Biology 5357: Chemistry & Physics of Biomolecules
Fall 2021

Lecture 3: Membrane Structure & Mechanics

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Reading for this week:

Required reading:

*Phillips, R. (2018). Physics of Biological Membranes* [https://dx.doi.org/10.1007/978-3-030-00630-3_3](https://dx.doi.org/10.1007/978-3-030-00630-3_3)
The hydrophobic effect

- Water forms a network of hydrogen bonds with itself
- The number of hydrogen bonds can be described in a simplified tetrahedral network, showing 6 possible configurations of the central water molecule making a hydrogen bond with a neighbor
- Changing one of these water molecules to a non-polar molecule that does not form hydrogen bonds reduces the number of states to 3, just a single face of the triangle
- A methylene group adds 0.8 kcal/mole to the hydrophobic effect
- Drives association of non-polar molecules to reduce the water accessible surface area

Self-assembly of amphiphiles
Structures of lipid phases.

I. Lamellar phases: (A) subgel, $L_c$; (B) gel, $L_{\beta}$; (C) interdigitated gel, $L_{\beta}^{[\text{int}]}$; (D) gel, tilted chains, $L_{\beta}'$; (E) rippled gel, $P_{\beta}'$; (F) liquid crystalline, $L_\alpha$.

II. Micellar aggregates; (G) spherical micelles, $M_I$; (H) cylindrical micelles (tubules); (J) disks; (K) inverted micelles, $M_{II}$; (L) liposome;

III. Non-lamellar liquid-crystalline phases of various topology; (M) hexagonal phase $H_I$; (N) inverted hexagonal phase $H_{II}$; (O) inverted micellar cubic phase $Q_{II}[M]$; (P) bilayer cubic (Q$_n$) phase Im$3m$; (Q) bilayer cubic phase P$n$3m; (R) bilayer cubic phase Ia$3d$.

<table>
<thead>
<tr>
<th>Critical Packing Parameter ((v/a_0 l_c))</th>
<th>Critical Packing Shape</th>
<th>Structures Formed</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; (1/3)</td>
<td>Cone</td>
<td>Spherical micelles</td>
</tr>
<tr>
<td>(1/3 - 1/2)</td>
<td>Truncated cone</td>
<td>Cylindrical micelles</td>
</tr>
<tr>
<td>(1/2 - 1)</td>
<td>Truncated cone</td>
<td>Flexible bilayers, vesicles</td>
</tr>
<tr>
<td>(\approx 1)</td>
<td>Cylinder</td>
<td>Planar bilayers</td>
</tr>
<tr>
<td>(&gt; 1)</td>
<td>Inverted truncated cone or wedge</td>
<td>Inverted micelles</td>
</tr>
</tbody>
</table>
Purifying membrane proteins

1. Native membrane
2. Solubilization
3. Purification
4. Reconstitution
   - Dialysis
   - Gel filtration
   - Dilution
   - Polystyrene beads
The Critical Micelle Concentration (CMC)

Figure from “Cell Membranes” by Lukas Buehler

below CMC

above CMC

Surfactant molecule
\[ \text{Hydrophobic portion} \]
\[ \text{Hydrophilic portion} \]

Critical micelle concentration (CMC)

Air

Surface at surface

Surface saturated

Micelles formed

Water at 20 °C

Surface tension (mN/m)

Concentration (mg/L)

[SDS] mM

[SDS]_{total} mM
Structure of detergent micelles

R - radius
Nagg - aggregation number

ACS Omega 2017, 2, 8, 4524-4530

https://doi.org/10.1371/journal.pone.0062488
What defines the CMC?

