Comparing Simulations of Lipid Bilayers to Scattering Data: The GROMOS 43A1-S3 Force Field

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Supplementary Information

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Table S1. Comparison of results for six simulations at fixed projected areas A_P = 62, 64, 66, 68, 70, and 72 Å^2 as well as the NPT simulation that had a mean A_P=65.8 Å^2 and experimental ranges for some of the properties. The parsing of DOPC involved seven components as defined in the text. The component volumes were directly transcribed from the SIMtoEXP program and the number of significant figures is exaggerated. As originally noted[1] there is statistical noise in the volumes of small components that is smoothed when volumes of two contiguous groups are added, such as Chol+PO4 and Carb(2)+Gly, and even more smoothing occurs upon addition to obtain volumes of chains, heads and total lipid. The Gibbs dividing surface values for DC and DB were obtained by an app in SIMtoEXP.[2] Distances from the bilayer center for the components and for DHH/2 were obtained manually by locating the peak in the profiles plotted in SIMtoEXP. The distances from the bilayer center of N (nitrogen) and P (phosphorus) were obtained manually from the position of the maximum in their number density distributions.

7 components								
Properties	Simulated	values						Exp
Projected Area	62	64	65.8	66	68	70	72	--
Volumes	--	--	--	--	--	--	--	--
water	30.155	30.14	30.15	30.153	30.102	30.148	30.164	30
Chol	151.22	152.78	150.7	151.3	157.09	152.73	152.37	--
PO4	36.159	35.87	37.884	35.729	28.629	33.177	32.327	--
Carb(2)	77.972	83.145	85.378	77.589	75.35	77.133	77.669	--
Gly	62.953	58.676	57.025	64.094	68.846	66.947	68.4	--
CH2	26.842	26.801	26.693	26.988	27.086	27.041	26.917	--
CH1	23.82	24.152	24.619	23.797	23.558	23.976	24.503	--
CH3	53.701	53.766	54.294	53.021	52.668	52.873	53.228	--
r = CH3/CH2	2	2.01	2.03	1.96	1.94	1.96	1.98	1.8-2.1
Lipid Volume	1283	1285	1286	1286	1288	1289	1289	1303
Head Volume	329	330	331	329	330	330	331	319-331
chain volume	954	955	955	957	958	959	958	972-984
Distances	--	--	--	--	--	--	--	--
N	21.3	20.6	20.4	20.3	19.8	19.4	19	--
Choline	21.1	20.5	20.2	20.2	19.7	19.3	18.9	--
DB/2	20.5	20.1	19.5	19.5	18.9	18.4	17.9	19.35
PO4=P	20.1	19.6	19.1	19.1	18.7	18.2	17.7	--
DHH/2	19.3	18.9	18.5	18.4	18	17.6	17.2	17.7-18.4
glycerol	17.3	16.9	16.5	16.5	16.1	15.6	15.1	--
carbonyls	15.9	15.6	15.2	15.2	14.7	14.4	14	--
DC	15.2	14.9	14.5	14.4	14	13.6	13.3	--
CH1	7.8	7.6	7.3	7.3	7.1	6.7	6.3	--
DH1=DHH/2-DC	4.1	4	4	4	4	4	3.9	--
P-DC	4.9	4.7	4.6	5	4.7	4.6	4.6	--
DB/2-DC	5.3	5.2	5	5.1	4.9	4.8	4.6	--
P-DHH/2	0.8	0.7	0.6	0.7	0.7	0.6	0.5	--
DB/2-DHH/2	1.2	1.2	1	1.1	0.9	0.8	0.7	1.0-1.7

Table S2. Table S2 is similar to Table S1 except the parsing of DOPC followed the SDP model which is most appropriate for fitting both x-ray and neutron data simultaneously.[3] CholCH3 is just the three methyls on the choline and PCN is the remainder of the choline, while CG contains glycerol and both carbonyls.

