The Interaction between Lipid Bilayers and Biological Membranes

Chapter 18
Membrane & Phospholipid Bilayer Structure

**Introduction**

Membrane & Lipid bilayer

**FLUID**
Phosphatidyl Choline Bilayer

Carbon/Palmitic
Nitrogen
Oleic
Oxygen
Water Oxygens
Phosphorus

H Heller,
M Schaefer,
K Schulten,
J Phys Chem
97:8343, 1993

RasMol Image
by E Martz
Introduction

Forces Acting between Surfaces in Liquid

- **DLVO forces**
  - van der Waals force
    - permanent or induced dipole moment
  - electrostatic (double-layer) force
    - surface charge density (potential)

- **Non-DLVO forces**
  - solvation (hydration) force
    - ionization: $\text{Na}^+ \rightarrow [\text{Na(H}_2\text{O)}_n]^+$
  - steric force
    - thermal fluctuation
  - hydrophobic force
    - entropy effect: disordering
van der Waals Forces

- between two planar surfaces:

\[ W(D) = -\frac{A}{12\pi D^2} \text{ per unit area of surface} \]

- between amphiphilic structures: generally small

- Hamaker constant
  - Non-retarded: \( A = 4 \sim 7 \times 10^{-21} J \) for \( D < 3 \text{nm} \)
  - Retarded: \( A_{\nu=0}(D) = A_{\nu=0}(0)2\kappa De^{-2\kappa D} \)

Ionic screening of the zero-frequency
The double-layer repulsion is much more sensitive to the type and concentration of electrolyte present, the pH, temperature and the surface charge density or potential.

\[
P = kT \rho_0 = 2\varepsilon\varepsilon_0 (kT / ze)^2 K^2
\]

\[
K^2 = (ze)^2 \rho_0 / 2\varepsilon\varepsilon_0 kT
\]
- Measured repulsive forces between the DSPG bilayers in various aqueous solutions at 22°C due to attractive ion correlation force.

**Type & Concentration of Electrolyte Effect**

<table>
<thead>
<tr>
<th>Electrolyte</th>
<th>Surface charge</th>
<th>Ion binding</th>
<th>Measured forces</th>
</tr>
</thead>
<tbody>
<tr>
<td>CaCl₂</td>
<td>Surface charge</td>
<td>~ ion binding</td>
<td>more attractive than expected from the DLVO theory</td>
</tr>
</tbody>
</table>

DSPG : Distearoyl Phosphatidylglycerol
At higher monovalent electrolyte the double-layer repulsion generally diminishes. But between lipid bilayers it usually remains strong enough to keep the surface apart even for low surface potentials and in high salt, because of the relatively weak van der Waals attraction.

Theoretical DLVO interaction energy per unit area between two amphiphilic surfaces in 0.15 M NaCl.

- weak secondary minimum occurs at 4-6nm.
- Repulsive hydraton forces arise whenever water molecules bind strongly to hydrophilic surface groups.

- Between two solid crystalline surfaces the hydration force is oscillatory. Oscillations have a periodicity of the diameter of the water molecule (0.25 nm) and reflect the ordering of water molecules into semidiscrete layers between the smooth, rigid surfaces.

- Between bilayer surfaces:
  no such ordering into well-defined layers is possible
  1) the head groups are rough on the scale of a water molecule
  2) the surfaces are thermally mobile giving rise to a steric repulsion any oscillatory force becomes smeared out.

\[
P(D) \approx -kT \rho_s(\infty) \cos(2\pi D/\sigma)e^{-D/\sigma}
\]
- The range of the steric-hydration forces: between surfactant and lipid bilayers ~ 1-3nm

- The overlapping of the mobile headgroups protruding out from two approaching bilayers produces a variety of repulsive steric or osmotic-type forces between them. Roughly exponentially repulsive

- Forces between layers of di-hexadecyl phosphate in aqueous NaCl solutions

below $10^{-2}$ M: DLVO theory
D>2nm: double-layer repulsion dominate
D<2nm: van der Waals attraction dominate

above $10^{-2}$ M, high pH: repulsive hydration forces come in
Limitation of the hydration model

Hydration Model

- The origin of the monotonically repulsive hydration forces
  1) Marcelja theory: the polarization induced by surfaces or surface groups on the water molecules adjacent to them. Molecular dynamic simulations failed to reproduce
  2) Experimentally: more complex and less consistent

- Pressure between egg lecithin bilayers in water, formamide, and PDO

\[
P = P_0 e^{-D\lambda}
\]

not unique to water!!
- Repulsion forces in water between uncharged monolaidin bilayers in the gel state and monocaprylin bilayers in the liquid-crystalline state, as measured by the Osmotic Pressure technique.

- Temperature increasing gel liquid crystalline: increase in the magnitude and range of the repulsion

\[ F \approx \frac{(kT)^2}{2k_bD^3} \]
Limitation of the hydration model

Crystal/Gel/Fluid Lipid Bilayer(I)
**Limitation of the hydration model**

**Crystal/Gel/Fluid Lipid Bilayer (II)**

<table>
<thead>
<tr>
<th>Crystal</th>
<th>End view.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Center slice of one leaflet from molecular dynamics simulation of 200-PC lipid bilayer.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
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<tr>
<th>Side view of 20 phosphatidyl cholines (2 x 10).</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Gel</th>
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<tbody>
<tr>
<td>1-palmitoyl 2-oleoyl phosphatidyl choline</td>
</tr>
</tbody>
</table>

**Fluid**

**Water**

**Nitrogen**

**Phosphorus**

Other phospholipid atoms

*Figure by Eric Martz with RasMol by Roger Sayle*
Limitation of the hydration model

Temperature Effect

- Repulsion forces in water between various free phospholipid bilayers in water in the liquid-crystalline and fluid states, i.e., below and above the chain melting temperature, $T_c$, as measured by the Osmotic Pressure technique.

