Membranes and Lipids
Biophysical Chemistry 1, Fall 2009

Fundamentals of lipid/membrane structure
Membrane/protein interactions
Reading assignment: Chaps. 4 & 10
Back to the cell:

Eukaryotic cells are usually at least 10 times larger than prokaryotic cells and more complex. In eukaryotic cells, the basic prokaryotic cell structure with the plasma membrane and cytoplasm is upgraded with compartments, also called organelles. In the cytoplasm, additional distinctive structures can be found. In some cases their interior is segregated from each other by a membrane. The most common organelles are: (i) the nucleus storing the cell genetic material and where replication and gene expression take place; (ii) the cytosol, where protein synthesis and many essential biochemical reactions take place; (iii) the mitochondrion, a power plant and energy storage compartment; (iv) the endoplasmatic reticulum and Golgi apparatus, where proteins are packaged and sent to further locations; (v) the lysosomes or vacuoles, where polymeric macromolecules, such as proteins, are degraded into usable monomers (Fig. 1.3).

It is believed that all organisms on Earth originate from a single kind of unicellular organism. Today many millions of different kinds of organisms that do not interbreed with one another can be found and we call them species. They are all successfully adapted to their different environments and in this sense, perfect. However, some of them may not be perfect tomorrow and can thereby become extinct.
4.3 Amphiphile Self-Assembly Into Different Aggregate Structures

4.3.1 Lipid Packing and Spontaneous Curvature

A typical lipid structure is shown in (Fig. 4.10). Since polar lipids are composed of two parts, a hydrophilic part and a hydrophobic part, connected by a backbone residue, they are referred to as amphiphiles. In water, they assemble into different types of aggregates that form phases.

One of the most useful concepts for a qualitative understanding of the phase behavior in amphiphilic systems is based on the geometry or general shape of a lipid molecule (Fig. 4.11). The self-assembly of lipid molecules depends on a dimensionless packing parameter defined by the ratio:

\[ P = \frac{v}{al} \]

where \( v \) is the volume of the fluid hydrocarbon chains, \( l \) is the length of the hydrophobic chains and \( a \) is the optimal cross-sectional area of the polar head group as shown in Fig. 4.11.

When the packing parameter (sometimes also called the surfactant number) is equal to unity (cylindrical-like molecules, Fig. 4.12), the conditions are optimal for the formation of a bilayer structure. If \( P > 1 \), the lipid molecules are wedge-shaped and the lipid monolayer prefers to curve towards the water region, i.e. it forms reversed micelles or an HII liquid crystalline phase (Fig. 4.12).

**FIGURE 4.10** As an example of a typical lipid, the figure shows a phospholipid (phosphatidylcholine, PC, often called lecithin). Its amphiphilic character is seen by the hydrophobic hydrocarbon acyl chains (tails) and the hydrophilic polar head group connected by the backbone, in this case glycerol.
Lipids self-assemble...

- Lipid molecule
- Micelles
- Reversed micelles
- Lipid bilayers
- Liposomes or vesicles

FIGURE 4.1: A cartoon of four representative lipid aggregate structures. A lipid bilayer may also form a closed structure called a lipid vesicle or liposome. Note that these drawings only show average geometrical structures. In reality, these structures are much more varied and dynamic.

FIGURE 4.2: Thylakoid membranes from a chloroplast illustrating the sharp bends (at the arrows) between the flat regions. Electron microscopy picture by C. Weibull provided by P. Å. Albertsson.
and make complex membranes:
Controlling the amount of unsaturation

4.2.1.1 Phospholipids

As major constituents of biological membranes, phospholipids play a key role in all living cells. The two principal groups of phospholipids are the glycerophospholipids that contain glycerol, and the sphingophospholipids that contain the alcohol, sphingosine (Fig. 4.6).

A number of different polar head groups can be found in phospholipids, for example, choline and ethanolamine that yield zwitterionic head groups at neutral pH, as well as negatively charged serine, glycerol, and phosphate.

