Accurately modeling ion–lipid interactions remains a persistent challenge in computational biophysics. Alkali and alkaline earth metal cations associate with zwitterionic membranes, modulating the electrostatic potential near the bilayer and influencing lipid packing, water structure, and the behavior of membrane-associated proteins. These subtle but consequential effects impact processes such as signaling, fusion, and membrane phase behavior. However, widely used molecular dynamics (MD) model parameters (force-fields) often differ substantially in their predictions of ion dehydration and coordination.

My dissertation focuses on improving and evaluating ion–lipid interaction terms in force-fields. I have developed parameters for Na^+ and Li^+, and am currently characterizing two distinct Mg^{2+} models in simulations of POPC and DMPC bilayers. Each Mg^{2+} parameter set (2024 and 2025) is paired with two water–ion interaction models developed by other groups: one reproducing hydration free energies and the other tuned to match experimental water residence times.

The cation–lipid interaction terms were developed from DFT-optimized clusters using ligands representing the ester and phosphate fragments of the lipid. In our newer (2025) parameterization of Mg^{2+}, we preserve sixfold coordination by replacing missing ligands with water–an approach adapted from recent work with Mg^{2+} and ATP. Unexpectedly, simulations of DMPC with the 2025 model resulted in a larger number of Mg^{2+} adsorbed, despite DMPC having a smaller area per lipid than POPC. Tighter packing was expected to increase inner-shell coordination between Mg^{2+} and lipid oxygens, but not necessarily increase adsorption overall. This result has prompted a comparative study using the 2024 model in the same DMPC systems, which is currently ongoing and represents the final analysis needed to complete my dissertation.

Beyond resolving force field behavior, this project supports a longer-term goal: enabling multiscale simulations of membrane organization. Our lab has previously used this lipid force field to develop parameters for mean-field modeling of cholesterol–phospholipid systems and systems containing lipid-like molecules such as sphingomyelin. However, we lacked reliable and experimentally validated parameters for ion–lipid interactions, preventing their inclusion in these models. My current work addresses this limitation by identifying which ion observables–adsorption modes, and adsorbed charge density–may translate into new terms in mesoscopic models. Together with our validated monovalent ion models, these results will lay essential groundwork for future study of membrane, and membrane protein dynamics and organization at the mesoscopic and cellular scale.

During the Dissertation Completion Fellowship semester, I will complete the analysis of the DMPC+2024 simulations, finalize the POPC/DMPC comparison, and integrate this work into my dissertation's final chapter. I will also finish and submit the associated manuscript, prepare for my defense, and complete formatting and final revisions. I expect to defend by late September 2025 and submit my final ETD by early October.