Supporting Information: An Averaged Polarizable Potential for Multiscale Modeling in Phospholipid Membranes

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Lipid Structures

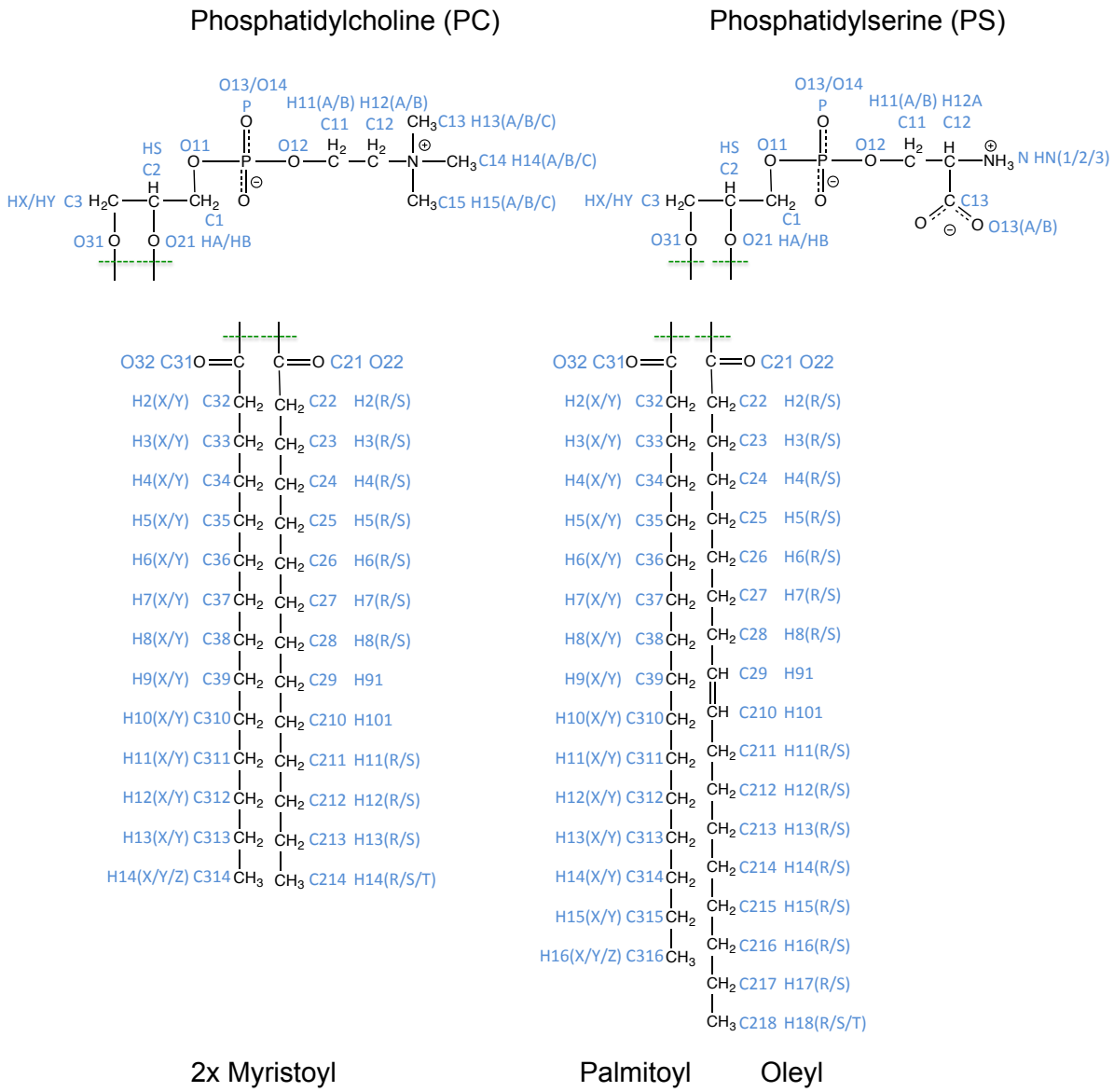

Figure S1: Chemical structure of the phosphatidylchole (PC) and phosphatidylserine (PS) headgroups as well as the myristoyl, palmitoyl and oleyl chains with CHARMM36 atom names indicated.

Initial Bilayer Structures, Equilibration and Simulation Protocol

Starting structures of the membranes were built with the CHARMM-GUI Membrane Builder[1] with compositions shown in Table S1. The Amber tool CHAMBER[2] was used to create in-

put files in Amber format. The POPC membrane was simulated both in a 150 mM NaCl solution and in pure water to see whether a salt concentration has an effect on the average lipid conformation. The simulations were run with Amber 12[3] using the CHARMM36[4] force field, water molecules are of the TIP3P[5] model.

