Cell Biology

Unit 2 · Lesson 1 · The fluid mosaic membrane

The notes for Lesson 1 of Unit 2: chapters 2.1 to 2.2 of the unit book, with their figures, worked examples, exam traps and quizzes, in one file. The full unit book, with every chapter, the exam question bank and the glossary, is linked at the end.

Lesson 1 of 3 | 2 chapters | Chapters 2.1 to 2.2

About these notes

These are the notes for **Lesson 1 · The fluid mosaic membrane** of the University free n easy video lessons on Cell Biology Unit 2, Membranes and Membrane Transport. They are chapters 2.1 to 2.2 of the unit book, unchanged, so a page here is the same page in the full book.

2.1 Plasma membrane structure: fluid mosaic model

The plasma membrane is a sheet of lipid two molecules thick, about 5 nm across, with proteins floating in it and sugar chains on its outer face. The fluid mosaic model, proposed by S. J. Singer and Garth Nicolson in 1972, says two things: the lipids form a fluid bilayer in which molecules move sideways freely ("fluid"), and proteins of many kinds sit in or on that bilayer like tiles in a moving floor ("mosaic"). Every transport process in this unit happens through this structure, so it is the picture to draw first in any membrane answer.

> You need: the idea of polar and non-polar molecules and the cell compartments from Unit 1, Overview of cell organelles and compartments.

From sandwich to mosaic: how the model was built

In the 1890s Charles Overton noticed that substances which dissolve in oil enter cells faster than those which do not. He concluded that the cell surface is made of lipid.

In 1925 Gorter and Grendel extracted the lipids from red blood cells and spread them as a single layer on water. The layer covered about twice the surface area of the cells. Their conclusion: the membrane is a lipid **bilayer**.

In 1935 Davson and Danielli proposed a "sandwich": a lipid bilayer coated on both faces by flat sheets of protein. In the late 1950s J. D. Robertson's electron micrographs showed membranes as two dark lines with a light band between (the trilaminar **unit membrane**).

The sandwich failed on three points: many membrane proteins are globular and partly hydrophobic, freeze-fracture electron microscopy showed protein particles inside the bilayer, and in 1970 Frye and Edidin fused a mouse cell with a human cell, labelled the two sets of surface proteins with different fluorescent antibodies, and watched the colours mix over the whole hybrid cell within an hour at 37 °C. Proteins were moving sideways. Singer and Nicolson put these facts together into the fluid mosaic model.

The parts of the model

The lipid bilayer. A membrane phospholipid is **amphipathic**: it has a polar (hydrophilic) head and two non-polar (hydrophobic) fatty acid tails. In water, the tails hide from water and the heads face it, so the molecules assemble on their own into two layers (leaflets) with tails meeting in the middle. This hydrophobic core, about 3 nm thick, is the barrier to ions and large polar molecules. A bilayer also closes on itself to avoid exposed edges, so membranes always form sealed compartments.

Proteins. Integral proteins are embedded in the bilayer; most cross it completely (transmembrane proteins). **Peripheral proteins** sit on one face, held by ionic bonds and hydrogen bonds to the heads or to integral proteins. Proteins make up roughly half the mass of a typical plasma membrane (Alberts gives lipid as about 50% of the mass of most animal cell membranes). Their types are the subject of chapter 2.2.

Carbohydrates. Short sugar chains are attached to proteins (glycoproteins) and lipids (glycolipids) on the **outer face only**. Together they form the **glycocalyx**, a sugar coat used in cell recognition, for example the ABO blood group antigens on red cells.

Cholesterol. In animal plasma membranes cholesterol sits between the phospholipids, its small hydroxyl head at the surface and its rigid ring system among the tails. Alberts notes that eukaryotic plasma membranes can hold up to one cholesterol per phospholipid.

