NMRLipids VI: Polarizable Force Fields

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Abstract

For the initial project description, please refer to

https://github.com/batukav/NMRlipidsVIpolarizableFFs/blob/master/Manuscript/manuscript.pdf

Introduction

Conventional classical molecular dynamics (MD) simulations only consider electrostatics as interactions between static point charges, set by molecular dynamics models (force fields) as an input in the beginning of the simulation. The dynamic effects arising from polarizability are ignored or at most enter the simulations in an averaged fashion in the force field parametrization process. However, since decades work has been underway to make MD simulations explicitly polarizable in the hopes of reaching a more accurate description of the system. In the case of biomembranes (lipid bilayers), spesifically, including polarizability the molecular (dielectric) environment varies dramatically while crossing the membrane from the water phase across the dipolar/charged headgroup interface to the hydrophobic tail region and including explicit polarizability has the potential to provide more accurate description of membrane binding, membrane crossing, and behaviour and interactions of molecules residing within membranes, such as membrane protein folding. There certainly is room for improvement: efforts from the NMRlipids opens science community have showed that the

current classical lipid models cannot correctly reproduce the conformational ensemble, conformational dynamics, or ion biding within the simulations.

Historically, there has been three main approaches to modelling polarizability: 1) the induced point dipole/multipole model where polarizable point dipoles are placed on chosen sites on a molecule, 2) the classical Drude oscillator model where polarization is modelled by separating a core and a shell charge with a spring which stretches according to the enviroment giving the site a dipole moment, and 3) electronegativity equilization (fluctuating charge) model where atomic charges are no longer constant but can change according to the electronegativities of the molecule atoms and the electric fields from the molecular enviroment. In recent years the first two have surpassed the third in popularity. However, all of these approaches result in an increasing computational cost, e.g, by introducing new types of interactions, more interactions sites, or by requiring a shorter time step in the simulations.

Considering the increasing popularity of both implicitly and explicitly polarizable force fields and the increased computational computational cost that they require, systematic benchmark study polarizable force field quality is in high need. A few published studies reviewing the state of the polarizable force fields for biomolecules did not go beyond citing the results from the existing studies.[1?],[2] Recent publications show that implicit inclusion of polarizability improves cation binding simulations when evaluated against NMR data.[3,4] These results suggest that ion binding would be better captured in simulations with polarizable force fields. At the moment, there are three main polarizable lipid force fields with explicit electronic polarization: CHARMM-Drude,[5] AMOEBA,[6,7] and CHARMM-Fluctuating Charge (FQ).[8] Here we evaluate the performance of two polarizable force fields with lipid parameters available, CHARMM-Drude[5] and AMOEBA,[6,7] against NMR data. We use NMR order parameters to evaluate structural properties and cation binding, whereas NMR relaxation rates and correlation times are utilized to benchmark the lipid conformational dynamics. Furthermore, we compare the results to the non-polarizable simulations from the NMRlipids databanks.