Table S1: System composition and simulation time of the four membranes.

lipid type	DMPC	POPC	POPC	POPS
NaCl concentration (mM)	150	0	150	150
# lipids per leaflet	100	100	100	100
# waters	10343	10343	10474	10744
# Na^+	28	0	28	28
# Cl^-	28	0	28	28
simulation time (ns)	118	111	108	115

The initial structures were minimized first with the steepest descent method and then conjugated gradient until either a total of ten thousand steps were reached or the gradient was less than $1{\cdot}10^{-4}$ kcal/(mol·Å). The systems were then heated gradually from 0 K to 100 K over 5 ps at a constant volume. A second step of heating over 100 ps raised the temperature from 100 K to 310 K as well as changing from constant volume to constant pressure (1.0 bar) with the Berendsen barostat[6] using anisotropic pressure scaling and a relaxation time of 2.0 ps. Afterwards the systems were simulated between 108 and 118 ns (Table S1) with a time step of 2 fs, constant temperature at 310 K and an anisotropic pressure scaling set at 1.0 bar (relaxation time of 1.0 ps). For all simulations the temperature was controlled with the Langevin thermostat[7] (collision frequency of 1.0 ps^{-1}), bonds to hydrogens were constrained with SHAKE,[8] the real space cutoff was 10 Å, periodic boundary conditions were used in all three dimensions and the electrostatic interactions were treated with the Particle Mesh Ewald (PME)[9] method beyond 10 Å.

Simulation of Prodan in a lipid bilayer

Atomic charges for Prodan were derived using the RESP[10] procedure at the HF/6-31+G*[11–14] level through the program Antechamber[15] from AmberTools12.[3] The remainder of the force

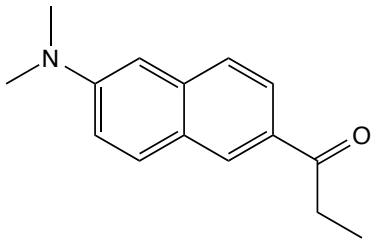

Figure S2: Chemical structure of Prodan.

field parameters for Prodan were taken from the Generalized Amber Force Field (GAFF).[16] The CHARMM-GUI Membrane Builder[1] was used to generate a pure DMPC and a pure POPC bilayer, each having 50 lipids per leaflet, see system composition in Table S2. The obtained pdb files were converted to the format used in Lipid 14[17] with the program 'charmmlipid2amber' included in Amber 14.[18] The lipids were described by the Lipid 14 force field,[17] water by the TIP3P[5] model and the ion parameters are from the work of Joung and Cheatham.[19]

Table S2: System composition and simulation time for Prodan in two lipid bilayers.

lipid type	DMPC	POPC
# lipids per leaflet	50	50
# waters	6425	6475
# K^+	19	20
# Cl^-	19	20
simulation time (ns)	160	75

Prodan was placed in the water phase around the membrane using VMD 1.9.1.[20] The initial structures were minimized in two steps, each using the same classical minimization protocol as described for the lipid bilayer above. The lipid molecules and Prodan were restrained with a force constant of 500 kcal/mol in this first minimization. A second energy minimization was carried out on the whole system, *i.e.* without restraints. The equilibration protocol was carried out in the same way as described for the lipid bilayer above. The DMPC system was simulated for 160 ns and the POPC system for 75 ns, using the same simulation protocol as described for the lipid bilayer above.

The Prodan molecule inserted into the membrane after ~10 ns and ~30 ns in the DMPC and the POPC membrane, respectively. During the course of the simulation the Prodan molecule occupied several positions and orientations in the membranes, both parallel with the lipid tails and horizontal in the interface. From each simulation we chose a snapshot with a close-to-vertical orientation of Prodan with the amino group pointing towards the interface and the carbonyl group pointing towards the hydrophobic core. This choice is based on a wish to probe the electrostatic potential (ESP) as deep into the membrane as possible. We note that a thorough sampling would be needed if a comparison to experimental results was wanted.

From this snapshot the Prodan structure was replaced with the original geometry-optimized version. The lipids were allowed to adapt to the slightly altered conformation of Prodan through a round of classical energy minimization as described above with the geometry of the Prodan molecule constrained. Snapshots of the minimized systems were used in the subsequent analysis.

Fragmentation Procedure

Table S3: RMSD values [kJ mol^{-1}] for the ESP from classical parameters (calculated with different fragmentation procedures) with respect to a full QM reference ESP on three conformations of DMPC (**1**, **2** and **3**). Classical conformation-specific parameters and the QM reference were calculated with B3LYP/aug-cc-pVDZ. The classical ESPs are based on LoProp multipoles up to quadrupoles (denoted M2), or by LoProp multipoles up to quadrupoles and LoProp anisotropic dipole–dipole polarizabilities (denoted M2P2). The right column gives averaged RMSD values over the three conformations.

