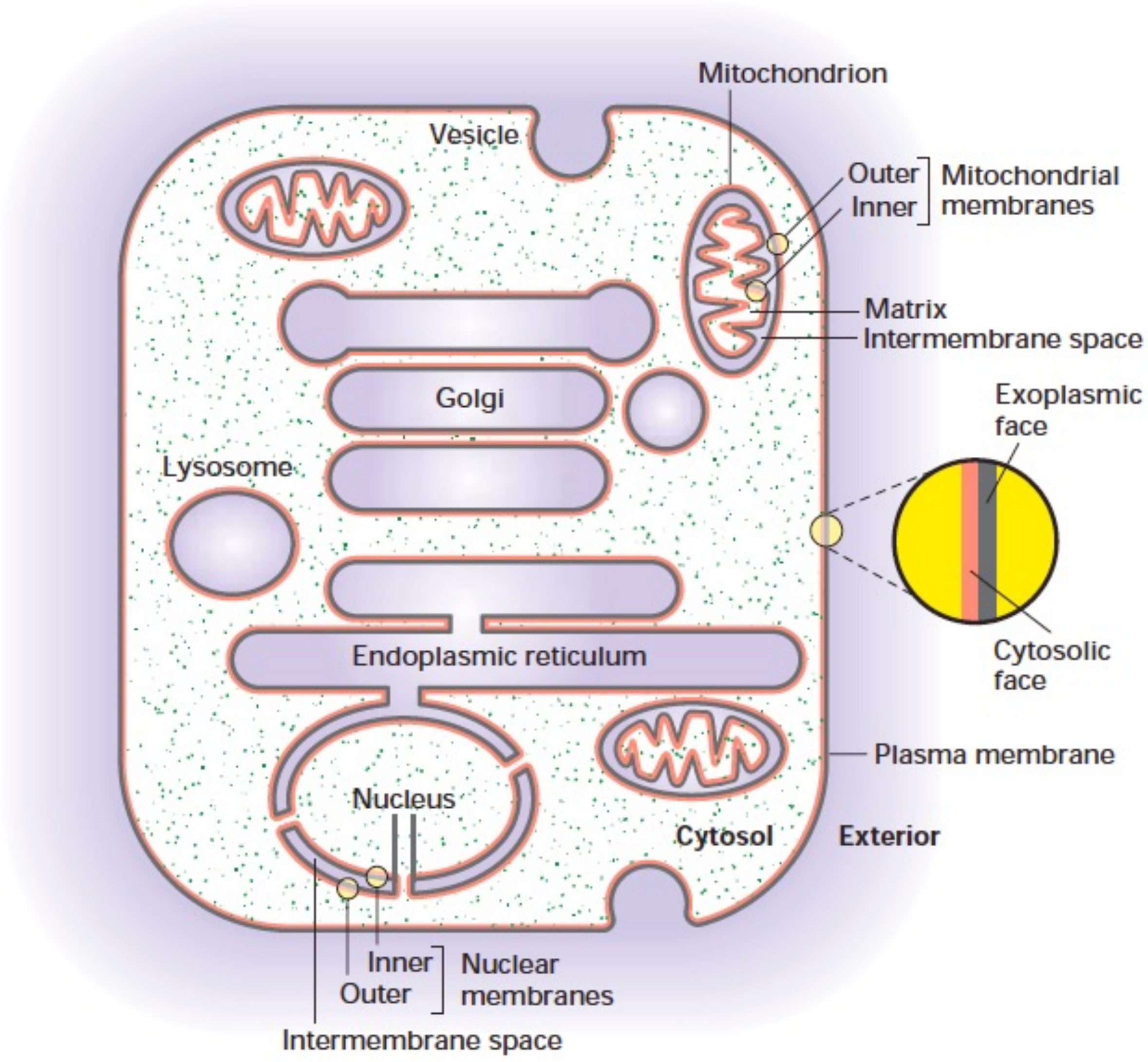
Cell membranes

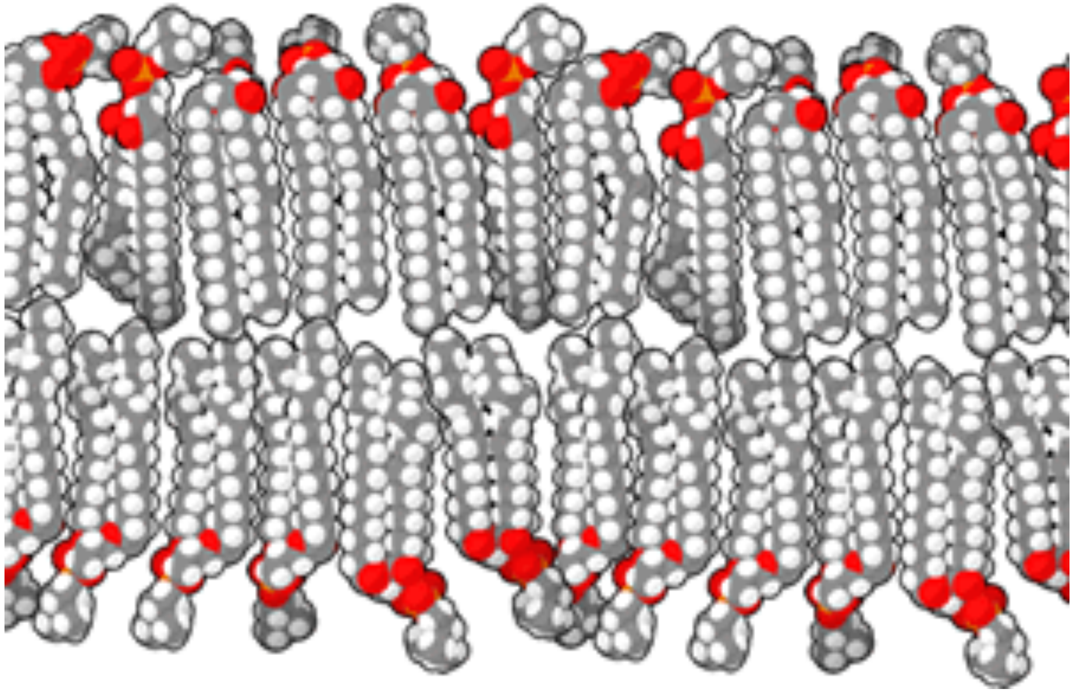
▶ **FIGURE 5-4 The faces of cellular membranes.** The plasma membrane, a single bilayer membrane, encloses the cell. In this highly schematic representation, internal cytosol (green stipple) and external environment (purple) define the cytosolic (red) and exoplasmic (black) faces of the bilayer. Vesicles and some organelles have a single membrane and their internal aqueous space (purple) is topologically equivalent to the outside of the cell. Three organelles—the nucleus, mitochondrion, and chloroplast (which is not shown)—are enclosed by two membranes separated by a small intermembrane space. The exoplasmic faces of the inner and outer membranes around these organelles border the intermembrane space between them. For simplicity, the hydrophobic membrane interior is not indicated in this diagram.



Cell membranes

Membranes are made of strongly anisotropic molecules
Strongly anisotropic molecules like to self-organizing.

- a typical eukaryotic cell membrane contains 500–2000 different lipid species



The Lipid Bilayer Is a Two-dimensional Fluid

Around 1970, researchers first recognized that individual lipid molecules are able to diffuse freely within the plane of a lipid bilayer. The initial demonstration came from studies of synthetic (artificial) lipid bilayers, which can be made in the form of spherical vesicles, called **liposomes** (**Figure 10–9**); or in the form of planar bilayers formed across a hole in a partition between two aqueous compartments or on a solid support.

Various techniques have been used to measure the motion of individual lipid molecules and their components. One can construct a lipid molecule, for example, with a fluorescent dye or a small gold particle attached to its polar head group and follow the diffusion of even individual molecules in a membrane. Alternatively, one can modify a lipid head group to carry a "spin label," such as a nitroxide

