

# Supporting Information: A high dimensional parameter search method to determine force field mixing terms in molecular simulations

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Table S1: Total energies of systems of small molecules from QM calculations. These energies are computed by taking the total energy from the final step of geometry optimization on clusters of our selected small molecules around a single  $\text{Na}^+$  following the procedure outlined in the methods section. We computed binding energies using these values.

Cluster Size	Water (kJ/mol)	MeAc (kJ/mol)	DePh (kJ/mol)
1	$-9.048 \times 10^5$	$-1.130 \times 10^6$	$-2.528 \times 10^6$
2	$-1.609 \times 10^6$	$-1.834 \times 10^6$	$-4.630 \times 10^6$
3	$-2.313 \times 10^6$	$-2.538 \times 10^6$	N/A
4	$-3.018 \times 10^6$	$-3.243 \times 10^6$	N/A

Table S2: Self energies of isolated molecules. These are computed by performing geometry optimization on an isolated molecule following the procedure outlined in the methods.

	Water	$\text{Na}^+$	MeAc	DePh
Energy (kJ/mol)	-2.006E+05	-4.253E+05	-7.042E+05	-2.102E+06

Figure S1: Distances from  $\text{Na}^+$  to each component atom in sample clusters. We compute the geometry of our sample clusters by computing the distance from the ion to each other atom in the system, shown per atom type. These distances are used in combination with the substitution energies in figure 2 to compute the error for the NM optimization.

Table S3: Nelder–Meade constraints. These values were used to constrain the parameter search space during the NM-optimization.

	NA-CH3		NA-CH2		NA-CO*		NA-OA,-OM*,-O*,-P		Additional Con- straints
	Min	Max	Min	Max	Min	Max	Min	Max	N/A
$\sigma_{ij}$ (nm)	0.2	0.5	0.2	0.5	0.2	0.5	0.2	0.5	$\sigma_{ij}^{\text{NA-OM*}} \leq \sigma_{ij}^{\text{NA-P}}$
$\epsilon_{ij}$ (kJ/mol)	0	0.79	0	0.81	0	0.83	0.05	7	N/A

Figure S2: Lipid chain deuterium order parameters.  $S_{CD}$ s are computed for each carbon for the chains Sn1 (a) and Sn2 (b), starting at the second carbon in the chain. We see that the optimized system is still showing significant ordering in the lipid chains as a result of ion binding; however, the ordering is less pronounced than in the system simulated with LB rules, and is closer to that of the simulation without salt. This result corresponds with the smaller bilayer thickness in the optimized system.

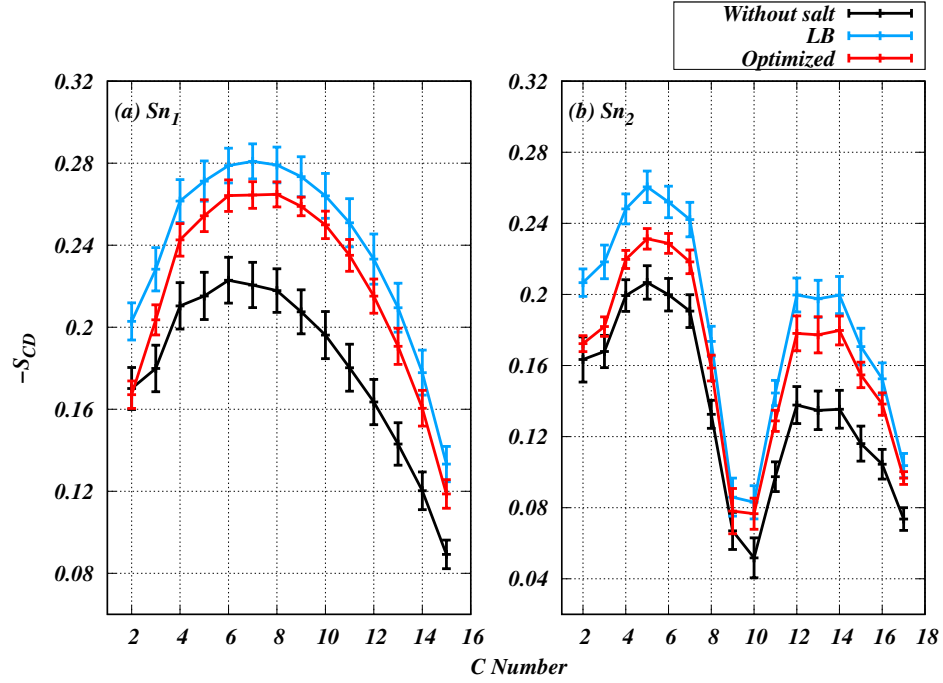


Figure S3: Electrostatic potential as a function of distance from bilayer center. The optimized cross terms yield a small change in the location of the peak of the potential in the bilayer simulated with optimized cross terms, as well as the loss of the valley behind the peak.

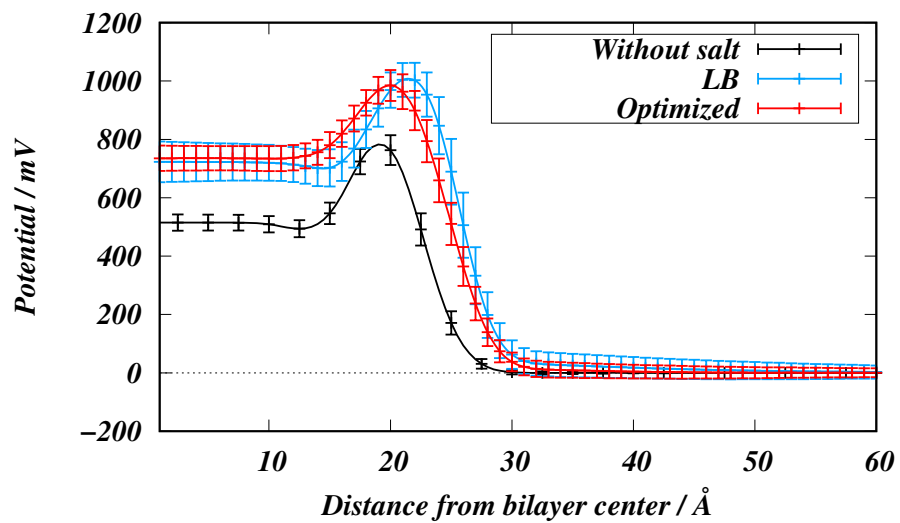


Figure S4: Poisson-Boltzmann theory predictions and simulation results. (a) shows a snapshot of the system simulated with optimized cross terms, translated to center the solvent occupied region. Water has been hidden for clarity. (b) and (d) show the number density of ions in the solvent occupied region of the box. (c) and (e) show the corresponding electrostatic potential in solvent. We illustrate theoretical predictions as solid lines, with corresponding simulation results as points with error bars. Red vertical lines denote the *hydration boundary* of the lipid bilayer. Cl<sup>-</sup> density data is used for fitting in both systems.

