiological and cellular processes. However, despite several decades of research, many details about the mechanism of ion transport by ClC proteins are not well understood at the molecular level. Our recent quantum calculations[1,2] revealed significant charge delocalization in Cl- binding, which contributes significantly to the effectiveness of the broken helical structure of the binding sites to coordinate Cl- ions. The marked loss of partial charges of the Cl- ions to the surroundings, especially to the residues having π bonds, may impact Cl- transport. Here we report a molecular dynamics study of the movement of Cl- through Escherichia coli ClC where we compare the free energy profiles obtained by employing both the molecular mechanics (MM) and combined quantum mechanics/molecular mechanics (QM/MM) methods.
[1] Smith, M.; Lin, H. Chem. Phys. Lett. 2011, 502, 112-117.
[2] Church, J.; Pezeshki, S.; Davis, C.; Lin, H. J. Phys. Chem. B 2013, 117, 16029-16043.
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