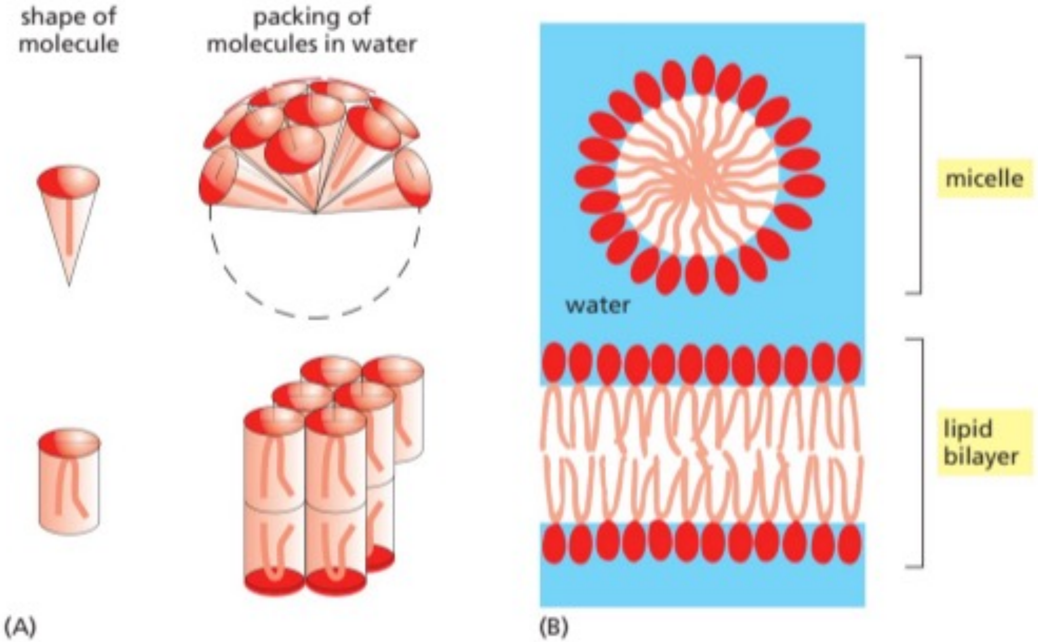
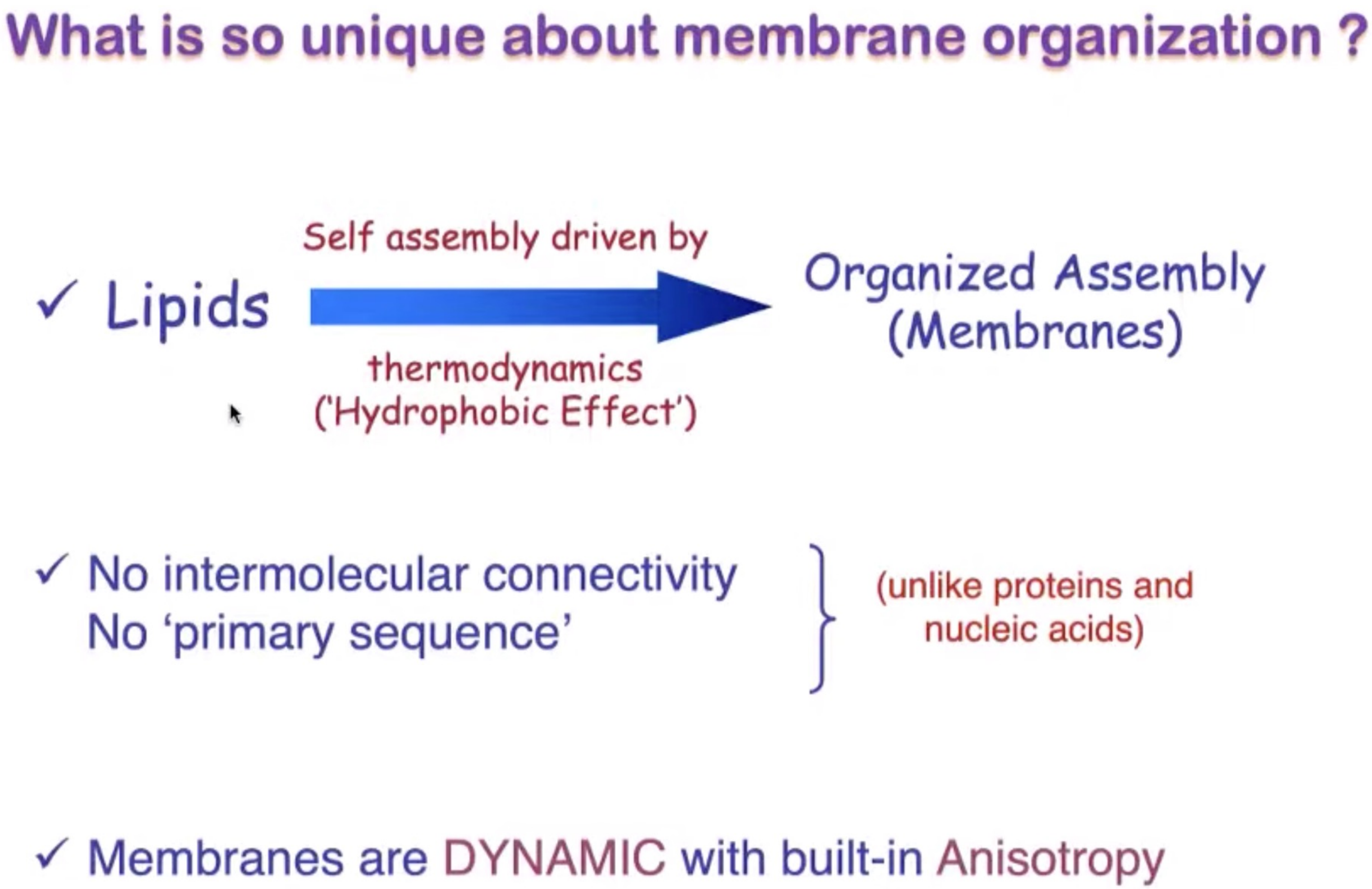


Figure 10–7 Packing arrangements of amphiphilic molecules in an aqueous environment. (A) These molecules spontaneously form micelles or bilayers in water, depending on their shape. Cone-shaped amphiphilic molecules *(above)* form micelles, whereas cylinder-shaped amphiphilic molecules such as phospholipids *(below)* form bilayers. (B) A micelle and a lipid bilayer seen in cross section. Note that micelles of amphiphilic molecules are thought to be much more irregular than drawn here (see Figure 10–26C).

Cell membranes



What is so unique about membrane organization ?

✓ Lipids

Self assembly driven by

thermodynamics

('Hydrophobic Effect')

Organized Assembly

(Membranes)

✓ No intermolecular connectivity

No 'primary sequence'

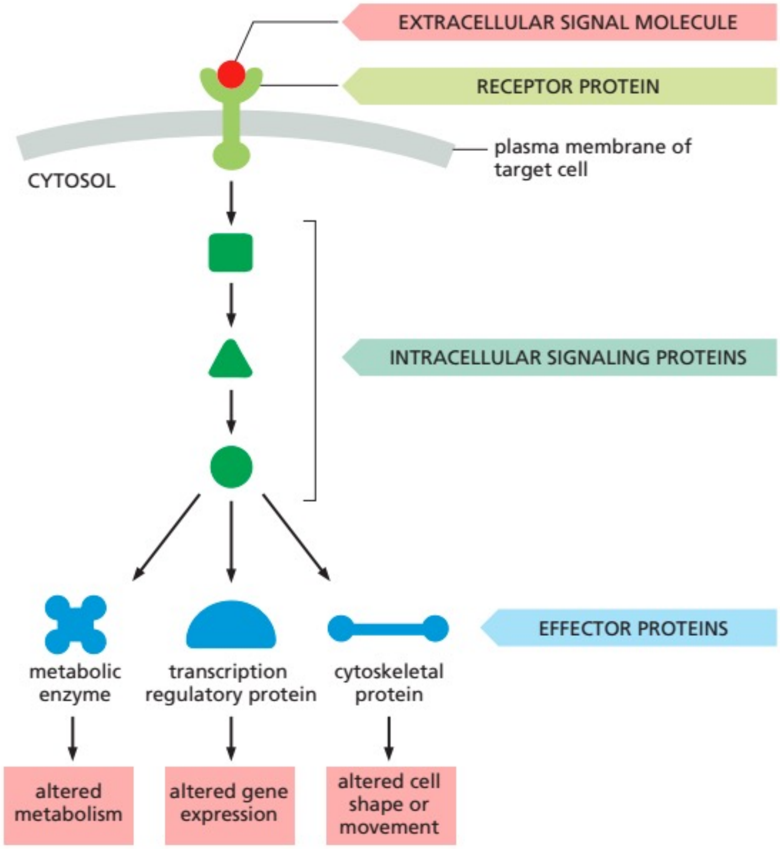
(unlike proteins and nucleic acids)

✓ Membranes are DYNAMIC with built-in Anisotropy

However, dynamics does not implicitly implies randomness and disorder!

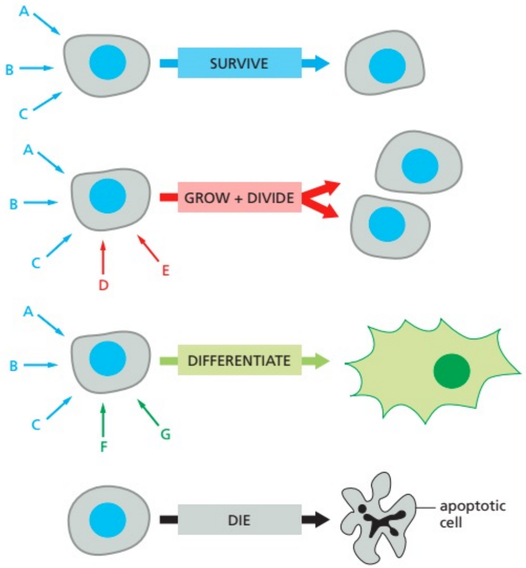
It is a many body problem with LOCAL (nm scale) order and structure

Cell-cell communication

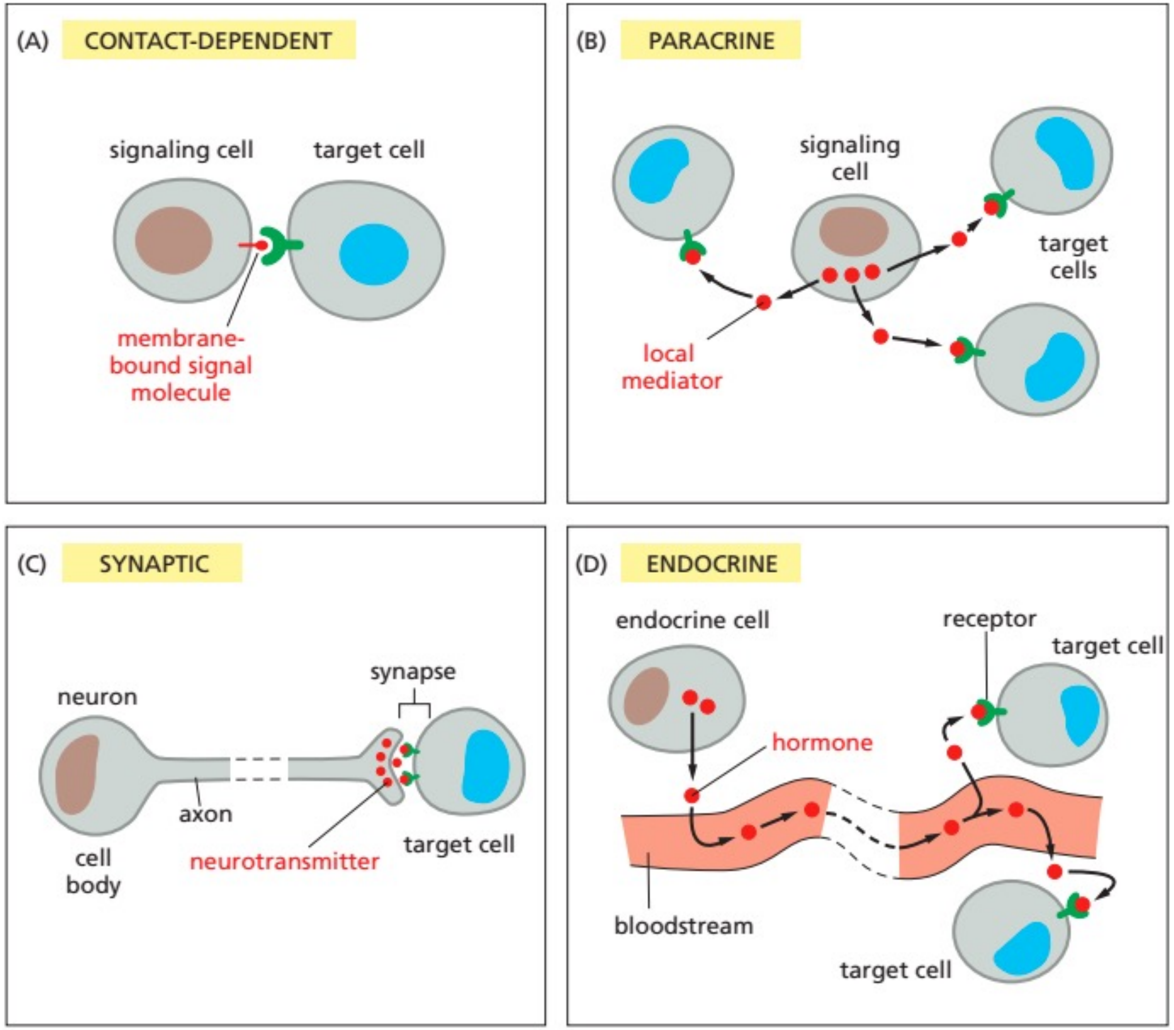


When things change, cell respond! Every cell, monitors its intracellular and extracellular environment, processes the information it gathers, and responds accordingly. (homeostasis).