Results

Evaluation of lipid bilayer properties simulated with polarizable force fields

1.Batuhan: Do we want to have a table showing the area per lipid, volume per lipid etc. type of values from these simulations?
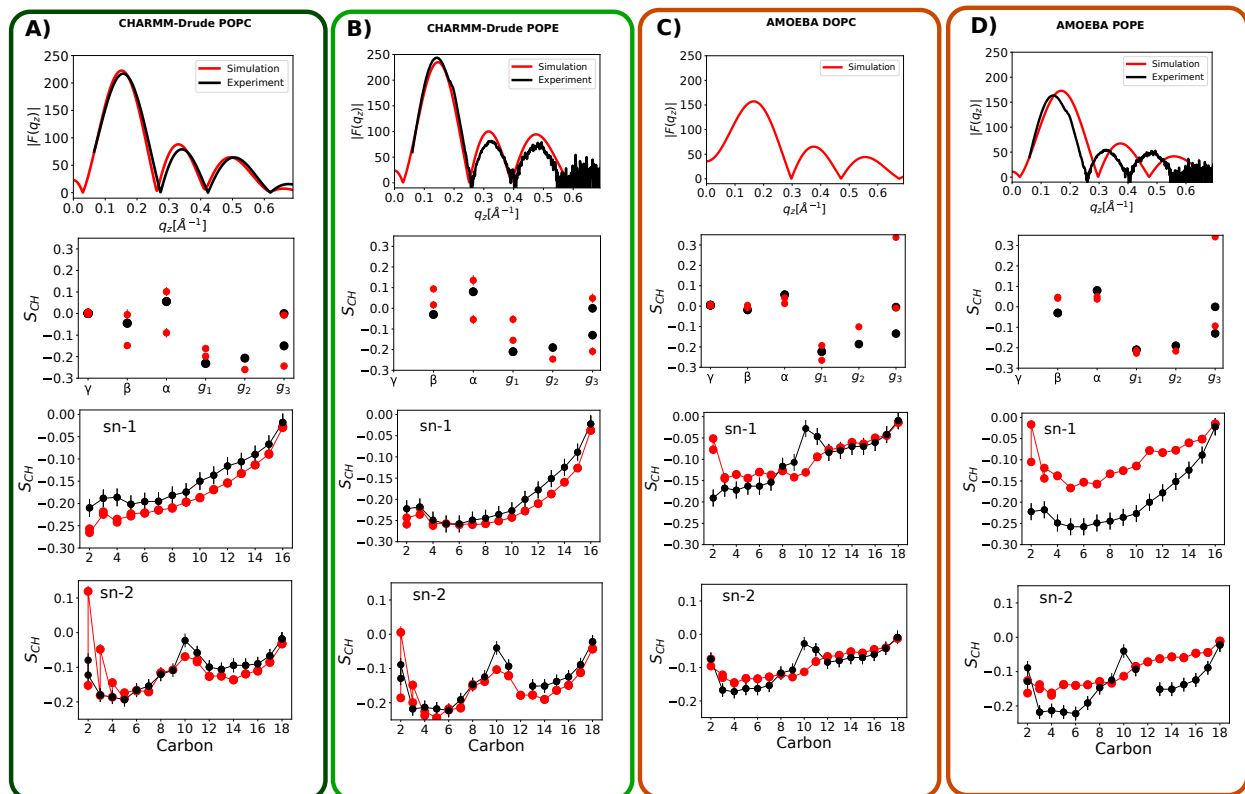

Figure 1: Order parameters calculated from the simulations

2.Batuhan: Exp for DOPC? 3.Batuhan: Charmm or any other simulation data for DOPC?
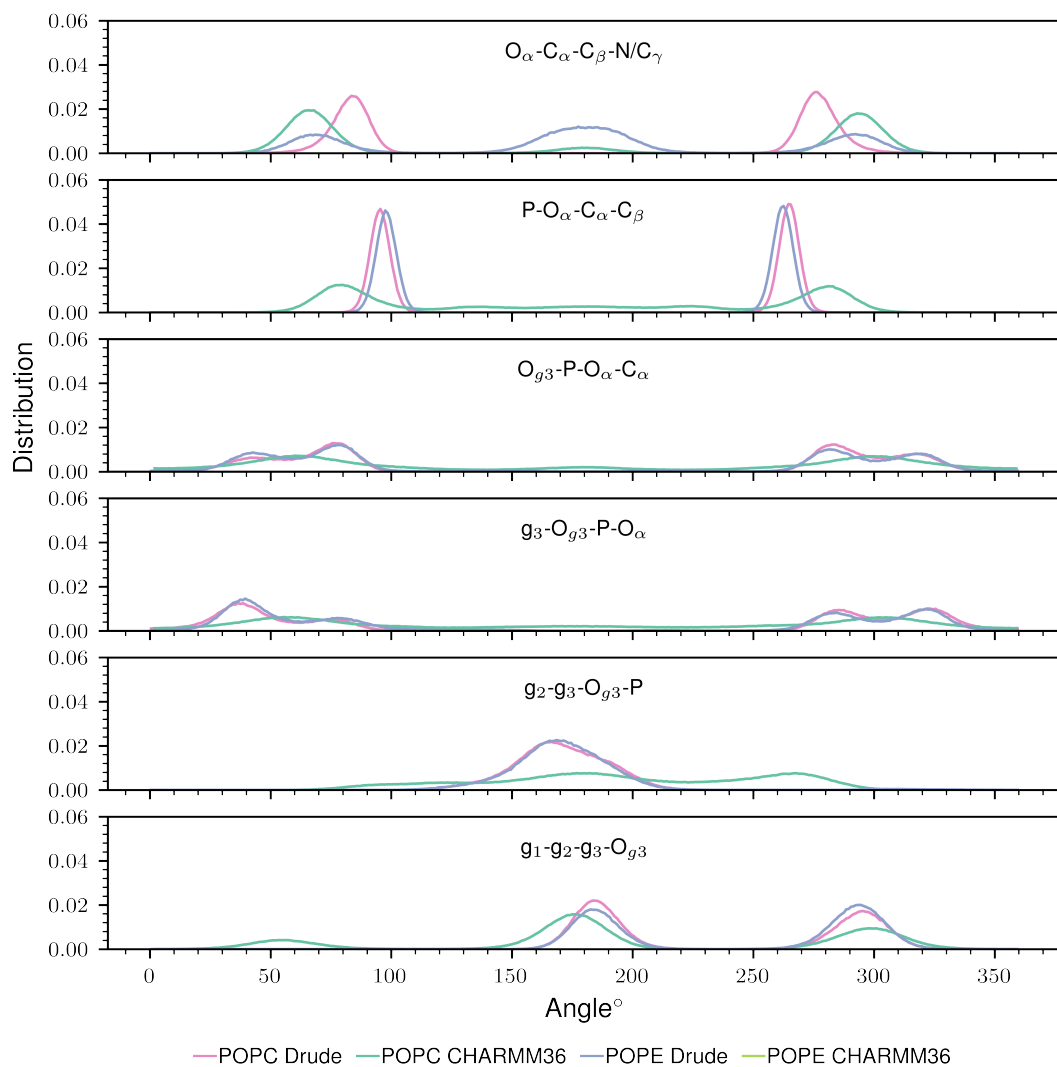
Figure 2: The distributions of the torsion angles for the head group atoms without the presence of salt.

