Accurate binding of calcium to phospholipid bilayers by effective inclusion of electronic polarization

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Cellular membranes are complex systems that are hard to study both experimentally and theoretically. Classical molecular dynamics simulations (MD) give detailed information about membrane structure, dynamics and its interactions with other biomolecules. However, there is still a room for improvements in the current force fields, especially in the hydrophilic region of membrane. According to the results reported in NMRlipids, Open Collaboration project running at nmrlipids.blogspot.fi, biologically relevant Na+ and Ca2+ generally overbind to zwitterionic phophatidylcholine (PC) membranes in current MD models [Ollila 2016]. Here we suggest that the PC lipid membrane-ion interactions can be corrected by implicitly inducing electronic polarizability in the lipid models by using a simple electrostatic continuum correction (ECC) for partial charges [Leontyev 2010], which is successfully applied already to monovalent and divalent ions in bulk water [Kohagen, 2015]. Our results show that applying ECC to existing force fields significantly improved PC lipid–cation interactions when compared against NMR data by using the electrometer concept [Ollila 2016,Seelig87]. However, also other force field parameters have to be made consistent for ECC correction to preserve the area per molecule and other relevant bilayer properties. This work is carried as Open Collaboration in NMRlipids VI project (http://nmrlipids.blogspot.fi).

I. INTRODUCTION

Cations were shown to generally overbind in PC lipid bilayers in NMRlipids II project. Here we propose that the cation overbinding can be corrected by implicitly inducing electronic polarizability in lipid headgroups by scaling the partial charges.

II. EFFECT OF SCALING OF HEADGROUP AND GLYCEROL BACKBONE PARTIAL CHARGES ON LIPID BILAYER PROPERTIES AND CATION BINDING

Headgroup and glycerol backbone partial charges of Slipids and Lipid14 models were scaled with various scaling factors and cation binding was monitored by using the electrometer concept. Headgroup order parameter changes as a function of ion concentration are shown in Fig. 1. The order parameter decrease seemst to be proportional to the headgroup charges: the smaller the charges (larger scaling factor), the less change is observed in order parameters. According to the electrometer concept, this means that the headgroup scaling decreases cation binding affinity. However, from this data only we cannot exclude the possibility that order parameters are changing less because headgroup becomes less sensitive for cation binding.

The best models from Fig. 1 are shown in Fig. 2. Based on these results we choose two models for more careful studies: Slipids and Lipid 14 models with headroup and glycerol backbone partial charges scaled with 0.8 and 0.85, respectively.

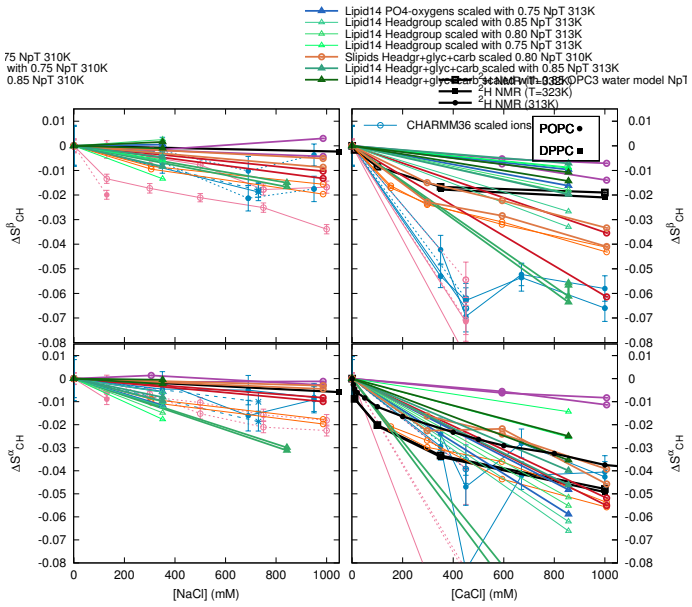

FIG. 1: Headgroup order parameter changes as a function of cations from models with modified headgroup partial charges.

While scaling seems to improve ion binding, it changes the lipid bilayer properties without ions. The glycerol backbone and headgroup order parameters are plotted in Fig **??** for reference models and EEC models. The difference, i.e. the effect of scaling on these parameters, is shown in Fig. 4. The area per lipid from different models are shown in Table I The conclusion is that the charge scaling has only a marginal effect on headgroup order parameters, while area per lipid is significantly decreased. Area per lipid decrease is more pronounced in Lipid14 than in Slipids.

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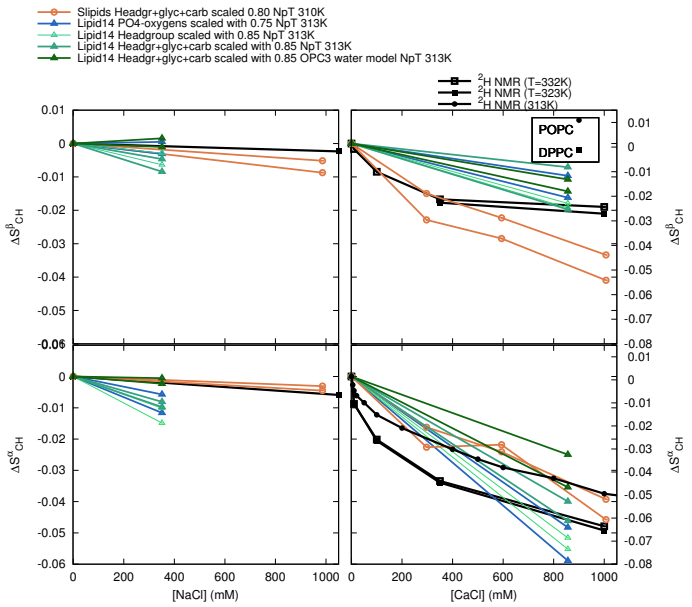

FIG. 2: Headgroup order parameter changes as a function of cations from models with modified headgroup partial charges.

