# Cell Biology

**Unit 2 · Lesson 2 · Downhill free, uphill paid**

The notes for Lesson 2 of Unit 2: chapters 2.3 to 2.4 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 2 of 3 | 2 chapters | Chapters 2.3 to 2.4

## About these notes

These are the notes for **Lesson 2 · Downhill free, uphill paid** of the University free n easy video lessons on Cell Biology Unit 2, Membranes and Membrane Transport. They are chapters 2.3 to 2.4 of the unit book, unchanged, so a page here is the same page in the full book.

## 2.3 Passive transport: simple and facilitated diffusion, osmosis

Passive transport is any movement across a membrane that runs downhill, from where a substance is more concentrated to where it is less, so it needs no ATP. Small non-polar molecules slip straight through the bilayer (simple diffusion). Glucose, ions and most nutrients need a protein door (facilitated diffusion). Water moves by osmosis, mostly through water channels. These three explain how oxygen reaches mitochondria, how glucose enters a red cell, and why a red cell bursts in pure water.

> You need: the bilayer and its hydrophobic core from chapter 2.1.

### Simple diffusion through the bilayer

Molecules move at random. Where there are more of them on one side, more cross from that side per second, so the net flow is down the concentration gradient. **Fick's first law** describes it:

```
J = −D (dC/dx)
```

Here J is the flux (amount crossing unit area per second), D the diffusion coefficient, C the concentration and x the distance. The minus sign says flow goes from high to low C. For a

membrane of thickness x it becomes $J = P (C_1 - C_2)$, where $C_1$ and $C_2$ are the concentrations on the two sides and P is the **permeability coefficient** (units cm/s). P is larger when the molecule dissolves well in lipid (a high oil–water partition coefficient K) and when the membrane is thin: $P = K D / x$.

So the bilayer sorts molecules by size and polarity. Small non-polar gases ($O_2$, $CO_2$, $N_2$) and lipid-soluble drugs and steroid hormones cross fast. Small uncharged polar molecules (water, urea, ethanol, glycerol) cross slowly. Large polar molecules (glucose, amino acids) hardly cross. Ions ($Na^+$, $K^+$, $Cl^-$) are almost stopped, because a charge carries a shell of water that would have to be stripped off to enter the oily core.

Simple diffusion has three signatures: rate rises in a straight line with the concentration difference, it never saturates, and it has no specificity (no protein, so no binding site to compete for).

## Facilitated diffusion: channels and permeases

Molecules the bilayer blocks cross passively through transport proteins. There are two kinds:

- **Carrier proteins** (also called **transporters** or **permeases**. The binding site is open to one side at a time, the **alternating access** mechanism. The glucose transporter GLUT1 of red cells is the textbook example. A carrier that moves one solute on its own is a uniporter (chapter 2.5).
- **Channel proteins** form a water-filled pore that is open to both sides at once when it is open. They select by size and charge and are much faster than carriers (chapter 2.6).

Facilitated diffusion is still passive: the direction is always down the gradient, and it stops when concentrations are equal (for an uncharged solute). The protein only lowers the barrier. Because a carrier has a limited number of binding sites, its rate follows the same curve as an enzyme:

```
v = Vmax [S] / (Km + [S])
```

Here v is the rate of transport, [S] the solute concentration, Vmax the maximum rate when every carrier is busy, and Km the concentration that gives half of Vmax (a low Km means high affinity). The carrier also shows **specificity** (GLUT1 carries D-glucose but not its mirror image L-glucose) and **competitive inhibition** by similar molecules.

