Lipids and Membrane Proteins
Biophysical Chemistry 1, Fall 2010

Fundamentals of lipid/membrane structure
Fundamentals of membrane protein structure
Channels and pores
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 takes 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...
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...

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:

![Image of complex membranes with arrows indicating bends.](image-url)
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 \( \text{sn}-1 \) position but an unsaturated acid, which may contain between one to six double bonds, at \( \text{sn}-2 \). Hydrolysis of the ester linkage at \( \text{sn}-2 \) 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 4.5** 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 palmitoyldocosahexaenoyl-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

**FIGURE 4.7** A partial phase diagram of DPPC and water. At low temperature the gel, \( L_{β'} \), phase is formed and at high temperature and relatively high water content, a lamellar liquid crystalline, \( L_{α} \), phase is stable. In the middle of the phase diagram the ripple \( P_{β'} \) 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

FIGURE 4.11 A schematic drawing of the shape of a lipid molecule forming spherical micelles as shown in Fig. 4.12. The red sphere is the polar headgroup and the hydrophobic tail is shown in gray. The components defining the packing parameter are indicated.

FIGURE 4.12 Lipid molecules of different shapes and packing parameters. The possible aggregate structures in different phases (micellar solutions and liquid crystalline phases) are shown to the left. A liquid crystalline phase has the properties of a liquid and at the same time shows a long-range order as in a crystal.

This simple approach is very useful for explaining the kind of shapes certain molecules assume. However, one has always to remember that the surface area might have a complex dependence on temperature, charge, and concentration, and more sophisticated considerations may be needed. For example, a change in...
Lamellar (membrane) phases have curvature. The molecular shape does not fully explain why a reversed hexagonal, H II, 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 (entropic) ($\pi > 0$)

![Diagram of lateral pressure profile in a lipid bilayer](image)

**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

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

The stored elastic energy of the lipid bilayer modifies the activity of curvature-sensitive enzymes through interaction with amphipathic α-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.

Figure 4.27: A cartoon of the fluid mosaic model of a biological membrane from 1972 according to Singer and Nicolson. The yellow transmembrane molecules represent cholesterol and the green parts sticking out into the solution represent sugar molecules. (Courtesy of Vanessa Kunkel.)
Basic classification scheme for membrane proteins

FIGURE 10.1 Different categories of membrane proteins.
What we knew 5-10 years ago

First crystallization of the photosynthetic reaction center from *Rhodopseudomonas viridis* — this soon turned out to be a very good move. Despite repeated failures to obtain diffraction by X-rays, Michel succeeded after having obtained better crystal forms by changing detergents and testing micelle modulating additives. In fact, most people at that time had considered his quest for a crystal structure of a membrane protein to be rather impossible. The atomic structure determination of the photosynthetic reaction center with all its ligands and metal centers revealed a new world of electron chains and transport pathways across the membrane and close interactions with lipid molecules — a gigantic achievement even by today’s standards — and Michel shared the Nobel prize with his colleagues Deisenhofer and Huber in 1988 (Fig. 10.3). Three-dimensional crystals of the *E. coli* outer membrane protein porin (later termed OmpF) diffracting X-rays at medium resolution had been reported already in 1980, but it was not until 1992 that the structure of OmpF was determined, showing 16 β-stands arranged in a large barrel embedded in the membrane as a very illustrative representation of a transmembrane pore (Fig. 10.4; see also Chap. 2 and App. C).

Lipid molecules surrounding the structure of bacteriorhodopsin. The structure gives a nearly complete view of the lipidation of a membrane protein and is a basis for understanding the complex nature of protein-lipid-water interfaces. The retinal molecule is shown in blue and the lipids are in yellow (carbon atoms) and red (oxygen atoms) (PDB: 1C3W, 1QJH).

FIGURE 10.6
The photosynthetic reaction center

The first membrane protein structures — bacteriorhodopsin (see Sec. 10.5.1), the photosynthetic reaction center (Fig. 10.3) and porin/OmpF (Fig. 10.4) — revealed that there are two fundamentally different classes of membrane proteins: α-helix and β-barrel proteins. These two frameworks fulfill a fundamental requirement: minimizing the energy cost of localization of protein structure to the hydrophobic environment of the membrane as compared to aqueous environments. The polypeptide backbone has a hydrogen-bonding potential at the carbonyl and amide positions. This potential is satisfied in a systematic way in the membrane by β-barrels or α-helices generating the hydrogen bonds through intramolecular interactions (see Chap. 2). At the same time, these two frameworks are very...
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FIGURE 10.7 Left: Schematic overview of transport mechanisms. Top: A primary transporter (a pump) establishes an electrochemical gradient for the red cation. Middle: A secondary transporter exploiting the electrochemical gradient for active symport of the yellow solute (e.g. other ions, metabolites, sugar, neurotransmitters). Bottom: A channel allowing for the downhill transport of the red cation with rates being limited by diffusion through the selectivity filter.

