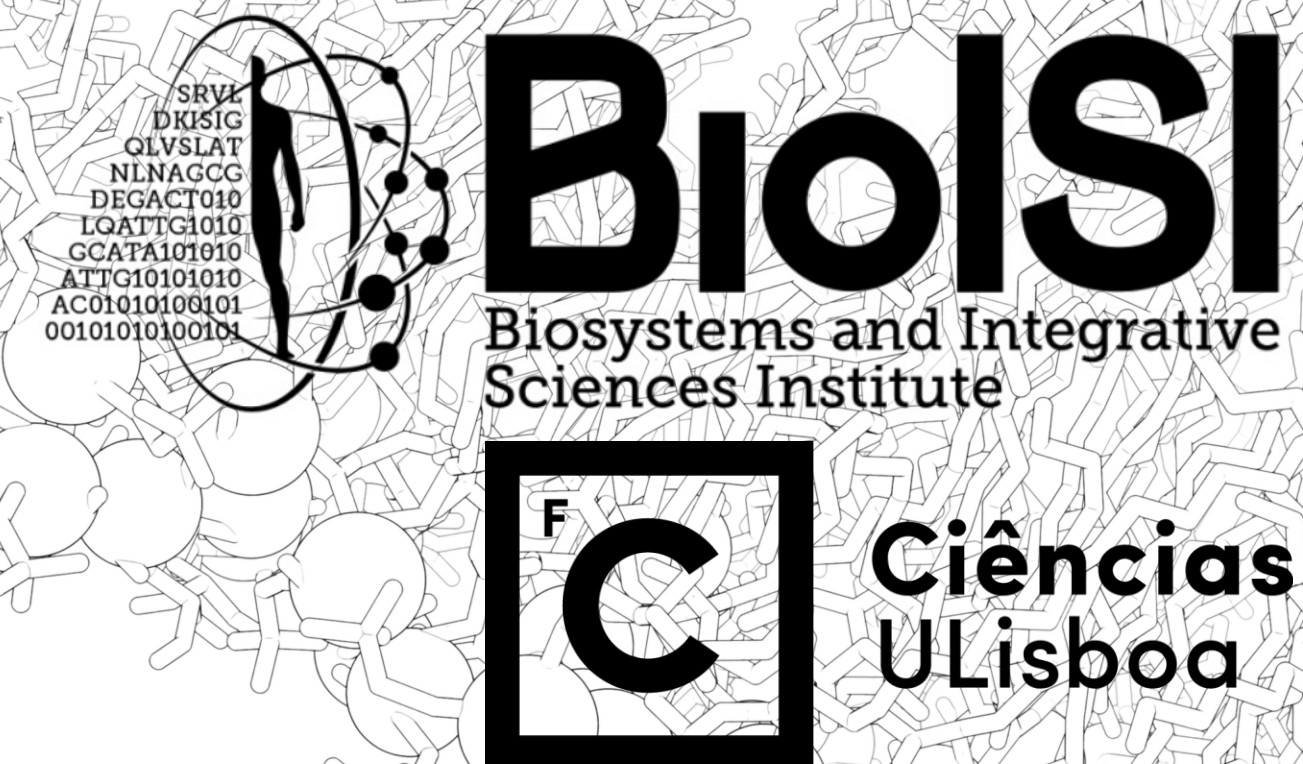


pH effects on PG/PC and PS/PC lipid binary mixtures

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Introduction

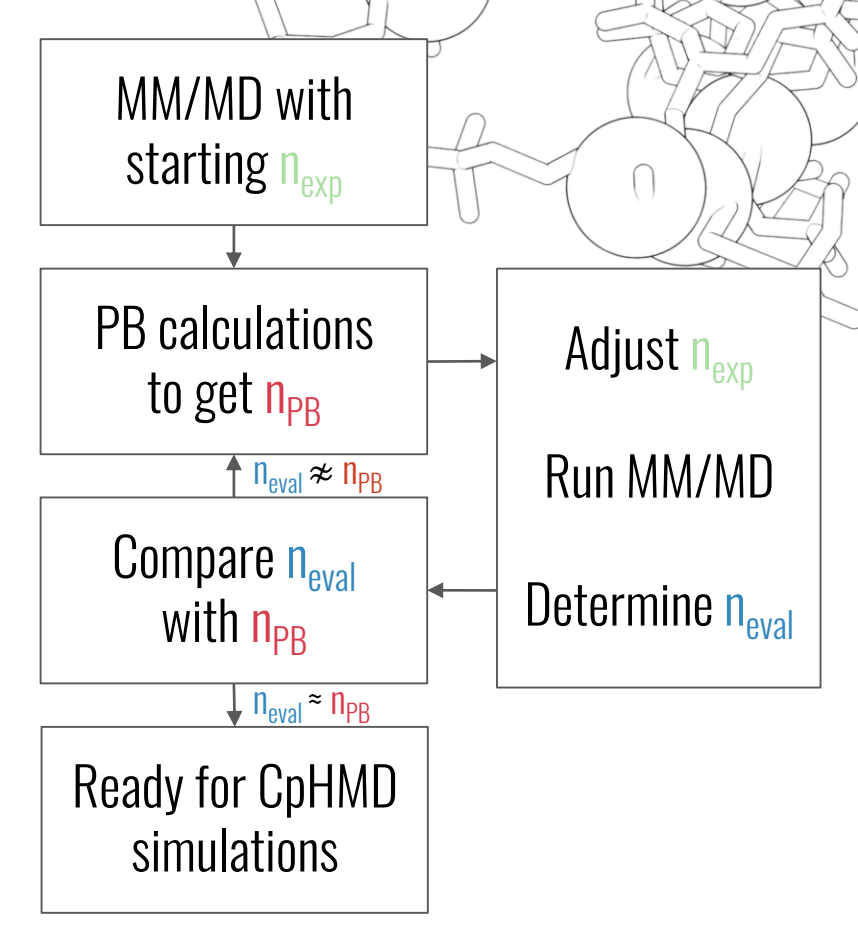
Membranes are vital biological components, fulfilling many roles in cells [1]. Although highly diverse, they are primarily comprised of zwitterionic and anionic lipids, making them sensitive to changes in pH. In computational methods, these systems are often simplified via model membranes composed of a single lipid type or, in some cases, by binary or ternary mixtures [2]. While these approximations are generally adequate, there are particular cases where pH plays a key role in membrane function and stability, which highlights the importance of developing more realistic membrane models where pH effects are accounted for.