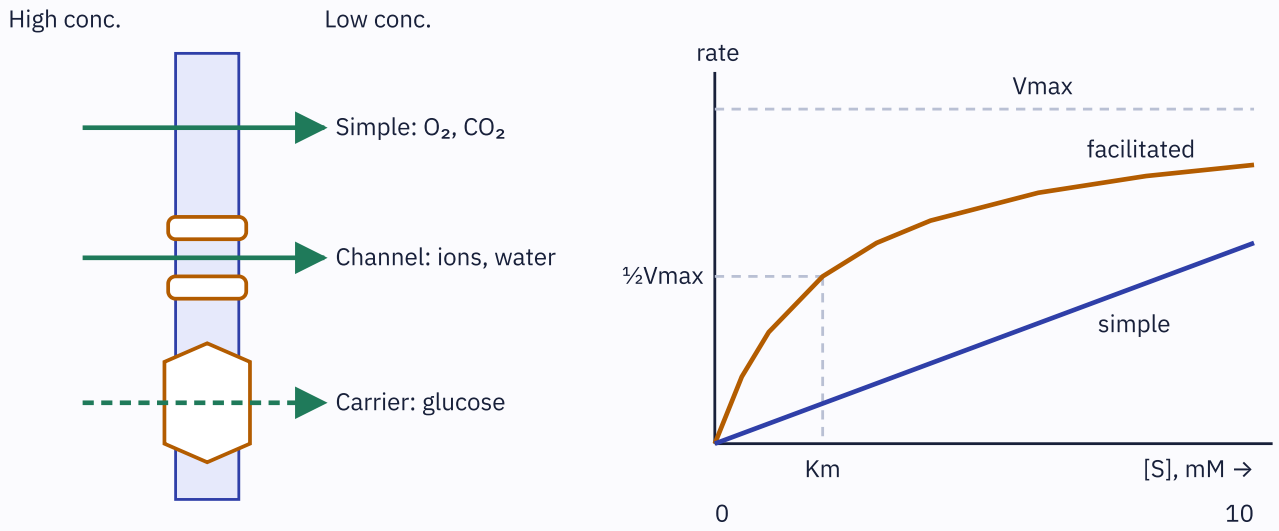



**Figure 2.3.1** Left: the three passive routes, all running from high to low concentration. Right: rate against concentration, plotted from v = 100[S]/(2 + [S]) for a carrier (orange; Km = 2 mM) and v = 6[S] for simple diffusion (blue). Notice that the carrier is faster at low concentration but levels off at Vmax, while simple diffusion never saturates.

## Osmosis

**Osmosis** is the net movement of water across a selectively permeable membrane from the side with lower solute concentration to the side with higher solute concentration. Water itself moves down its own concentration gradient. Some water diffuses through the bilayer, but most crosses through **aquaporins**, water channels discovered by Peter Agre (Nobel Prize in Chemistry, 2003). Kidney tubules and red cells are rich in them.

The pressure that would have to be applied to stop water entering is the **osmotic pressure**, π. For dilute solutions, the van 't Hoff equation gives:

```
π = i C R T
```

Here i is the number of particles each formula unit gives in solution (about 2 for NaCl, 1 for glucose), C the molar concentration, R the gas constant (0.0821 L·atm·mol⁻¹·K⁻¹) and T the absolute temperature. The product iC is the **osmolarity**.

**Tonicity** describes what a solution does to a cell, and it depends only on solutes that cannot cross the membrane:

- **Isotonic**: no net water flow; the cell keeps its volume (0.9% NaCl for human cells).
- **Hypotonic**: water enters. An animal cell swells and may burst (a red cell bursting is **haemolysis**). A plant cell swells against its wall and becomes **turgid**, which keeps leaves firm.

- **Hypertonic**: water leaves. A red cell shrinks and becomes spiky (**crenation**). In a plant cell the membrane pulls away from the wall (**plasmolysis**); this is why salted mango pickle draws water out of the fruit.

### WORKED EXAMPLE 1

**Question.** Calculate the osmolarity and osmotic pressure of normal saline (0.9% w/v NaCl) at body temperature, 37 °C. Molar mass of NaCl = 58.44 g/mol; take i = 2. `4 marks`

1. 0.9% w/v means 0.9 g per 100 mL, that is 9 g/L.
2. Molarity C = 9 g/L ÷ 58.44 g/mol = 0.154 mol/L.
3. Osmolarity = iC = 2 × 0.154 = 0.308 osmol/L, about 308 mOsm/L, close to that of blood plasma, which is why this saline is isotonic.
4. T = 37 + 273 = 310 K.
5. π = iCRT = 0.308 × 0.0821 × 310 = **7.84 atm**.

### WORKED EXAMPLE 2

**Question.** A glucose carrier has Km = 2 mM and Vmax = 100 µmol per minute per gram of cells. Find the rate at 1 mM and at 10 mM glucose. Why does a tenfold rise in glucose not give a tenfold rise in rate? `4 marks`

1. At 1 mM: v = 100 × 1 / (2 + 1) = 33.3 µmol/min/g.
2. At 10 mM: v = 100 × 10 / (2 + 10) = 83.3 µmol/min/g.
3. Ratio = 83.3 / 33.3 = 2.5, not 10.
4. Reason: at 10 mM most carriers are already occupied, so the rate approaches Vmax. Saturation is the mark of carrier-mediated transport.