Right: The different principles of gated channels and an active transporter. The transporter (bottom) is represented as an inverted dimer, providing a simple basis for the design of inward and outward facing conformations. Combined with an energy source such as ATP hydrolysis or an electrochemical gradient, the transporter achieves a vectorial component. The kinetics of channels and transporters are typically very different — limited by diffusion rates versus large conformational changes, respectively.
Some nomenclature

- **Channels**
- **Transporters**
  - primary transporters (pumps) create gradients
  - secondary transporters use existing gradients
- **Coupled transport**
  - symporters take two species (often ions) in the same direction (sodium/glucose transport)
  - antiporters (exchangers) allow ions to exchange (e.g. sodium/calcium exchanger)
- **Signal transduction** (mostly G-protein coupled receptors)
β-barrel channels; porins

β-barrels are defined by “long-range” hydrogen bonds between individual strands that leave little room for conformational changes while keeping the hydrogen bonds intact; in contrast, α-helices form local \((n+4)\) hydrogen bonds that allow for conformational changes in the helix configurations across the membrane to be exploited (Fig. 10.5). Indeed, β-barrel proteins mostly serve as pores for passive transport across the membrane while more advanced transmembrane modules, like ion channels and transporters, are based on α-helical structures.

**FIGURE 10.4** The structure of the bacterial outer membrane protein porin, subsequently named OmpF, showing a transmembrane β-barrel structure (PDB: 2OMF).
The iron-citrate outer membrane transporter

**FIGURE 10.8** The *E. coli* FecA iron-citrate outer membrane transporter (PDB: 1KMO, 1PO3) is based on a 22-stranded \( \beta \)-barrel structure (cyan to red spectrum) with an N-terminal domain (blue) plugged in the middle of the barrel that acts as a gating domain for two citrate-chelated \( \text{Fe}^{3+} \) ions (white sticks and magenta spheres in the substrate-bound complex to the right).
α vs. β secondary structure in channels

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**FIGURE 10.5** ■ Left: A comparison of the hydrogen-bonding schemes of α-helical and β-barrel structures. Right: An illustration of the very different patterns of exposure of side chains to the lipid phase. The α- and β-structures are not drawn to scale. The α-helical structure represents a 21-residue transmembrane helix. (Figure courtesy of Dr. Maike Bublitz.)
The aquaporin channel

Predicted long ago and discovered in the early 1990s by Peter Agre. These channels are called aquaporins and are abundant proteins of many related types. Many cells have these membrane channels with specificity for water molecules. Within the family there are proteins that are also permeable to glycerol. Aquaporin solves a case of a difficult selectivity problem: how can the passage of small ions or protons be avoided while permitting water to pass?

The aquaporins are tetramers, where the pores go through each subunit. The protein is composed of six transmembrane helices and two shorter helices "meet" at the center of the membrane (Fig. 10.9). The N- and C-terminal halves seem to have originated through a gene duplication and are related by an approximate two-fold axis in the plane of the membrane. The channel has an hourglass structure with two vestibules connected by a 20 Å long channel, which at its narrowest point is no more than 2.8 Å wide. Water molecules have to travel through this channel in a single file. Two loops are symmetry-related and contain a highly conserved signature motif, NPA, which is situated at the channel with the two NPA sequences juxtaposed.

![Aquaporin tetramer](image)
The KcsA potassium channel

**FIGURE 10.10** The KcsA potassium channel. The tetramer as viewed from above (left) and from the side (right). The tetramer defines a selectivity filter and a central vestibule in the membrane stabilized by the dipoles of the helices forming the filter. Because of this, the effective transmembrane distance is significantly reduced. The conformation of the lower passage of the channel defines whether the gate is open or closed (PDB: 1K4C).
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FIGURE 10.11 The selectivity filter of KcsA at high potassium concentration. Only two subunits are drawn. A number of K⁺ ions (lilac) are filling the filter, but only every second position in the filter can be occupied by one ion at a time. Carbonyl oxygens are facing the channel and restricting the passage to ions of suitable size to match the coordination distances provided by the tetrameric arrangement of carbonyl groups at the filter. Below the filter, one ion is found in the vestibule, coordinated again by eight water molecules and stabilized by the negatively charged end of four helix dipoles (two of which are shown).
The leucine transporter

![Diagram of the leucine transporter](image)