	DMPC 1		**DMPC 2**		**DMPC 3**		**Average**	
	M2	M2P2	M2	M2P2	M2	M2P2	M2	M2P2
F1C2	2.26	2.36	2.85	2.57	2.31	2.38	2.47	2.43
F1C3	2.18	2.54	2.60	3.31	2.30	3.13	2.36	2.99
F2C2	2.19	3.08	2.61	3.43	2.28	3.22	2.36	3.24
F2C3	2.19	2.27	2.51	2.55	2.31	2.36	2.34	2.39
F3C1	2.27	2.16	2.72	2.71	2.56	2.52	2.52	2.46
F3C3	2.18	2.70	2.50	2.91	2.33	2.76	2.33	2.79

Averaged Lipid Embedding Parameters

Below we present the classical parameters for each of the three lipids used in this study. We refer to the exclusion lists presented in ref. 21 for each lipid to correctly avoid double-counting intramolecular polarization effects.

Table S4: Averaged embedding parameters for 1,2-dimyristoyl-*sn*-glycero-3-phosphocholine (DMPC). The list gives the lipid name in three-letter code (DMC), atom name (see Figure S1 for the chemical structure and atom names), averaged RESP charge and averaged isotropic polarizability, both in atomic units. The numbers are averages over 200 lipid conformations and have been calculated with B3LYP/aug-cc-pVDZ. Average parameters and exclusion lists are also given as separate supporting files. See the main text for details.

```
DMC, C1, 0.03716, 7.97663
DMC, C11, 0.39593, 8.06069
DMC, C12, -0.10528, 7.70902
DMC, C13, -0.32653, 5.89853
DMC, C14, -0.32653, 5.89853
DMC, C15, -0.32653, 5.89853
DMC, C2, 0.24835, 8.38848
DMC, C21, 0.74569, 7.42465
DMC, C210, -0.01464, 7.78764
DMC, C211, -0.02749, 7.73344
DMC, C212, -0.06066, 7.62789
DMC, C213, 0.18563, 7.46784
DMC, C214, -0.28337, 7.34751
DMC, C22, -0.29618, 8.02618
DMC, C23, 0.04668, 7.82164
DMC, C24, 0.04863, 7.80341
DMC, C25, -0.07811, 7.85417
DMC, C26, 0.01701, 7.82394
DMC, C27, -0.00203, 7.82818
DMC, C28, -0.01820, 7.85395
DMC, C29, -0.00072, 7.83648
DMC, C3, 0.03364, 7.65611
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DMC, C38, -0.03737, 7.86703
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DMC, H11S, 0.01010, 2.53968
DMC, H11X, 0.00903, 2.53706
DMC, H11Y, 0.00903, 2.53706
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DMC, O31, -0.38908, 6.52443
DMC, O32, -0.56415, 5.35035
DMC, P, 1.31453, 11.77389
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Table S5: Averaged embedding parameters for 1-palmitoyl-2-oleyl-*sn*-glycero-3-phosphocholine (POPC). The list gives the lipid name in three-letter code (POC), atom name (see Figure S1 for the chemical structure and atom names), averaged RESP charge and averaged isotropic polarizability, both in atomic units. The numbers are averages over 200 lipid conformations and have been calculated with B3LYP/aug-cc-pVDZ. Average parameters and exclusion lists are also given as separate supporting files. See the main text for details.

