Part 2: Rippled Membranes (with a side of water)

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“Every single year since 1840, physics alone has used successfully more (incompatible) models of phenomena in its day-to-day business, than it used in preceding years.

_The ideal end of science is not unity but absolute plethora._

- Ian Hacking in Representing & Intervening (Cambridge Univ. Press, 1983)
A brief review of Phospholipid Chemistry

<table>
<thead>
<tr>
<th>Phospholipid</th>
<th>Chemical Formula</th>
<th>Fatty Acid</th>
</tr>
</thead>
<tbody>
<tr>
<td>DMPC</td>
<td>1,2-DiMyristoyl-sn-glycero-3-PhosphatidylCholine</td>
<td>Myristic: CH₃(CH₂)₁₂COOH</td>
</tr>
<tr>
<td>DPPC</td>
<td>1,2-DiPalmtoyl-sn-glycero-3-PhosphatidylCholine</td>
<td>Palmitic: CH₃(CH₂)₁₄COOH</td>
</tr>
<tr>
<td>DSPC</td>
<td>1,2-DiStearoyl-sn-glycero-3-PhosphatidylCholine</td>
<td>Stearic: CH₃(CH₂)₁₆COOH</td>
</tr>
</tbody>
</table>
Phases of Phospholipid / Water mixtures

Micelle  Bilayer  Vesicle  Inverted Micelle

Increasing Lipid Fraction
The Ripple Phase

What do we know about the *structure* of the Ripple phase?

Not much!

1) Are the lipid bodies parallel to the bilayer normal?
2) Is there chain disorder?
3) Is this a co-existence phase?

X-ray crystallography doesn’t give us atomistic detail:

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AFM studies of supported bilayers also exhibit ripple phase

Images of the interfacial region between a \( \Lambda/2 \)-ripple domain and several \( \Lambda \)-ripple domains in a 7:3 DMPC-DSPC lipid bilayer at 26.0°C.

<table>
<thead>
<tr>
<th>Ripple phase</th>
<th>Periodicity</th>
<th>Amplitude</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \Lambda/2 )</td>
<td>150 Å</td>
<td>( \geq 12 ) Å</td>
</tr>
<tr>
<td>( \Lambda )</td>
<td>280 Å</td>
<td>( \geq 50 ) Å</td>
</tr>
<tr>
<td>2( \Lambda )</td>
<td>( \approx 550 ) Å</td>
<td>( \geq 110 ) Å</td>
</tr>
</tbody>
</table>

The Helfrich bending free energy

For planar, tensionless membranes subject to local perturbations:

$$H = \int \int dxdy \left\{ \frac{K_c}{2} \left( \nabla^2 h(x, y) \right)^2 + V(h(x, y)) \right\}$$

$h(x, y)$ is the displacement of the interface from a flat surface at point $x, y$

$K_c$ is the bending modulus

$V(h(x, y))$ : all external perturbations

$$\langle h^2(\rho) \rangle = \frac{T}{2\pi K_c} \log \frac{L}{a}$$

The mean-square real-space fluctuations of the surface away from a flat surface are limited by the ratio between the finite state of the system, $L$, and the molecular size, $a$.

If there are fluctuations from a flat surface that don’t follow the Helfrich-derived behavior, then we must look for a microscopic (or external) cause for this behavior.
A Simple tethered-dipole Model

\[
V = \sum_i \left[ \frac{k_z}{2} (z_i - z_0)^2 + \frac{k_{\theta}}{2} (\theta_i - \theta_0)^2 \right] + \sum_i \sum_{j > i} \frac{|\mu_i||\mu_j|}{4\pi \epsilon_0 r_{ij}^3} \left[ \hat{u}_i \hat{u}_j - 3(\hat{u}_i \cdot \hat{r}_{ij})(\hat{u}_j \cdot \hat{r}_{ij}) \right]
\]

- Rough approximation to the Hydrophobic effect
- Mimics in-plane headgroup orientation in the fluid phase
- Dipole-Dipole interaction

Dipoles are locked (in x-y plane) to lattice points of a hexagonal (or distorted) lattice.