In this work, we assembled binary mixtures of 128 lipids, either phosphatidylglycerol (PG) or phosphatidylserine (PS) in phosphatidylcholine (PC) in different molar fractions: 10%, 25%, 50% and 75% and equilibrated them using MM/MD simulations, in preparation for constant -pH MD simulations.

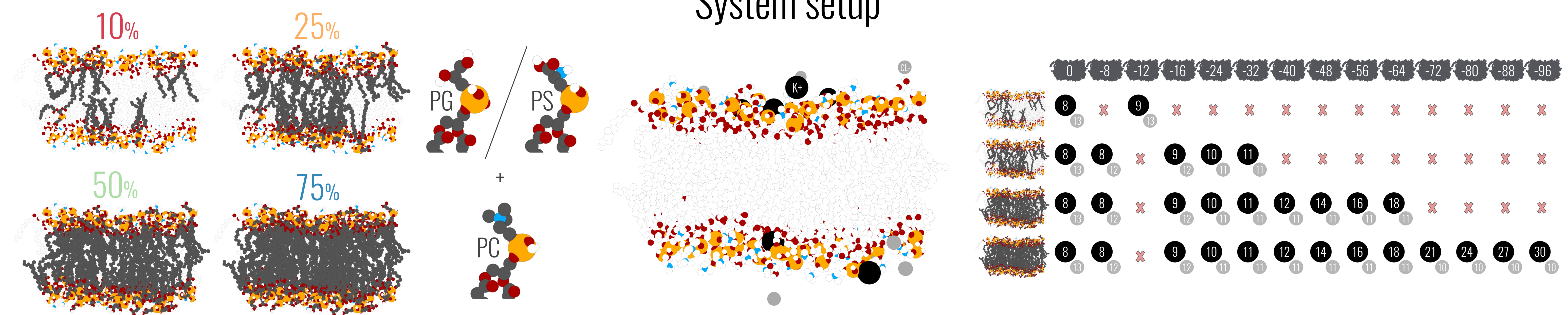
Methods

MM/MD simulations were performed using a modified [3, 4] GROMACS 4.0.7 distribution [5,6] and the GROMOS 54A7 force field [7]. PG and PS parameters were adapted from G54A7 and ref. [2]. Simulation settings were the ones described in ref. [2], but with an ionic strength of 0.15M. Explicit ions used in GRF were also estimated according to ref. [2], using DelPhi V5.1 [8,9] and Petit V1.6.1 [10] for PB and MC calculations, respectively.