SDP components								
Properties	Simulated	values						Exp
Projected Area	62	64	65.8	66	68	70	72	--
Volumes	--	--	--	--	--	--	--	--
water	30.101	30.093	30.096	30.101	30.102	30.092	30.109	30
CholCH3	107.07	107.93	107.42	106.27	107.64	106.52	106.88	--
PCN	90.267	89.534	89.717	90.824	89.331	90.521	89.205	--
CG	134.53	135.32	136.18	135.3	136.71	137.19	139.13	--
CH2	26.603	26.687	26.605	26.708	26.713	26.701	26.563	--
CH1	24.559	24.5	24.89	24.663	24.723	25.015	25.561	--
CH3	54.558	54.192	54.626	54.095	54.113	54.226	54.681	--
r = CH3/CH2	2.05	2.03	2.05	2.03	2.02	2.03	2.06	1.8-2.1
Lipid Volume	1284	1287	1287	1287	1289	1290	1290	1303
Head Volume	332	333	333	332	334	334	335	319-331
chain volume	952	954	954	955	955	956	955	972-984
Distances	--	--	--	--	--	--	--	--
N	21.3	20.6	20.4	20.3	19.8	19.4	19	--
CholCH3	21.2	20.5	20.4	20.3	19.8	19.6	19.1	--
DB/2	20.5	20.1	19.5	19.5	18.9	18.4	17.9	19.35
PCN	20.3	19.8	19.3	19.5	18.9	18.5	18	--
P	20.1	19.6	19.1	19.1	18.7	18.2	17.7	--
DHH/2	19.3	18.9	18.5	18.4	18	17.6	17.2	17.7-18.4
CG	16.4	16.1	15.6	15.7	15.3	14.7	14.4	--
DC	15.2	14.9	14.5	14.4	14	13.6	13.2	--
	7.8	7.6	7.3	7.3	7.1	6.7	6.3	--
DH1=DHH/2-DC	4.1	4	4	4	4	4	4	--
P-DC	4.9	4.7	4.6	5	4.7	4.6	4.5	--
PCN-DC	5.1	4.9	4.8	5.1	4.9	4.9	4.8	--
DB/2-DC	5.3	5.2	5	5.1	4.9	4.8	4.7	--
P-DHH/2	0.9	0.7	0.6	0.7	0.7	0.6	0.5	--
PCN-P	0.2	0.2	0.2	0.4	0.2	0.3	0.3	--
DB/2-DHH/2	1.2	1.2	1	1.1	0.9	0.8	0.7	1.0-1.7

Comment: Differences in the lipid, head, and chain volumes and the *r* value for the two parsings in Tables S1 and S2 indicate the level of volumetric uncertainty due to the parsing.

Table S3. SDP analysis

In Table S3 the column labelled Sim shows results obtained from the SIMtoEXP program for the various model SDP properties, including the values of reduced χ^2, Chi2N and Chi2X, obtained by comparing to the neutron and x-ray form factors, respectively. Subsequent columns list the results obtained from fitting the SDP model simultaneously to the experimental data. Different columns show the SDP results obtained under different constraints. Constrained values are shown in red, fitted values are shown in black and softly constrained values are shown in purple. Green fill indicates constraints that were changed or released compared to the column to the immediate left.