## EXAM TRAPS

- Facilitated diffusion uses a protein but no energy. Do not call it active because a protein is involved.
- In osmosis water moves towards the *higher* solute concentration. Writing "from high to low concentration" without saying of what is a common lost mark.
- Osmolarity counts particles: 0.1 M NaCl is about 0.2 osmol/L, 0.1 M glucose is 0.1 osmol/L.
- Tonicity is not the same as osmolarity. A solute that enters the cell (urea) does not hold water out, so an iso-osmotic urea solution is hypotonic.
- Remember to convert °C to kelvin in π = iCRT.

## CHECK YOURSELF

– REMEMBER **State Fick's first law.** 1 mark

J = −D (dC/dx): flux is proportional to the concentration gradient, from high to low concentration.

– REMEMBER **What are aquaporins?** 1 mark

Channel proteins that let water cross the membrane rapidly; discovered by Peter Agre.

– UNDERSTAND **List three differences between simple and facilitated diffusion.** 3 marks

Facilitated diffusion uses a protein, simple does not; facilitated saturates (Vmax, Km), simple is linear; facilitated is specific and can be competitively inhibited, simple is not.

– UNDERSTAND **Why do ions not cross a pure lipid bilayer?** 2 marks

An ion is surrounded by a hydration shell; entering the non-polar core would mean stripping that water off, which costs a great deal of energy.

– APPLY **Find π for 0.30 M glucose at 27 °C.** 2 marks

i = 1, T = 300 K: π = 0.30 × 0.0821 × 300 = **7.39 atm**.

– APPLY **For a carrier with Km = 2 mM, at what concentration is the rate 80% of Vmax?** 2 marks

0.8 = S/(2 + S), so 0.8 × 2 = 0.2S, giving S = **8 mM**.

– ANALYZE **Red cells are put in 0.3 M sucrose and in 0.3 M urea. Predict and explain the result in each.** 4 marks

Both are close to the cell's osmolarity. Sucrose cannot cross, so it is isotonic and the cells keep their shape. Urea crosses the membrane; as it enters, water follows, so the cells swell and haemolyse: 0.3 M urea is iso-osmotic but hypotonic.

**BEYOND THE SYLLABUS**

This is not for the exam. Drug designers use permeability rules (small, not too polar, not too many hydrogen-bond donors) to predict which molecules can be taken as tablets, and screen compounds through artificial membranes in the PAMPA assay. Reverse osmosis, used in Indian household RO water purifiers and in desalination plants such as those near Chennai, pushes water against its osmotic pressure through a polymer membrane. Aquaporin-embedded membranes are being tested for water treatment. Search next for "Lipinski rule of five" and "aquaporin biomimetic membranes".

## 2.4 Active transport: primary and secondary; ATP pumps

Active transport moves a solute uphill, against its concentration or electrochemical gradient, so it needs an energy source. In **primary** active transport a pump spends ATP directly; the $Na^+/K^+$-ATPase is the model. In **secondary** active transport a carrier spends the energy stored in an ion gradient that a primary pump built, as when your intestine absorbs glucose together with $Na^+$. Every animal cell runs on this pair: pumps build gradients, and the gradients power the rest.

You need: passive transport and carrier kinetics from chapter 2.3.

### Gradients and the energy to climb them

For a charged solute, two forces act: the concentration difference and the membrane voltage. Together they form the **electrochemical gradient**. The free-energy change for moving one mole of an ion into the cell is:

```
ΔG(in) = R T ln(C_in / C_out) + z F Vm
```

Here R = 8.314 J·mol$^{-1}$·K$^{-1}$ is the gas constant, T the absolute temperature, C_in and C_out the concentrations inside and outside, z the charge of the ion (+1 for $Na^+$, +2 for $Ca^{2+}$), F = 96 485 C/mol the Faraday constant, and Vm the membrane potential (inside minus outside, about −70 mV in many animal cells). If ΔG is negative the move is downhill and can be passive; if positive it must be driven.

A typical mammalian cell keeps (Alberts' standard values): $Na^+$ about 5–15 mM inside and 145 mM outside; $K^+$ about 140 mM inside and 5 mM outside; free $Ca^{2+}$ about $10^{-4}$ mM ($10^{-7}$ M) inside and 1–2 mM outside.