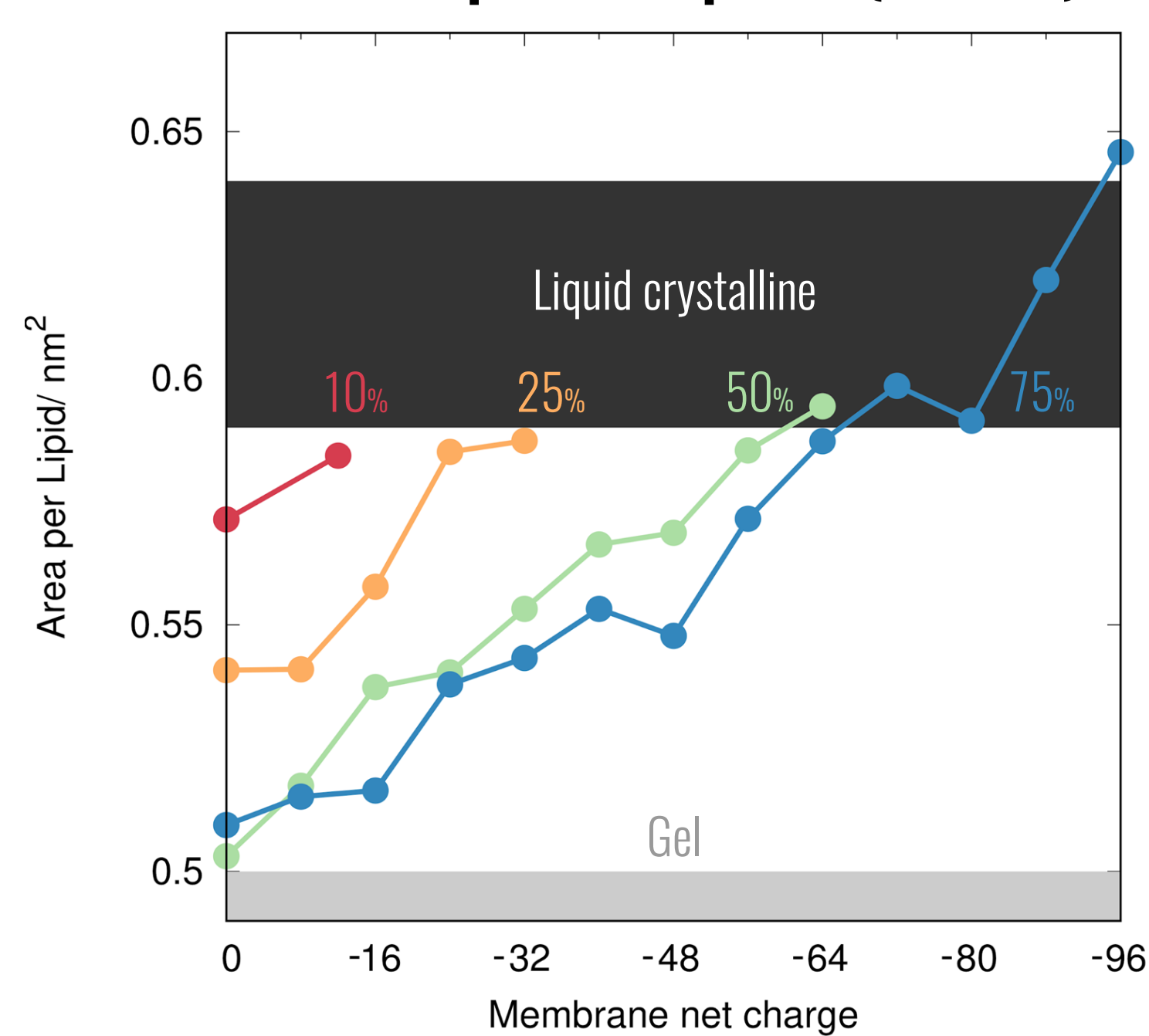
Long-range electrostatics were treated using either generalized-reaction-field (GRF) [11] with a PB estimated number of explicit K⁺/Cl⁻ ions shown below, or Particle Mesh Ewald (PME) [12] in a fully neutralized system (number of K⁺ ions equal to the net membrane charge). 30 ns-long MD simulations were performed for equilibration of all systems.



