robustness of the model by folding different WALP transmembrane helical peptides starting from stretched, unstructured conformations using both simple canonical simulations and enhanced-sampling techniques [4]. Finally, the method is used to fold the 50-residue-long major pVIII coat protein (fd coat) of the filamentous fd bacteriophage. The results show excellent agreement with experimental structures and atomistic simulations in implicit membrane, demonstrating that such a protocol can serve as a starting point for better-refined atomistic simulations in a multiscale framework.


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Opening the Lateral Gate of the Rhomboid Protease Couples to Lipid Binding
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Rhomboid intramembrane proteases dock and cleave transmembrane substrates within the lipid bilayer. The conformational dynamics of the lipids, substrate and rhomboid during substrate binding are poorly understood. A particularly important question is whether during substrate binding the protease must open a lateral gate - its transmembrane helix 5 - toward the lipid bilayer, and if so how opening of the lateral gate couples to rearrangements of the surrounding lipids.

Experiments on the Hemophilus influenzae GbgP have identified mutations that either promote or inhibit the catalytic activity of the protease. We thus reasoned that understanding the conformational dynamics of active vs. inactive rhomboids can give insight into the motions compatible with productive substrate binding. We performed prolonged all-atom simulations of wild type and mutant H. influenzae GbgP for time scales of up to ~250ns. We find that, relative to the wild type, in a triple mutant with enhanced catalytic activity the gate helix 5 displaces laterally. This displacement creates an opening at the substrate-docking site that lipid molecules fill. The strong coupling between lipid and protease dynamics revealed by the simulations suggests that lipid dynamics can shape the energetics of substrate binding to the active site.

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High Resolution Model of HDL Wrapped with Tetrafoil apoA-I: A Coarse-Grained Simulation Study
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High density lipoproteins (HDL) prevent the formation of plaques in arteries by transporting excess cholesterol from peripheral tissues to liver for excretion. Hence, elevated levels of HDL is vital in controlling the progression of cardiovascular diseases (CVD). Inspite of HDL’s preventive role in coronary artery disease (CAD), very less is known about its structure and function. Recent chemical cross-linking and mass spectrometry studies revealed that the core structure of HDL is wrapped by three to five apoA-I proteins, which influence the binding of various metabolic enzymes like LCAT and CETP. A sophisticated model of HDL wrapped with four to five apoA-I chains is still missing in the literature, although some effort has been put forward to design the structure of HDL wrapped with smaller number of apoA-I chains [5]. In the present work, we propose a model of HDL that resembles the experimentally measured composition of POPC, PPC, cholesterol, cholesteryl ester and triglyceride molecules. The self-assembled droplet from coarse-grained simulation was subsequently wrapped with four apoA-I chains (tetrafoil model) and reverse transformed. The lipid-protein interactions and the structural organization of lipids in HDL were analysed through multi-microsecond coarse-grained and united atom simulations. The model is validated by reproducing various experimentally determined properties, such as the density of HDL, apoA-I chemical cross links, diffusion coefficients of lipid fractions and order parameter of lipid acyl chains.