## The ATP pumps

| CLASS | HOW IT WORKS | EXAMPLES |
|---|---|---|
| P-type | Phosphorylates itself on an aspartate residue in every cycle; the phosphate switches its shape | $Na^+/K^+$-ATPase; $Ca^{2+}$-ATPases (SERCA of the sarcoplasmic reticulum, PMCA of the plasma membrane); gastric $H^+/K^+$-ATPase |
| V-type | Rotary pump; moves $H^+$ only, no phosphorylated intermediate | Acidifies lysosomes, endosomes and plant vacuoles |
| F-type | Rotary; related to V-type but normally runs backwards, using an $H^+$ gradient to make ATP | ATP synthase of mitochondria, chloroplasts, bacteria (Unit 3) |
| ABC transporters | Two ATP-binding cassettes; ATP binding brings them together, hydrolysis separates them | Multidrug resistance pump MDR1 (P-glycoprotein); CFTR, which acts as a $Cl^-$ channel |

## The $Na^+/K^+$-ATPase

Discovered by Jens Skou (Nobel Prize in Chemistry, 1997), this P-type pump moves **3 $Na^+$ out and 2 $K^+$ in for each ATP** hydrolysed. Its cycle has two shapes, E1 (sites face the cytosol, high affinity for $Na^+$) and E2 (sites face outside, high affinity for $K^+$):

1. In the E1 form, 3 $Na^+$ bind from the cytosol.
2. ATP transfers its terminal phosphate to an aspartate on the pump; ADP leaves.
3. Phosphorylation flips the pump to E2; the $Na^+$ sites open outward and lose affinity, so 3 $Na^+$ are released outside.
4. 2 $K^+$ bind from outside.
5. The aspartyl phosphate is hydrolysed and Pi leaves.
6. The pump returns to E1 and releases 2 $K^+$ into the cytosol.

Because 3 positive charges go out and only 2 come in, the pump is **electrogenic**; it adds a little directly to the negative inside voltage, though most of the resting potential comes from $K^+$ leaking out through channels (chapter 2.6). The pump has three jobs: it keeps the $Na^+$ and $K^+$ gradients; it controls cell volume, because by keeping $Na^+$ out it balances the many impermeant molecules inside that would otherwise draw water in until the cell burst; and it supplies the $Na^+$ gradient for secondary transport. Alberts estimates that it uses almost a third of a typical animal cell's energy, and close to two-thirds in nerve cells. **Ouabain** and **digoxin** (cardiac glycosides, from plants) block it from the outside.

## $Ca^{2+}$ and $H^+$ pumps

$Ca^{2+}$ is a signal (Unit 5), so its cytosolic level is kept about ten thousand times lower than outside. The plasma membrane $Ca^{2+}$-ATPase pumps it out, and SERCA pumps it into the sarcoplasmic reticulum of muscle, where it is stored for the next contraction; Alberts notes that this pump makes up about 90% of the membrane protein of that organelle. In the stomach, the $H^+/K^+$-ATPase of parietal cells pumps $H^+$ into the gastric lumen in exchange for $K^+$, making the acid of gastric juice. Proton pump inhibitors such as omeprazole, common acidity drugs in India, block it.

## Secondary active transport

$Na^+$ outside "wants" to come in: both its concentration gradient and the negative inside pull it. A secondary carrier lets $Na^+$ in only if it brings another solute with it, or sends one out. The energy of $Na^+$ running downhill pays for the second solute running uphill. If the pump stops, secondary transport stops too.

- **SGLT1** (sodium–glucose linked transporter) on the gut-facing side of intestinal cells moves 2 $Na^+$ and 1 glucose in together. Glucose is concentrated inside, then leaves the other face of the cell passively through GLUT2.
- **$Na^+/Ca^{2+}$ exchanger** (NCX) of heart muscle lets 3 $Na^+$ in and sends 1 $Ca^{2+}$ out.
- In bacteria and plants the driving ion is usually $H^+$, not $Na^+$; the *E. coli* lactose permease brings in lactose with $H^+$.

The direction rules (uniport, symport, antiport) and the stoichiometry calculation are in chapter 2.5.