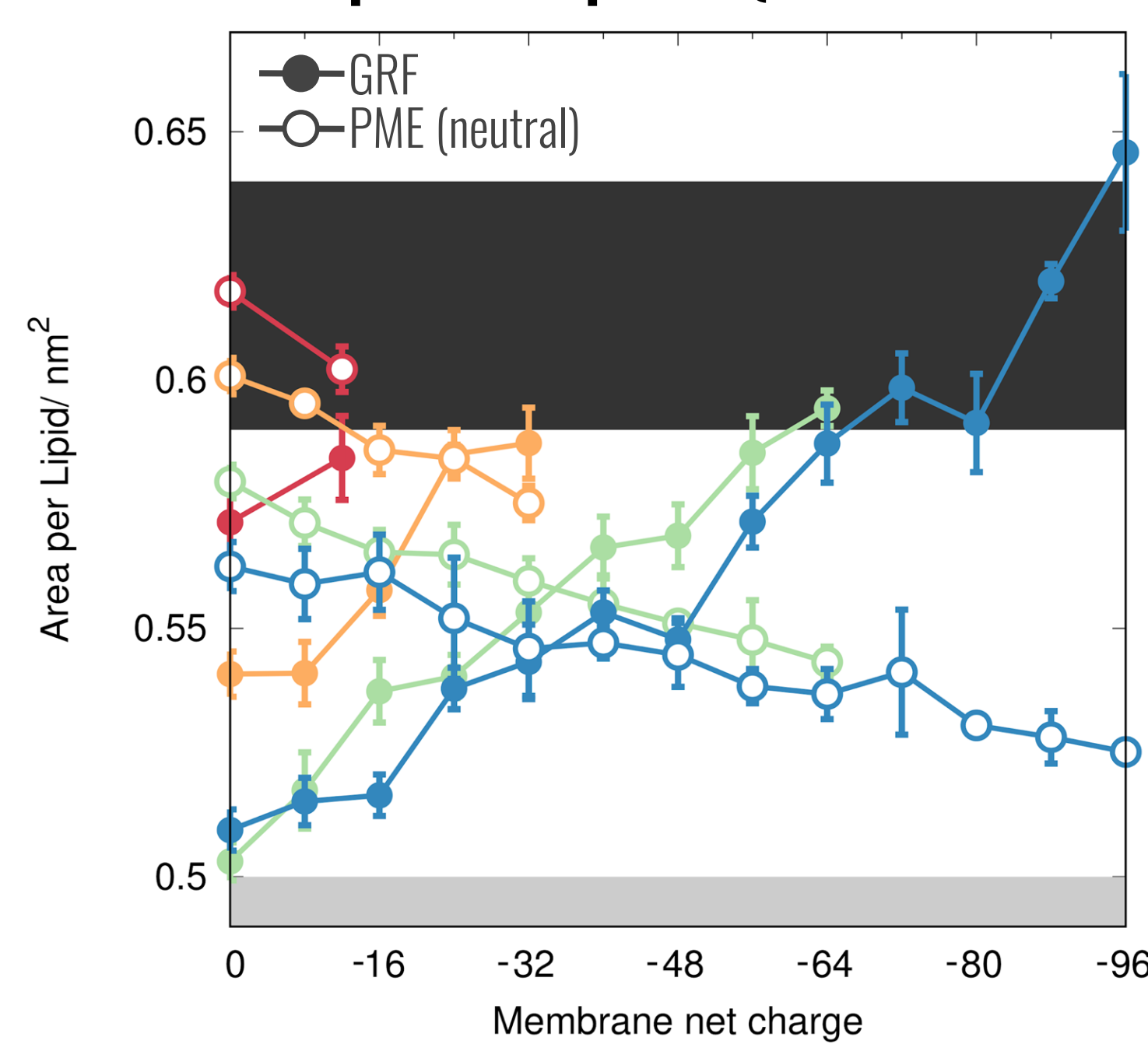
System setup