This is a modified X-Y (actually X-Y-Z) model with translational (and orientational) freedom along the z-axis.
Even simple dipolar systems can ripple...

Rippling allows hexagonally-packed dipoles to assume local antiferroelectric ordering!

Distorted hexagonal lattices don’t need rippling to have orientational order.
Timescale Issues

Time scale for “flip” translocation is unattainable via standard all-atom MD techniques.

Transport of small molecules across the bilayer is normally too slow to study with simulation methodologies.

The mechanism of segregation of head-groups between the exo and endo monolayers is poorly understood.

Can we treat these phenomena with realistic model lipids?

Since dipolar ordering appears to be vital for rippling, we have designed model lipid systems which use only dipoles for electrostatic interactions.
Other mesoscopic approaches:

Essex et al. (Southampton) - GB models for hydrocarbon regions of lipids

Goetz & Lipowski - LJ and soft-core ball & chain models

Klein et al. (Penn) - LJ Ball & Chain models

Ayton & Voth (Utah) - continuum mechanics methods & GB molecular bodies

Brown (UCSB) - Undulations and mobility in continuum models:

Laaksonen et al. - Dissipative Particle Dynamics
  *Soft Materials* 1, 121 (2003).
**Dipolar Ball & Chain**

\[ V_{\text{l lipid}} = \sum_i V_{i, \text{internal}} + \sum_i \sum_{j>i} \sum_{\alpha_i} \sum_{\beta_j} V_{\text{LJ}}(r_{\alpha_i\beta_j}) + \sum_i \sum_{j>i} V_{\text{dp}}(r_{1i1j}, \hat{u}_{1i}, \hat{u}_{1j}) \]

\[ V_{i, \text{internal}} = \sum_{\text{bends}} V_{\text{bend}}(\theta_{\alpha\beta\gamma}) + \sum_{\text{torsions}} V_{\text{tors}}(\phi_{\alpha\beta\gamma\delta}) + \sum_{\alpha_i} \sum_{\beta_i>\alpha_i+4} V_{\text{LJ}}(r_{\alpha_i\beta_j}) \]
Where does a membrane simulation spend its time?

- Consider a bilayer simulation with 1000 lipid molecules and 25,000 water molecules.
- Each lipid has approximately $n=134$ atoms.
- Each water molecule has approximately $m=4$ atoms.

<table>
<thead>
<tr>
<th>Interaction</th>
<th>Scaling</th>
<th>Approximate Number</th>
<th>Fraction of Computational Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>lipid-lipid</td>
<td>$N^2n^2$</td>
<td>11,222,500</td>
<td>0.07 %</td>
</tr>
<tr>
<td>lipid-water</td>
<td>$25N^2nm$</td>
<td>13.4 billion</td>
<td>87 %</td>
</tr>
<tr>
<td>water-water</td>
<td>$125N^2m^2$</td>
<td>2 billion</td>
<td>13 %</td>
</tr>
</tbody>
</table>

- Nearly all of the computational time in a bilayer simulation involves calculations with the particular water model that is chosen.
Which water model?

To compliment our simplified lipid models, we want a water model that is:

1) **Very Fast** (i.e. relatively short-range interactions)
2) Maintains the *correct densities* at different temperatures
3) Maintains the **hydrogen bonding network** correctly
4) Has reasonable **transport** properties

The best candidates are the single-point dipolar models:

1) BBL (Bratko, Blum, and Luzar) - Hard spheres with point dipoles

2) SSD (Soft Sticky Dipole):
   Variants on SSD:
   SSD: Parameterized to Soper’s x-ray data