**FIGURE 10.24** A possible mechanism for transport of leucine and two sodium ions by the symporter LeuT. At least three states are needed: Open to outside when leucine and sodium can be exchanged with the solvent outside the cell; Occluded state when the transported ions are enclosed in LeuT; Open to inside when leucine and sodium can be exchanged with the solvent inside the cell. TCA inhibitors lock the transporter in the occluded state (Adapted with permission from Singh SK, Yamashita A, Gouaux E. (2007) Antidepressant binding site in a bacterial homologue of neurotransmitter transporters. *Nature* 448: 952–956. Copyright (2007) Nature Publishing group).
FIGURE 10.17 ■ The structure of bacteriorhodopsin with arrows and side chain indicating the proton translocation pathway, coupled to the light-driven cis-trans isomerization of retinal coupled by a Schiff’s base link to the side chain amine of Lys216.
The first membrane protein structures — bacteriorhodopsin (see Sec. 10.5.1), the photosynthetic reaction center (Fig. 10.3) and porin/OmpF (Fig. 10.4) — revealed that there are two fundamentally different classes of membrane proteins: α-helix and β-barrel proteins. These two frameworks fulfill a fundamental requirement: minimizing the energy cost of localization of protein structure to the hydrophobic environment of the membrane as compared to aqueous environments. The polypeptide backbone has a hydrogen-bonding potential at the carbonyl and amide positions. This potential is satisfied in a systematic way in the membrane by β-barrels or α-helices generating the hydrogen bonds through intramolecular interactions (see Chap. 2). At the same time, these two frameworks are very...
The photosynthetic reaction center

Insight has been obtained on how the optimum wavelength for photoabsorption at the special pair is tuned (Fig. 10.19). By mutagenesis of the *R. viridis* photosynthetic reaction center on the L-chain His168 position to Phe, a significant blue-shift and increase in the initial electron transfer rate were observed. The His168 residue plays a pivotal role as hydrogen bond donor to the special pair, which then becomes stabilized in polarized forms. Replacing His for a Phe residue, the stabilization of a polarized form of the special pair is diminished, thus demanding a higher energy for excitation.

10.5.3 ATP-driven Pumps, P-ATPases

Cation pumps of the P-ATPase family form electrochemical gradients across biological membranes and maintain the homeostasis of cation levels and osmotic control in the cell. They transform chemical energy of ATP to electrochemical potential in the form of cation gradients and eventually membrane potential. Members include Na\(^{+}\)-ATPase, K\(^{+}\)-ATPase, H\(^{+}\)-K\(^{+}\)-ATPase, and Ca\(^{2+}\)-ATPases, which are all of key importance in physiology. It is worth noting that the P-type ATPases account for approximately one third of the ATP turnover in the body. However, plasma membranes of fungi and plants are also energized by a P-ATPase, the H\(^{+}\)-ATPase forming a strong potential and steep pH gradients that drive the uptake of nutrients from the acidified medium. Skou characterized the Na\(^{+}\)-K\(^{+}\)-ATPase as the first member.

**FIGURE 10.19** The special pair of the L-chain His168Phe mutant of the photosynthetic reaction center from *R. viridis* displays a significant blue-shift and increased initial electron transfer rate. His168 (position indicated by Phe168 in white stick) interacts with the special pair (green sticks with Mg\(^{2+}\) ions as cyan spheres). The Phe side chain will provide poor stabilization of the polarized special pair (PDB: 1XDR).
Getting more complex: photosystem I

Figure 10.18: Structure of photosystem 1 as seen from the thylakoid lumen onto the membrane (top) and from the side in the plane of the thylakoid membrane (bottom). This is only a monomer of the trimeric protein. There are 12 protein subunits, of which two (called A and B) have 11 membrane-spanning helices and form the core of the protein. The monomer binds 96 chlorophylls, three Fe4S4 iron-sulfur clusters, two phylloquinones, 22 carotenoids and four lipid molecules. The protein subunits are indicated by the white cartoon, and ligands by stick or sphere representation with chlorophylls in green (with Mg²⁺ ions in cyan), β-carotene in orange, lipids in yellow, phylloquinones in magenta, Fe₄S₄ clusters as orange and yellow spheres, and Ca²⁺ in blue. Note the pseudosymmetry around the special pair (center of top panel) and the involvement of deeply buried lipid molecules as cofactors. This structure represents the most complete view of a large antenna-system for direction of excited electrons to an electron transport chain providing charge separation and the establishment of potent redox equivalents (PDB: 1JB0).
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The mitochondrion

Diagram illustrating the electron transport chain and ATP synthesis within the mitochondrion. The diagram shows the outer and inner membranes, with components such as ATP synthase, NADH, O₂, H₂O, and various electron carriers like Cyt c and Fumarate. The process involves the transfer of electrons through a series of carrier proteins (I, II, III, IV) and the synthesis of ATP from ADP and Pi. The citric acid cycle is also depicted, connecting to the electron transport chain at different points.
Complex electron transport chains

**COMPLEX I**
NADH-CoQ oxidoreductase

**COMPLEX II**
succinate dehydrogenase

**COMPLEX III**
cytochrome bc₁ complex

**COMPLEX IV**
cytochrome c oxidase

NAD⁺, H⁺  →  NADH  →  succinate  →  fumarate  →  Q  →  cytochrome  →  H⁺, e⁻  →  O₂  →  H₂O