Phosphatidylcholines and related phospholipids usually contain a saturated fatty acid in the \( sn-1 \) position but an unsaturated acid, which may contain between one to six double bonds, at \( sn-2 \). Hydrolysis of the ester linkage at \( sn-2 \) yields a 1-acyl-3-phosphoglycerol, known as a lysophospholipid. It works like a powerful surfactant or detergent and leads to lysis of cells. Some snake venoms, for example, contain phospholipases that synthesize lysophosphatidylcholine.

**Figure 4.4** A dipalmitoylphospholipid molecule where the chiral carbon on the glycerol moiety is indicated.

**Figure 4.5** Phosphatidylcholine with some of the most common fatty acyl chains. DPPC stands for dipalmitoyl-PC; POPC for palmitoyloleoyl-PC; PLPC for palmitoyllinoleoyl-PC; PAPC for palmitoylarachidonyl-PC; and PDPC for palmitoyldocosahexaenooyl-PC.
For three components at constant pressure, we have $F = 4 - p$, and it is necessary also to fix the temperature to be able to illustrate the phase diagram on a two-dimensional page. Therefore, for a three-component system we utilize a triangular diagram with the pure compounds in the corners of the triangle (not shown; see a textbook in physical chemistry). The maximum number of phases in equilibrium is three, and a typical characteristic of the ternary phase diagram is the areas of three-phase triangles that occur as compared with the three-phase lines present in the two-component systems.

In the construction of phase diagrams the so-called lever rule is very useful. A point in a two-phase region of a phase diagram (binary or ternary) indicates not only, qualitatively, that two phases are present but represents, quantitatively, the relative amounts of each one. The relative amounts of the two phases that are in equilibrium are determined by the relative distances of the particular point on its tie line from the respective phase boundaries — this is called the lever rule. For a binary system, tie lines are always horizontal, but for a ternary system, their directions are not always easily predicted, and they have to be determined experimentally. Here, the NMR method is particularly useful.

**FIGURE 4.7** A partial phase diagram of DPPC and water. At low temperature the gel, $L_{\beta'}$, phase is formed and at high temperature and relatively high water content, a lamellar liquid crystalline, $L_\alpha$, phase is stable. In the middle of the phase diagram the ripple $P_\beta'$ phase is stable in a narrow region of temperature and water content. (Adapted with permission from Ulmius J, Wennerström H, Lindblom G, Arvidson G. (1977) Deuteron NMR studies of phase equilibria in a lecithin-water system. *Biochemistry* 16: 5742–5745. Copyright (1997) American Chemical Society.)
Types of structures

- Reversed Micelles
- Reversed Hexagonal $H_{II}$
- Cubic
- Lamellar $L_{\alpha}$
- Hexagonal $H_{I}$
- Micelles

$P = \frac{v}{a l}$

- $P > 1$
- $P = 1$
- $P < 1$
- $P < 1/3$
Lamellar (membrane) phases have curvature. The molecular shape does not fully explain why a reversed hexagonal, HII, phase is formed at high water content when an alkane or hydrophobic peptide is added to seemingly stable lamellar liquid crystalline phases of phosphatidylcholine (PC), an apparently "cylindrical" lipid molecule. Obviously, this has to mean that even the PC molecules in multilayers have a packing parameter that is slightly larger than one, but other factors restrain them from forming a curved monolayer. The reason is that it is not possible to pack the PC molecules in a large HII cylinder without creating a large interstitial volume of vacuum as will be discussed below.

Bilayers that are formed by such PC molecules are said to be "frustrated" (see below). This is explained by a concept known as lipid monolayer curvature that is related to the packing parameter but has a more general character not involving the lipid molecules specifically. The energy needed to deform a membrane is determined by the structure and elasticity of the membrane. The non-deformed unstressed state of the membrane is referred to as the spontaneous state. Deviations from the spontaneous state, the forces required for these deviations, and the accumulated energy in the new shape determine the membrane elastic properties.

