the accurate mechanism of how EIIC transports a sugar has not been clearly demonstrated yet. To investigate more detailed and accurate transportation mechanisms, we performed collective variable-based steered molecular dynamics (CVSMD) simulations. Our simulation shows the spontaneous transportation of the sugar toward the opposite side of the membrane with the preserved H-bonding interactions, supporting the ''Elevator'' type transport mechanism. A set of cross-linking experiments was carried out on the basis of the CVSMD model structures, and we were able to acquire a few of stable cross-linked structures.

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Molecular Basis of GLUT4 in Glucose Transport: Atomistic Molecular Dynamics Study

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The glucose transporter 4 (GLUT4) is one of the most important glucose transporter proteins for the absorption of glucose from the plasma circulation after a meal or during exercise. It is present in skeletal muscle, adipose tissue cells, cardiac muscle, and it has also been found in brain cells. It plays a significant role in the development of various diseases such as type 2 diabetes, cancer, and cardiac diseases. Inside a cell, GLUT4 is transported towards the cell membrane upon an insulin stimulus, leading to a 10- to 40-fold increase in the glucose uptake. In spite of its importance, the molecular mechanism of glucose transport by GLUT4 is still not clear. There is no crystal structure available for the GLUT4 protein either. However, using existing structural information of the other solved glucose transporter structures, we have modeled and validated the GLUT4 structure in three conformations: the outward-open, outward-occluded, and inward-open conformation. The GLUT4 models with glucose bound were subsequently embedded in a 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine (POPC) membrane and simulated over microsecond time scales using unbiased atomistic molecular dynamics simulations. In addition, we also carried out random acceleration molecular dynamics simulations to explore all possible pathways for glucose transport across the membrane. Our simulation studies revealed specific GLUT4 residues that captured the conformational changes in GLUT4 structure on glucose binding. Overall, the study provides atomistic level structural information on glucose transport and also provides one with ideas for the development of therapeutic agents blocking the function of GLUT4. This development work is important given that cancer cells express elevated levels of glucose transporter proteins and depend on increased glucose uptake for proliferation.

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Ions in Action - Studying Ion Channels by Computational Electrophysiology in GROMACS

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Ion channels play a fundamental role in maintaining vital electrochemical gradients across the cell membrane and in enabling electrical signaling in cells. Understanding their functional mechanism is crucial for facilitating drug design on this important class of membrane proteins. Key characteristics of ion channel function that are commonly quantified experimentally are ionic permeation rates and selectivities. The Computational Electrophysiology (CompEL) protocol allows the investigation of ion channels in GROMACS all-atom molecular dynamics simulations. By employing an ion/water exchange protocol in a double-membrane simulation setup, a steady state with a continuous flow of ions through the channels is achieved. The recorded ion permeation events directly reveal conductance, selectivity, and rectification behavior, which all allow a straightforward comparison to experimental quantities. In addition, the ionic pathways through the channels are readily revealed. CompEL is available in GROMACS and has a negligible impact on the simulation performance even in parallel.

Recent application to the bacterial channel PorB resulted in conductance and selectivity values and revealed the pathways of traversing ions. For a mutant, pathway disruption was observed, thereby explaining its resistance to certain antibiotics. The conductance calculated from the simulations agreed very well with measured conductances. Other successful examples of CompEL include the discovery of an unexpected ionic pathway in the anti-microbial peptide dermcidin as well as the identification of a novel conduction mechanism in the potassium channel KcsA. We finally investigated the conductance and the gating mechanism of pentameric ligand-gated ion channels such as GLIC. We constructed a reaction coordinate from two crystal structures, which have been proposed to represent the open and closed states of the channel, respectively. Constraining the pore to specific positions on that reaction coordinate allowed us to sample the conductivity at these positions. CompEL confirms that the assumedly open structure is indeed conducting and cation-selective (with conductances in the pS range, comparable to published experimental values), whereas the closed structure is indeed non-conducting. Moreover, conductance values steadily increase along the closed-to-open transition and are correlated with the amount of water in the pore.

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Modeling Membrane Associated Proteins through Neutron Reflectivity Augmented Molecular Dynamics

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The structural characterization of membrane-associated proteins on fluid lipid bilayers remains a challenge to most modern biophysical techniques. Neutron reflectivity (NR) has emerged as a method that provides sub-nanometer resolution of proteins in a functional lipid environment. Interpretation of NR data gives an envelope structure related to the distribution of protein density along the membrane normal direction and further refinement using structural information may yield a full atomistic description of the protein-membrane complex. However, for flexible or intrinsically disordered protein domains, such information is often not available or multiple conformational states may contribute to the average density profile as resolved by NR. Thus, characterization of such systems requires more elaborate approaches. We previously demonstrated that molecular dynamics (MD) simulations can provide a full atomistic interpretation of NR results in cases where only partial internal protein structure is available, but such simulations are often plagued by long equilibration times. Here we present a procedure to steer MD simulations toward configurations that reproduce experimental NR results. Biasing potentials are calculated through a comparison of the one-dimensional densities from NR data with the evolving density profile derived from the MD trajectory at each time step. This results in steering forces that direct molecular conformations of the protein on the bilayer toward the experimental results. Steering becomes weaker as the density profiles match more closely, disappearing entirely for matched densities. The structure is guided toward the desired configuration, rather than rigidly confined to the experimental density. Here we show the application of our method to model peptide and small protein systems, also discussing the efficiency of the procedure and potential merits and pitfalls in its application.

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Characterization of Apolipoprotein Mimetic Peptides on Nascent High Density Lipoproteins

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A nascent high-density lipoprotein (HDL) is a discoidal bilayer composed of phospholipids, cholesterols, and two apolipoproteins that form a scaffold that stabilizes the assembly. Apolipoprotein mimetic peptides are short synthetic peptides that share features of apolipoproteins and have potential therapeutic value based on their ability to form and stabilize nascent HDL. A key question in designing mimetic peptides is why some are more efficient than others. We characterize the properties of four mimetic peptides rich in the amino acids E, L, and K (called ELK peptides), using a combination of Molecular Dynamics simulations and experimental techniques. Experiments show that the hydrophobic and neutral ELKs have a significantly higher ability to form nascent HDLs than the positive or negative peptides. An *in silico* model of a discoidal bilayer was developed by introducing a water slab perpendicular to the bilayer head group surface, leading to acyl chains of edges exposed to water. Simulations on this model discoidal bilayer with peptides indicate that hydrophobic and neutral ELKs stabilize the assembly by forming scaffolds at the edges in a picket fence