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: current FFs and MDEC/ECC

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? 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.

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 paradigm – 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. Hence it is non trivial, how large should be the scaling factor f_σ – it should lay between 1 and f_q, the limits for the original interaction energy and its limit when we neglect the ΔG_{el} term in ΔG_{hyd}.

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

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

Observations, how does the system behave, what are its macroscopic properties:

Accurate electrometer response to Na^+, Ca^{2+} and DHMDMAB cationic surfactant. The response of the headgroup order parameters is improved both through diminished affinity towards the cations and through lower headgroup response to the

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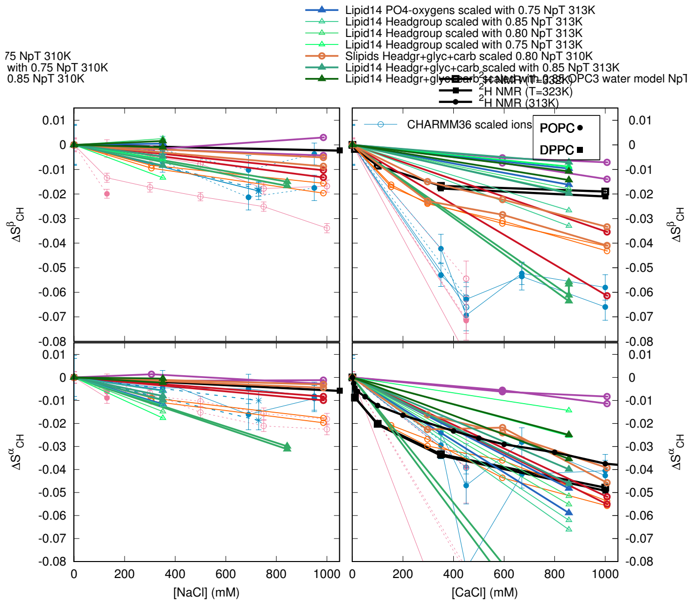

FIG. 1: Headgroup order parameter changes as a function of cations from models with modified headgroup partial charges.

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

model	A (^{2})
Lipid14 (literature)	65.6± 0.5
Lipid14ecc0.80+sigma0.875	64.3
Slipids (literature T=303K)	64.6 ± 0.4
SlipidsEEC0.8	57.8

bound charge (from simulations with DHMDMAB surfactant). The best models from Fig. 1 are shown in Fig. 2. Based on these results we choose

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

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

Provides/predicts 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. It is not obvious that RESP charges provide the best description, especially due to its non-uniqe solution. Shall we solve RESP fitting with the constraint of full charges and then scale down, or shall we rather solve the fitting with a scaled total charge target?

acheivable accuracy of the MD engines themselves (mainly Hector's worry) is another limiting factor in fine tuning parameters – solid physical ground helps.

application of the correction to other lipid models: The rule looks general, however, it depends on how accurate the original model was. From preliminary simulations with POPE, it looks that the rule works for Lipid14 FF, at least for zwitterionic headgroups.

Conclusion:

Reiterate what we did...

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

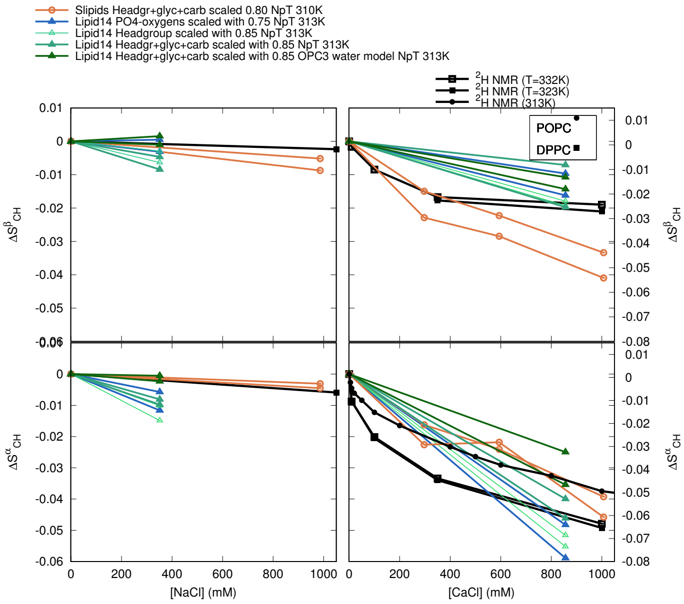

FIG. 2: Headgroup order parameter changes as a function of cations from models with modified headgroup partial charges.

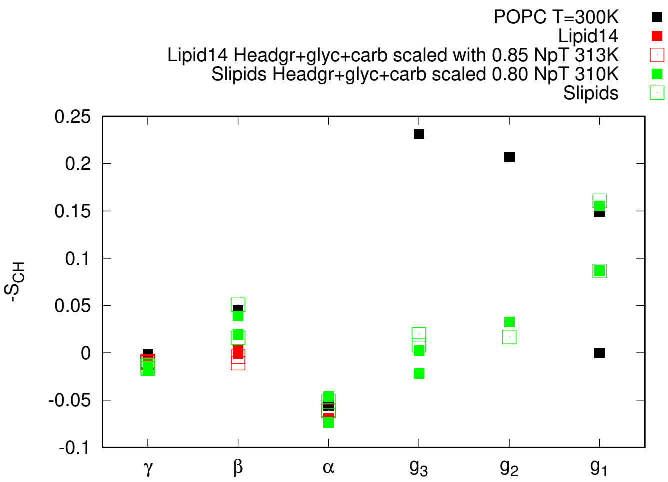

FIG. 3: Headgroup and glycerol backbone order parameters from standard and EEC models.

Acknowledgments

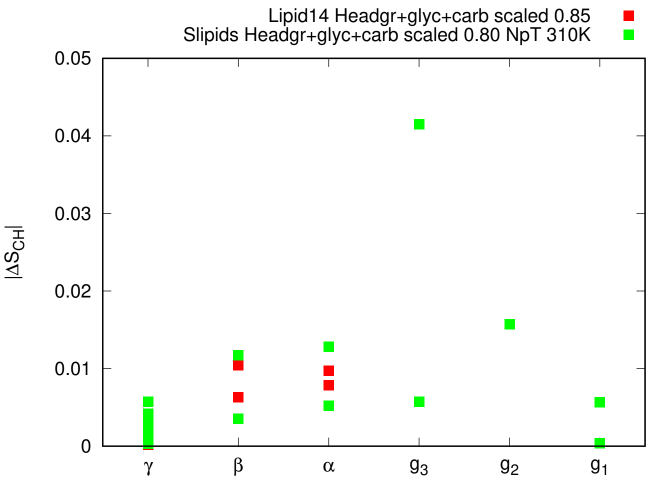

FIG. 4: Changes in headgroup and glycerol backbone order parameters due to EEC.

SUPPLEMENTARY INFORMATION

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