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Physical properties of mixed bilayers containing lamellar and nonlamellar lipids: insights from coarse-grain molecular dynamics simulations

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Contents

1 Shifted-force dipolar interaction

Considering two point dipoles $\vec{p}_i$ and $\vec{p}_j$, the shifted-force pair potential energy is:

$$E_{ij} = \left[1 - 4\left(\frac{r}{r_c}\right)^3 + 3\left(\frac{r}{r_c}\right)^4\right]\left[\frac{1}{r^3}(\vec{p}_i \cdot \vec{p}_j) - \frac{3}{r^5}(\vec{p}_i \cdot \vec{r})(\vec{p}_j \cdot \vec{r})\right]$$

where $\vec{r}$ and r are the pair distance vector and its magnitude, respectively, and r_c is the cutoff distance. Note that we use the convention $\vec{r} = \vec{r}_i - \vec{r}_j$. Forces and torques were derived following Appendix C.3 in Allen and Tildesley.[1] In particular, the pair forces are:

$$\begin{aligned}\vec{F}_{ij} = -\vec{F}_{ji} \quad = \quad & \frac{3}{r^5}\left\{\left[1 - \left(\frac{r}{r_c}\right)^4\right]\left[(\vec{p}_i \cdot \vec{p}_j) - \frac{3}{r^2}(\vec{p}_i \cdot \vec{r})(\vec{p}_j \cdot \vec{r})\right]\vec{r} + \right. \\ & \left. \left[1 - 4\left(\frac{r}{r_c}\right)^3 + 3\left(\frac{r}{r_c}\right)^4\right]\left[(\vec{p}_j \cdot \vec{r})\vec{p}_i + (\vec{p}_i \cdot \vec{r})\vec{p}_j - \frac{2}{r^2}(\vec{p}_i \cdot \vec{r})(\vec{p}_j \cdot \vec{r})\vec{r}\right]\right\}\end{aligned}$$

The pair torque $\vec{T}_{ij}$ is:

$$\vec{T}_{ij} = -\frac{1}{r^3}\left[1 - 4\left(\frac{r}{r_c}\right)^3 + 3\left(\frac{r}{r_c}\right)^4\right](\vec{p}_i \times \vec{p}_j) + \frac{3}{r^5}\left[1 - 4\left(\frac{r}{r_c}\right)^3 + 3\left(\frac{r}{r_c}\right)^4\right](\vec{p}_j \cdot \vec{r})(\vec{p}_i \times \vec{r})$$

The pair torque $\vec{T}_{ji}$ is:

$$\vec{T}_{ji} = -\frac{1}{r^3}\left[1 - 4\left(\frac{r}{r_c}\right)^3 + 3\left(\frac{r}{r_c}\right)^4\right](\vec{p}_j \times \vec{p}_i) + \frac{3}{r^5}\left[1 - 4\left(\frac{r}{r_c}\right)^3 + 3\left(\frac{r}{r_c}\right)^4\right](\vec{p}_i \cdot \vec{r})(\vec{p}_j \times \vec{r})$$

These expressions were implemented in the `pair_dipole_sf.cpp` module of the program LAMMPS.[2,3]

2 Force field parameters

Table 1 reports the parameter set for the *elba-1.1* force field. For convenience, the parameters are reported using different conventions. The “BRAHMS units” column reports the parameters in the units used by the program BRAHMS;[4] this highlights the hydrogen-bonding scale factors. The “LAMMPS units” column report the parameters in the format required by the LAMMPS program;[2,3] corresponding input files are available online.[5]

3 Tangential pressure profile for 2-body interactions: equivalence of “per-particle” and Harasima formulations

The “per-particle” pressure for the 2-body virial term in the main body of the paper can be rewritten in terms of the interparticle distance $r_{ij_x} = r_{i_x} - r_{j_x}$:

$$V_s P_{xx}(z_s) = \frac{1}{2}\left\langle \sum_{\substack{i=1\\ i\in V_s}}^{N} \sum_{\substack{j=1\\ j\neq i}}^{N} \left(r_{i_x} f_{ij_x} + r_{j_x} f_{ji_x}\right) \right\rangle = \frac{1}{2}\left\langle \sum_{\substack{i=1\\ i\in V_s}}^{N} \sum_{\substack{j=1\\ j\neq i}}^{N} r_{ij_x} f_{ij_x} \right\rangle = \left\langle \sum_{\substack{i=1\\ i\in V_s}}^{N-1} \sum_{j>i}^{N} r_{ij_x} f_{ij_x} \right\rangle = -\left\langle \sum_{\substack{i=1\\ i\in V_s}}^{N-1} \sum_{j>i}^{N} \frac{r_{ij_x}^2}{r_{ij}} \frac{\partial v(r_{ij})}{\partial r_{ij}} \right\rangle \tag{1}$$