Properties	Sim	1a	1b	2	3	4	5	6
Chi2N	1.06	1.01	1.12	7.5	2.11	3.17	1.16	0.92
Chi2X	20.1	15.5	17	2.05	1.43	1.65	1.22	1.12
VL	1287	1287	1303	1303	1303	1303	1303	1303
VH	332	332	331	331	331	331	331	331
r	1.95	1.95	1.95	1.95	1.95	1.95	1.95	1.95
r12	0.91	0.91	0.91	0.91	0.91	0.91	0.91	0.91
RCG	0.41	0.41	0.41	0.41	0.41	0.41	0.41	0.32
RPCN	0.27	0.27	0.27	0.27	0.27	0.27	0.27	0.27
zCH1	7.24	7.24	7.24	7.24	7.24	7.24	7.24	7.24
sCH1	2.54	2.54	2.54	2.54	2.54	2.54	2.54	2.54
zCG	15.7	15.7	15.7	14.7	14.7	15.5	15.7	15.5
sCG	2.37	2.37	2.37	2.37	2.02	2.62	3.12	2.73
zPCN	19.3	19.3	19.3	19.1	19.5	19.2	18.6	19.5
sPCN	2.4	2.4	2.4	2.4	2.55	3.29	3.15	1.95
zCh	20.4	20.4	20.4	20	21.6	22.4	20.6	19.6
sCh	3.13	3.13	3.13	3.13	2.26	3.16	3.6	1.66
DC	14.4	14.4	14.4	13.9	14.2	14.2	14.4	14.2
sDC	2.25	2.25	2.25	2.25	2.25	2.25	2.83	2.49
sCH3	3.16	3.16	3.16	3.16	2.95	3.06	3.18	3.11
DB	39	38.8	38.6	37.4	38.1	38	38.5	38
DHH	36.8	36.8	36.8	36.6	36.9	34.8	35.4	35.7
(DB-DHH)/2	1.1	1	0.9	0.4	0.6	1.6	1.5	1.1
(DHH-2DC)/2	4	4	4	4.4	4.3	3.2	3	3.6
zPCN-zCG	3.6	3.6	3.6	4.2	4.8	3.7	2.9	4
zCh-zPCN	1.1	1.1	1.1	0.9	2.1	3.2	2	0.1
zCG-DC	1.3	1.3	1.3	0.8	0.5	1.3	1.3	1.3
zPCN-DHH/2	0.9	0.9	0.9	0.8	1.2	0.8	0.9	1.7
A	66	66.5	66.5	69.8	68.4	68.5	67.7	68.5

The volumetric properties embedded in the SDP model are the lipid volume VL, the headgroup volume VH, the ratio r of the volumes of the chain terminal methyl (the CH3 component) and chain methylenes, the ratio r12 of the volumes of the chain methines (the C1 component) and the chain methylenes, the ratio RCG of the carbonyl/glycerol (CG) volume to VH, and the ratio RPCN of the PCN moiety to VH.

PCN consists of the phosphocholine minus the choline methyls; the latter are the Ch component in the table. The properties z(component) give the distance z of the SDP component from the bilayer center and s(component) gives the Gaussian sigma width (HWHM/1.18) of these SDP distributions. DC is the z position of the Gibbs dividing surface for the total CH1 (methines) plus CH2 (methylenes) plus CH3 (terminal methyl) hydrocarbon chain components and sDC is the decay width of this surface. DB is the Gibbs dividing surface for the water distribution which does not have a predetermined functional form. DHH is the head-head thickness obtained from the model electron density profile. All quantities are in appropriate powers of Å.

SDP Commentary:

Column 1a constrained all values to those of the simulation. The χ^2 values (CHI2N and CHI2X) should not be the same as obtained in the Sim column because the model uses Gaussian functional forms and the simulated functional forms are not exactly Gaussians, the largest deviation being for the terminal methyls on the hydrocarbon chains. It is a bit surprising that the CHI2N and CHI2X values actually decrease in column 1a, but the disparity between the neutron and x-ray errors are faithful to the simulation.

Column 1b imposes the experimental volumes resulting in only small changes. The increase in the errors is not significant because all other quantities remain constrained to values that the experimental volumes make less compatible.

As already seen in the main text, the Sim column results are not optimal, especially for the x-ray data, because the bilayer is too thick. The fit in Column 2 releases four thickness/z distance constraints. This results in a substantial improvement in Chi2X but a worsening of Chi2N. We hold zCH1 fixed because, when released, zCH1 decreases to zero, the required fixed value for zCH3.

Column 3 shows that the fits again improve dramatically upon releasing constraints on the widths of the headgroup and the terminal methyl distributions, all of which become smaller, especially sCh. It should be noted that if the sDC constraint is also released, sCh becomes unphysically small while further improving the errors. This emphasizes the deficiency that one can obtain excellent fits with unphysical parameters.