Communication between cells in multicellular organisms is mediated mainly by extracellular signal molecules.



Communication needs long and short range signaling



To **coordinate their answer**, cells needs to react fast and efficiently. For that, they use chemical signaling.

Integration and coordination occurs in the **nervous** system and in the **endocrinus** and **immuno** systems.

Many of the same types of signaling molecules are used in ***paracrine, synaptic, and endocrine signaling***; the crucial differences lie in the speed and selectivity with which the signals are delivered to their target.

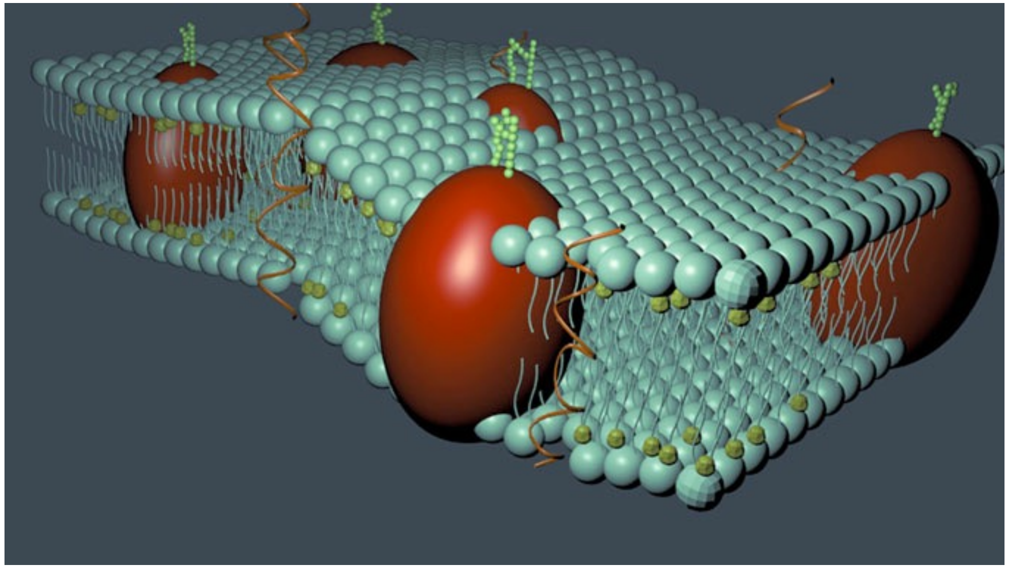
Autocrine signaling. Cancer cells, for example, often produce extracellular signals that stimulate their own survival and proliferation

Cell-cell communication over large distances occurs mainly through nerve cells, or ***neurons***, which typically extend long, branching processes (***axons***) that enable them to contact target cells far away, where the processes terminate at the specialized sites of signal transmission known as ***chemical synapses***.

When a neuron is activated by stimuli from other nerve cells, it sends electrical impulses (***action potentials***) rapidly along its axon; when the impulse reaches the synapse at the end of the axon, it ***triggers secretion of a chemical signa***l that acts as a ***neurotransmitter.*** The tightly organized structure of the synapse ensures that the neurotransmitter is delivered specifically to receptors on the postsynaptic target cell.

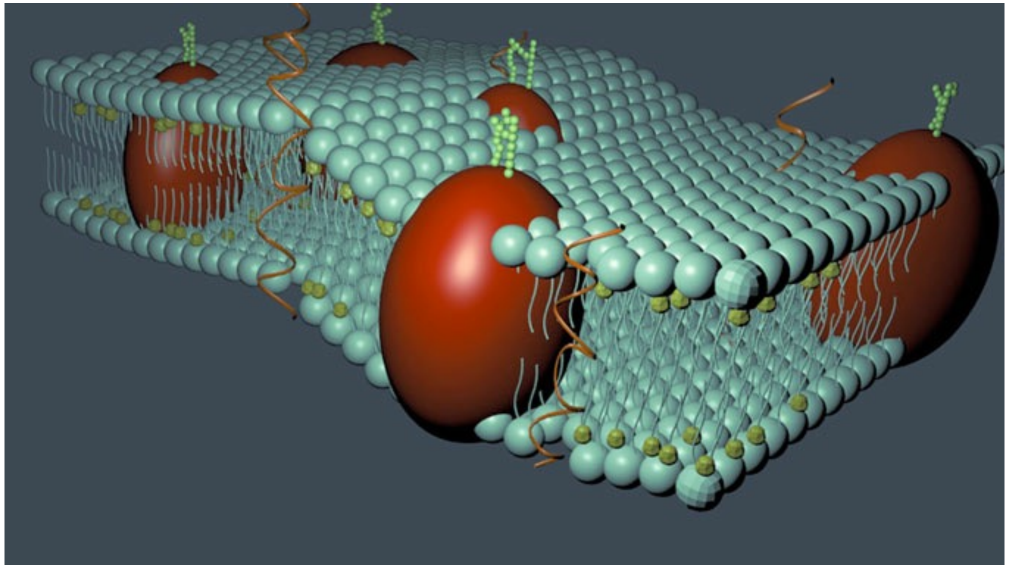
Membranes play a fundamental role in neural and more generally in cell-cell communications

Cell membranes



Membranes are very thin, typically ranging from **3-6 nm** across. Most membranes are **selectively permeable**; that is, they allow only certain substances to cross them because there are pores through which substances diffuse.
These **pores** are so **small (0.7-1.0 nm wide)** that only small molecules can get through. Other factors contributing to the semi-permeable nature of membranes have to do with the chemistry of the membrane, **cohesive and adhesive forces, charges on the ions involved**, and the existence of carrier molecules. Diffusion through membranes is relatively slow.

Cell membranes



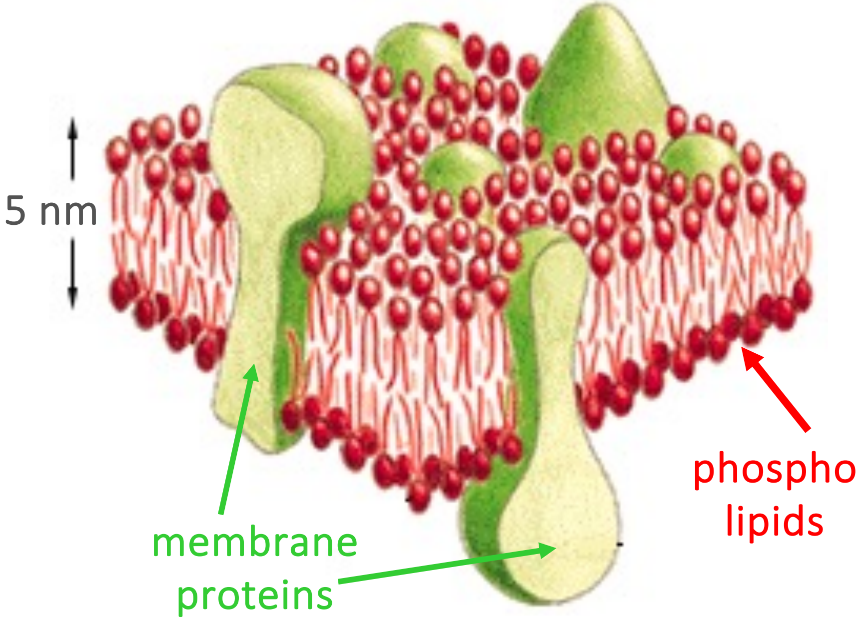
3-6 nm, 100 mV

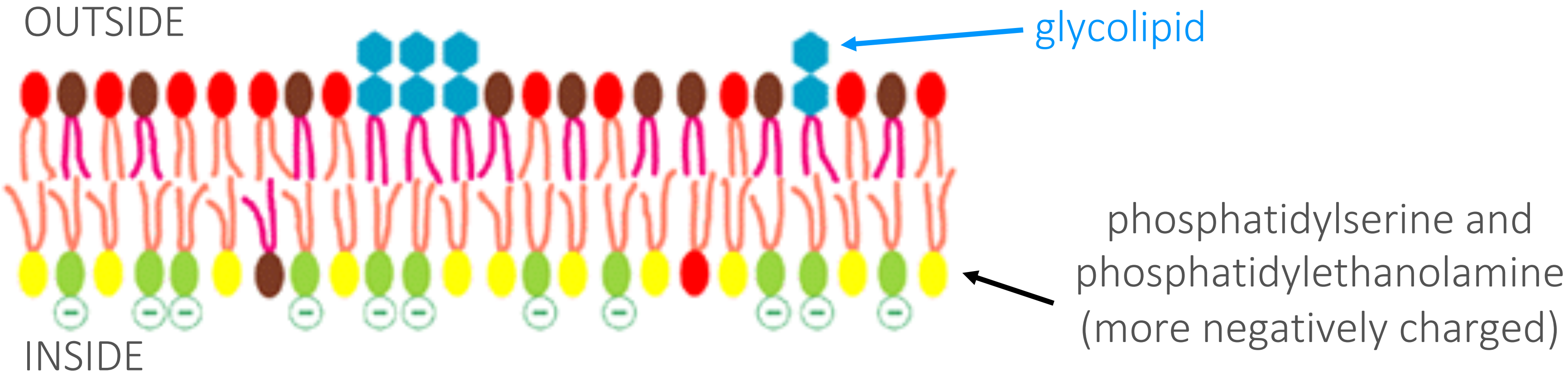
$E = 10^7$ V/m!!