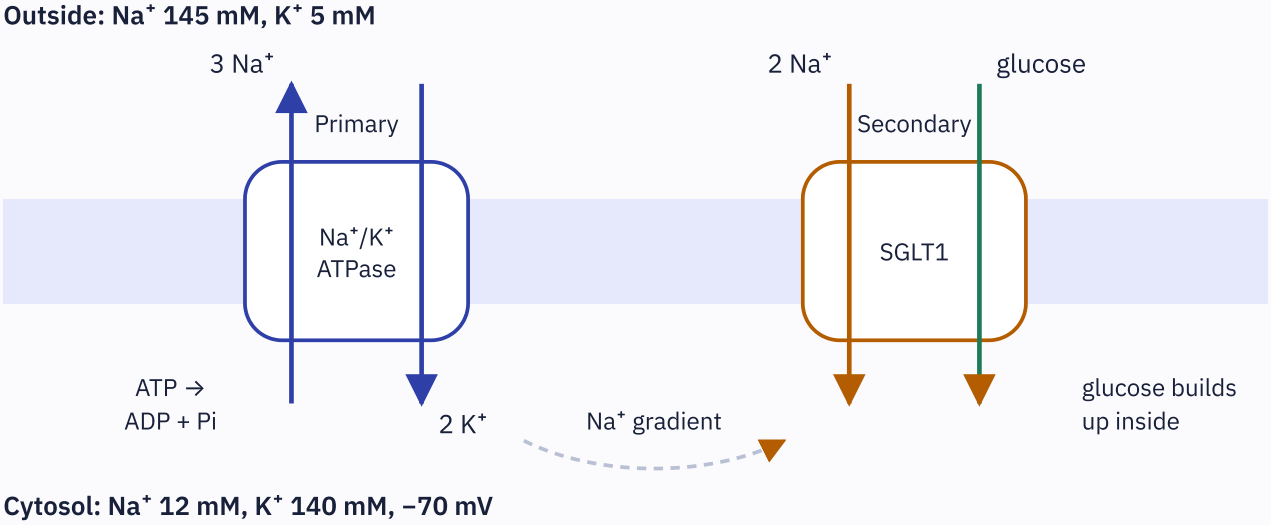



**Figure 2.4.1** The pump (left) spends ATP to push $Na^+$ out and $K^+$ in, against both gradients. The symporter (right) uses no ATP: $Na^+$ flowing back in, down its gradient, drags glucose in against its gradient. The dashed arrow is the energy link: no pump, no gradient, no glucose uptake.

### WORKED EXAMPLE

**Question.** Using $Na^+$ 12 mM inside and 145 mM outside, $K^+$ 140 mM inside and 5 mM outside, Vm = −70 mV and T = 310 K, find the free energy needed for one cycle of the $Na^+/K^+$-ATPase. Can the hydrolysis of one ATP, taken as −50 kJ/mol under cell conditions, pay for it? `8 marks`

1. RT = 8.314 × 310 = 2577 J/mol. zFVm for a +1 ion = 96 485 × (−0.070) = −6754 J/mol.
2. $Na^+$ moving *in*: ΔG = 2577 × ln(12/145) − 6754 = 2577 × (−2.492) − 6754 = −6422 − 6754 = −13 176 J/mol. Entry is downhill.
3. So moving $Na^+$ *out* costs +13.18 kJ/mol; for 3 $Na^+$: 3 × 13.18 = +39.5 kJ.
4. $K^+$ moving *in*: ΔG = 2577 × ln(140/5) − 6754 = 2577 × 3.332 − 6754 = 8588 − 6754 = +1834 J/mol. The voltage helps, but the concentration gradient wins, so it is slightly uphill. For 2 $K^+$: +3.7 kJ.
5. Total per cycle = 39.5 + 3.7 = **+43.2 kJ/mol**.
6. ATP supplies about 50 kJ/mol, more than 43.2, so one ATP per cycle is enough.

## EXAM TRAPS

- The ratio is 3 $Na^+$ out : 2 $K^+$ in : 1 ATP. Swapping the 3 and 2, or the directions, is the commonest slip.
- Secondary active transport does use energy, from an ion gradient, not from ATP directly. Do not call it passive.
- F-type ATP synthase normally makes ATP; it is listed among pumps because it can run in reverse.
- Vm is inside minus outside, so it is negative. A wrong sign in zFVm changes the answer completely.
- The favourite question: "Explain the mechanism of the $Na^+/K^+$ pump with a neat diagram and state its significance."

## CHECK YOURSELF

– REMEMBER **Name the four classes of ATP-powered pumps.** 2 marks

P-type, V-type, F-type and ABC transporters.

