Modifying Membrane Permeability with Ionic Liquids

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Room temperature ionic liquids (ILs) have been proven to have a range of biological applications, from influencing protein folding and structural stability, to affecting enzyme activity, to modifying the permeability profile of lipid bilayers. In this work we use all-atom molecular dynamics simulations to study the effects of the ionic liquid choline geranate (CAGE) on lipid bilayers composed of POPE and POPC lipid types. CAGE was chosen based on previous experimental work that demonstrated this IL is effective at eradicating bacterial biofilms and at increasing the permeability of the biofilms to several antibiotics and other small molecules. Our group previously carried out simulations of lipid bilayer assembly in the presence of CAGE, which demonstrated that the geranate and geranic acid components of the IL embed in the lipid bilayer, while choline predominantly remains in the aqueous phase.

In order to expand on those initial simulations, we are using an enhanced sampling technique known as adaptively biased molecular dynamics (ABMD) to measure the free energy associated with the motion of the choline, geranate, and geranic acid components of the IL through pure POPE and POPC membranes. In the ABMD method, an energetic bias is applied to the system that accelerates the exploration of the ionic liquid molecules between the aqueous and lipid phases of the system, similar to the principles of the metadynamics method. The free energies calculated from ABMD will also be compared to the results of umbrella sampling (US) simulations. By comparing the ABMD and US methods we will be able to demonstrate whether the ABMD approach is well-suited for studying membrane permeability to ILs.

The next phase of the project seeks to contrast the permeability of several pharmaceutical compounds in the same membranes with and without ILs. From these simulations we will be able to determine how the presence of ILs impact the free energy profile of small drugs across the membrane.

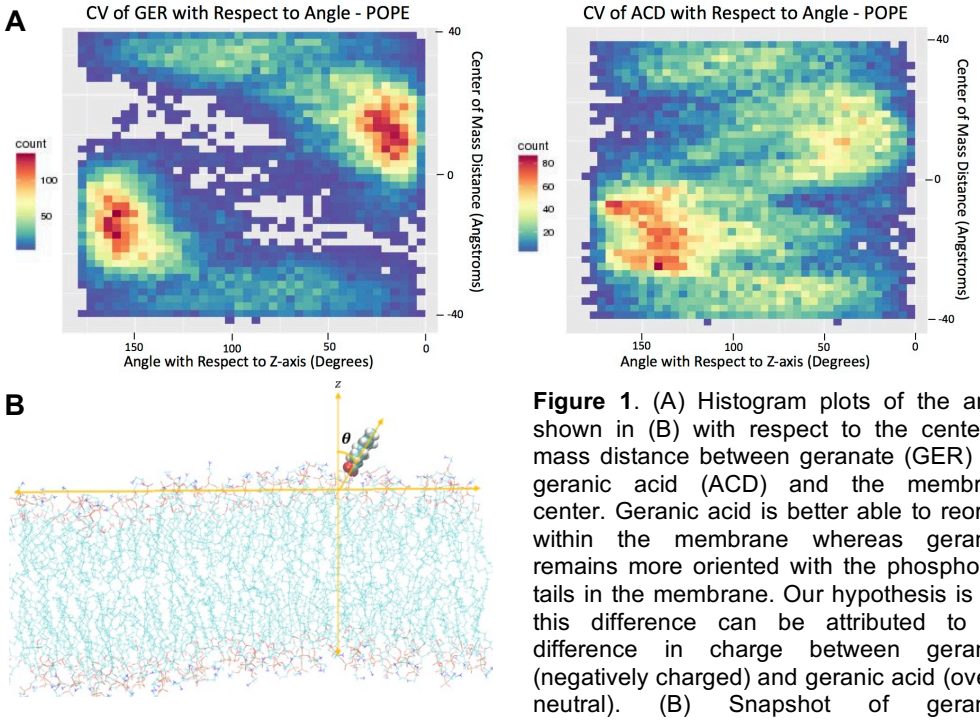

Figure 1. (A) Histogram plots of the angle shown in (B) with respect to the center of mass distance between geranate (GER) and geranic acid (ACD) and the membrane center. Geranic acid is better able to reorient within the membrane whereas geranate remains more oriented with the phospholipid tails in the membrane. Our hypothesis is that this difference can be attributed to the difference in charge between geranate (negatively charged) and geranic acid (overall neutral). (B) Snapshot of geranate approaching the membrane, with the angle of the molecule with respect to the z-axis shown.