Cell membrane is a power plant!
The electric energy created in this power plant is enough to regulate the functions of many biological processes such as ion movements across membranes, membrane protein dynamics, exclusion of large molecules and pathogens, etc.
All membrane constituents such as lipids, membrane proteins, hydrocarbons, etc., reside in the presence of the electric field created by the membrane's electric power plant.
Naturally, the electrostatic properties of all the membrane constituents are sensitive to its electric field. The presence of strong polarizing effects on the charges of individual atoms within any molecule and the overall charges of these molecules leads to directed molecular process.

Cell membranes

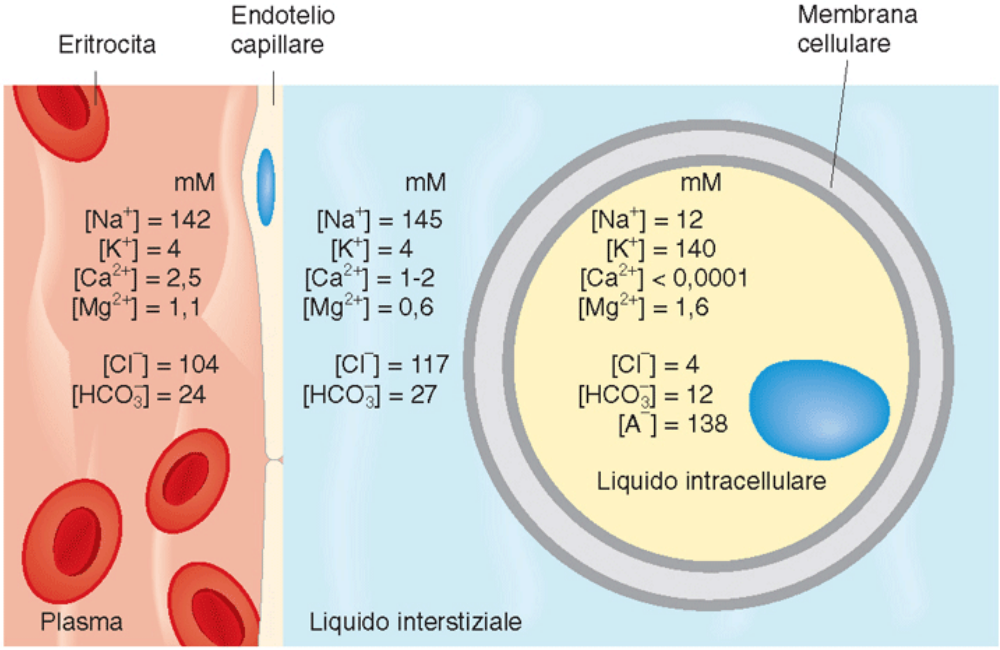
- biological membranes are fluid
- the fluidity is controlled by the % of saturated/unsaturated fatty acid and the % of cholesterol
- membranes are impermeable to ions and most polar molecules
- **many proteins are embedded in the membrane**
- the membrane is highly asymmetric





phosphatidylserine and phosphatidylethanolamine (more negatively charged)

Membrane electrical properties



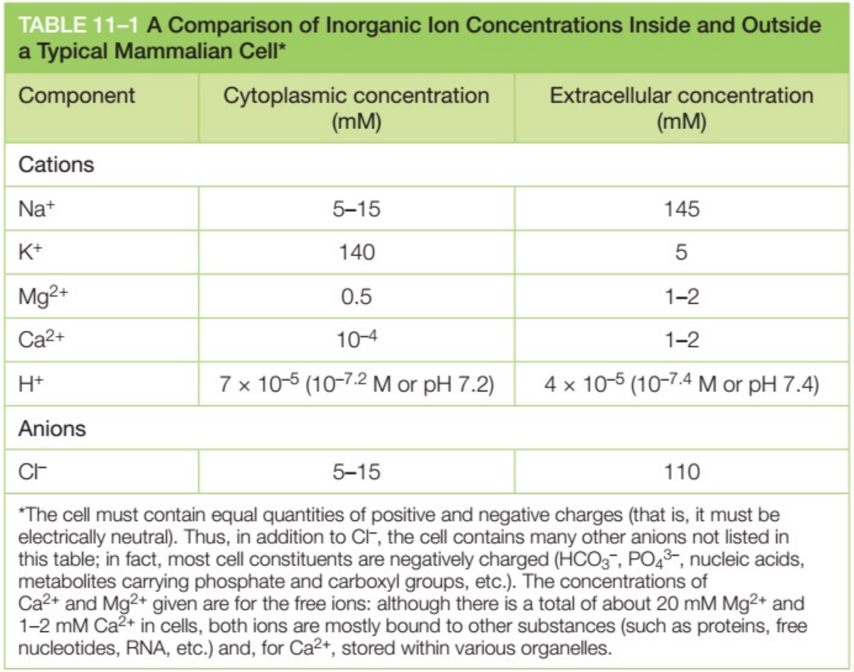
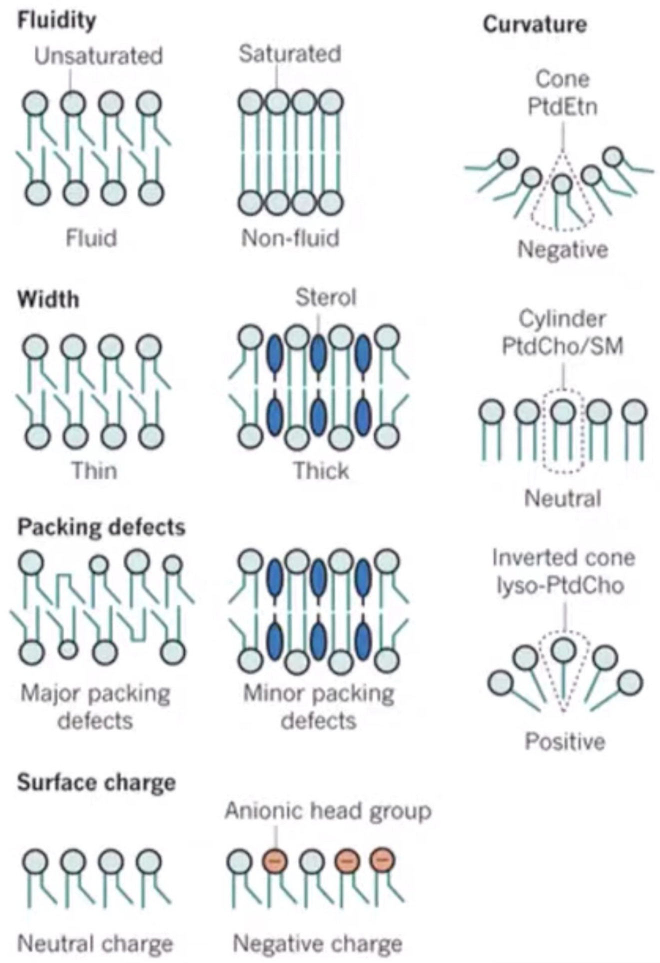


TABLE 11–1 A Comparison of Inorganic Ion Concentrations Inside and Outside a Typical Mammalian Cell*

Component	Cytoplasmic concentration (mM)	Extracellular concentration (mM)
Cations		
Na^+	5–15	145
K^+	140	5
Mg^{2+}	0.5	1–2
Ca^{2+}	10^{-4}	1–2
H^+	7×10^{-5} ($10^{-7.2}$ M or pH 7.2)	4×10^{-5} ($10^{-7.4}$ M or pH 7.4)
Anions		
Cl^-	5–15	110

*The cell must contain equal quantities of positive and negative charges (that is, it must be electrically neutral). Thus, in addition to Cl^-, the cell contains many other anions not listed in this table; in fact, most cell constituents are negatively charged (HCO_3^-, PO_4^{3-}, nucleic acids, metabolites carrying phosphate and carboxyl groups, etc.). The concentrations of Ca^{2+} and Mg^{2+} given are for the free ions: although there is a total of about 20 mM Mg^{2+} and 1–2 mM Ca^{2+} in cells, both ions are mostly bound to other substances (such as proteins, free nucleotides, RNA, etc.) and, for Ca^{2+}, stored within various organelles.

Membrane physical properties



Membrane Physical Properties are Determined by its Lipid Composition

Nature (2014) 510: 48-57

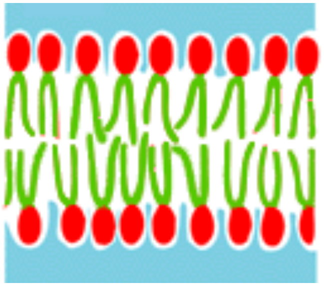
Phospholipids and membranes

Phospholipids are the major constituent of cell membranes.

When in aqueous environment the heads have affinity for the water molecules, while the tails tend to avoid water by sticking together.

Cellular membranes are essentially made up by phospholipid bilayers.

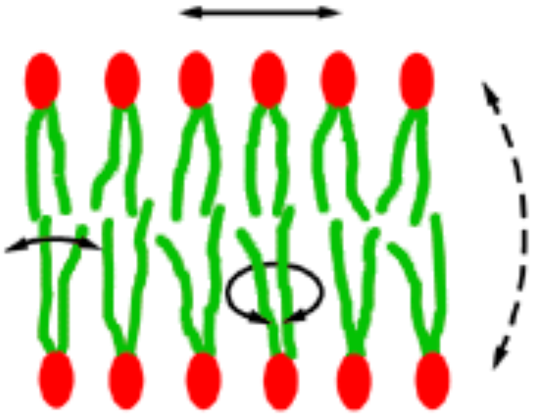
micelle



lipid bilayer

Phospholipid mobility

lateral diffusion

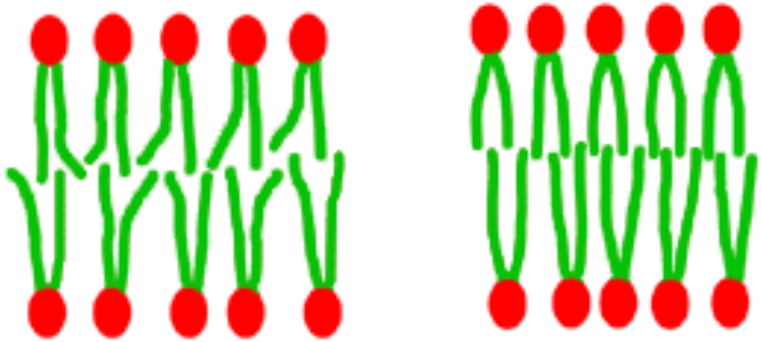


flip-flop (occurs very rarely)