- **Structure of hydrophobic group**: increase in carbon chain increases micellar size, decreases CMC
- **Increase in hydrophilic head group**: increases hydrophilicity and increases CMC
- **Addition of electrolytes** for ionic surfactants decrease CMC and increase micellar size due to a reduction in head group repulsion
- **Temperature**: mainly affects nonionic surfactants, increases in temperature up to the cloud point increase micellar size and decrease CMC
- **Concentration**: aggregation number in micelle can change above CMC making non-spherical micelle structures
### CMCs of Detergents

<table>
<thead>
<tr>
<th>Detergent</th>
<th>MW</th>
<th>CMC</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHAPS</td>
<td>614.88</td>
<td>8 mM</td>
</tr>
<tr>
<td>CHAPSO</td>
<td>630.88</td>
<td>8 mM</td>
</tr>
<tr>
<td>BIGCHAP</td>
<td>878.06</td>
<td>2.9 mM</td>
</tr>
<tr>
<td>DeoxyBIGCHAP</td>
<td>862.06</td>
<td>1.4 mM</td>
</tr>
<tr>
<td>Octylglucoside</td>
<td>292.37</td>
<td>25 mM</td>
</tr>
<tr>
<td>Heptylthioglucoside</td>
<td>294.41</td>
<td>30 mM</td>
</tr>
<tr>
<td>Octylthioglucoside</td>
<td>308.44</td>
<td>9 mM</td>
</tr>
<tr>
<td>Decylmaltoside</td>
<td>482.57</td>
<td>1.8 mM</td>
</tr>
<tr>
<td>Dodecylmaltoside</td>
<td>510.62</td>
<td>0.17 mM</td>
</tr>
<tr>
<td>Nonylthiomaltoside</td>
<td>484.60</td>
<td>2.4 mM</td>
</tr>
<tr>
<td>MEGA-8</td>
<td>321.41</td>
<td>-</td>
</tr>
<tr>
<td>MEGA-9</td>
<td>335.44</td>
<td>25 mM</td>
</tr>
<tr>
<td>MEGA-10</td>
<td>349.46</td>
<td>7 mM</td>
</tr>
<tr>
<td>Sucrose monocholate</td>
<td>732.85</td>
<td>4.7 mM</td>
</tr>
<tr>
<td>Sodium cholate</td>
<td>448.57</td>
<td>14 mM</td>
</tr>
</tbody>
</table>
Mixtures of detergent & lipids - bicelles

Schema of bicelle structure

DMPC

DHPC

CHAPSO

Increasing DMPC/DHPC (q)

q=1.0

q=0.5

q>3

Prosser et al., 2006. DOI: 10.1021/bi060615u
• Lipids, with two acyl chains, undergo the same type of self-assembly behavior, but the CMC values are now much lower.

• The exchange between free monomers and the lipid bilayer is slow.

• Furthermore, liposomes are stable and do not fuse spontaneously.
Bilayer & Lipid structural parameters

- $A_L$ - surface area of lipid
- $D$ - primary lamellar repeat spacing (multilamellar structures)
- $D_b$ - bilayer thickness
- $D_h$ - hydrophobic thickness
- $\Theta$ - tilt angle of the hydrophobic tails
Small angle scattering to measure membrane structure

Figure 1. Illustration of lipid bilayer structure determination through the joint refinement of X-ray and neutron scattering data. The scattering density profile (SDP) representation of a bilayer in real space is shown on the left, where the top panels show X-ray scattering length density (XSLD) with amplitudes calculated from the number of electrons and electron radius (A), and neutron scattering length density (NSLD) based on neutron coherent scattering amplitudes (B) of lipid component distributions (see e.g., [33] for detailed description). The total scattering length densities are denoted by the thick red lines. Panel (C) shows volume probability distributions, where the total probability is equal to 1 at each point across the bilayer, and the location where the shaded areas are equal defines the Gibbs dividing surface between the lipid bilayer and the water phase (effectively Dₐ). Graphs on the right show the experimentally determined X-ray (D) and contrast varied neutron (E) scattering form factors (points), together with the best fits to the data (solid lines).