4.SAMULI: I am not sure if I see POPE CHARMM36 lines in this figure. Also, colors, lines styles and/or widths could be better used to distinguish common and different elements in each line. For example, CHARMM36 with thick lines, drude thin lines, POPC black, POPE red, or something like that. 5.Batuhan: I'll fix the color scheme, add amoeba results, and move it to the SI section
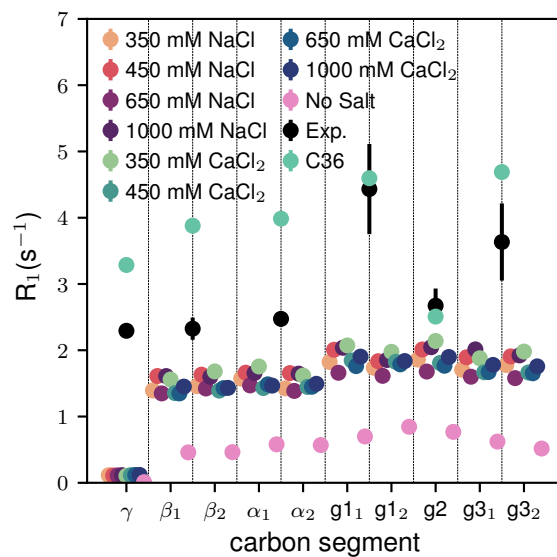
Figure 3: R1 times calculated for the POPC system. Experimental values are obtained from Ref.[23]

6.SAMULI: Are "No Salt" and all ion containing systems from Drude? Is it really true that addition of any salt increases the values to the same independently on the amount? 7.HANNE: are you going to add the teffs? You got the lower limit out of them right? Or maybe we can just mention that the correlation times were super slow which compounds to the already heavy computational load (one needs to simulate even longer to get convergence)