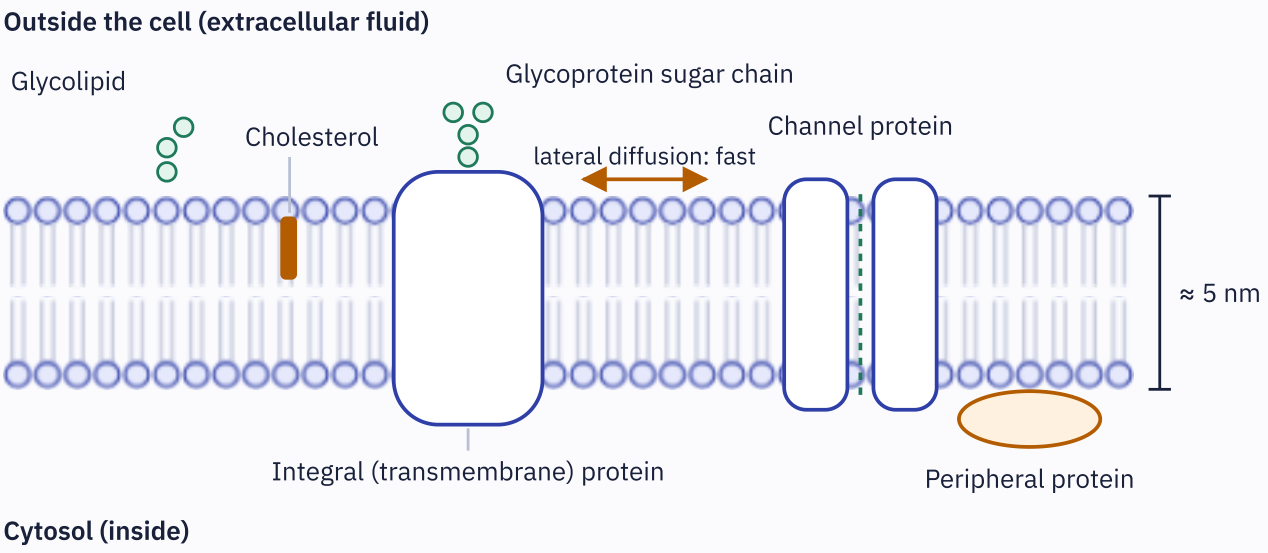


Figure 2.1.1 The fluid mosaic model. Blue circles are polar heads and grey lines are fatty acid tails; the tails form the hydrophobic core. Notice that sugar chains (green) are only on the outside, the peripheral protein sits only on the cytosolic face, and the integral and channel proteins cross the whole bilayer. Lipids and many proteins drift sideways within their own leaflet.

Fluidity and what controls it

The bilayer behaves like a two-dimensional liquid. A lipid swaps places with its neighbours about 10^7 times per second and has a lateral diffusion coefficient D of about 10^{-8} cm²/s (that is, 1 μm²/s). In contrast, **flip-flop**, the movement of a lipid from one leaflet to the other, is rare: for a given phospholipid it happens less than once a month unless an enzyme helps (Alberts). The polar head would have to pass through the oily core, which costs too much energy.

Four factors set fluidity:

1. **Temperature.** Cooling below a transition temperature makes the bilayer go from a fluid state to a rigid, crystal-like gel state.
2. **Unsaturation.** A cis double bond puts a kink in a tail, so tails pack loosely and the membrane stays fluid at lower temperature.
3. **Tail length.** Shorter tails have fewer contacts with each other, so they increase fluidity.
4. **Cholesterol.** It acts as a fluidity buffer. At body temperature its rigid rings restrain the tails and make the bilayer less fluid and less permeable to small water-soluble molecules. At low temperature it keeps the tails from packing into a gel.

Cells adjust these settings. Bacteria and fish grown in the cold make more unsaturated fatty acids, keeping their membranes fluid (homeoviscous adaptation). Many membrane proteins stop working when a membrane gels, so fluidity is not optional.

