Simple Models for Biomembrane Structure and Dynamics

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Limitations of Fully Atomic Molecular Dynamics Simulation

A recent “large” membrane simulation (Pitman et. al., JACS, 127, 4576 (2005))
• 1 rhodopsin, 99 lipids, 24 cholesterols, 7400 waters (43,222 atoms total)
• 5.5 x 7.7 x 10.3 nm periodic box for 118 ns duration

Length/time scales relevant to cellular biology
• ms, μm (and longer)
• A 1.0 x 1.0 x 0.1 μm simulation for 1 ms would be approximately 2 x 10⁹ more expensive than our abilities in 2005
• Moore’s law: this might be possible in 46 yrs.
Outline

• Elastic membrane model
  – Background and simulation methods
  – Protein motion on the surface of the red blood cell
  – Supported bilayer fluctuations and diffusion of curved proteins

• Molecular membrane model
  – Correspondence with experimental physical properties and stress profile
  – Protein induced deformation of the bilayer and detailed elastic models
Linear response, curvature elasticity model

Helfrich bending free energy:

\[ E = \frac{K_c}{2} \int (\nabla^2 h(\mathbf{r}))^2 dxdy = \frac{K_c}{2L^2} \sum_k k^4 |h_k|^2 \]

Linear response for normal modes:

\[ \frac{d}{dt} h_k(t) = -\omega_k h_k + \zeta(t) \]

\[ \omega_k = \frac{K_c k^3}{4\eta} \]

Ornstein-Uhlenbeck process for each mode:

\[ P(h_k) = \sqrt{\frac{K_c k^4}{2\pi k_B TL^2}} \exp\left[ -\frac{K_c k^4}{2k_B TL^2} |h_k|^2 \right] \]

\[ P(h_k(t) | h_k(0)) = \sqrt{\frac{K_c k^4}{2\pi k_B TL^2}} \frac{1}{(1 - e^{-2\omega_k t})} \exp\left[ -\frac{K_c k^4}{2k_B TL^2} \frac{|h_k(t) - h_k(0)e^{-\omega_k t}|^2}{(1 - e^{-2\omega_k t})} \right] \]

\( K_c \): Bending modulus

\( L \): Linear dimension

\( T \): Temperature

\( \eta \): Cytoplasm viscosity
Relaxation frequencies

Solve for relaxation of membrane modes coupled to a fluid in the overdamped limit:

Non-inertial Navier-Stokes eq:
\[ \nabla p - \eta \nabla^2 \mathbf{u} = f_{\text{ext}} \]
\[ \nabla \cdot \mathbf{u} = 0 \]

Nonlocal Langevin equation:
\[ \dot{h}(\mathbf{r}, t) = \int d\mathbf{r}' H(\mathbf{r} - \mathbf{r}') f(\mathbf{r}', t) + \zeta(\mathbf{r}, t) \]
\[ H(\mathbf{r}) = \frac{1}{8\pi\eta r} \]
\[ f(\mathbf{r}) = -\frac{\delta E}{\delta h(\mathbf{r})} \]

Oseen tensor (for infinite medium)
Bending force

\[ \omega_k = \frac{K_c k^3}{4\eta} \]

\[ \dot{h}_k(t) = -(K_c k^4) \left( \frac{1}{4\eta k} \right) h_k(t) + \zeta(k, t) \]

Membrane Dynamics

QuickTime™ and a decompressor are needed to see this picture.
Extension to non-harmonic systems

Helfrich bending free energy + additional interactions:

\[ E = \frac{K_c}{2} \int \left( \nabla^2 h(\vec{r}) \right)^2 dxdy + V[h(r)] = \frac{K_c}{2L^2} \sum_k k^4 |h_k|^2 + V[h_k] \]