To understand this, let us briefly review the physical chemistry of membrane bending and the energetics involved. First, we need to look at some definitions. At any point on a sheet in three-dimensional space, two principal radii of curvature $R_1$ and $R_2$ and local curvatures $c_1 = 1/R_1$ and $c_2 = 1/R_2$ can be defined (Fig. 4.13). The sign of the curvature is arbitrary, and by convention one uses a definition as shown in Fig. 4.13, where a region that bulges "outward" from the volume enclosed from the surrounding medium has a positive curvature. Thus, spherical micelles have uniformly positive curvature, since $R_1$ and $R_2$ are both positive and equal. Saddle-shaped membranes, found, for example, on the bicontinuous cubic phase structure (illustrated in Fig. 4.15 below) or at the necks of budding vesicles,
FIGURE 4.17 Illustration of the lateral pressure, $p(z)$, profile in a lipid bilayer. A coordinate system, $z$, along the normal to lipid bilayer, showing the pressure distribution across the bilayer is schematically indicated to the right. The lateral pressure in the middle of the bilayer can be very high. However, the total pressure over the bilayer is zero. (Courtesy of Ole Mouritsen.)
Pressure and conformation

The Basics of Lipids and Membrane Structure

Head group repulsion \((\pi > 0)\)

Interfacial tension \((\pi < 0)\)

Chain repulsions \((\text{entropic}) \ (\pi > 0)\)

Interfacial tension

\[ \gamma(z) \]

**FIGURE 4.17**

Illustration of the lateral pressure, \(p(z)\), profile in a lipid bilayer. A coordinate system, \(z\), along the normal to lipid bilayer, showing the pressure distribution across the bilayer is schematically indicated to the right. The lateral pressure in the middle of the bilayer can be very high. However, the total pressure over the bilayer is zero. (Courtesy of Ole Mouritsen.)

**FIGURE 4.18**

High lateral pressure, \(p(z)\), can result in a change in the conformation of an integral membrane protein (striped or dashed) as illustrated by the cross-section \(A(z)\). The protein can be in any of two states; \(r\) or \(t\). \(\gamma\) is the interfacial tension. (Reprinted with permission from Cantor RS. (1997) Lateral pressures in cell membranes: a mechanism for modulation of protein function. *J Phys Chem B* 101: 1723–1725. (Copyright (1997) ACS.))
Membrane fusion

4.4.4 Lipid Synthesizing Enzymes

The structure of fatty acid synthase is described in Sec. 5.4. The regulation of the membrane lipid composition implies that the activity of the enzymes synthesizing the lipids (lipid synthases) is adjusted to the prevailing growth conditions of the cells. Some kind of signal(s), reflecting the status of the lipid bilayer, must thus be transferred from the bilayer to the lipid synthases. The lipid synthases are generally more or less tightly associated to the lipid bilayer, and one possibility is that the activity of these enzymes is directly influenced by the properties of the lipid bilayer (see Fig. 4.26). Another possibility is that the synthase activity is regulated...
Lipid domains and rafts of the membrane enzymes of A. laidlawii. The model suggests that the stored elastic energy of the lipid bilayer modifies the activity of curvature-sensitive enzymes through interaction with amphipathic \( \alpha \)-helices. As their binding depends on the lipid composition, this results in a biophysical feedback mechanism for the regulation of the stored elastic energy that depends on the packing of the lipids in the bilayer. Thus, restrictions are imposed on the balance between lamellar- and non-lamellar-forming lipids in the plasma membrane and on the concentrations of particular lipids. By using measured values of lipid curvatures from A. laidlawii, the theoretical model gives quite a good, although as yet not fully quantitative, description of the membrane process.

4.4.5 Lipid Domains and Rafts in Membranes

In 1972, Singer and Nicolson launched their classical model of the membrane as a matrix in which the proteins have a degree of motional freedom in a lipid “sea.” This “fluid mosaic model” became the framework and benchmark for our current understanding of membrane bilayers and their physiological function (Fig. 4.27).

However, the homogeneous nature of the membrane proposed in this model, characterized by random distribution of molecular components in the membrane, has later been altered. Many recent studies have revealed that cell membranes possess a rather complex lateral organization. For example, it was discovered by single-particle tracking techniques, that labeled lipid or protein molecules perform a lateral diffusive motion, and that they are temporarily confined into a corral on the membrane.