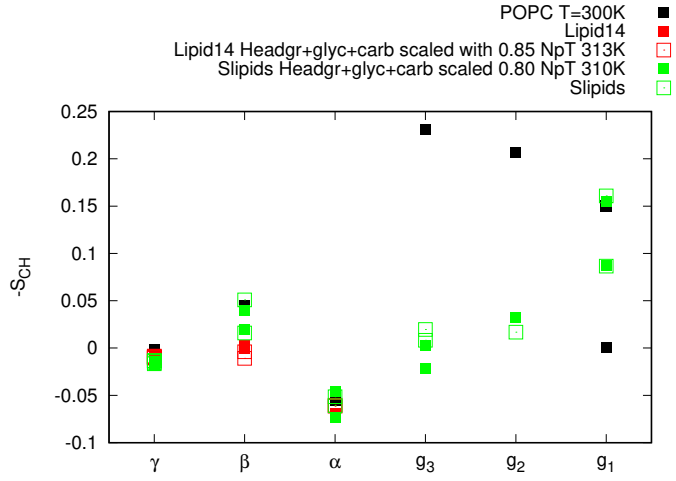

FIG. 3: Headgroup and glycerol backbone order parameters from standard and EEC models.

The Calcium densities from new models and standard models are compared in Fig 5. It seems to me that Ca binding in Lipid14 model is not reduced by scaling the partial charges even thought the order parameter response is better. On the other hand, in Slipids the binding seems to be reduced. Possible interpretation is that Lipid14 result gets better because headgroup gets less sensitive for bound charge, while in Slipid the binding is reduced.

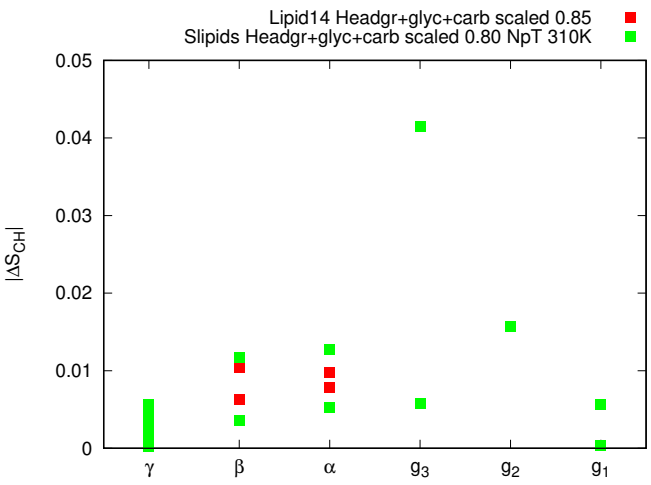

FIG. 4: Changes in headgroup and glycerol backbone order parameters due to EEC.

TABLE I: Area per lipid from different models for POPC without ions

model	A (^{2})
Lipid14 (literature)	65.6± 0.5
Lipid14eec0.85	55.5
Slipids (literature T=303K)	64.6 ± 0.4
SlipidsEEC0.8	57.8

III. CONCLUSIONS

Acknowledgments

SUPPLEMENTARY INFORMATION

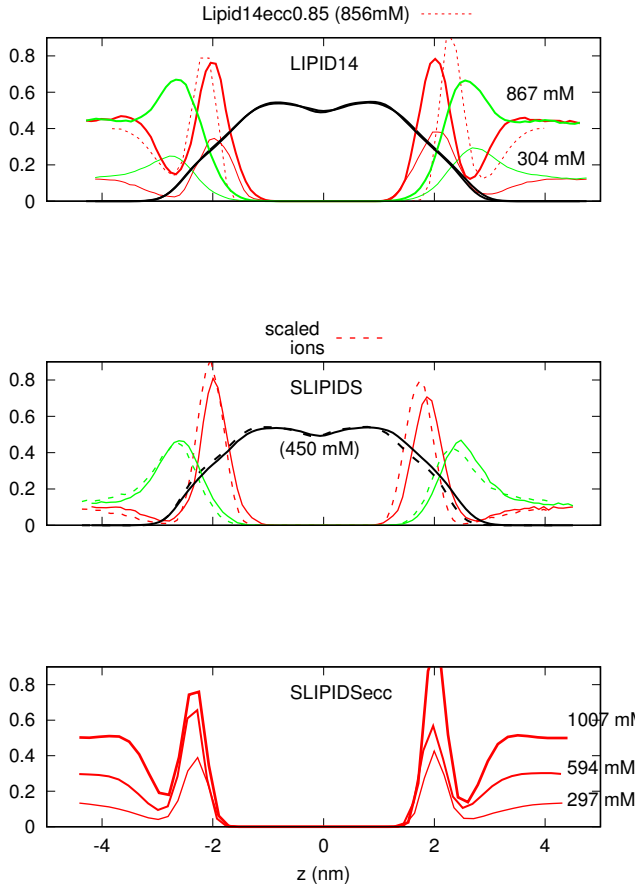

FIG. 5: Calcium densities from different simulations with new and standard models.

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