The modern view

The model is still correct in outline, with three refinements. The membrane is **asymmetric**: the two leaflets carry different lipids and proteins face one way only (chapter 2.2). Proteins are not all free: many are tethered to the cytoskeleton beneath or to the extracellular matrix, or fenced into regions such as the apical and basolateral faces of a gut epithelial cell. And cholesterol with sphingolipids can gather into small, short-lived ordered patches called **lipid rafts**.

WORKED EXAMPLE

Question. (a) The lipids extracted from 1.0×10^9 red blood cells are spread as a monolayer on water and cover 0.20 m². The surface area of one red cell is taken as 100 μm². What does this tell you about the membrane? (b) A lipid in a bilayer has D = 1 μm²/s. Using the two-dimensional diffusion relation $\langle r^2 \rangle = 4Dt$, how long does it take to travel 2 μm, the length of a bacterium? 6 marks

1. Total cell surface = $1.0 \times 10^9 \times 100$ μm² = 1.0×10^{11} μm².
2. Convert: 1 m² = 10^{12} μm², so 1.0×10^{11} μm² = 0.10 m².
3. Ratio = monolayer area / cell surface = 0.20 m² / 0.10 m² = 2.0.
4. Conclusion (a): there is enough lipid for exactly two layers over the cell surface, so the membrane is a lipid bilayer. This is the logic of Gorter and Grendel.
5. (b) Here r is the distance moved, t the time, D the diffusion coefficient. Rearranging, $t = r^2 / 4D = (2\ \mu m)^2 / (4 \times 1\ \mu m^2/s) = 4 / 4$ s = 1 s.
6. Conclusion (b): a lipid can cross a whole bacterium in about one second, which shows how fluid the bilayer is.

EXAM TRAPS

- "Fluid" refers to sideways movement within a leaflet. Flip-flop between leaflets is slow; do not write that lipids move freely between the two layers.
- Carbohydrate is only on the extracellular (non-cytosolic) face. A diagram with sugar chains facing the cytosol loses marks.
- Cholesterol does not simply "increase fluidity". It reduces fluidity at high temperature and prevents gelling at low temperature.
- Davson–Danielli is the protein–lipid–protein sandwich; Singer–Nicolson (1972) is the fluid mosaic. Examiners ask you to compare them.
- The favourite question: "Describe the fluid mosaic model with a neat labelled diagram, and give the evidence for it." Draw Figure 2.1.1 and quote the Frye–Edidin experiment.

CHECK YOURSELF

– REMEMBER **Who proposed the fluid mosaic model, and when?** 1 mark

S. J. Singer and G. L. Nicolson, in 1972.

– REMEMBER **Name the three kinds of molecule in a plasma membrane.** 2 marks

Lipids (phospholipids, cholesterol, glycolipids), proteins (integral and peripheral) and carbohydrates (as glycoproteins and glycolipids).

– UNDERSTAND **Why does a phospholipid bilayer form on its own in water?** 3 marks

Phospholipids are amphipathic. The hydrophobic tails are pushed together away from water (the hydrophobic effect) while the polar heads face water on both sides. Two leaflets tail to tail is the lowest-energy arrangement, and the sheet closes into a sealed compartment to avoid exposed edges.

– UNDERSTAND **How did the Frye–Edidin experiment support the fluid mosaic model?** 3 marks

Mouse and human cells were fused, and their surface proteins were tagged with two different fluorescent labels. Within about an hour at 37 °C the labels were mixed over the whole hybrid cell, showing that membrane proteins move sideways in a fluid bilayer. Mixing was blocked at low temperature.

– APPLY **How long does a lipid with D = 1 μm²/s take to move 6 μm by 2-D diffusion?** 2 marks

$t = r^2 / 4D = 36 / 4 =$ **9 s**. Note that tripling the distance multiplies the time by nine.

– APPLY **A bacterium is moved from 37 °C to 20 °C. Predict the change in its membrane lipids.** 2 marks

It makes more unsaturated (kinked) and shorter fatty acid tails so the membrane stays fluid at the lower temperature.