where we have used $f_{ij_x} = -f_{ji_x}$ (Newton’s third law), and:[1]

$$\mathbf{f}_{ij} = -\nabla_{\mathbf{r}_{ij}} v(r_{ij}) = -\frac{\partial v(r_{ij})}{\partial r_{ij}} \nabla_{\mathbf{r}_{ij}} r_{ij} = -\frac{\partial v(r_{ij})}{\partial r_{ij}} \frac{\mathbf{r}_{ij}}{r_{ij}} \Rightarrow f_{ij_x} = -\frac{\partial v(r_{ij})}{\partial r_{ij}} \frac{r_{ij_x}}{r_{ij}}$$

with $v(r_{ij})$ the interaction potential.
The $P_{yy}(z_s)$ term can be obtained trivially by simply replacing x with y in equation 1.
The tangential pressure $P_T(z_s)$ can then be written as:

$$P_T(z_s) = \frac{1}{2}\left[P_{xx}(z_s) + P_{yy}(z_s)\right] = -\frac{1}{4V_s}\left\langle \sum_{\substack{i=1\\ i\in V_s}}^{N} \sum_{\substack{j=1\\ j\neq i}}^{N} \frac{r_{ij_x}^2 + r_{ij_y}^2}{r_{ij}} \frac{\partial v(r_{ij})}{\partial r_{ij}} \right\rangle = -\frac{1}{2V_s}\left\langle \sum_{\substack{i=1\\ i\in V_s}}^{N-1} \sum_{j>i}^{N} \frac{r_{ij_x}^2 + r_{ij_y}^2}{r_{ij}} \frac{\partial v(r_{ij})}{\partial r_{ij}} \right\rangle \tag{2}$$

which is the expression first developed by Harasima[6] and later reported in several publications.[7–12]

4 Mean square displacements and diffusion coefficients

The mean square displacement (*MSD*) in the plane of the bilayer was calculated with:

$$MSD = \frac{1}{N}\sum_{i=1}^{N}\left[\mathbf{r}_i(t) - \mathbf{r}_i(0)\right]^2 \tag{3}$$

with N the number of lipids, t the time, and $\mathbf{r}_i$ is the 2-dimensional vector defining the position of lipid i in the xy-plane (parallel to the bilayer plane by construction). In practice, we make the (reasonable) assumption that the position of a lipid corresponds with the position of its glycerol CG particle, so $\mathbf{r}_i$ in Eq. 3 is really the position of the glycerol particle of lipid i. The lateral diffusion coefficient D was obtained through:

$$D = \frac{MSD}{4t} \tag{4}$$

where *MSD* is defined in Eq. 3 and $t = 1\,\mu$s is the simulation time.

Fig. 1 reports the *MSDs* calculated for the mixed bilayer systems simulated. The plot shows that the lipids in all the systems studied diffuse laterally in a similar way, showing no apparent sensitivity to composition. Diffusion coefficients computed using Eq. 4 are reported in Table 2, together with corresponding literature data from atomistic simulation and experiment.