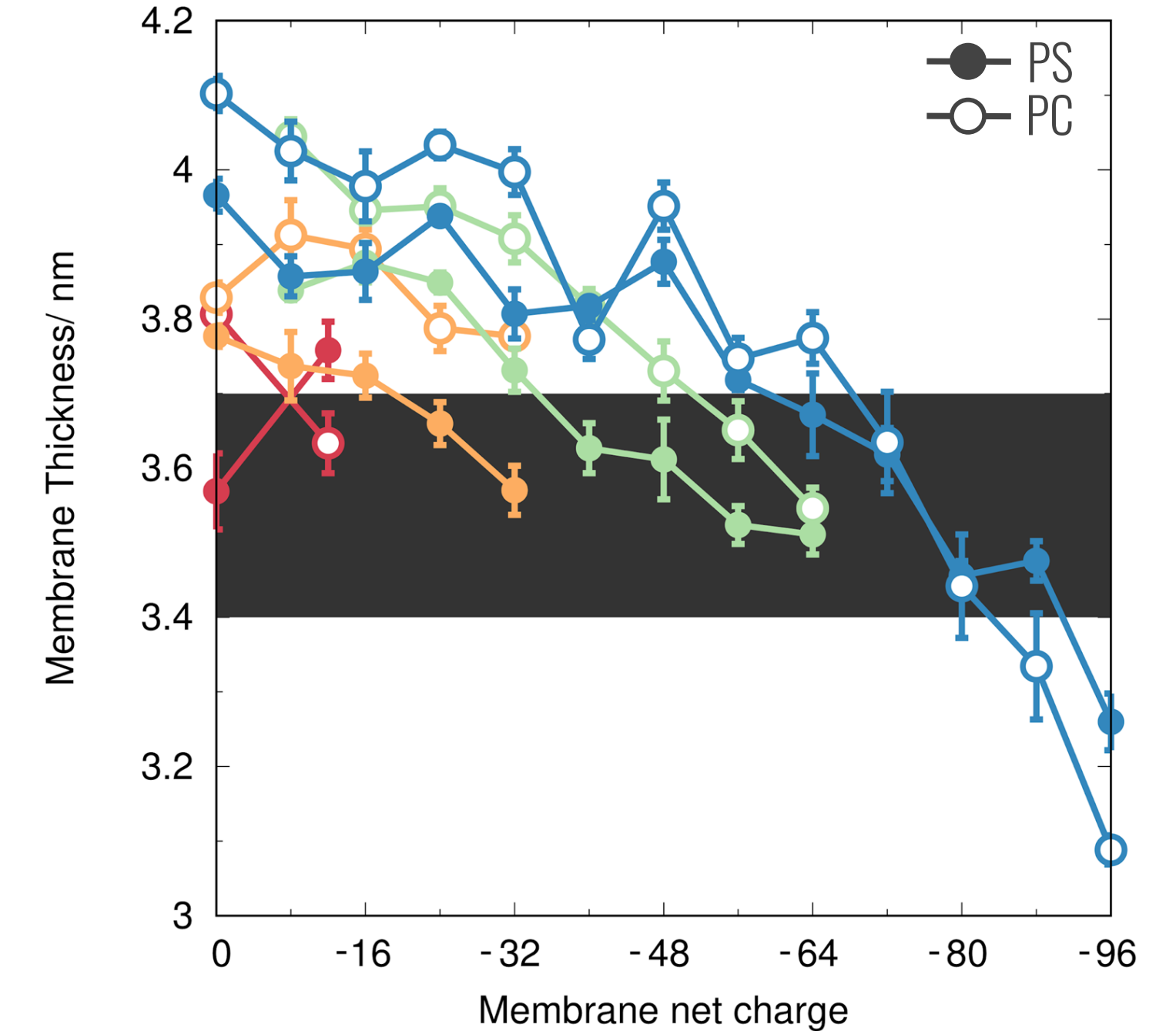
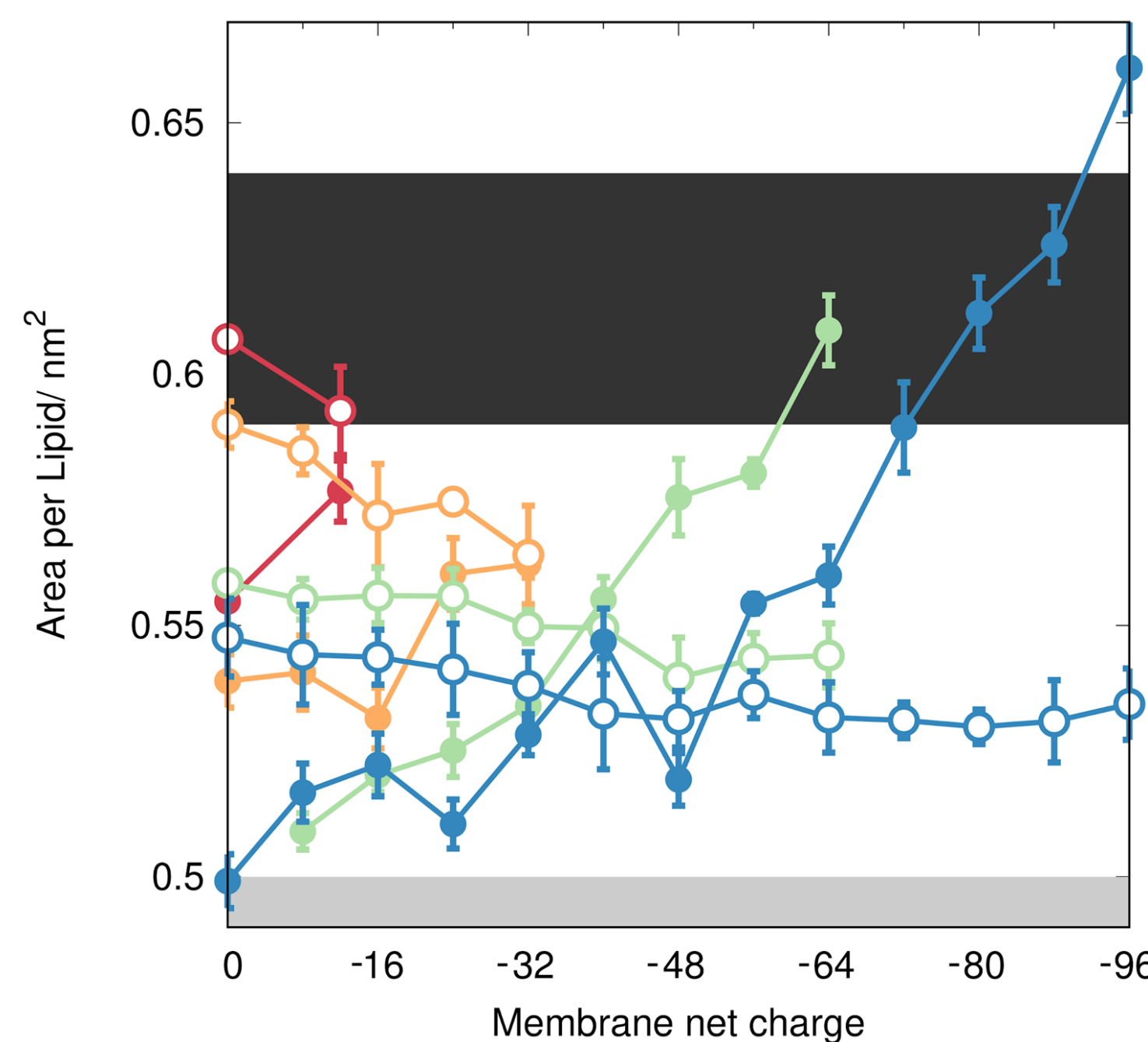