– ANALYZE **Give two observations the Davson–Danielli sandwich model cannot explain.** 4 marks

Freeze-fracture shows protein particles inside the bilayer, not only on its faces; many membrane proteins are hydrophobic and globular and could not lie on a water-facing surface; and proteins diffuse sideways (Frye–Edidin), which a fixed protein coat would not allow.

BEYOND THE SYLLABUS

This is not for the exam. Researchers now study membranes with cryo-electron microscopy, super-resolution fluorescence and molecular dynamics computer simulations that follow every lipid. Artificial bilayers are a technology in themselves: liposomes carry drugs, and the lipid nanoparticles that deliver mRNA vaccines are built on the same self-assembly you met here. Search next for "lipid nanoparticles mRNA", "FRAP fluorescence recovery after photobleaching" and "lipid rafts debate".

2.2 Membrane proteins and lipids

The bilayer of chapter 2.1 is built from three families of lipid, and its work is done by proteins attached to it in six distinct ways. Lipids set the barrier and its fluidity; proteins carry out transport, signalling, enzyme reactions and anchoring. Others cover it under "membrane structure".

The lipids and their asymmetry

- **Phosphoglycerides**: glycerol carrying two fatty acids and a phosphate-linked head. The main ones are phosphatidylcholine (PC), phosphatidylethanolamine (PE), phosphatidylserine (PS, negatively charged) and phosphatidylinositol (PI).
- **Sphingolipids**: built on sphingosine instead of glycerol. Sphingomyelin carries a phosphocholine head; glycolipids carry sugars (gangliosides carry sialic acid and are common in nerve cell membranes).

- **Sterols**: cholesterol in animals; plants use related phytosterols, and bacteria generally lack sterols.

The two leaflets differ. In the human red cell, the outer leaflet holds nearly all the PC, sphingomyelin and glycolipids, while the inner leaflet holds nearly all the PE and PS (Alberts). Enzymes keep it so: **flippases** use ATP to move PS and PE to the cytosolic leaflet, and **scramblases** mix the leaflets when activated. Asymmetry carries information: when a cell dies by apoptosis, PS appears on the outer face and acts as an "eat me" signal to macrophages (see Unit 4, Apoptosis), and inositol phospholipids on the inner face are raw material for second messengers (Unit 5).