flexion

rotation

Saturated vs unsaturated lipids



unsaturated, more difficult to pack, more fluid

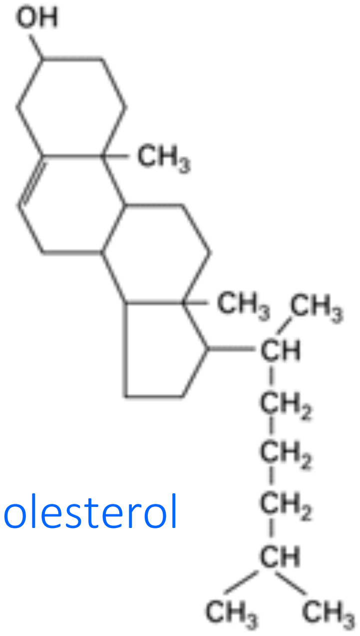
saturated, easier to pack, less fluid

Membranes are highly dynamic

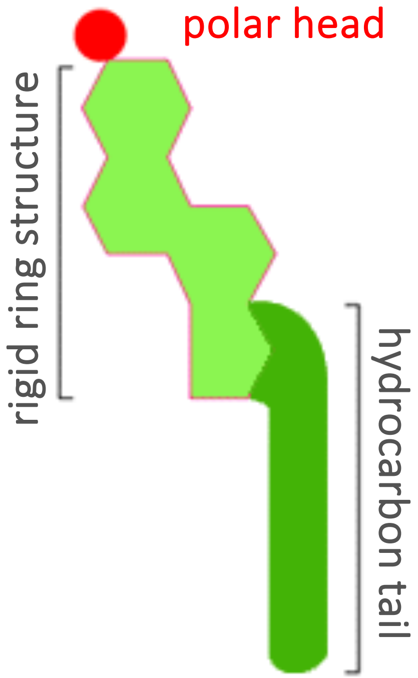
The various components of membranes are subject to rapid movements.
Rapid lateral movement of lipids is characterized by a diffusion constant of approximately 10^{-8} cm^2/s, while those of **proteins** range between 10^{-10} and 10^{-12} cm^2/s.
On the other hand, **flip-flop** movements across the membrane are slow, of the order of 10^{-5} s.
Indeed, the phospholipids of the membrane may undergo a phase transition from a gel phase to a liquid crystal phase. This may take place as a result of changing the ambient temperature, external pressure, or even membrane composition: **especially CHOL!**

Cholesterol and steroids

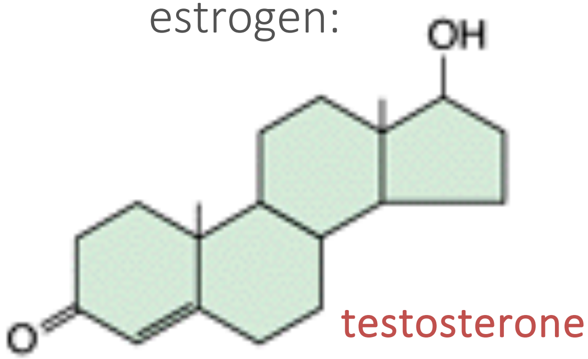
Steroids (such as cholesterol) have a rigid structure made up by 4 rings.



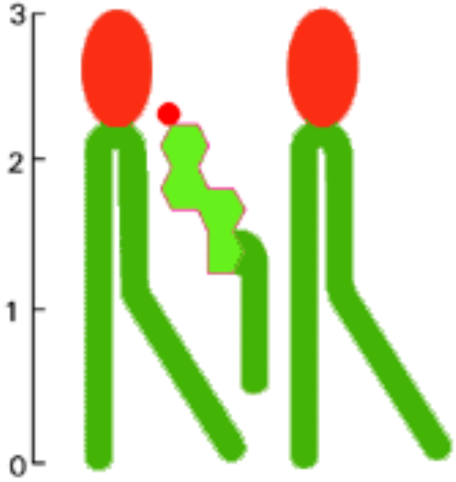
Cholesterol



Other important steroid are the sex hormones, such as testosterone and estrogen:



Cholesterol is an important component of the eukaryotic membranes and **has a key role in controlling the membrane fluidity.**



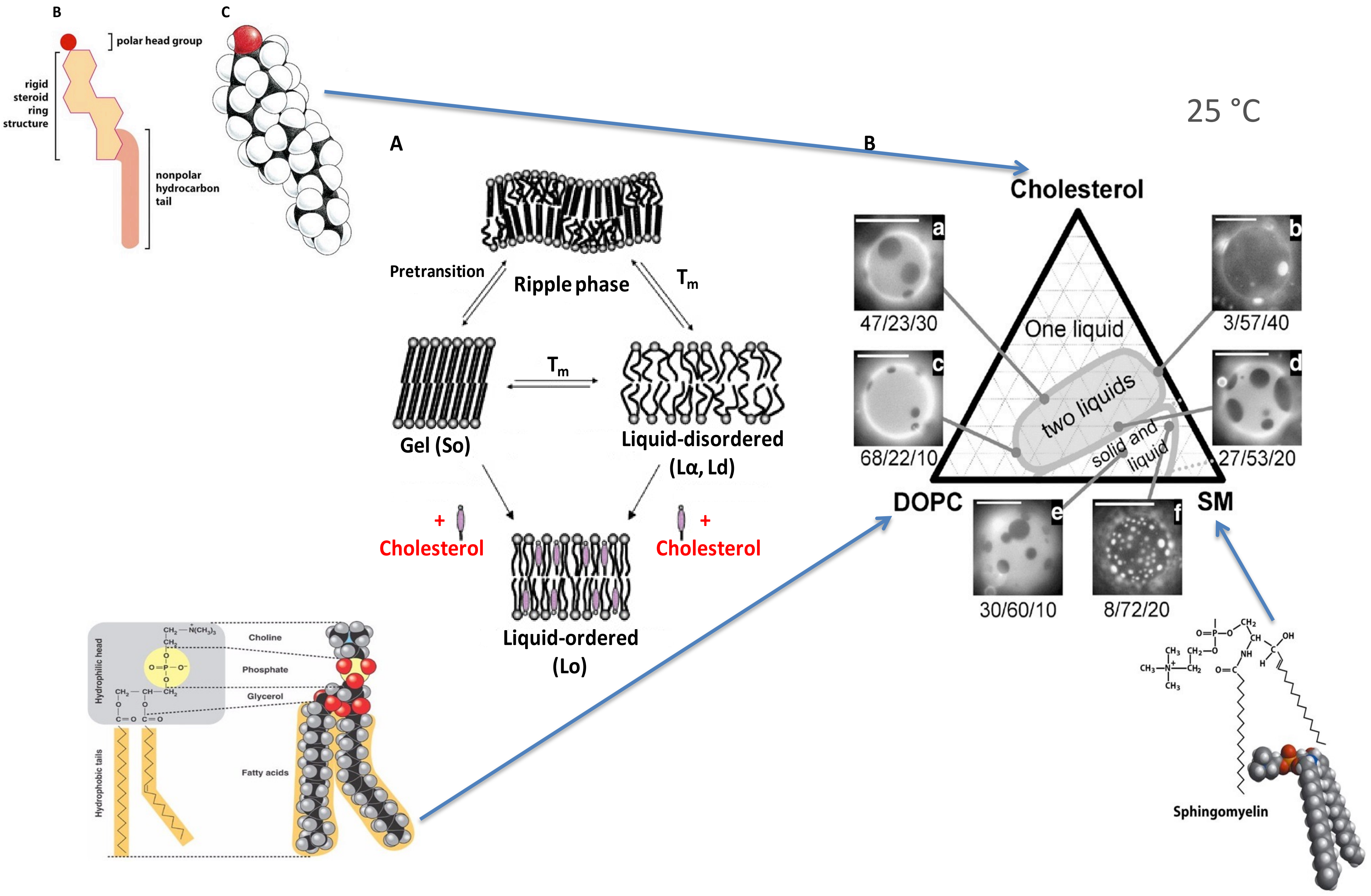
Cell membrane: an optimized 2D fluid system

Membrane fluidity depends on the type of lipid:

Saturated lipid are more ordered, therefore mode rigid then the **unsaturated** ones
Cholesterol is hydrophobic, but reacts with a OH^- group with the hydrophilic heads of neighbor phospholipids

Low T: chol is a spacer, keeping fluidity high
High T: chol stabilize the membrane (sealing)

Cell membrane: an optimized 2D fluid system

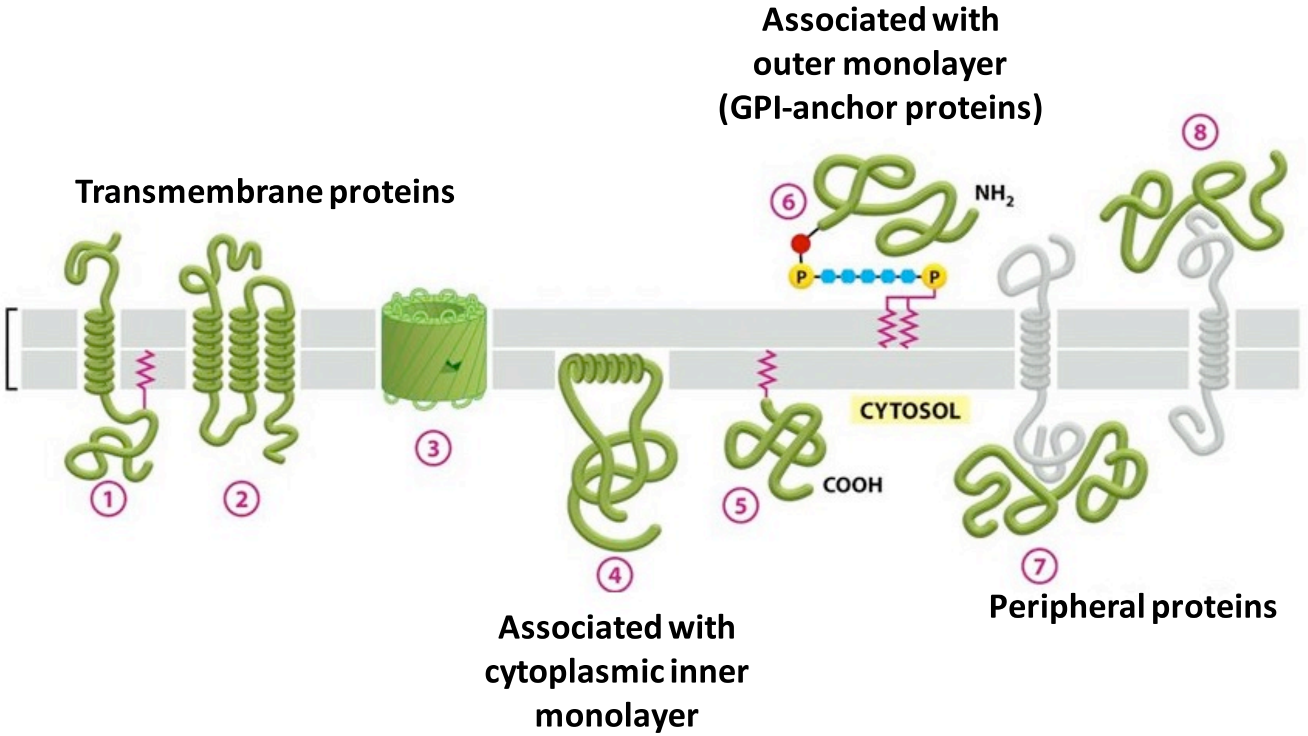


Membranes are highly dynamic

Membrane constituents such as proteins and hydrocarbons, together with lipids continuously form, break, and translocate between different complex structures (e.g., ion channels, defects, etc.) inside and across membranes, which can be responsible for

