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

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Classical molecular dynamics simulations give detailed information about membrane structure and dynamics. However, there is still a room for improvements in current force fields it is known from the literature, that the binding of ions, especially cations, to phopholipid membranes is overestimated in all classical models [1]. We suggest that the membrane-ion interactions can be corrected by including implicit electronic polarizability into the lipid models through the electronic continuum correction (ECC) [2], which was already applied to monovalent and divalent ions yielding models that feature correct ion pairing [3]. Using the electrometer concept [3, 4], our simulations point out that our hypothesis is correct and ECC is indeed a missing important contribution in current classical lipid models. Moreover, the solid physical principles behind ECC are found not to hamper other relevant properties of a phospholipid bilayer. The new lipid model, "ECClipids", shows accurate affinity to sodium and calcium cations. This work will continue as an open collaboration project NMRlipids IV (http://nmrlipids.blogspot.fi).

[1] Catte, A., Girych, M., Javanainen, M., Melcr J., Miettinen, M. S., Oganesyan, V. S. and Ollila H. S., PCCP 18(47) 32560-32569 (2016) [2] Leontyev, I. V., and Stuchebrukhov, A. A., JCTC 6(5) 14981508 (2010) [3] Kohagen, M., Mason, P. E., and Jungwirth, P., J. Phys. Chem. B 120(8) 145460 (2015) [4] Seelig, J., MacDonald, P. M., and Scherer, P. G., Biochemistry 26(24) 75357541 (1987)

General Introduction

motivation, significance of membranes, phospholipids and simulation.

assumptions (so that we have structure of the paper like in a mathematical proof) – MD simulation is a good tool for studying molecules. classical MD models can describe lipids accurately,

MD is ... and it serves ... it is useful for ... (describe throuhg references)

Lipid membranes, especially phospholipid membranes; their significance for life, sciences, society, pharma ...

Specific introduction: MDEC and current FFs

Current force fields – pros and cons, at a good shape in many aspects, agree on various properties

lipid force fields fail in description of membrane-cation interaction – could be answered by ECC?

MDEC – or – ECC **1.choose one** MD in electronic continuum as in [**?**] or electronic continuum correction as in [**?**]

Describe ECC: good physical concept for treating part of the polarizability (electronic) in a simple mean-field way.

Succesful application: Works for cations [**? ?**]**2.REF** – motivation for its application to zwitterionic lipids like POPC.

Hypothesis: ECC helps in describing even zwitterionic molecules like POPC, will be demonstrated through headgroup order parameter response to cationic molecules.

Main body starts:

ECC and solvation ΔG.(from [**?**]: hydration ΔG can provide good structure and energetics, but will fail in good interactions – already proved for cations) In addition, ΔG_{hyd} – the usual target for parametrization of small molecules in classical force fields – is not the right target in the MDEC/ECC framework – part of ΔG is already included in the polarization of electrons, and only the remining part of ΔG belongs to the polarization of the nuclei. Interestingly, the part of ΔG due to electrons is approximately $1/2$ of it, which is what I observe in my simulations – if I assume that half of this energy is already accounted for by the water model (which is rather a MDEC model already), than I should recover approximately $3/4$ of the original interaction energy. When I write the formula for interaction energy for two particles at a distance $r = \sigma$ (approximate equilibrium position), I get

$$W(f_\sigma r, f_q q) = \kappa \frac{q_i q_j}{r} \frac{f_q^2}{f_\sigma} \tag{1}$$

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When I apply $3/4$-assumption for the intereaction energy, I require:

$$\frac{3}{4}W(r,q) = W(f_\sigma r, f_q q) \tag{2}$$

So for $f_q = 0.8$ I obtain $f_\sigma = \frac{4}{3}f_q^2 = 0.853$ – which is very close to the value I use, $f_\sigma = 0.875$. This is a crude derivation neglecting the true position of energy minimum and the LJ mixing rules. However, the formula for f_σ does not depend on the absolute position and I believe that the assumption that the minimum is relatively shifted by scaling with f_σ holds pretty well.

How I apply ECC on Lipid14 POPC and why such choice (i.e. f_σ, f_q and definition of the scaled region).

why Lipid 14 – good ratio of α/β response.

Observations:

Accurate electrometer response to Na^+, Ca^{2+} and DHMDMAB cationic surfactant.