Overdamped dynamics:

\[ \dot{h}(\vec{r},t) = \int d\vec{r}' H(\vec{r} - \vec{r}') f(\vec{r}',t) + \zeta(\vec{r},t) \]
\[ f(\vec{r}) = -\frac{\delta E}{\delta h(\vec{r})} \]
\[ \frac{d}{dt} h_k(t) = \Lambda_k \{ F_k[h(r,t)] + \zeta_k(t) \} \]

Solve via Brownian dynamics

• Handle bulk of calculation in Fourier Space (FSBD)
• Efficient handling of hydrodynamics
• Natural way to coarse grain over short length scales

Fourier Space Brownian Dynamics

\[ \frac{d}{dt} h_k(t) = \Lambda_k \{ F_k[h(r,t)] + \zeta_k(t) \} \]

\[ \Gamma_k(\Delta t) = \Lambda_k \int_t^{t+\Delta t} d\tau \xi_k(\tau) \]

1. Evaluate \( F(r) \) in real space (use \( h(r) \) from previous time step).
2. FFT \( F(r) \) to obtain \( F_k \).
3. Draw \( \Gamma_k \)'s from Gaussian distributions.
4. Compute \( h_k(t+\Delta t) \) using above e.o.m..
5. Inverse FFT \( h_k(t+\Delta t) \) to obtain \( h(r) \) for the next iteration.
Protein motion on the surface of red blood cells
Spectrin “corrals” protein diffusion

- $D_{\text{micro}} = 5 \times 10^{-9} \text{ cm}^2/\text{s}$ (motion inside corral)
- $D_{\text{macro}} = 7 \times 10^{-11} \text{ cm}^2/\text{s}$ (hops between corrals)


Proposed Models

- Cell membrane
- Extracellular region
- Intracellular region
- Cytoskeleton

Key markers:
- a
- b
- c
- d
- e

Approximate distances:
- ~6 nm
- ~150 nm
Dynamic undulation model

$K_c = 2 \times 10^{-13}$ ergs

$\eta = 0.06$ poise

$L = 140$ nm

$T = 37^\circ C$

$D_{micro} = 0.53 \, \mu m^2/s$

$h_0 = 6$ nm
Explicit Cytoskeletal Interactions

- Harmonic anchoring of spectrin cytoskeleton to the bilayer

\[ E = \int_A d\mathbf{r} \left\{ \frac{K_c}{2} \left[ \nabla^2 h(\mathbf{r}) \right]^2 + \frac{1}{2} V(\mathbf{r})h^2(\mathbf{r}) \right\} \]

\[ V(\mathbf{r}) = \gamma \sum_i \delta(\mathbf{r} - \mathbf{R}_i) \]

- Additional repulsive interaction along the edges of the corral to mimic spectrin

\[ F_{rep} = \varepsilon \int_A d\mathbf{r} \; e^{-h(\mathbf{r})/\lambda} \sum_i \delta(ax_i + by_i + c_i) \]

Dynamics with repulsive spectrin

QuickTime™ and a decompressor are needed to see this picture.
Information extracted from the simulation

- Probability that thermal bilayer fluctuation exceeds $h_0=6\text{nm}$ at equilibrium (intracellular domain size)
- Probability that such a fluctuation persists longer than $t_0=23\mu\text{s}$ (time to diffuse over spectrin)

- Escape rate for protein from a corral
- Macroscopic diffusion constant on cell surface (experimentally measured)
Calculated $D_{\text{macro}}$

- Used experimental median value of corral size $L=110$ nm

<table>
<thead>
<tr>
<th>System Size</th>
<th>Simulation Type</th>
<th>Simulation Geometry</th>
<th>$D_{\text{macro}} \text{ (cm}^2\text{s}^{-1})$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$L$</td>
<td>Free Membrane</td>
<td>Square</td>
<td>$9 \times 10^{-12}$</td>
</tr>
<tr>
<td>$L$</td>
<td>Pinned</td>
<td>Square</td>
<td>$5 \times 10^{-12}$</td>
</tr>
<tr>
<td>$\infty$</td>
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<td>Square</td>
<td>$7 \times 10^{-10}$</td>
</tr>
<tr>
<td>$\infty$</td>
<td>Pinned &amp; Repulsive</td>
<td>Square</td>
<td>$3.4 \times 10^{-10}$</td>
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<tr>
<td>$\infty$</td>
<td>Pinned &amp; Repulsive</td>
<td>Triangular</td>
<td>$2 \times 10^{-10}$</td>
</tr>
</tbody>
</table>