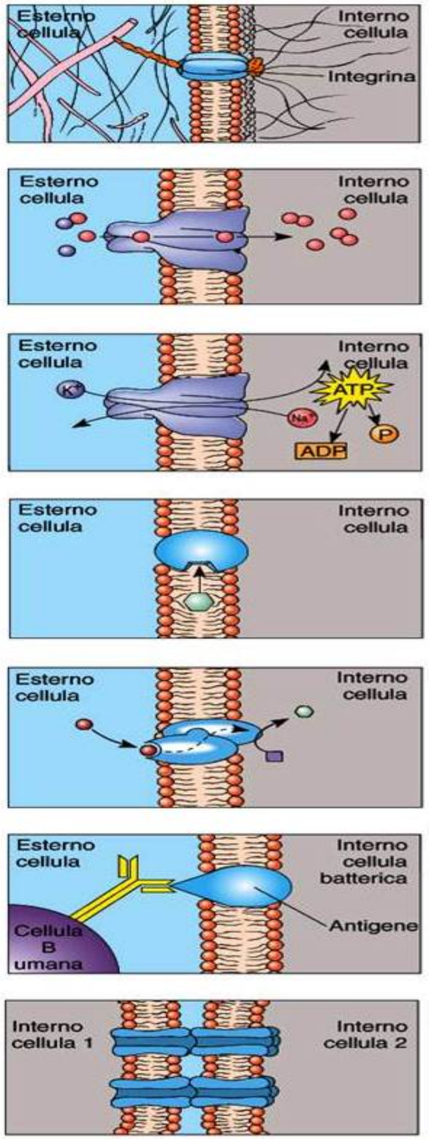
changing the membrane’s insulating properties. As a result, materials such as ions, water molecules, other small molecules, etc. may pass through membranes.

Type and function of membrane proteins



Trans-membrane proteins cross the bilayer:
(1) a single α helix, **(2)** as multiple α helices, or **(3)** as a β barrel.
Other membrane proteins are exposed at only one side of the membrane:
(4) anchored to the cytosolic surface by an amphipathic α helix that partitions into the cytosolic monolayer of the lipid bilayer through the hydrophobic face of the helix, **(5)** attached to the bilayer solely by a covalently attached lipid chain or, **(6)** via an oligosaccharide linker, to phosphatidylinositol in the non-cytosolic monolayer.
(7, 8) proteins are attached to the membrane only by non-covalent interactions with other membrane proteins.

Type and function of **transmembrane proteins**



(a) Ancoraggio. Alcune proteine di membrana, per esempio le integrine, ancorano la cellula alla matrice extracellulare ed inoltre si connettono ai microfilamenti intracellulari.

(b) Trasporto passivo. Certe proteine formano canali che permettono il passaggio selettivo di ioni o molecole.

(c) Trasporto attivo. Alcune proteine di trasporto pompano i soluti attraverso la membrana, un processo che richiede un apporto di energia.

(d) Attività enzimatica. Molti enzimi legati alla membrana catalizzano reazioni che avvengono all'interno o sulla superficie della membrana.

(e) Trasduzione del segnale. Alcuni recettori legano molecole segnale come gli ormoni e trasmettono l'informazione all'interno della cellula.

(f) Riconoscimento cellulare. Alcune proteine recettoriali funzionano come siti per il riconoscimento cellulare. Per esempio, le cellule batteriche posseggono proteine superficiali, o antigeni, che vengono riconosciuti come estranei dalle cellule umane.

(g) Giunzione intercellulare. Le proteine di adesione legano le membrane di cellule adiacenti.

Ancoraggio (integrine)

Trasporto passivo

Trasporto attivo

Attività enzimatica

Attività recettoriale e trasduzione del segnale

Riconoscimento cellulare

Giunzione intercellulare

Passive and Active Transport

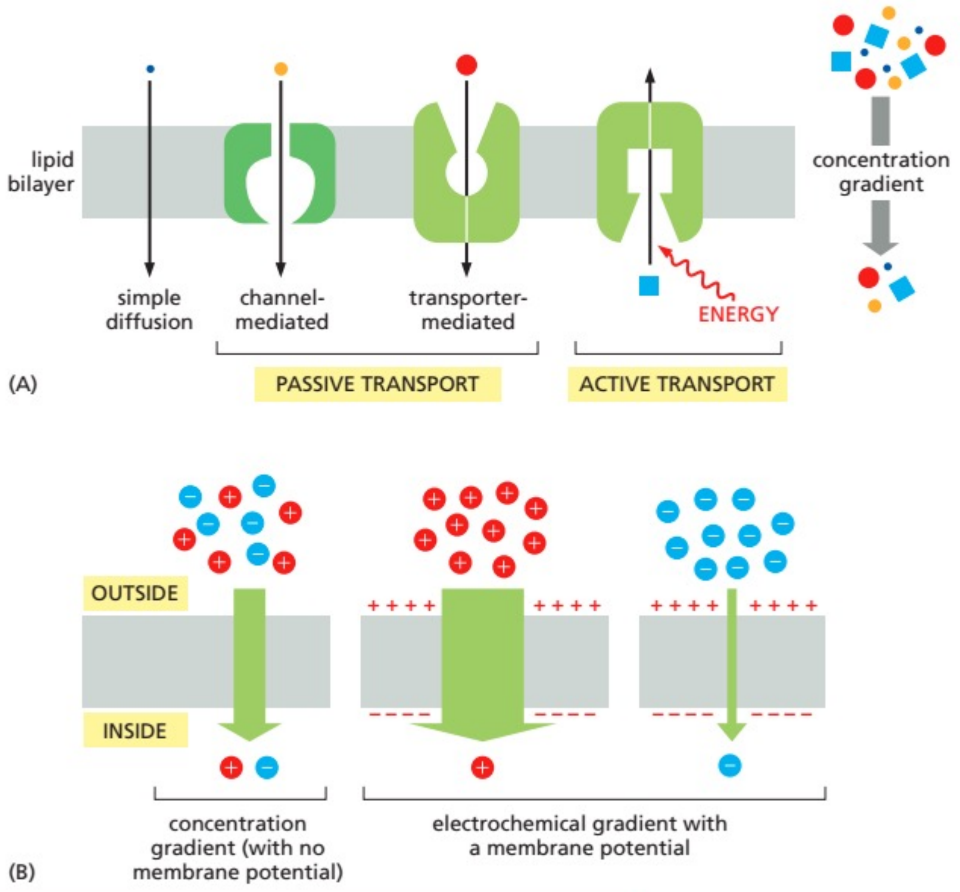
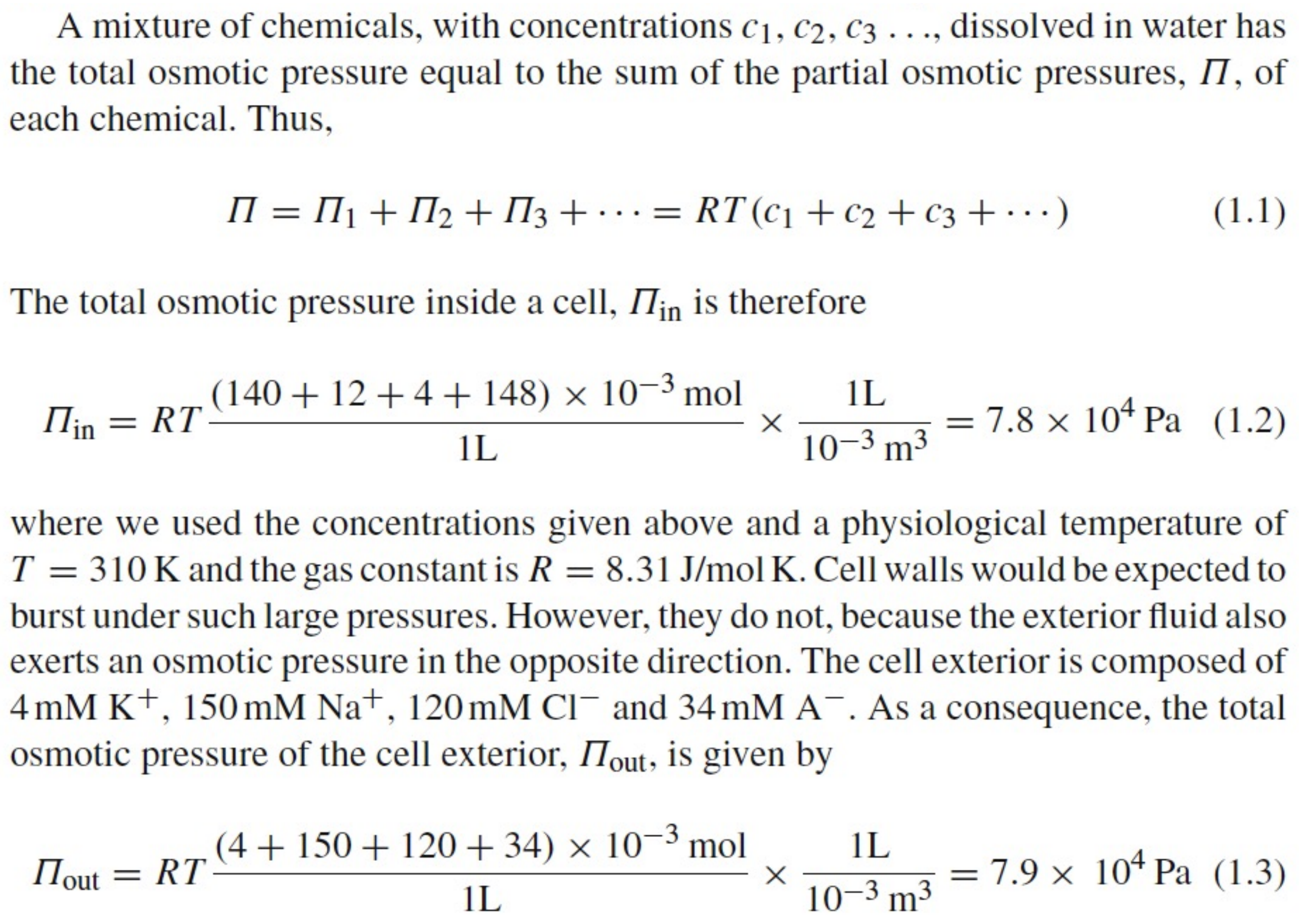


Figure 11–4 Different forms of membrane transport and the influence of the membrane. Passive transport down a concentration gradient (or an electrochemical gradient—see B below) occurs spontaneously, by diffusion, either through the lipid bilayer directly or through channels or passive transporters. By contrast, active transport requires an input of metabolic energy and is always mediated by transporters that pump the solute against its concentration or electrochemical gradient. (B) The electrochemical gradient of a charged solute (an ion) affects its transport. This gradient combines the membrane potential and the concentration gradient of the solute. The electrical and chemical gradients can work additively to increase the driving force on an ion across the membrane (*middle*) or can work against each other (*right*).