Preserves other relevant properties: APL, Order Parameters (OPs), diffusion? 3., elasticity? 4. – however, it is still garbage in-garbage out

Gives correct scattering form factor – good groud for interpretting experimental data.

Provides correct stoichiometry for Na^+, Ca^{2+} and their interaction energies with the lipid membrane.

Discussion:

other lipids: charged lipid? – ongoing research in our lab (starting to do something with Aniket on POPE for curved membranes)

Role of water model: we use OPC3 (current best), it would be worth giving an estimate how results change when we use say SPCE or even TIP3p at least in the SI (so that the reader knows what errors to expect comming from these sub-optimal models). In addition, there is protein force field Amber15-FB, which uses water close to OPC3, TIP3pFB 5.REFs.

questionable charge distribution from RESP – a leeway for further tweaks of the FF

acheivable accuracy of the MD engines themselves (mainly Hector's worry).

application of the correction to other lipid models: The rule looks general, however, it depends on how accurate the original model was.

Conclusion:

Say what we did...

This will be a foundation stone of a new open-collaboration project NPRlipid 6 in 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.

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.

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.

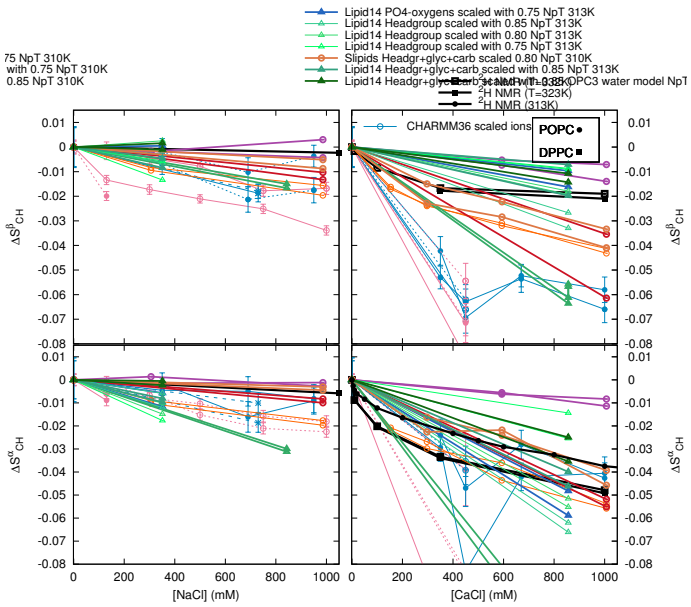

FIG. 1: Headgroup order parameter changes as a function of cations from models with modified headgroup partial charges.

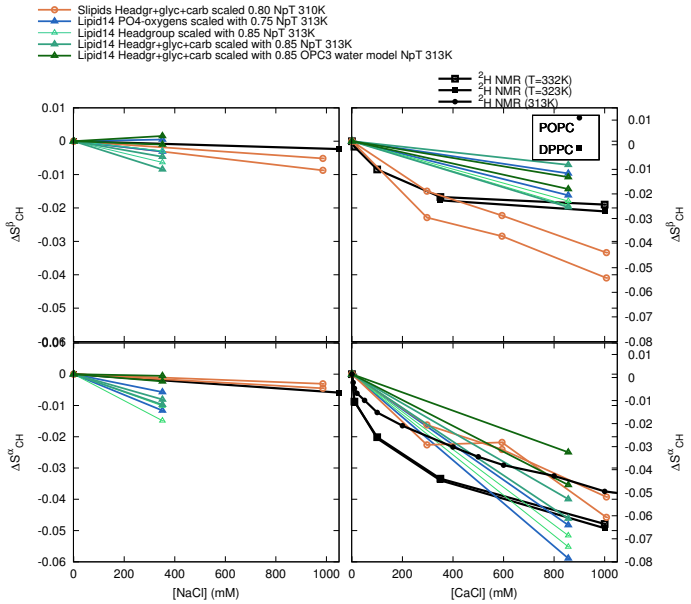

FIG. 2: Headgroup order parameter changes as a function of cations from models with modified headgroup partial charges.