A result that already appears implausible in the Column 3 fit is the distance between the CG group and the hydrocarbon core, given by zCG-DC. It is unphysical for the center of the CG group to become too close to the hydrocarbon core interface. In column 4, we therefore constrained zCG-DC to its simulated value, which ought to be a physically possible value. Of course, adding a constraint compared to column 3 worsens the errors, but not as much as might have been expected. Apparently, the error increases are compensated by the widths of the headgroup Gaussians becoming larger, even larger than the simulated values instead of smaller as in column 3.

Column 5 shows that the fit again improves dramatically when sDC is allowed to increase. When sDC is allowed to be completely free, starting from other columns, it often becomes unphysically broad. Even here, sDC was softly constrained as described by Kucerka et al. 2008.[3]

As was emphasized by Kucerka et al. 2008, there are too many parameters to be determined by unconstrained SDP model fitting and constraints must be imposed from experiment, especially the volume constraints, as well as from simulations. The additional simulation constraints most likely to be valid are for the simulated volumetric ratios, r12, RCG and RPCN. However, even here, different simulations give different values; CHARMM 27 gives r12=0.82 and RCG=0.48.[3] We therefore explored releasing these one at a time starting from the fit in column 5. The errors decrease when r12 decreases to 0.88 (not included in table S3). The larger improvement is shown in column 6 where RCG was allowed to decrease under a soft constraint. However, such a small CG volume appears to be unphysical and it leads to rather small s widths of the headgroup components.

Our preferred SDP fit in Table S3 is in column 5. However, it should be cautioned that different pathways give different fits. For example, starting with col 1b and proceeding directly to the constraints shown in column 5 results in a poorer fit and a too narrow sCh, indicating that there are secondary chi2 minima in parameter space. Possibly, a different pathway to a different set of constraints would improve the fit and lead to better physical values for the parameters (this is explored in Table S4).

The column 5 fit suggests that the simulations give s widths of the component distributions that are too small because releasing those widths results in χ^2 that are much smaller than those in column 2. It also suggests that the simulated value of (DB-DHH)/2 may be too small. The root difference is that zPCN is closer to DC in column 5 and that would suggest a difference in the headgroup conformations. It may also be noted that the area A is different for the different fits, but it is only 0.3 $Å^2$ larger in column 5 compared to the original SDP model paper.[3]

It may be noted that the SDP fitting program allows weighting the neutron data versus the x-ray data to achieve roughly equal values of Chi2X and Chi2N, as occurred in the column 5 fit.

Table S4 on the next page shows results for a variety of fits with different combinations of constraints. The Table S4 results are consistent with the column 5 fit in Table S3 and provide a feeling for the uncertainties in the SDP values of the parameters.

Table S4. More SDP results

The quantities have the same definitions as in Table S3 and the color coding is the same; black type gives results of fits, red type shows hard constrained values and blue type shows results obtained using soft constraints that typically allow 10% variations from target values. The estimated uncertainties in the data were adjusted so that neutron and x-ray data were weighted on an equal footing so that χ^2_X (Chi2X) and χ^2_N (Chi2N) were more nearly equal. The quantity X2fractN in the last row is the fraction of the total χ^2 from the neutron data which is theoretically derivable to be 0.2 when Chi2N = Chi2X.