```
POC, C1, 0.02133, 7.96015
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POC, C14, -0.32324, 5.89373
POC, C15, -0.32324, 5.89373
POC, C2, 0.36325, 8.40321
POC, C21, 0.73033, 7.46244
POC, C210, -0.23365, 10.50043
POC, C211, 0.12881, 8.00110
POC, C212, -0.05812, 8.06332
POC, C213, -0.01578, 7.89216
POC, C214, -0.00536, 7.84086
POC, C215, -0.03499, 7.74208
POC, C216, -0.03720, 7.66999
POC, C217, 0.15843, 7.50917
POC, C218, -0.21225, 7.36512
POC, C22, -0.19668, 8.02223
POC, C23, -0.00377, 7.86563
POC, C24, 0.03579, 7.82671
POC, C25, -0.06876, 7.86703
POC, C26, -0.01298, 7.89255
POC, C27, -0.07270, 8.06196
POC, C28, 0.16450, 7.99647
POC, C29, -0.25728, 10.51216
POC, C3, 0.13278, 7.63313
POC, C31, 0.74848, 7.62857
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POC, C32, -0.25147, 8.15964
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POC, C34, 0.00950, 7.86137
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POC, C36, -0.03203, 7.88114
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Table S6: Averaged embedding parameters for 1-palmitoyl-2-oleyl-*sn*-glycerol-3-phospho-L-serine (POS). The list gives the lipid name in three-letter code (POS), atom name (see Figure S1 for the chemical structure and atom names), averaged RESP charge and averaged isotropic polarizability, both in atomic units. The numbers are averages over 200 lipid conformations and have been calculated with B3LYP/aug-cc-pVDZ. Average parameters and exclusion lists are also given as separate supporting files. See the main text for details.

```
POS, C1, 0.02905, 8.20360
POS, C11, 0.38499, 8.18597
POS, C12, -0.37578, 10.36373
POS, C13, 0.83249, 10.10036
POS, C2, 0.40685, 8.57176
POS, C21, 0.75190, 7.52183
POS, C210, -0.25591, 10.59231
POS, C211, 0.15377, 8.05756
POS, C212, -0.05179, 8.09573
POS, C213, -0.01689, 7.95315
POS, C214, 0.00052, 7.86746
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POS, C216, -0.04554, 7.70116
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POS, C218, -0.20491, 7.42258
POS, C22, -0.20878, 8.08187
POS, C23, 0.01878, 7.92481
POS, C24, 0.01470, 7.91490
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POS, C29, -0.22400, 10.57213
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POS, C31, 0.76625, 7.69454
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POS, C311, -0.00602, 7.85945
POS, C312, -0.01214, 7.81528
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POS, H11B, 0.01219, 2.31733
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POS, H11X, 0.00570, 2.53892
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POS, H12S, 0.01577, 2.58087
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POS, H14X, 0.01137, 2.56782
POS, H14Y, 0.01137, 2.56782
POS, H15R, 0.01122, 2.54155
POS, H15S, 0.01122, 2.54155
POS, H15X, -0.02487, 2.59661
POS, H15Y, -0.02487, 2.59661
POS, H16R, 0.01152, 2.58498
POS, H16S, 0.01152, 2.58498
POS, H16X, 0.04630, 2.67933
POS, H16Y, 0.04630, 2.67933
POS, H16Z, 0.04630, 2.67933
POS, H17R, -0.02477, 2.58933
POS, H17S, -0.02477, 2.58933
POS, H18R, 0.04127, 2.68430
POS, H18S, 0.04127, 2.68430
POS, H18T, 0.04127, 2.68430
POS, H2R, 0.06646, 2.42207
POS, H2S, 0.06646, 2.42207
POS, H2X, 0.07249, 2.43157
POS, H2Y, 0.07249, 2.43157
POS, H3R, 0.01076, 2.49489
POS, H3S, 0.01076, 2.49489
POS, H3X, -0.00092, 2.45826
POS, H3Y, -0.00092, 2.45826
POS, H4R, 0.00145, 2.50696
POS, H4S, 0.00145, 2.50696
POS, H4X, -0.00708, 2.56432
POS, H4Y, -0.00708, 2.56432
POS, H5R, 0.02300, 2.53082
POS, H5S, 0.02300, 2.53082
POS, H5X, 0.01965, 2.52319
POS, H5Y, 0.01965, 2.52319
POS, H6R, 0.01040, 2.50584
POS, H6S, 0.01040, 2.50584
POS, H6X, 0.01073, 2.54305
POS, H6Y, 0.01073, 2.54305
POS, H7R, 0.02282, 2.57966
POS, H7S, 0.02282, 2.57966
POS, H7X, 0.00790, 2.53536
POS, H7Y, 0.00790, 2.53536
POS, H8R, 0.00630, 2.50866
POS, H8S, 0.00630, 2.50866
POS, H8X, 0.01085, 2.55000
POS, H8Y, 0.01085, 2.55000
POS, H91, 0.10845, 2.69356
POS, H9X, 0.00536, 2.54181
POS, H9Y, 0.00536, 2.54181
POS, HA, 0.02955, 2.45988
POS, HB, 0.02955, 2.45988
POS, HN1, 0.28680, 1.93541
POS, HN2, 0.28680, 1.93541
POS, HN3, 0.28680, 1.93541
POS, HS, 0.01277, 2.07789
POS, HX, 0.04078, 2.29699
POS, HY, 0.04078, 2.29699
POS, N, -0.31375, 6.65416
POS, O11, -0.46250, 7.09856
POS, O12, -0.50502, 7.03264
POS, O13, -0.80572, 7.04161
POS, O13A, -0.71884, 6.90879
POS, O13B, -0.71884, 6.90879
POS, O14, -0.80572, 7.04161
POS, O21, -0.44614, 6.26548
POS, O22, -0.57059, 5.22329
POS, O31, -0.44644, 6.54700
POS, O32, -0.56420, 5.32514
POS, P, 1.31175, 12.15811
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