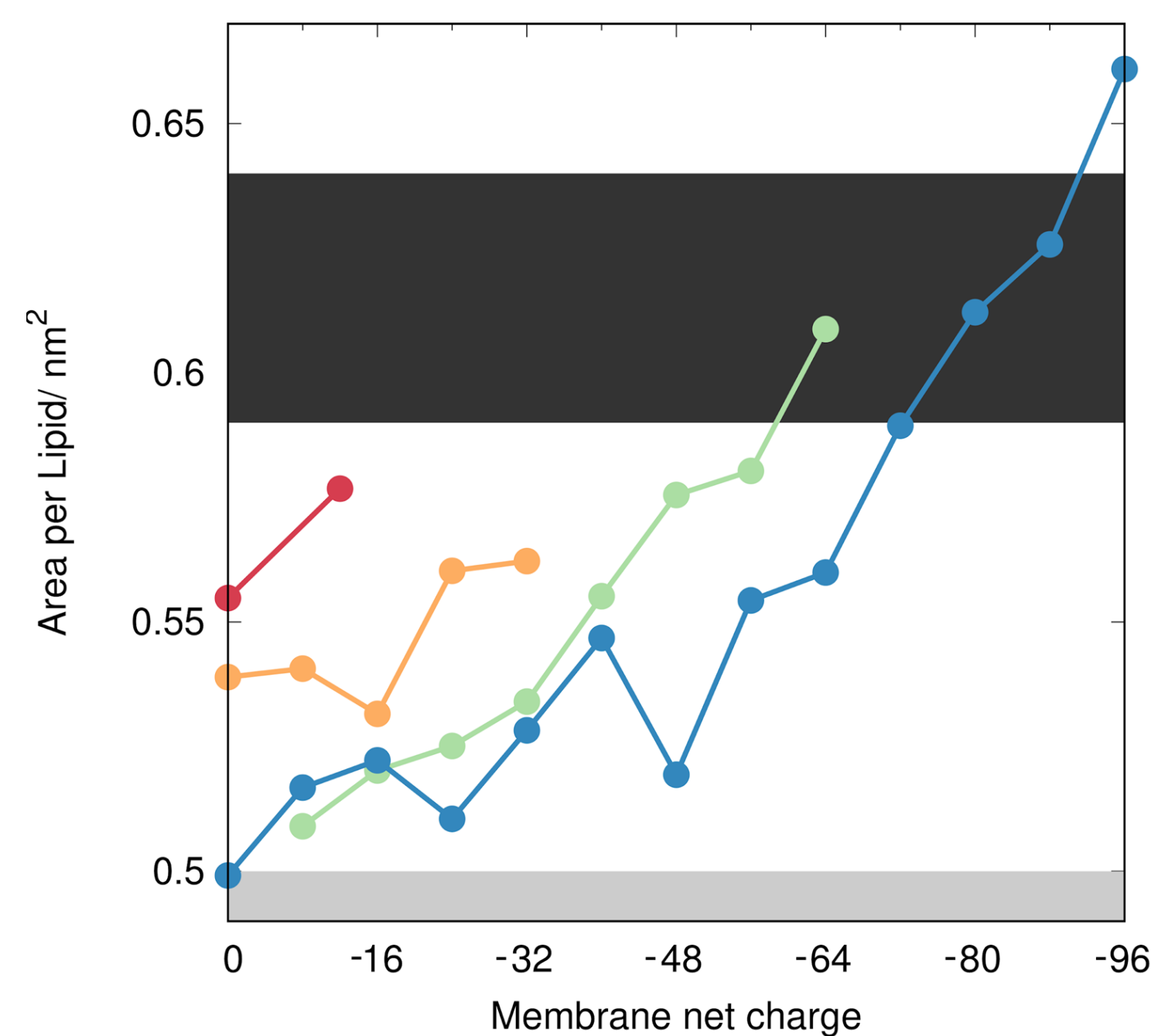