Six ways a protein meets the bilayer

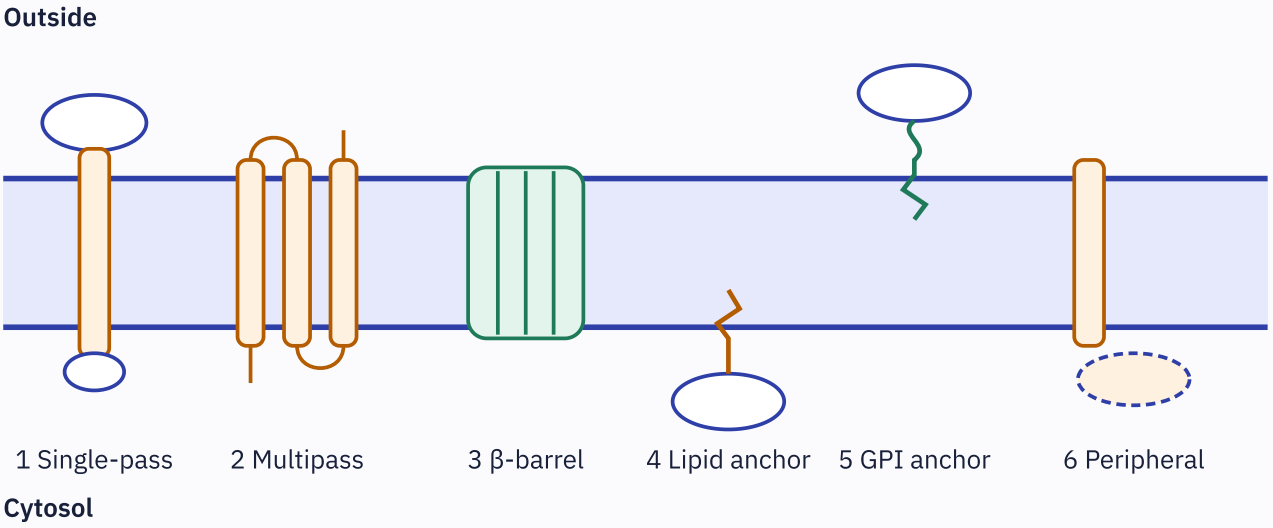


Figure 2.2.1 Orange bars are α-helices crossing the hydrophobic core; the green barrel is a rolled β-sheet. Types 1 to 3 are transmembrane (integral). Type 4 hangs on the cytosolic face by a fatty acid or prenyl chain, type 5 on the outer face by a GPI glycolipid. Type 6 (dashed) binds non-covalently to another protein and comes off with salt.

1. **Single-pass**: one α-helix of about 20 hydrophobic amino acids crosses the core. Example: glycophorin of the red cell.
2. **Multipass**: several helices, joined by loops. Most transporters and receptors are multipass; band 3 (the red cell Cl^-/HCO_3^- exchanger) and the seven-helix bacteriorhodopsin are examples.
3. **β-barrel**: a β-sheet rolled into a tube. Porins of the outer membranes of Gram-negative bacteria, mitochondria and chloroplasts are of this kind.
4. **Lipid-anchored on the cytosolic face**: a myristoyl, palmitoyl or prenyl chain is covalently attached. Ras (Unit 4) is held this way.

5. **GPI-anchored on the outer face**: attached to a glycosylphosphatidylinositol lipid; the enzyme phospholipase C can cut it free.
6. **Peripheral**: bound by ionic and hydrogen bonds to heads or to integral proteins. Spectrin, the network under the red cell membrane, is the classic case.

Integral proteins are removed only by **detergents** that dissolve the bilayer (SDS, which denatures, or the milder Triton X-100); peripheral proteins come off with high salt or a change of pH, leaving the membrane intact. This is the working definition of the two classes.

WORKED EXAMPLE

Question. An α-helix rises 0.15 nm per amino acid. The hydrophobic core of a bilayer is 3.0 nm thick. (a) How many residues are needed to span it? (b) A hydropathy plot of a new protein shows four stretches of hydrophobic residues of length 21, 8, 22 and 20. How many transmembrane helices does it probably have? `4 marks`

1. (a) Residues = core thickness / rise per residue = 3.0 nm / 0.15 nm = **20 residues**.
2. (b) A stretch must be about 20 hydrophobic residues to cross the core. The stretches of 21, 22 and 20 qualify; the 8-residue stretch (8 × 0.15 = 1.2 nm) is too short.
3. Conclusion: probably **three** transmembrane helices, so a multipass protein.

EXAM TRAPS

- "Integral" means needs detergent to remove; it is not the same as "transmembrane". A lipid-anchored protein is integral by some books and peripheral by others; say which definition you use.
- GPI anchors are on the outer face; myristoyl and prenyl anchors are on the cytosolic face.
- PS and PE are inner-leaflet lipids; glycolipids are outer only.
- Examiners like: "Classify membrane proteins by their mode of association with a labelled diagram."

CHECK YOURSELF

– `REMEMBER` **Name the three main classes of membrane lipid.** `1 mark`

Phosphoglycerides, sphingolipids and sterols.

– REMEMBER **Which lipids are mainly in the cytosolic leaflet of a red cell?** 1 mark

Phosphatidylethanolamine and phosphatidylserine.

– UNDERSTAND **Why does a transmembrane segment need to be hydrophobic?** 2 marks

It lies in the oily core of the bilayer. Hydrophobic side chains interact well with fatty acid tails; polar or charged groups there would cost a large amount of energy.