All channels and many transporters allow solutes to cross the membrane only passively (“downhill”), a process called **passive transport.**

Membrane physical properties

Cell membrane osmotic pressure:



A mixture of chemicals, with concentrations $c_1, c_2, c_3 \ldots$, dissolved in water has the total osmotic pressure equal to the sum of the partial osmotic pressures, Π, of each chemical. Thus,

$$\Pi = \Pi_1 + \Pi_2 + \Pi_3 + \cdots = RT(c_1 + c_2 + c_3 + \cdots) \quad (1.1)$$

The total osmotic pressure inside a cell, Π_{in} is therefore

$$\Pi_{in} = RT \frac{(140 + 12 + 4 + 148) \times 10^{-3}\,\text{mol}}{1\text{L}} \times \frac{1\text{L}}{10^{-3}\,\text{m}^3} = 7.8 \times 10^4\,\text{Pa} \quad (1.2)$$

where we used the concentrations given above and a physiological temperature of $T = 310\,\text{K}$ and the gas constant is $R = 8.31\,\text{J/mol K}$. Cell walls would be expected to burst under such large pressures. However, they do not, because the exterior fluid also exerts an osmotic pressure in the opposite direction. The cell exterior is composed of 4 mM K^+, 150 mM Na^+, 120 mM Cl^- and 34 mM A^-. As a consequence, the total osmotic pressure of the cell exterior, Π_{out}, is given by

$$\Pi_{out} = RT \frac{(4 + 150 + 120 + 34) \times 10^{-3}\,\text{mol}}{1\text{L}} \times \frac{1\text{L}}{10^{-3}\,\text{m}^3} = 7.9 \times 10^4\,\text{Pa} \quad (1.3)$$

For fragile animal cells, it therefore becomes vitally important to keep their interior and exterior osmotic pressures closely matched. The cell has a sophisticated control mechanism to do this.

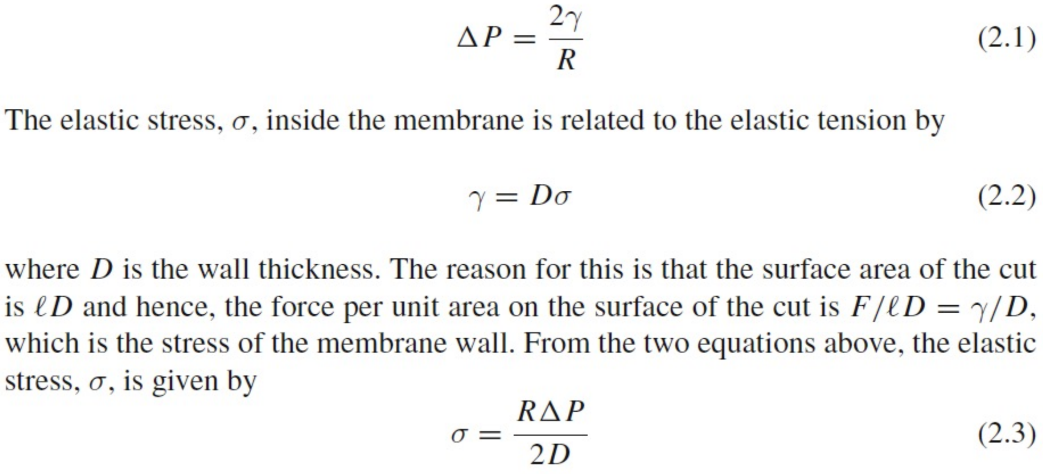
Membrane physical properties

Membrane mechanical rigidity is one of the most fundamental physical properties investigated.

Suppose we increase the osmotic pressure of a cell. The cell will try to swell but this is prevented because the surface area of the plasma membrane is nearly fixed, i.e., **an elastic stress will be built up inside the membrane and if this is too great the cell will burst**—a condition called lysis.

Membrane physical properties

Which is the stress at which the membrane will burst?
Suppose we cut the membrane along some **line of length l**.
To prevent the two sides of the cut from separating, a force, F, must be present which is proportional to l, **F = γl** where **γ** is called the **elastic tension in the wall**. This tension is not the surface tension, T , of a fluid, but it does play a similar role. The excess pressure inside a bubble of radius R, above atmospheric pressure, is 2T/R. A similar relation to this may be used to compute the excess pressure P inside a spherical pressure vessel, such as a membrane, if we **replace the surface tension T with the elastic tension γ**. Thus we have:



$$\Delta P = \frac{2\gamma}{R} \tag{2.1}$$

The elastic stress, σ, inside the membrane is related to the elastic tension by

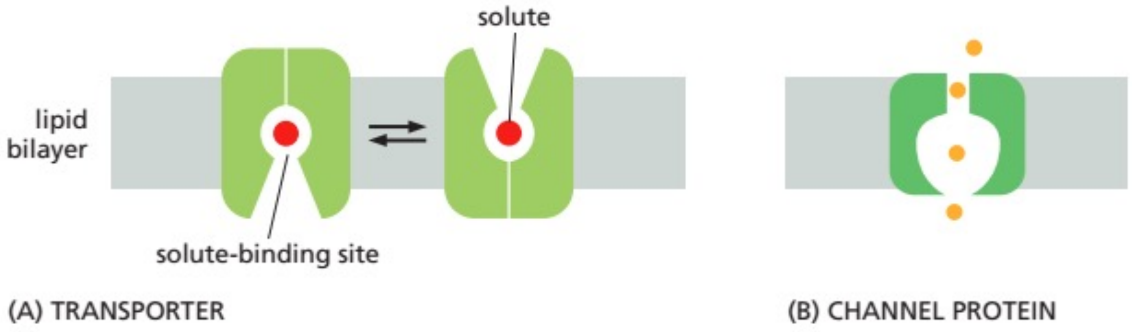
$$\gamma = D\sigma \tag{2.2}$$

where D is the wall thickness. The reason for this is that the surface area of the cut is ℓD and hence, the force per unit area on the surface of the cut is $F/\ell D = \gamma/D$, which is the stress of the membrane wall. From the two equations above, the elastic stress, σ, is given by

$$\sigma = \frac{R\Delta P}{2D} \tag{2.3}$$

i.e. the fracture stress of the material from which the cell membrane is made.

Passive Transport Is driven by concentration gradient



(A) TRANSPORTER

(B) CHANNEL PROTEIN

Figure 11–3 Transporters and channel proteins. (A) A transporter alternates between two conformations, so that the solute-binding site is sequentially accessible on one side of the bilayer and then on the other. (B) In contrast, a channel protein forms a pore across the bilayer through which specific solutes can passively diffuse.

Transporters (carriers, or permeases) bind the specific solute to be transported and undergo a series of conformational changes that alternately expose solute-binding sites on one side of the membrane and then on the other to transfer the solute across it.

Channels, interact with the solute to be transported much more weakly. They form continuous pores that extend across the lipid bilayer. When open, these pores allow specific solutes to pass through them and thereby cross the membrane. Much faster rate than transport mediated by transporters. Cells use dedicated channel proteins (called water channels, or aquaporins) that greatly increase the permeability of their membranes to water.

Membrane permeability: simple diffusion

Non selective; No saturation; Drives to equilibrium
- Small hydrophobic molecules (impermeable to polar molecules)
- Small non charged polar molecules (H2O, ethanol)
- Gas (CO2, O2, N2)

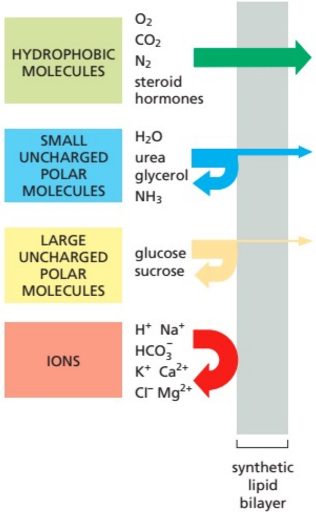
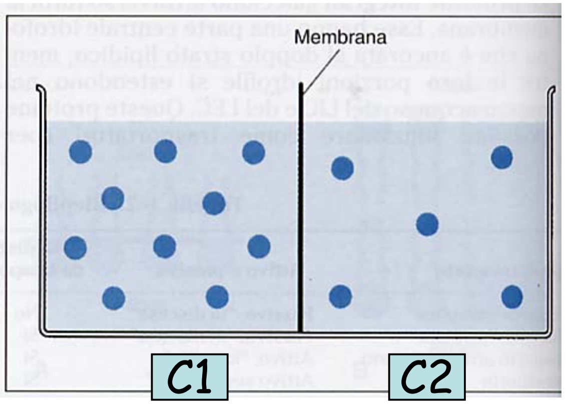


Figure 11–1 The relative permeability of a synthetic lipid bilayer to different classes of molecules. The smaller the molecule and, more importantly, the less strongly it associates with water, the more rapidly the molecule diffuses across the bilayer.