Ion binding to membranes in simulations with polarizable force fields
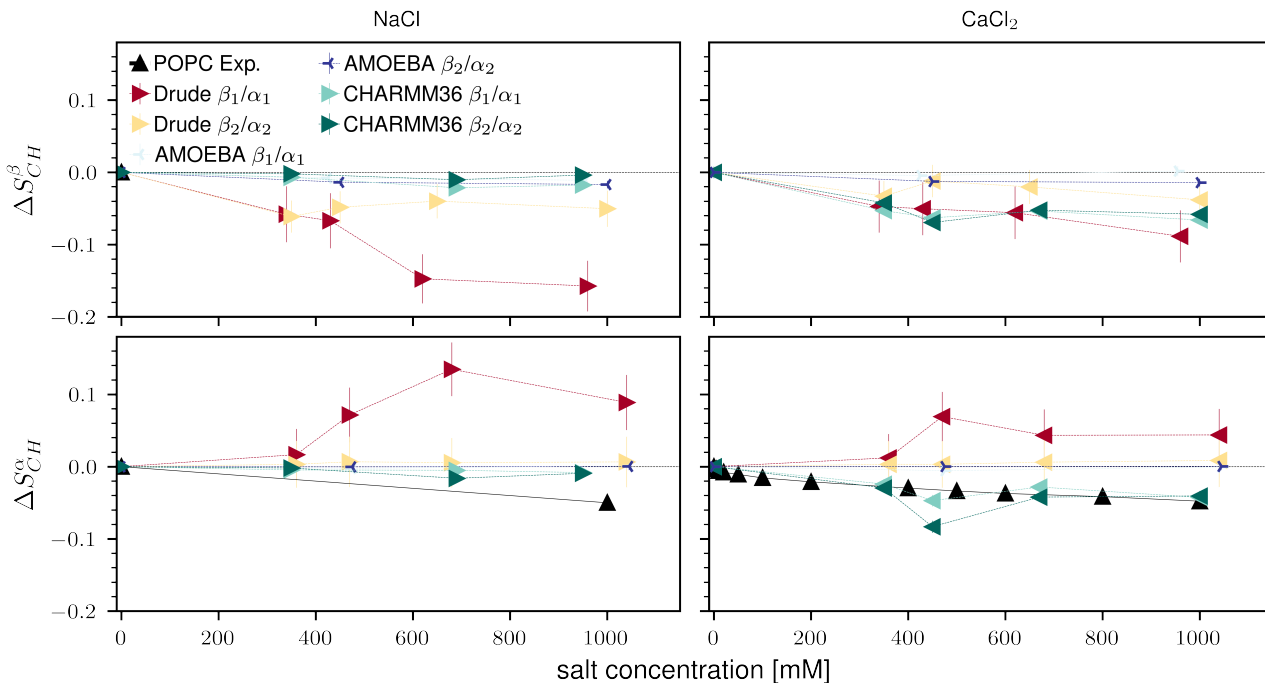

Figure 4: The change in the head group order parameters with respect to the simulations without salt as a function of the salt concentration.

8.SAMULI: y-axis scale should be much more zoomed in here, particularly the difference in experiments between sodium and calcium must be visible.

9.SAMULI: We should also show the ion density profiles along membrane normal and compare the ones with 1000 mM NaCl and 350 mM CaCl$_2$ (concentration in bulk water) to the best profiles in the literature (Fig. 5 in http://dx.doi.org/10.1021/acs.jpcb.7b12510). This will show the actual difference in ion binding to the best performing models available.
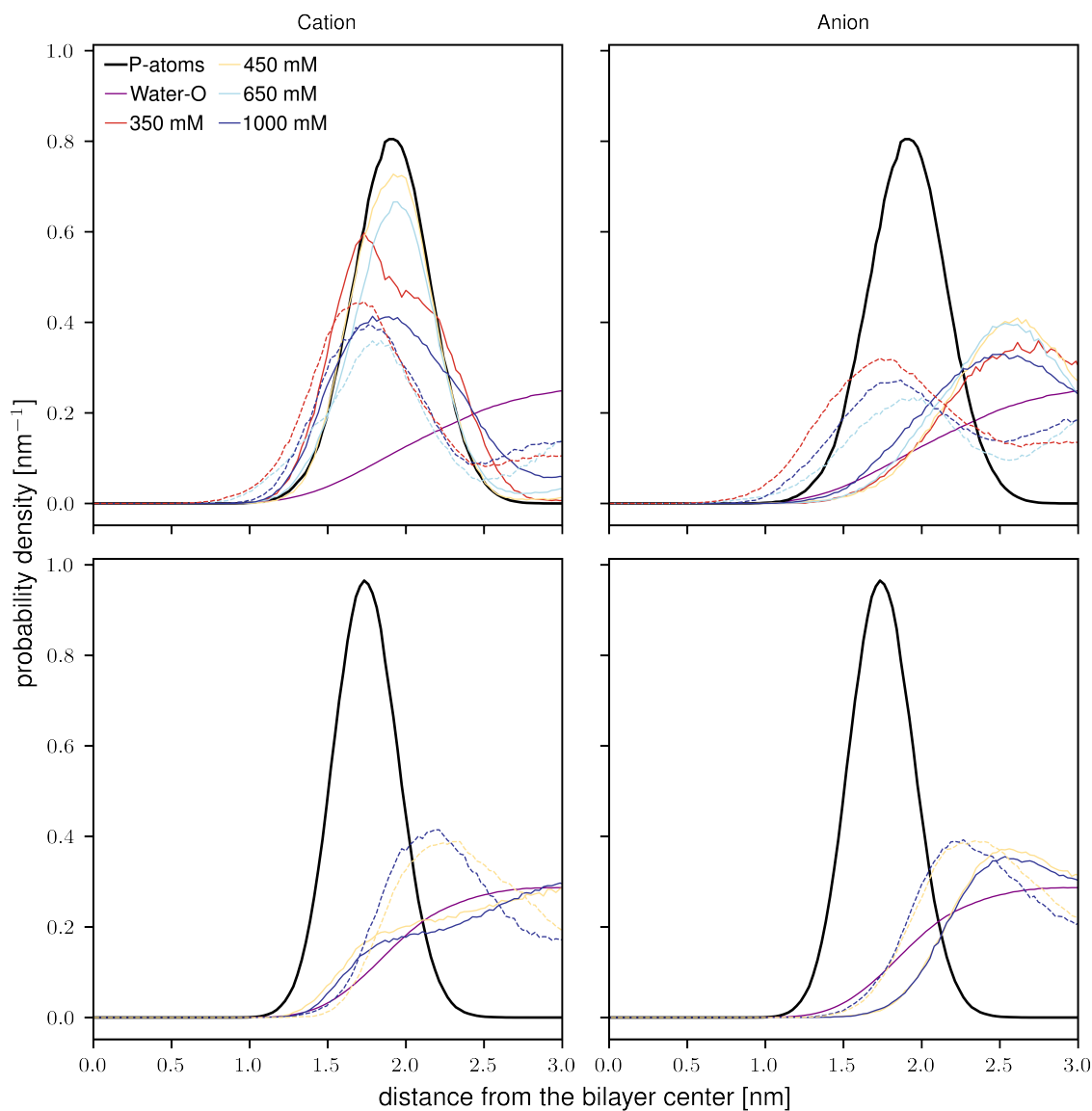
Figure 5: Density profiles alongside the membrane normal for the Drude POPC (first row) and AMOEBA DOPC (second row). Solid and dashed lines are for the systems with the NaCl and CaCl$_2$, respectively.

