Towards an implicit model to capture electrostatic features of membrane environment

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Membrane proteins play a critical role in our body, constituting about a third of all human protein. They are targets for more than half of all drugs. Membrane proteins are challenging to predict structure or design due to lipid layers. Implicit models accelerate this complex biomolecular problem by representing the solvent as a continuous medium. However, such models often do not consider the effect of pH, lipid head group, or dielectric constant of membrane environment. In this work, we are developing an implicit approach that captures the crucial electrostatic interactions due to the membrane, such as the effect of lipid head groups the influence of pH and dielectric variations inside the membrane layer. Our energy function franklin2022 is built upon franklin2019, an existing energy function based on experimentally derived hydrophobicity scales that could capture the anisotropic structure, the shape of water-filled pores, and nano-scale dimensions of membranes with different lipid compositions. Our method uses a constant-pH algorithm to sample the protonated and deprotonated states of protein residues. Further, it captures the effect of lipid head group using a mean-field based approach and uses a depth-dependent dielectric constant to characterize the membrane environment.

Relative to soluble proteins, the model development of membrane proteins particularly lag behind due to the sparse and low-quality data, leading to overfit tools and specific models. To overcome this challenge, we assembled a suite of 12 tests on independent datasets ranging from predicting structural property, stability to protein-protein docking and design. We test the performance of franklin2022 on this benchmark suite to evaluate its ability to predict the stability, structure, and design membrane proteins.

The speed of such implicit models and the model calibration based on diverse tests will help access biophysical phenomena at different time and length scales to accelerate the design pipeline for membrane proteins.