III. CONCLUSIONS

Acknowledgments

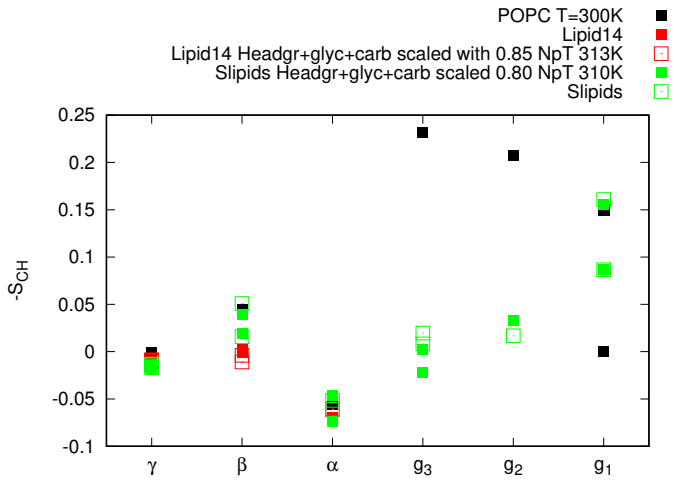

FIG. 3: Headgroup and glycerol backbone order parameters from standard and EEC models.

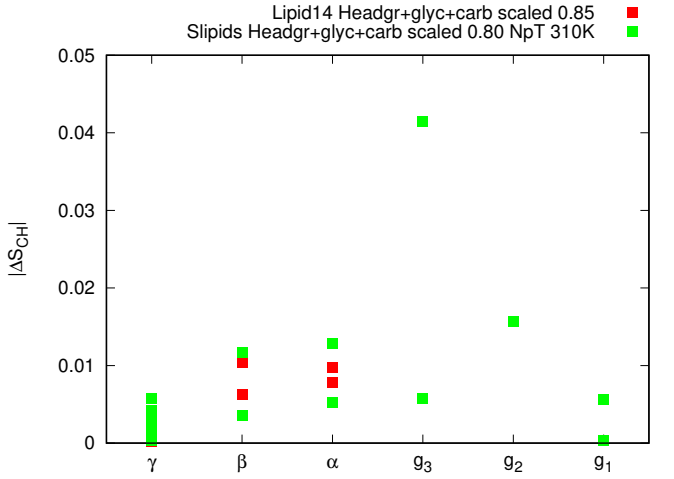

FIG. 4: Changes in headgroup and glycerol backbone order parameters due to EEC.

SUPPLEMENTARY INFORMATION

ToDo

P.

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

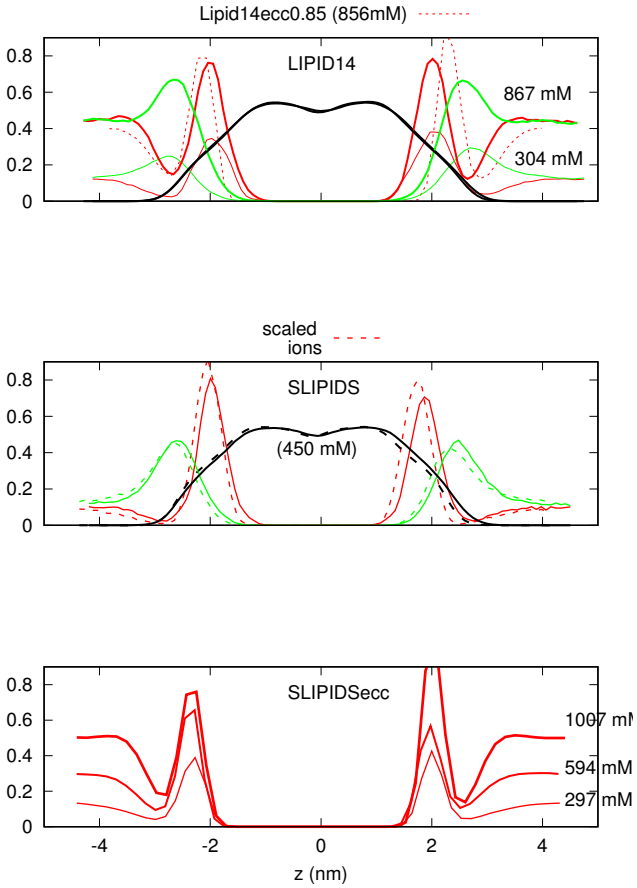

FIG. 5: Calcium densities from different simulations with new and standard models.