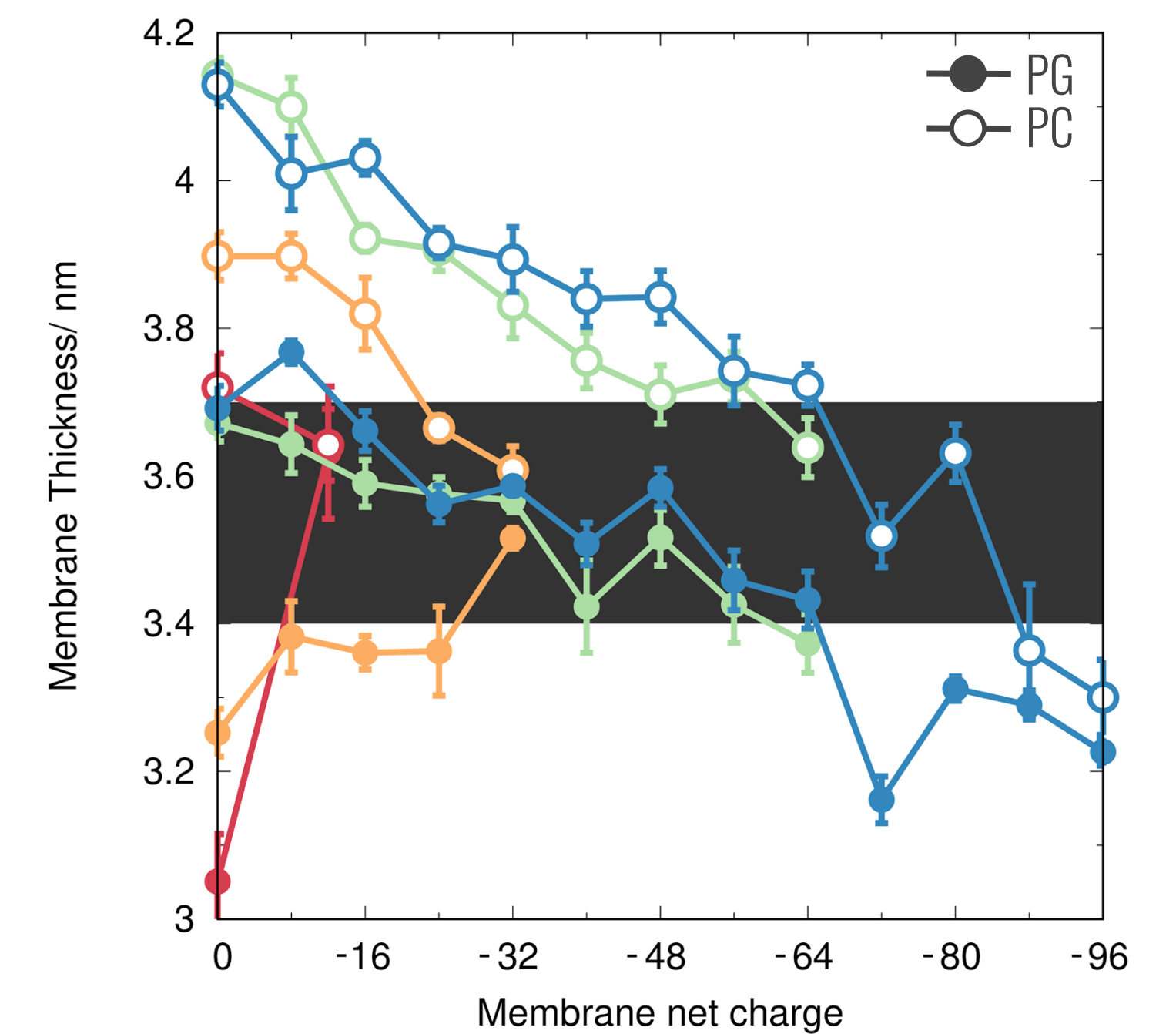
Area per Lipid (GRF)



