well-understood. To provide insight on oleic acid self-aggregation, we used molecular dynamics simulations with the coarse-grained MARTINI model to simulate oleic acid aggregates in various concentrations and protonation states. Starting from a random configuration of oleic acid, protonated oleic acid yield oils, charged oleate yields micelles, and mixtures of oleate and oleic acid form vesicles. We then performed free energy calculations using umbrella sampling to determine the relative thermodynamic preference of oleic acid and its conjugated base, oleate, for each aggregate type. Oleic acid prefers charged micelles over neutral while oleate prefers neutral over charged. Both oleate and oleic acid show preference for 80 mM vesicles and oils, but oleate prefers the oil over the vesicle whereas oleic acid prefers a vesicle. Reproducing oleic acid self-aggregates and calculating free energies for monomer-aggregate interactions suggests thermodynamic driving forces for oleic acid aggregation.

Investigation of Shiga-Like Toxin Subunit B using Coarse-Grained Modeling
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We investigate the structural properties of the Shiga-like toxin (SLT1) subunit B in the bulk and bound to a lipid membrane using coarse-grained (CG) molecular dynamics simulations. SLT1 consist of a cytotoxic A subunit that shuts down protein synthesis and five B subunits forming a homo-pentamer responsible for ferreting the A subunit into the cell. With or without the A unit attached, the B3 complex binds to specific glycolipids on the cell membrane and leads to toxin uptake by cooperatively driving membrane invagination. Unfortunately, the size of the protein-lipid system needed to investigate SLT1 driven vesiculation makes all-atom simulations impractical. Instead, CG models hold promise, having previously succeeded in simulating events even though at a much lower resolution [1]. We use an intermediate resolution systematic CG model of proteins and lipids, which improves the efficiency of our simulations while providing the necessary specificity to relate the results directly to SLT1 [2,3]. To ensure that the monomer structure resembles all-atom simulations, we augment the protein model with an intra-monomer elastic network that is parameterized using a novel iterative process. In addition, we explore ways to best represent the bonds between binding sites on the monomers and glycolipids. With the completed model, we investigate the stability and fluctuation modes of the Shiga B subunit in the bulk and on a membrane. In addition, we investigate the effect of the protein on the lipid bilayer, specifically its local bending deformation and lipid diffusion around the protein.

References:

Window Exchange Umbrella Sampling to Enhance Conformational Samplings and Quantify Energetics in Transmembrane Helix Assembly
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The method of window exchange umbrella sampling molecular dynamics (WEUSMD) with a pre-optimized parameter set was recently used to obtain the most probable conformations and the energetics of transmembrane (TM) helix assembly of a generic TM sequence. When applied to glycoporphin A TM domain (Gpa-TM) using the window potentials along the helix-helix distance, however, tight interfacial packing of GpA-TM resulted in insufficient conformational sampling at short helix-helix separation. To address this sampling issue, we approached in two directions: (i) Extension of WEUSMD into two dimensions with the restraint potentials along the rHH and crossing angle (G) to bypass barriers for hidden variables; (ii) Design of another scheme for the window spacing rather than a uniform one to control the averageAcceptance probability (Pa) between neighboring windows systematically. The two-dimensional WEUSMD results demonstrate that the incomplete sampling in the one-dimensional WEUSMD arises from high barriers along the crossing angle between the Gpa-TM helices. In principle, the multi-dimensional WEUSMD is suitable for modeling TM helix assembly. However, for three or higher dimensions, this approach becomes prohibitively intensive. To avoid this issue, one may consider the latter approach, the variable window spacing for WEUSMD, where the (highest) restraint force constant for the window at the shortest rHH geometrically decreases with rHH and the first passage time optimized parameter set is estimated by using an analytic approximation of Pa in general case (different window force constants for the exchange pairs). To demonstrate the improved sampling power of WEUSMD that in turn provides trustworthy potential of mean force, we applied WEUSMD with variable window spacing for the assembly of GpA-TM, and indeed obtained the improved sampling power compared to that with uniform window spacing.

The Conformational Energy Landscape of Aqueous Polyglutamine Peptides from Metadynamics Calculations
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One pathological effect of polyglutamine (polyQ) diseases, such as Huntington’s disease, is the aggregation of polyQ tracts in nerve cells. These aggregates form larger fibrils in the cells called inclusions. Though the exact pathological role these inclusions play is unknown, an increase in their development is directly correlated to progression of these diseases. The solution structure and aggregation mechanism of polyQ aggregates is poorly understood and, consequently, is a subject of interest in the biophysics community. Understanding the conformational stability and dynamic properties of polyQ peptides is an important component along the path towards pathological polyQ aggregation. Metadynamics simulation was used to explore the energy landscape of DD(Q6)-K peptides in vacuum, implicit and explicit solvent environments. Initial results from the implicit solvent simulations yield an energy landscape populated by extended and hairpin structures. The results from all simulations will be presented.

Conformational Diversity of N-Glycans in Solution Studied by REMD Simulations
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Conformational diversity of glycans is essential for the specific binding to their receptor proteins. Each of multiple conformers of a glycan could serve a “key” for specific binding to a target protein. However, the labile nature of glycans makes characterizing their conformational states a challenging issue. Here, we performed replica-exchange molecular dynamics (REMD) simulations to identify a family of multiple conformers of N-glycans in solution. The results provide new insights into the conformational equilibria of N-glycans and their alteration by chemical modification, supporting the concept of “conformer selection” in protein-glycan recognition. We also emphasize the importance of statistical averaging over the multiple conformers of glycans for comparing simulation results with experimental observables. Further theoretical developments prompt to explore the relationship between the flexibility of glycans and their specific recognition.

Conformational Diversity of N-Glycans in Solution Studied by REMD Simulations
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Molecular dynamics (MD) simulation is a powerful tool and widely used to elucidate dynamic behavior of proteins. Protein motions occur over a wide range of time scales, but not all are important for protein functions, which time scales are generally longer. Thus, it would be reasonable to consider that slower motions of proteins are more relevant to their functions. To identify such slow protein dynamics from simulation results, we have proposed the time-structure based independent component analysis (tICA) and have validated its usefulness. It was found that the motions detected by tICA were classified into two types: slowly changing motions and rare events. In the present study, we focused on rare events in protein simulation and investigated their variety and robustness. As a target protein, we selected lysine-, arginine-, ornithine-binding protein (LAO), which undergoes a large structural change upon ligand binding. One-microsecond MD simulation of apo-LAO in explicit water was performed three times using MARBLE and the CHARMM22/CMAP force field parameters. By applying the tICA to the simulation results, several rare events were identified as local motions, and confirmed with additional analyses to be actually occurred. We will discuss their underlying mechanism and functional significance.

Improvement of Sampling Efficiency through Combined use of Molecular Dynamics Simulations with Implicit and Explicit Solvent Models
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The molecular dynamics (MD) simulation is a powerful tool for analyzing the dynamical or physicochemical properties of biomolecules that are not accessible experimentally. It is however that the time scale of the MD simulation is not enough for examining the biologically significant events such as protein...