– APPLY **A protein is released from membranes by 1 M NaCl. Classify it.** 2 marks

Peripheral: salt breaks the ionic bonds that hold it, without dissolving the bilayer.

– ANALYZE **Why is PS appearing on the outer leaflet a useful death signal?** 3 marks

Living cells use flippases to keep PS inside, so outer PS is normally absent. In apoptosis the flippase stops and a scramblase acts, exposing PS; macrophage receptors recognise it, so dying cells are eaten before they burst and cause inflammation.

BEYOND THE SYLLABUS

This is not for the exam. Roughly a quarter to a third of human genes are commonly estimated to code for membrane proteins, and a large share of drug targets are membrane proteins. Their structures are now solved by cryo-EM in detergent micelles or lipid nanodiscs, and AlphaFold predicts transmembrane topology. Search next for "nanodisc membrane protein" and "TMHMM topology prediction".

Key terms of this lesson

TERM	MEANING OR FORMULA	CHAPTER
Fluid mosaic model	Fluid lipid bilayer with proteins embedded in or attached to it; Singer and Nicolson, 1972	2.1
2-D diffusion	$\langle r^2 \rangle = 4Dt$; lipid $D \approx 1\ \mu m^2/s$	2.1
Integral vs peripheral	Removed only by detergent vs removed by salt or pH change	2.2

Glossary (terms used in this lesson)

Amphipathic	Having both a water-loving (polar) part and a water-avoiding (non-polar) part, like a phospholipid.
Flip-flop	Movement of a lipid from one leaflet of the bilayer to the other; rare without enzymes.
Flippase	ATP-using enzyme that moves specific lipids (PS, PE) to the cytosolic leaflet.
Glycocalyx	Sugar coat on the outer cell surface formed by glycoproteins and glycolipids.
Integral protein	Membrane protein that can be removed only by dissolving the bilayer with detergent.
Peripheral protein	Protein bound to a membrane surface by non-covalent bonds; removable by salt or pH.

The full unit book

Every chapter of Unit 2, the unit summary, the exam question bank with model answers and the full glossary: Cell Biology · Unit 2 · Membranes and Membrane Transport (one file, works offline).

Sources and further reading

- B. Alberts, A. Johnson, J. Lewis and others, *Molecular Biology of the Cell*, Garland Science; chapters on membrane structure and membrane transport. The 4th edition (2002) is free to read on NCBI Bookshelf; values quoted in this book from Alberts were checked there.
- H. Lodish, A. Berk and others, *Molecular Cell Biology*, W. H. Freeman; chapters on biomembranes and transmembrane transport (from memory; check the transport-rate figures against your edition).
- G. Karp, *Cell and Molecular Biology: Concepts and Experiments*, Wiley; chapter on the plasma membrane (from memory; check).
- G. M. Cooper, *The Cell: A Molecular Approach*, Sinauer; chapter on the plasma membrane (from memory; check).
- S. J. Singer and G. L. Nicolson, "The fluid mosaic model of the structure of cell membranes", *Science*, 1972 (from memory; check).
- Alberts et al., *Molecular Biology of the Cell*, 4th ed., "The Lipid Bilayer", NCBI Bookshelf: https://www.ncbi.nlm.nih.gov/books/NBK26871/ (opened; lipid diffusion, flip-flop, cholesterol and asymmetry figures).

- Alberts et al., *Molecular Biology of the Cell*, 4th ed., "Carrier Proteins and Active Membrane Transport", NCBI Bookshelf: https://www.ncbi.nlm.nih.gov/books/NBK26896/ (opened; Na^+/K^+ pump stoichiometry and energy share, P-type and ABC pumps, Ca^{2+} levels).

Syllabus: the University free n easy universal syllabus, built from top universities' syllabi.

Built for the University free n easy YouTube channel from the universal syllabus of Cell Biology (Oct 2026). Written with top universities' syllabi and standard textbooks; check a formula against your prescribed book before an exam, and report mistakes on the channel.