Area per Lipid (GRF/PME)



Membrane Thickness



Conclusions

Neutral PG and PS generally decrease the overall area per lipid. Upon ionization, the *A/l* increases significantly.

At 75% molar fraction, both PG and PS ionization induce a complete phase transition from Gel to highly Fluid phases.

In PME simulations the ionization-induced phase transition is abolished due to the relatively high number of counterions in such small systems, resulting in unphysical results.

Thickness results show that both lipids (anionic and PC) react to the ionization, unlike what we have previously observed for PA [2].

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PTDC/QEQCOM/5904/2014



References: [1] Edidin, M. 2003 NRMCB 4:414 [2] Vila-Viçosa, D. 2014 JCTC 10:5483 [3] Baptista, A.M. 2002 JCP 117:4184 [4] Machuqueiro, M. 2006 JPCB 110:2927 [5] van der Spoel, D. 2005 JCC 26:1701 [6] Hess, B. 2008 JCTC 4:435 [7] Schmid, N. 2011 EBJ 40:843 [8] Rocchia, W. 2002 JCC 23:128 [9] Li, L. 2012 BMCB 5:9 [10] Baptista, A.M. 2001 JPCB 105:293 [11] Tirion, I.G. 1995 JCP 98:10089 [12] Darden, T. 1993 JCP 98:10089