Discussion

Conclusions

Methods

Practical pitfalls of polarizable biomembrane simulations

Building a polarizable force field

The atomic point charges describing the electrostatics in non-polarizable force fields are typically parameterized by fitting to the electrostatic potential energy surface around one or few conformers obtained from ab initio calculations. One then proceeds to build on top of that the parameters for Lennard-Jones interactions and the dihedrals using a mixture of experimental (such as heats of vaporizations) and quantum mechanical information. For a polarizable force fields, this process has to be redone as in the first step the polarizable contribution has to be separated from the "static" one. Furthermore, for the polarization models considered here, an additional cutoff/damping scheme needs to be introduced to prevent polarization catastrophe—a phenomenon where close-by dipoles feed of each others and their dipole moments (and energy) grows into infinity.

Both polarizable lipid force fields considered here use a bottom up approach where parameters are first obtained for smaller molecules or molecular fragments from which the lipid models are then built. In the CHARMM-Drude model, the polarizabilities, the Thole damping factors used to prevent polarization catastrophe, and the partial charges where determined by fitting to a discretized QM potential energy surface around the molecule. More spesifically, the pertubations of the potential energy surface in the presence of a small charge where observed to separate the dynamic polarizability contribution. They then proceeded to use enthalpies of vaporation along with QM calculations of molecular interaction enegies to obtain the Lennard-Jones parameters, and on top of that dihedral potentials were intro-

duced to reproduce the QM potential energy profiles along a dihedral rotation. Finally, the dihedrals of the lipid head groups where refined targetting the NMR order parameters.

In the Amoeba force field, a set of atomic multipoles were first obtained based on the QM electron densities using Stone's distributed multipole analysis. The atoms were then assigned polarizabilities according to the AMOEBA atom types and induced dipole contribution was self consistently substracted from the permanent dipoles.[9] The charges (monopoles) were then kept constant while the multipoles were refined against the electrostatic potential energy surface around few conformers of the molecular fragments. After electrostatic parameters were set, the Lennard-Jones parameters were taken from previous AMOEBA parameterizations of smaller molecules containing same functional groups,[10,11] and then refined against molecule - water (gas phase) interaction energies. After settling all the nonbonded parameters, dihedral potentials were parameterised based on the QM conformational energy profiles.