Table 1 *Elba-1.1* force field

Symbol	BRAHMS units	LAMMPS units	Other units
σ_{CC}	0.54 nm	5.4 Å	
σ_{PP}	0.52 nm	5.2 Å	
σ_{GG}, σ_{EE}	0.46 nm	4.6 Å	
σ_{AA}, σ_{TT}	0.45 nm	4.5 Å	
σ_{WW}	0.305 nm	3.05 Å	
ε_{CC}, ε_{PP}	6.0 kJ/mol	1.434 kcal/mol	
ε_{GG}, ε_{EE}	4.0 kJ/mol	0.956 kcal/mol	
ε_{AA}, ε_{TT}	3.5 kJ/mol	0.837 kcal/mol	
ε_{WW}	1.534 kJ/mol	0.367 kcal/mol	
ε_{WW}^{tot}	$1.5\,\varepsilon_{WW}$	0.550 kcal/mol	
ε_{WP}	$1.3\sqrt{\varepsilon_{WW}\,\varepsilon_{PP}}$	0.943 kcal/mol	
ε_{WG}	$1.1\sqrt{\varepsilon_{WW}\,\varepsilon_{GG}}$	0.651 kcal/mol	
ε_{WE}	$1.2\sqrt{\varepsilon_{WW}\,\varepsilon_{EE}}$	0.710 kcal/mol	
ε_{AW}	$1.1\sqrt{\varepsilon_{AA}\,\varepsilon_{WW}}$	0.609 kcal/mol	
ε_{AP}	$1.3\sqrt{\varepsilon_{AA}\,\varepsilon_{PP}}$	1.424 kcal/mol	
ε_{AG}	$1.1\sqrt{\varepsilon_{AA}\,\varepsilon_{GG}}$	0.984 kcal/mol	
ε_{AE}	$1.3\sqrt{\varepsilon_{AA}\,\varepsilon_{EE}}$	1.163 kcal/mol	
Q_C, Q_A	+0.7 e	+0.7 e	1.12×10^{-19} C
Q_P	−0.7 e	−0.7 e	-1.12×10^{-19} C
μ_G	1.6 D	0.333 e Å	
μ_E	2 D	0.416 e Å	
μ_W	2.6 D	0.541 e Å	
k	1260 kJ/(mol nm^2)	2*1.506 kcal/(mol Å^2)	
w	30 kJ/mol	2*3.585 kcal/mol	
c	10 kJ/mol	2*1.195 kcal/mol	
$\alpha_{0_{CPG}}$, $\alpha_{0_{APG}}$	115°	115°	2.01 rad
$\alpha_{0_{PGE}}$	90°	90°	1.57 rad
$\alpha_{0_{GET}}, \alpha_{0_{ETT}}, \alpha_{0_{TTT}}^{saturated}$	180°	180°	3.14 rad
$\alpha_{0_{TTT}}^{cis-unsaturated}$	120°	120°	2.09 rad
m_C, m_P	90 amu	90 g/mol	14.9×10^{-23} g
m_G, m_E	62 amu	62 g/mol	10.3×10^{-23} g
m_T, m_A	42 amu	42 g/mol	7.0×10^{-23} g
m_W	40 amu	40 g/mol	6.6×10^{-23} g
$I_{G,E}$	10 amu nm^2	1000 g Å^2/mol	
I_W	1 amu nm^2	100 g Å^2/mol	

Subscripts C, A, P, G, E, T and W stand for the site types *choline*, *amine*, *phosphate*, *glycerol*, *ester*, *tail* and *water*, respectively. Lennard-Jones cross-terms are calculated by the standard Lorentz-Berthelot rule except for increased ε terms representing hydrogen bonding; in particular, $\varepsilon_{WP}, \varepsilon_{WG}, \varepsilon_{WE}$, ε_{AW}, ε_{AP}, ε_{AG}, ε_{AE} are set as reported in the table. Charges and dipoles are identified by Q and μ; cross terms are obtained via standard electrostatic formulae. Within the same lipid molecule, nonbonded interactions between bonded pairs are zero (1-2 LJ and electrostatic interactions are excluded). The rigidity of the Hooke harmonic potential is identified by k; reference lengths are set to $0.9\sigma_{ij}$. The rigidity of the angle potential is identified by w. The rigidity of the dipole orientation-restraining potential is c. Masses and principal moments of inertia are identified by m and I, respectively.

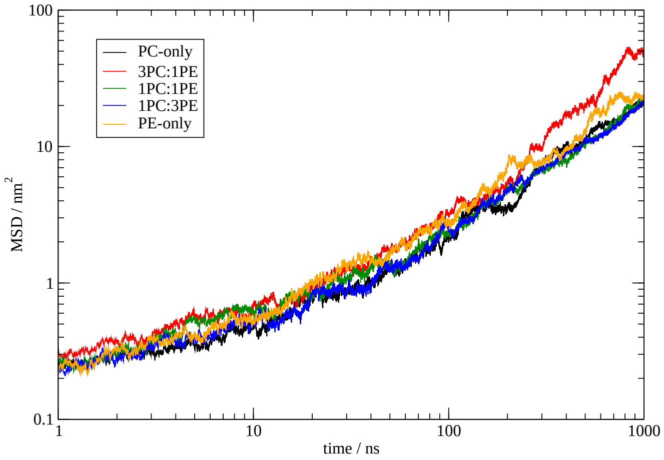

Figure 1 Mean square displacements, in the *xy*-plane, for mixed lipid bilayers at different PC:PE fractions (see main body of the paper for details).