Properties	08o	08e	NK6b	ave1	ave2	ave4
Chi2N	1.02	1.17	1.16	1.27	1.16	1.15
Chi2X	1.31	1.16	1.22	1.26	1.23	1.19
VL	1303	1303	1303	1303	1303	1303
VH	331	331	331	331	331	331
r	1.92	1.92	1.95	1.93	1.93	1.91
r12	0.814	0.83	0.91	0.85	0.85	0.92
RCG	0.42	0.354	0.41	0.39	0.39	0.41
RPCN	0.25	0.28	0.27	0.27	0.27	0.27
zCH1	7.24	7.24	7.24	7.24	7.24	7.24
sCH1	3.05	3.05	2.54	2.88	2.88	2.88
zCG	15.8	15.45	15.7	15.5	15.7	15.7
sCG	3.07	2.77	3.12	3	3	3.2
zPCN	18.2	19.4	18.6	18.8	18.7	18.5
sPCN	3.24	2.72	3.15	3	3.2	3.2
zCh	19.3	20.3	20.6	20.1	20.4	20.5
sCh	4.05	2.98	3.6	3.5	3.7	3.74
DC	14.45	14.15	14.36	14.2	14.4	14.37
sDC	3.02	2.88	2.83	2.9	2.77	2.89
sCH3	3.48	3.33	3.18	3.3	3.3	3.1
DB	38.8	37.9	38.5	38.2	38.6	38.5
DHH	35.2	35.6	35.4	35.5	35.5	35.4
(DB-DHH)/2	1.8	1.15	1.55	1.4	1.6	1.5
(DHH-2DC)/2	3.15	3.6	3.3	3.6	3.4	3.3
zPCN-zCG	2.4	3.9	2.9	3.3	3	2.8
zCh-zPCN	1.1	0.9	2	1.3	1.7	2
zCG-DC	1.3	1.3	1.3	1.3	1.3	1.3
zPCN-DHH/2	0.6	1.6	0.9	1.1	1	0.8
A	67.2	68.7	67.7	68.3	67.6	67.6
X2fractN	0.161	0.2	0.189	0.2	0.189	0.193

Table S5. Still more SDP results

Same format as Tables S3 and S4. The first column shows results from 2008.[3] Subsequent fits evolved from that result. The result in the final column 8b is similar to the results in Column 5 in Table S3 and to the results in Table S4.

Properties	BJ 2008	2	3	3b	4	4b	7b	8b
Chi2N	1.637	3.22	1.84	1.35	1.26	1.08	1.06	1.26
Chi2X	2.936	1.71	1.22	1.19	1.59	1.47	1.36	1.26
VL	1303	1303	1303	1303	1303	1303	1303	1303
VH	331	331	331	331	331	331	331	331
r	1.9575	1.9575	1.9575	1.9575	1.9575	1.9575	1.9575	1.9575
r12	0.7931	0.7931	0.7931	0.7931	0.7931	0.7931	0.7931	0.7931
RCG	0.4213	0.4213	0.4213	0.4213	0.4213	0.4213	0.4213	0.4213
RPCN	0.2575	0.2575	0.2575	0.2575	0.2575	0.2575	0.2575	0.2575
zCH1	9.595	9.595	9.595	9.595	9.595	9.595	7.24	7.24
sCH1	3.05	3.05	3.05	3.05	3.05	3.05	3.05	3.05
zCG	14.847	14.7	14.6	14.6	15.8	15.9	15.8	15.7
sCG	2.0481	2.0481	2	2	2.84	2.89	3.03	2.97
zPCN	19.113	19.1	19.2	19.2	18.4	18.3	18.2	18.5
sPCN	2.4132	2.4132	2.34	2.3	3.18	3.22	3.24	3.32
zCh	20.589	20	20.3	20.2	19.6	19.4	19.3	20.9
sCh	2.98	2.98	2.07	2.1	3.65	4.11	4.05	3.83
DC	14.421	14.3	14.34	14.4	14.5	14.6	14.5	14.4
sDC	2.4836	2.4836	2.4836	2.61	2.66	2.86	2.92	2.75
sCH3	3.0924	3.0924	3.35	3.37	3.5	3.52	3.63	3.6
DB	38.664	38.3	38.5	38.6	38.9	39.1	38.8	38.6
DHH	36.6	36.8	36.7	36.6	35.1	35.2	35.2	35.2
(DB-DHH)/2	1	0.8	0.9	1	1.9	1.9	1.8	1.7
(DHH-2DC)/2	3.9	4.1	4	3.9	3.1	3	3.1	3.2
zPCN-zCG	4.266	4.4	4.8	4.8	3.9	2.4	2.4	2.8
zCh-zPCN	1.456	0.969	1.1	1	1.2	1.1	1.1	2.4
zCG-DC	0.426	0.38	0.3	0.24	1.3	1.3	1.3	1.3
zPCN-DHH/2	0.8	0.7	0.8	0.9	0.9	0.7	0.6	0.9
A	67.4	68.03	67.8	67.5	67	66.6	67.2	67.4

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