Using a polarizable force field

The increased level of detail portrayed by explicit treatment of electronic polarizability comes with certain costs. The first cost is the increased computational complexity reduces the simulation speed. For the Drude force field, this slowdown occurs both because the addition of the Drude particles increases the number of interaction pairs and the employed extended dual-Langevin thermostat requires 1 fs integration time step. Current AMOEBA force field can use a multi time-step integration algorithm where the non-electronic interactions are iterated with a 2 fs time step whereas more computationally unstable polarization terms are iterated with a smaller time step. Yet, this usage of a multi-time step integration scheme does not overcome the slowdown resulting from the computationally demanding polarization calculations. As a result, one experiences almost a ten-fold decrease in the simulation speed while using the polarizable force fields. The second cost is due to the limited software support for both running and analyzing the simulations. Currently only

OpenMM supports both AMOEBA and Drude force fields. NAMD can only run the Drude force field whereas TINKER is only valid for AMOEBA force field and it does not support semi-isotropic pressure coupling, which decouples the pressure tensor in xy and z-direction and is crucial for correctly evaluating the ion binding properties of the bilayers (**10.This needs a reference, I remember Samuli mentioning this during a chat**). On the other hand, GROMACS, which has been the most popular MD engine within the bilayer simulation field, does not support any polarizable force field simulations. This is particularly important, as GROMACS also comes with many built-in functions for analyzing the trajectories and many of these functions require a GROMACS tpr file and subsequently cannot be utilized for analyzing the trajectories generated by other MD engines. This hinders the researchers from using well-tested analysis tools creating an overhead during the trajectory analysis while making results more prone to error. Therefore, open-source Python libraries for trajectory analysis like MDAnalysis, MDtraj, and LiPhyphilic (based on MDAnalysis) that can work on multiple trajectory and topology formats are gaining more attention.

Thanks to its recent update, CHARMM-GUI now can generate the topology and input parameters for the Drude force field, which greatly simplifies the employment of this model.

Simulations with CHARMM-Drude parameters

Current versions of the polarizable force fields require "good" starting structures. To achieve this, for every system, 200 ns long MD simulations with the non-polarizable CHARMM36 force field are run. The last frames from these simulations are fed into the CHARMM-GUI Drude Prepper to generate the input structures and OpenMM run files. Each bilayer contains 36 lipids in each leaflet. Simulations are run with the OpenMM MD engine.

The trajectories are publicly available on Zenodo.

Simulations with AMOEBA parameters

AMOEBA parameters are obtained from Githb [ref].

Analysis of simulations

Order parameters are calculated using the script "OrderParameters.py" under

"https://github.com/batukav/NMRlipidsVIpolarizableFFs/tree/master/scripts".

The order parameters are first calculated for each lipid as an average over time, and then averaged over the lipids. The error estimates are calculated as the standard error of the mean from the second average. Dihedral distributions are calculated using the script "calcDihedral.py" under

"https://github.com/batukav/NMRlipidsVIpolarizableFFs/tree/master/scripts" .

The R_1 rates and effective correlation times, along with the accompanying error estimates, are quantified from the trajectories as elaborated in Ref. 12. In-house python script available at XXX was used for this purpose.

Simulation Details and data availability

This project is performed using the "NMRLipids Databank" format and all related files, except the trajectories, are available under

"https://github.com/batukav/NMRlipidsVIpolarizableFFs/"

Lipid/counter-ions	force field	Ion (M)	N_l	N_w	N_{ion}	T (K)	t_{sim} (ns)	$t_{analysis}$ (ns)	
POPC	CHARMM-Drude	NA	NA	6400	0	303	500	400	
POPE	CHARMM-Drude	NA	NA	6400	0	303	350	300	
POPC:NaCl	CHARMM-Drude	0.350	144	6400	41	303	500	400	
	CHARMM-Drude	0.450	144	6400	51	303	500	400	
	CHARMM-Drude	0.650	144	6400	77	303	500	400	
	CHARMM-Drude	1.0	144	6400	115	303	500	400	
POPC:CaCl$_2$	CHARMM-Drude	0.350	144	6400	41	303	500	400	
	CHARMM-Drude	0.450	144	6400	52	303	500	400	
	CHARMM-Drude	0.650	144	6400	76	303	500	400	
	CHARMM-Drude	1.0	144	6400	114	303	500	400	

Acknowledgement

Supporting Information Available

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