Table 2 Lateral diffusion coefficients in units of nm$^2/\mu$s

System	*CG (this work)*	*Atomistic*	*Experiment*
PC-only	8 ± 2	$2-12$[13]	9.5,[14] 11.5,[15] 12[16]
3_{PC}:1_{PE}	17 ± 7		
1_{PC}:1_{PE}	8 ± 3		
1_{PC}:3_{PE}	8 ± 2		
PE-only	9 ± 3		

5 Kinetic energy pressure term from velocity vs. number density

The kinetic energy contribution to the tangential pressure $P_{xx}^{\mathrm{KE}}(z_s)$ can be obtained in two different yet equivalent ways. The first approach involves the use of the particles' velocities through:

$$P_{xx}^{\mathrm{KE}}(z_s) = \frac{1}{V_s}\left\langle \sum_{\substack{i=1 \\ i\in V_s}}^{N} m_i v_{i_x} v_{i_x} \right\rangle \tag{5}$$

where m_i and v_i represent the mass and velocity of particle i, V_s is the slab volume, and N is the total number of particles. The pressure profiles obtained using Eq. 5 are displayed in Fig. 2.
Alternatively, the following expression can be used:

$$P_{xx}^{\mathrm{KE}}(z_s) = k_B T \langle \rho(z_s) \rangle \tag{6}$$

where $\rho(z_s)$ is the number density, k_B is Boltzmann's constant, and T is the temperature. The pressure profiles obtained using Eq. 6 are displayed in Fig. 3.

6 Composition of self-assembled mixed bilayers

Table 3 reports the number of PC/PE lipids per monolayer in the bilayers formed through self-assembly.

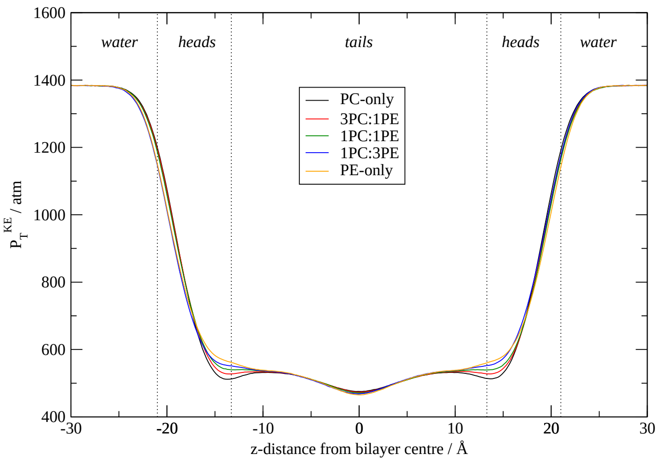

Figure 2 Tangential pressure. Kinetic energy contribution obtained from particles' velocities.

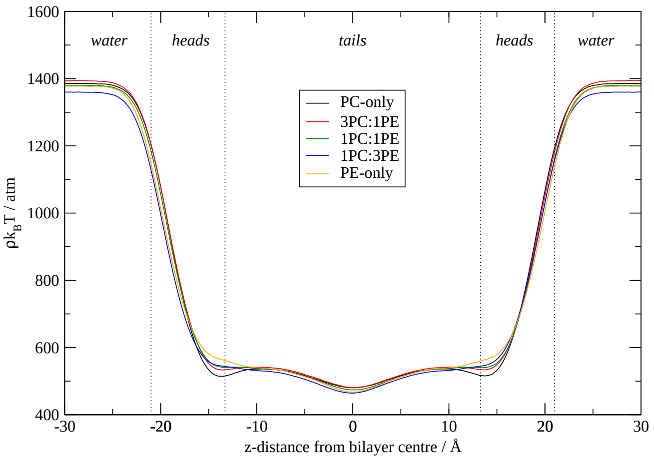

Figure 3 Tangential pressure. Kinetic energy contribution obtained from number density profiles.

Table 3 Composition of mixed DOPC/DOPE bilayers after self-assembly from random solution

System	N_{lipids} layer1 / layer2	N_{DOPC} layer1 / layer2	N_{DOPE} layer1 / layer2
PC-only	63/65	63/65	0/0
3_{PC}:1_{PE}	63/65	45/51	18/14
1_{PC}:1_{PE}	64/64	27/37	37/27
1_{PC}:3_{PE}	62/66	12/20	50/46
PE-only	66/62	0/0	66/62

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