- Median experimental value

$$D_{\text{macro}} = 6.6 \times 10^{-11} \text{ cm}^2\text{s}^{-1}$$
Explicit diffusion of membrane "proteins"

Explicit diffusion of membrane proteins

Numerically, the membrane shape is defined on a discrete grid. Protein position is continuously variable.

Numerically, proteins A, B, & C are not equivalent.
This problem can be solved…

\[ \int d\mathbf{r} F G(\mathbf{r} - \mathbf{r}_0) = F \]

P. Atzberger et. al., J Comp Phys, 224, 1255 (2007).

Blood P. D., Voth G. A. PNAS 2006;103:15068-15072
Curved proteins diffuse more slowly than flat proteins.

- For $D/D_0$ vs $C_p$ [nm$^{-1}$]:
  - Open circles: with noise
  - Triangle: without noise
  - Square: Adiabatic approx

- For $D/D_0$ vs $K_p/K_m$:
  - Open circles: with noise
  - Triangle: without noise
  - Square: Adiabatic approx

- For $D/D_0$ vs $\eta/\eta_w$:
  - Open circles: with noise
  - Triangle: without noise
  - Square: Adiabatic approx
Summary (elastic modeling)

- Elastic models for membrane undulations can be extended to complex geometries and potentials via Brownian dynamics simulation.
- “Thermal” undulations appear to be able to promote protein mobility on the RBC.
- Curved proteins diffuse more slowly than flat proteins.
- Other biophysical and biochemical systems are well suited to this approach.

Molecular membrane models with implicit solvent
Why?

• Study the basic (minimal) requirements for bilayer stability and elasticity.
• A particle based method is more versatile than elastic models.
  – Incorporate proteins, cytoskeleton, etc.
  – Non “planar” geometries
• Computational efficiency.
A range of resolutions...

W. Helfrich, Z. Naturforsch, 28c, 693 (1973)


Motivation

Fig. 1. Schematic representation of the balance of forces in a phospholipid bilayer. The repulsive internal two-dimensional pressures arising from headgroup and chain interactions ($\pi_{\text{int}}$ and $\pi_{\text{hyd}}$) balance the cohesive hydrophobic tension ($\gamma_{\text{phob}}$) which acts at the polar-apolar interface. The net lateral tension in the bilayer is therefore zero (cf. [6]). In practice, the lateral pressure components ($\pi_{\text{int}}$ and $\pi_{\text{hyd}}$) result from integration over the appropriate sections of the lipid molecule, e.g. over the chain profile.

A solvent free model

\[ U_{\text{flat}} = -C_{\text{flat}} \left( \frac{\sigma}{|r_{ij} - r_{i2}|} \right)^2 \]

Self-Assembly

QuickTime™ and a YUV420 codec decompressor are needed to see this picture.

(128 lipids)
Flexible (and tunable)

$k_c: 1 - 8 \times 10^{-20} \text{ J}$

$k_A: 40-220 \text{ mJ/m}^2$
Stress Profile
(-surface tension vs. height)

Atomistic DPPC bilayer
Protein Inclusions

Single protein inclusion in the bilayer sheet

Inclusion is composed of rigid “lipid molecules”
Deformation of the bilayer

\[ \delta = \frac{h(r) - h_0}{h_0} \]

The correspondence is meaningful

Deformation profile has three independent constants formed from combinations of elastic properties:

- \( h_0 \) monolayer thickness
- \( \Sigma_0 \) area/lipid
- \( k_c \) bending modulus
- \( k_A \) stretching modulus
- \( c_0 \) spontaneous curvature (monolayer)
- \( c_0' \) area derivative of above