– REMEMBER **Which drug blocks the $Na^+/K^+$-ATPase from outside the cell?** 1 mark

Ouabain (and digoxin, a related cardiac glycoside).

– UNDERSTAND **Why is the $Na^+/K^+$ pump called electrogenic?** 2 marks

Each cycle moves 3 positive charges out and only 2 in, a net transfer of one charge out, which makes the inside slightly more negative.

– UNDERSTAND **Why does an animal cell swell and burst if its $Na^+/K^+$ pump is blocked for long?** 3 marks

$Na^+$ (and $Cl^-$) leak in and are no longer pumped out. Together with the impermeant molecules already inside, they raise the internal osmolarity, water follows by osmosis, and with no cell wall the cell swells until it lyses.

– APPLY **Find ΔG for moving one mole of $Ca^{2+}$ into a cell: $Ca^{2+}$ $10^{-4}$ mM inside, 1 mM outside, Vm = −70 mV, T = 310 K.** 3 marks

RT ln($10^{-4}$) = 2577 × (−9.210) = −23 738 J; zFVm = 2 × 96 485 × (−0.070) = −13 508 J. ΔG = **−37.2 kJ/mol**: entry is strongly downhill, which is why opening a few $Ca^{2+}$ channels floods the cytosol so quickly.

– APPLY **Why does oral rehydration solution (ORS) contain both glucose and salt?** 3 marks

SGLT1 in the gut wall absorbs $Na^+$ and glucose together (2 $Na^+$ per glucose), and this route keeps working in diarrhoea such as cholera. Water follows the absorbed solutes by osmosis, so the patient rehydrates.

– ANALYZE **Ouabain is added to intestinal cells. Explain why glucose uptake falls even though SGLT1 itself is not blocked.** 4 marks

Ouabain stops the $Na^+/K^+$ pump. $Na^+$ leaks in, the $Na^+$ gradient runs down, and SGLT1 loses its energy source. Uptake of glucose against its gradient fails, showing that secondary transport depends on the primary pump.

**BEYOND THE SYLLABUS**

This is not for the exam. SGLT2, the kidney's version of SGLT1, is the target of the gliflozin drugs (such as dapagliflozin and empagliflozin) used in type 2 diabetes: blocking it makes the kidney pass glucose in urine. ABC pumps such as P-glycoprotein throw anticancer drugs out of tumour cells and are a major cause of multidrug resistance. Cryo-EM structures of pumps caught in each step of their cycle are a current research theme. Search next for "SGLT2 inhibitors mechanism" and "P-glycoprotein multidrug resistance".

## Key terms of this lesson

| TERM | MEANING OR FORMULA | CHAPTER |
|---|---|---|
| Fick's law | J = −D dC/dx; across a membrane J = P($C_1$ − $C_2$) | 2.3 |
| Carrier kinetics | v = Vmax[S]/(Km + [S]) | 2.3 |
| Osmotic pressure | π = iCRT (R = 0.0821 L·atm·$mol^{-1}$·$K^{-1}$) | 2.3 |
| Ion transport energy | ΔG(in) = RT ln(C_in/C_out) + zFVm | 2.4 |
| $Na^+/K^+$-ATPase | 3 $Na^+$ out, 2 $K^+$ in per ATP; P-type; electrogenic; blocked by ouabain | 2.4 |

## Glossary (terms used in this lesson)

| | |
|---|---|
| **Antiport** | Carrier that moves two solutes in opposite directions. |
| **Aquaporin** | Channel protein for fast water movement across membranes. |
| **Crenation** | Shrinking and wrinkling of a red cell in a hypertonic solution. |
| **Electrochemical gradient** | Combined driving force on an ion from its concentration difference and the membrane voltage. |
| **Electrogenic** | Moving net charge across the membrane, as the $Na^+/K^+$ pump does. |
| **Endosome** | Acidic compartment that receives endocytosed vesicles and sorts their contents. |
| **Haemolysis** | Bursting of red cells, for example in a hypotonic solution. |
| **Km** | Solute concentration at which a carrier works at half its maximum rate. |
| **Osmosis** | Net movement of water across a selectively permeable membrane towards higher solute concentration. |
| **Permease** | Older name for a carrier protein (transporter). |
| **Symport** | Carrier that moves two solutes in the same direction. |
| **Tonicity** | Effect of a solution on cell volume, set by solutes that cannot cross the membrane. |
| **Uniport** | Carrier that moves a single solute down its gradient. |

## 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).

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