Figure 3. Comparison of the scattering length density profile of liposome for X-ray (left) and neutron (right). Adapted from [11].

doi:10.3390/pharmaceutics8020010
Bilayer thickness vs. acyl chain

Relative Bilayer Thickness [Å]

chain length

k=1.9 Å per CH₂
Bilayer thickness vs. chain modification

- di-monounsaturated [65]
- DOPC
- DEiPC
- DErPC
- DMoPC
- DPOPC
- SOPC
- POPC mixed [62]
- saturated [62]
- DLPC
- DMPC
- DPPC
- DSPC

Lipid Area [Å²]

chain length
Hydrophobic thickness vs. cholesterol

DMPC

DOPC

POPC

Cholesterol

Distance $D_{HH}$ (Å)

Molar fraction cholesterol

Sim

Exp
Lipid Bilayer Properties - Curvature

**a. Membrane curvature**

- Lipid species and spontaneous membrane curvature
  - Cylindrical
    - Phosphatidylcholine
    - Phosphatidylserine
  - Conical
    - Phosphatidylethanolamine
    - Phosphatidic acid
  - Inverted-conical
    - Lyso-GPLs
    - Phosphoinositides

**Membrane curvature and fission**

- Flat membrane
- Negative curvature
- Positive curvature
- Flat
  - Positive
- Negative

*Image showing membrane curvature and fission with lipid species and spontaneous membrane curvature.*
Lipid Bilayer Properties - lateral pressure

A. Bilayer containing only bilayer lipids
   - Decreased headgroup pressure
   - Increased chain pressure

B. Bilayer containing a mixture of nonbilayer and bilayer lipids

C. Changes in lipid bilayer structure under lateral pressure
Material Properties of Lipid Bilayers

- **bend**
- **stretch**
- **shear**
- **thickness change**
Energetic consequence of bending membranes

Helfrich-Canham-Evans Free Energy

\[ G_{bend}[h(x, y)] = \frac{K_b}{2} \int da [\kappa_1(x, y) + \kappa_2(x, y)]^2 \]

- \( h(x, y) \) – membrane height at \((x, y)\) [length, nm]
- \( \kappa_{i,j}(x, y) = \frac{\partial^2 h}{\partial x_i \partial x_j} \) – principle curvature at \((x, y)\) [1/length, 1/nm]
- \( K_b \) – bending modulus [energy, \( k_B T \)]

(A)

(bending modulus (10^{-19}))

- poly-cis unsaturation
- ~24 \( k_B T \)
Energetic consequence of stretching membranes

\[ G_{\text{stretch}} = \frac{K_a}{2} \int da \left[ \frac{\Delta a}{a_0} \right]^2 \]

\( \Delta a \) – change in area [area, nm\(^2\)]

\( a_0 \) – reference area [area, nm\(^2\)]

\( K_a \) – area – stretch modulus [energy/area, \( k_B T / \text{nm}^2 \)]
Energetic consequence of compressing membranes

\[ G_{\text{thickness}}[w(x, y)] = \frac{K_t}{2} \int da \left[ \frac{w(x, y) - w_0}{w_0} \right]^2 \]

- \( w(x, y) \) = half-width of membrane [\( \text{length, nm} \)]
- \( w_0 \) = half equilibrium width of membrane [\( \text{length, nm} \)]
- \( K_t \) = stiffness modulus [\( \text{energy/area, } k_B T/\text{nm}^2 \)]
<table>
<thead>
<tr>
<th>technique</th>
<th>schematic illustration</th>
<th>results [ref]</th>
</tr>
</thead>
<tbody>
<tr>
<td>quantitative fluorescence microscopy</td>
<td><img src="image1.png" alt="Diagram" /></td>
<td>protein binding [102–104,106,107] lipid rafts [56,57]</td>
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<tr>
<td>micropipette aspiration</td>
<td><img src="image2.png" alt="Diagram" /></td>
<td>membrane tension [92–94] bending rigidity [73]</td>
</tr>
<tr>
<td>combined with optical tweezers</td>
<td><img src="image3.png" alt="Diagram" /></td>
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</tr>
<tr>
<td>optical trapping</td>
<td><img src="image4.png" alt="Diagram" /></td>
<td>bending rigidity [77–80]</td>
</tr>
<tr>
<td>atomic force microscopy</td>
<td><img src="image5.png" alt="Diagram" /></td>
<td>bending rigidity [82] membrane tension [83,84] area compressibility modulus [83,84]</td>
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