DPPC : DiphalmitoryPhosphatidylcholine
Steric forces

Four-type repulsive Steric forces (I)

With the apparent failure of models based on purely electrostatic or solvation interactions to explain these forces, attention has recently focused on the role of thermal fluctuation interactions.

Four-type repulsive Steric forces

Undulation
\[ F \approx \frac{(kT)^2}{2k_B D^2} \]

Identically long range

Peristaltic
\[ F \approx \frac{(kT)^2}{5k_a D^5} \]

Protrusion
\[ F \approx \frac{2.7 \Gamma kT e^{-D\lambda}}{\lambda}, \text{ where } \lambda \approx \frac{kT}{\alpha_p} \]

Headgroup overlap
\[ F \approx 100 \Gamma^2 kT e^{-D\lambda}, \text{ where } \lambda \approx \frac{\pi}{L} \]

L : effective thickness of fluctuating headgroup region
2L : range of interaction
Steric forces

Four-type repulsive Steric forces (II)

Theoretical plot of the four steric repulsion
(double-chained lipid bilayers in the fluid state)
Hydrophobic forces (I)

Attractive hydrophobic interaction
(between hydrocarbon molecule or surface in water)

At small D, much stronger than van der Waals attraction

When bilayer are subjected to a stretched force,
- lateral expansion of bilayer
- Exposition of increased hydrophobic area to the aqueous phase
- Hydrophobic interaction

Exposition of Hydrocarbon group to aqueous phase
$\propto$ strongly attractive hydrophobic force

Force between supported DLPC and DMPC layers in water
Hydrophobic forces

Hydrophobic forces (II)

Stress of bilayers and membranes

- Applying an electric field across bilayers and membranes
- Osmotic swelling of cells or vesicles
- Introduce local stresses on the lipid via ion binding or packing mismatches with other membrane components

Temperature (T)

- Ex) Interaction between certain non-ionic micells and bilayers
  surfactant: polyoxyethylene headgroup
Specific Interactions

Specific Interaction (I)

**Electrostatic**

- Some electrostatic interactions are unusually strong:
  - Ex) Adhesion of phosphatidylserine bilayers in the presence of Ca$^{2+}$ ions
- Certain divalent ions trigger conformational or chemical changes in proteins and membranes while others do not

**Bridging**

- Bridging forces also arise in biological systems
  - Ex) Polymer bridges: connect myelin membranes
    prevent from moving too far from each other.
Specific Interactions

Specific Interaction (II)

• *Lock-and-key or ligand-receptor interactions*

biological interactions: immunological recognition
(ligand-receptor interactions)
cell-cell contacts

biotin: a ligand
streptavidine: a protein receptor

binding energy: 88kJ/mol
(35kT per bond)

by a change in the pH or solution conditions
locked ⇔ unlocked
Interdependence of intermembrane and Intramembrane forces

$a_0$ (headgroup area)

$\rightarrow$ $a_0$, larger repulsive force, between bilayer,

Large hydration of the lecithin headgroup
- large surface area, $a_0 \approx 0.7 \text{ nm}^2$
- large swelling in fully hydrated lecithin multilayers

Headgroup repulsion in phosphatidylethanolamin is much less
- smaller headgroup area, $a_0 \approx 0.5 \text{ nm}^2$
- much reduced swelling

Low pH, Addition of divalent cation between two different bilayer $\rightarrow$ Charged lipid layer

Addition of divalent cation
Low pH condition

Electrostatic headgroup repulsion

Bilayer swelling, Adhesion of vesicle
1. Adhesion force – Vesicle Fusion

2. Vesicle fusion in a cell
   - Specific membrane or vesicle, specific time & space etc
     : Synaptic nerve transformation, Exocytosis(vesicle incorporation),
     Pinocytosis(vesicle shedding)

3. Kinetics (0.1 ~ 1 ms)
   - Fusion process - intermediate stage - trapVesicle
   - Electron microscope - sample freezing - sample fixing

4. Drug carrier systems
   - vesicle adhesion & fusion
   - vesicle planar membrane adhesion & fusion
**Vesicle Fusion (II)**

i) $T < T_c$ (chain melting temp.)

- Pure stable lipid vesicles
- Large, less curved vesicle
- Cooling

**T < $T_c$ vesicle fusion**
- Curved bilayer stress
- Vesicle Stress
  - Chain stretching
  - Large, less curved bilayer packing

**Intravesicle vs Internal Packing force**

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ii) Divalent cation

- CaCl$_2$ (1~10mM)
  - Electrostatic repulsion, Short range attraction
  - Vesicle Fusion lipid packing stress

- Biological vesicle membran charge, Ca concentration
  - 1~10uM, vesicle fusion
Probable molecular events taking place during the adhesion, fusion and fission of bilayers and membranes