SSD1: density corrected SSD

SSD/E: density, structure, and transport corrections

SSD/RF: SSD/E parameterized for use with reaction field
The “Soft Sticky Dipole” (SSD) model for Water

\[ u_{ij} = u_{ij}^{LJ}(r_{ij}) + u_{ij}^{dp}(r_{ij}, \Omega_i, \Omega_j) + u_{ij}^{sp}(r_{ij}, \Omega_i, \Omega_j) \]

\[ u_{ij}^{LJ}(r_{ij}) = 4\epsilon \left[ \left( \frac{\sigma}{r_{ij}} \right)^{12} - \left( \frac{\sigma}{r_{ij}} \right)^{6} \right], \]

\[ u_{ij}^{dp} = \frac{|\mu_i||\mu_j|}{4\pi\epsilon_0 r_{ij}^3} \left[ \hat{u}_i \cdot \hat{u}_j - 3(\hat{u}_i \cdot \hat{r}_{ij})(\hat{u}_j \cdot \hat{r}_{ij}) \right] \]
The “Sticky” Potential

\[ u_{ij}^{sp}(r_{ij}, \Omega_i, \Omega_j) = \frac{\nu_0}{2} [s(r_{ij})w(r_{ij}, \Omega_i, \Omega_j)] + \frac{\nu'_0}{2} [s'(r_{ij})w'(r_{ij}, \Omega_i, \Omega_j)] \]

Tetrahedral Attraction: \( w(r_{ij}, \Omega_i, \Omega_j) = \sin \theta_{ij} \sin 2\theta_{ij} \cos 2\phi_{ij} \)

Dipolar Repulsion: \( w'(r_{ij}, \Omega_i, \Omega_j) = (\cos \theta_{ij} - 0.6)^2(\cos \theta_{ij} + 0.8)^2 - w^0 \)
Symplectic Step Integration for Orientational Motion


The *entire* Rotation Matrix is propagated (instead of just the quaternions):

Splitting of rotational propagators is reversible:

\[ G(\Delta t) = G_x(\Delta t/2)G_y(\Delta t/2)G_z(\Delta t)G_y(\Delta t/2)G_x(\Delta t/2) \]

Where each propagator rotates about one axis:

\[ G_x(t) = \begin{cases} A(t) & \leftarrow A(0) \cdot R_x(\theta)^T \\ j(t) & \leftarrow R_x(\theta) \cdot j(0) \end{cases} \]

And the rotation angle is given by:

\[ \theta = tj_x/I_x \]

( \( R_x(\theta) \) is the appropriate rotation matrix around the x axis)
A few words about Parallel Simulation Methods

<table>
<thead>
<tr>
<th>Methodology</th>
<th>Atomic Decomposition</th>
<th>Spatial Decomposition</th>
<th>Force Decomposition</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Each processor does all forces for $N/p$ particles</td>
<td>Each processor does all forces for particles in one “cell”</td>
<td>Each processor does one block of the $N \times N$ pairwise force matrix</td>
</tr>
<tr>
<td>Communication Scaling</td>
<td>$N$</td>
<td>$(N/p)^{2/3}$</td>
<td>$N/(p)^{1/2}$</td>
</tr>
<tr>
<td>Memory Scaling</td>
<td>$N/p$</td>
<td>$N/p$</td>
<td>$N/p$</td>
</tr>
<tr>
<td>Computational Scaling</td>
<td>$N/p$</td>
<td>$N/p$</td>
<td>$N/p$</td>
</tr>
<tr>
<td>Advantages</td>
<td>Simple to program</td>
<td>Best for $N &gt; 10^6$ particles</td>
<td>Best choice for intermediate system sizes</td>
</tr>
</tbody>
</table>
**Force Decomposition**

Consider a 58 atom system divided among 16 processors:

<table>
<thead>
<tr>
<th>j</th>
<th>i</th>
<th>1-15</th>
<th>16-30</th>
<th>31-44</th>
<th>45-58</th>
</tr>
</thead>
<tbody>
<tr>
<td>j</td>
<td>1-15</td>
<td>P_0 (0,0)</td>
<td>P_1 (0,1)</td>
<td>P_2 (0,2)</td>
<td>P_3 (0,3)</td>
</tr>
<tr>
<td>1-15</td>
<td>P_4 (1,0)</td>
<td>P_5 (1,1)</td>
<td>P_6 (1,2)</td>
<td>P_7 (1,3)</td>
<td></td>
</tr>
<tr>
<td>16-30</td>
<td>P_8 (2,0)</td>
<td>P_9 (2,1)</td>
<td>P_{10} (2,2)</td>
<td>P_{11} (2,3)</td>
<td></td>
</tr>
<tr>
<td>31-44</td>
<td>P_{12} (3,0)</td>
<td>P_{13} (3,1)</td>
<td>P_{14} (3,2)</td>
<td>P_{15} (3,3)</td>
<td></td>
</tr>
<tr>
<td>45-58</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Processor P_6 = P_{1,2} is responsible for computing the forces on atoms 16-30 by atoms 31-44.

Communication costs can be kept to a minimum by cyclic relabeling of the column indices to avoid communication between transposed processors.
The original SSD model underestimates densities (with RF)

Turning off the reaction field increases the density, but also moves the density maximum from 255 K to 245 K. Densities at high temperatures remain low even with the Reaction Field turned off.
Transport Properties are Excellent!

- Gillen et al., *JCP* 57, 5117 (1972)
- Mills, *JPC* 77, 685 (1973)

Diffusion Constant ($10^{-5}$ cm$^2$/s) vs. T (K)

Graph showing the diffusion constant as a function of temperature. The graph includes data points from Gillen et al. (1972) and Mills (1973), with additional markers for SSD1 and SSD/RF.
New experimental X-ray data from Theresa Head-Gordon’s group suggests a less structured liquid than the original Soper data does.

SSD/E and SSD/RF track the Head-Gordon data surprisingly well in the first solvation shell.

Angular Correlations

The second solvation shell is *split* in all of the SSD-based models. This plot shows the two angular-distance correlation functions.

All of the SSD models allow an equatorial, anti-aligned dipolar structure in the second shell. The X-ray data leads us to believe that the dipoles are overstructuring the second shell.
SSD/E and SSD/RF compare well with other models

Time Savings for SSD:
- TIP3P: 6x
- TIP4P: 7x
- TIP5P: ~10x
A cautionary tale: SSD water and imaginary Ice

**Ice-\textit{I}_h**

- $\rho$: 1.020 g cm$^{-3}$
- $T_m$: 235 K
- $G$: -10.103 kcal mol$^{-1}$
- $C_p$: 13.42 kcal mol$^{-1}$ K$^{-1}$
- $r^{\text{donor-acceptor}}$: 2.71 Å
- Pore size: 5.18 Å

**Ice $\sqrt{-I}$**

- $\rho$: 0.922 g cm$^{-3}$
- $T_m$: 375 K
- $G$: -10.739 kcal mol$^{-1}$
- $C_p$: 14.1 kcal mol$^{-1}$ K$^{-1}$
- $r^{\text{donor-acceptor}}$: 2.71 Å
- Pore size: 6.59 Å
Concluding Remarks

1) The ripple phase appears to be caused by a competition between anti-ferroelectric ordering of the dipoles in the head group and the hydrophobic effect.

2) A more complete explanation will have to wait for our mesoscale modelling to reach relevant time and length scales.

3) An extremely fast single point dipolar water model is capable of competing with the rest of the candidates in the water model business.

4) However, it (along with some other popular models) can exhibit a non-physical ice structure that has the potential for causing problems in the supercooled regime
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Matt Meineke
Ball & Chain Lipids

Teng Lin
Head-group / Water Interactions

Xiuquan Sun
Tethered dipole model