Using physical constants inferred from homogeneous bilayer simulations we can predict the “fit” values:

- Direct from simulation
- Thermal fluctuations
- Infer from stress Profile & fluctuations
A consistent elastic model

- Begin with standard treatment for surfactant monolayers (e.g. Safran)
- Couple monolayers by requiring volume conservation of hydrophobic tails and equal local area/lipid between leaflets
- Include microscopic protrusions (harmonically bound to z fields & include interfacial tension)
A consistent elastic model

\[ \int_A dxdy \left\{ \frac{k_c}{2} \left( \nabla^2 z^+ \right)^2 + k_\lambda \lambda^2 + \gamma_{\text{int}} \left( \nabla \lambda^+ \right)^2 + 2 \gamma_{\text{int}} \nabla z^+ \cdot \nabla \lambda^+ \right. \]

\[ \left. + \frac{k_A}{2t_0^2} \left( z^- \right)^2 + 2k_c c_0 \nabla^2 z^- + 2k_c \left( c_0 - c_0' \Sigma_0 \right) \frac{Z}{t_0} \nabla^2 z^- + \frac{k_c}{2} \left( \nabla^2 z^- \right)^2 \right. \]

\[ + k_\lambda \lambda^2 + \gamma_{\text{int}} \left( \nabla \lambda^- \right)^2 + 2 \gamma_{\text{int}} \nabla z^- \cdot \nabla \lambda^- \right\} \]

Undulations (bending & protrusion)
Peristaltic bending
Peristaltic protrusions (and coupling to bending)

\( k_c \): Monolayer bending modulus
\( \frac{k_c}{2} \): Monolayer bending modulus
\( k_\lambda \): Protrusion binding constant
\( \gamma_{\text{int}} \): Interfacial (water/hydrocarbon) tension
\( \frac{k_A}{2} \): Monolayer compressibility modulus
\( c_0 \): Monolayer spontaneous curvature
Fits to fluctuation spectra

\[
\langle |h_q|^2 \rangle = \frac{k_B T}{k_c q^4} + \frac{k_B T}{2(k_\lambda + \gamma_{int} q^2)}
\]

\[
\langle |t_q|^2 \rangle = \frac{k_B T}{k_c q^4 - 4 \frac{k_c}{t_0} (c_0 - c_0' \Sigma_0) q^2 + k_A / t_0^2} + \frac{k_B T}{2(k_\lambda + \gamma_{int} q^2)}
\]
Positive spontaneous curvature & conservation of volume favors modulated thickness

These molecules are unhappy, but, there are relatively few of them.

These molecules are happy because they’re in their preferred curvature.
Fluctuation spectra: spontaneous curvature

Of the available simulation data, this effect is most pronounced for DPPC:

Lindahl, E. and O. Edholm. 
gramicidin A channel lifetimes


\[
\frac{k_d(z_0^{(1)})}{k_d(z_0^{(2)})} \approx \frac{e^{-\beta(F_{elas}(TS)-F_{elas}(D))}}{e^{-\beta(F_{elas}(TS)-F_{elas}(D))}}
\]


Rate vs. monolayer thickness

\[
\ln(k_d/k_{d,0}) = \begin{cases} 
0 & \text{microscopic fields neglected} \\
\frac{1}{2} & \text{microscopic fields considered}
\end{cases}
\]

\[
\Delta F^* = \begin{cases} 
2.27\text{nm} & \text{D} \\
2.17\text{nm} & \text{M}
\end{cases}
\]
Implicit solvent models can reproduce an array of bilayer properties and behaviors.

Computation is significantly reduced relative to explicit solvent models, enabling otherwise difficult (impossible) simulations.

Coarse-grained models are especially well suited for validating and suggesting analytical theory.

A single elastic model can explain peristaltic fluctuations, height fluctuations and response to a protein deformations.
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