Simple diffusion (PASSIVE!!) depends on the thermal motion of molecules

J = flux depends on:
- **C2-C1**
- Partition coefficient
- **Diffusion coefficient D** (m^2/s)
- **Membrane thickness d**
- Diffusion area A



molecular lipo-solubility: ratio between solubility in oil and water=partition coefficient
Depends on Lipid layer composition

Membrane permeability: simple diffusion

$$\boxed{dm/dt = D \times A/d \times (c1 - c2)}$$

Fick low

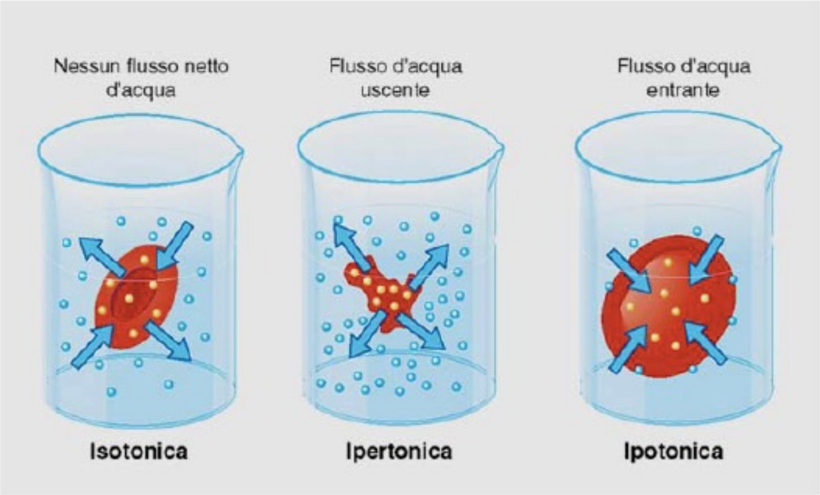
m = mass

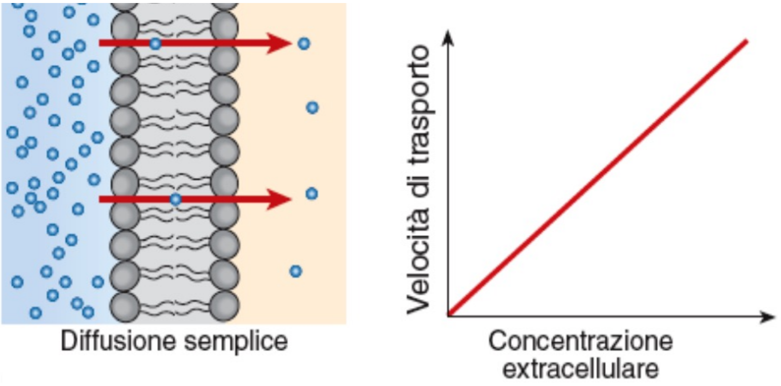
t= time

The Permeability P is defined as D/d :

$$dm/dt = P \times A \times \Delta c$$

$$J = P \times A \times Dc$$





La **diffusione semplice** ha una cinetica di **non saturazione**

Membrane permeability: simple diffusion

Per poter abbandonare la fase acquosa ed entrare nella fase lipidica, un soluto deve prima di tutto rompere i legami idrogeno con l'acqua (per la rottura di un legame idrogeno si richiedono 5 kcal/mol). Inoltre la molecola di soluto deve essere solubile nella fase lipidica ed il suo grado di solubilità sarà determinante per l'attraversamento della membrana. (la concentrazione in membrana aumenta all'aumentare del coefficiente di partizione olio/acqua, K)

Tutte le sostanze che formano pochi legami idrogeno con l'acqua possono entrare più facilmente nel doppio strato lipidico mentre gli ioni inorganici non avranno quasi mai la possibilità di farlo.

La pearmeabilità dell'acqua attraverso le membrane cellulari è molto maggiore di quanto si possa dedurre dal suo coefficiente di ripartizione.
l'acqua può passare attraverso canali selettivi che penetrano il doppio strato lipidico denominati acquaporine
Anche nei doppi strati lipidici artificiali, privi di canali, la permeabilità all'acqua è superiore a quanto ci si dovrebbe aspettare in base alla sua solubilità nella fase idrocarburica dovuta al passaggio attraverso
dei canali temporanei che si formano tra le molecole lipidiche.

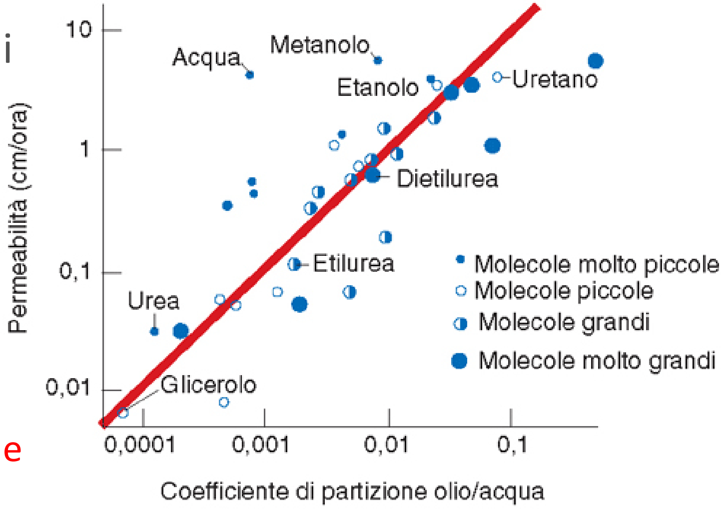
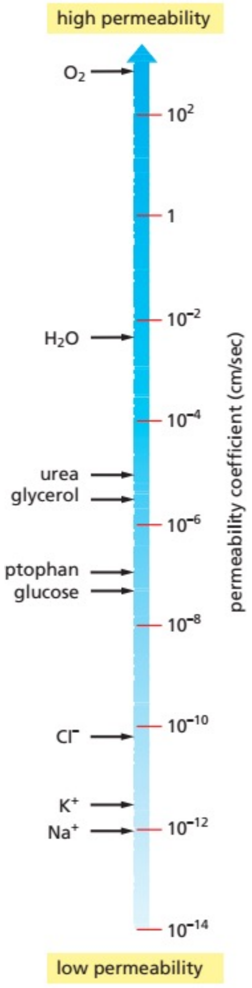


Figura 1.9 Relazione lineare tra coefficiente di partizione olio/acqua e permeabilità di membrana. Si noti come la permeabilità non dipenda dalla dimensione delle molecole. Due molecole piccole come glicerolo e uretano hanno permeabilità molto diverse perché i loro coefficienti di partizione differiscono di circa tre ordini di grandezza.



Passive Transport through Channels

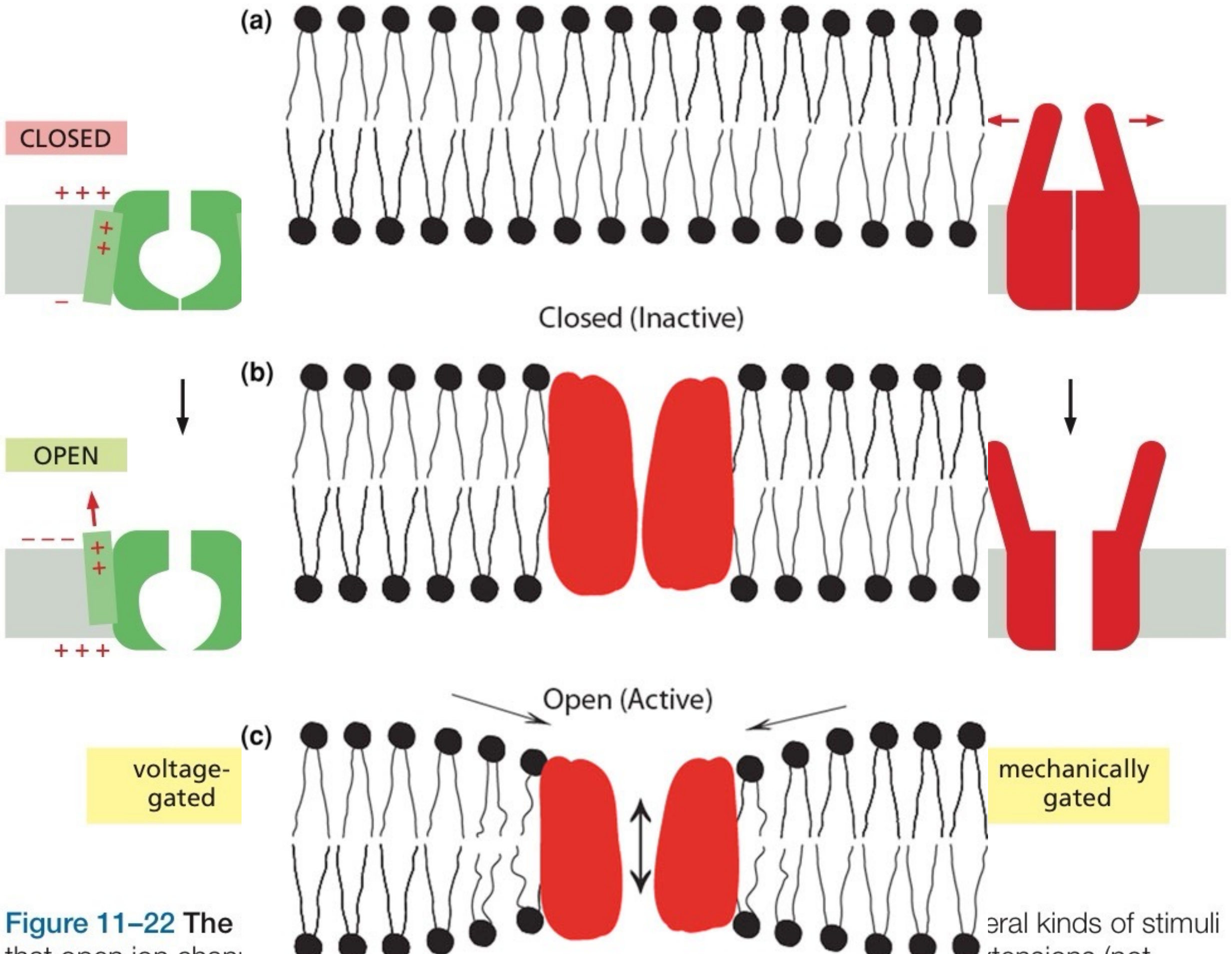


Figure 11–22 **The** eral kinds of stimuli that open ion chan xtensions (not shown) that link the channel to the cytoskeleton.

There are two families of channels: one always allowed, as for facilitating water transport (aquaporin, with a central “block” for H^+ ions) and gated channels as for transporting ions (voltage-gated)

Passive Transport through Channels

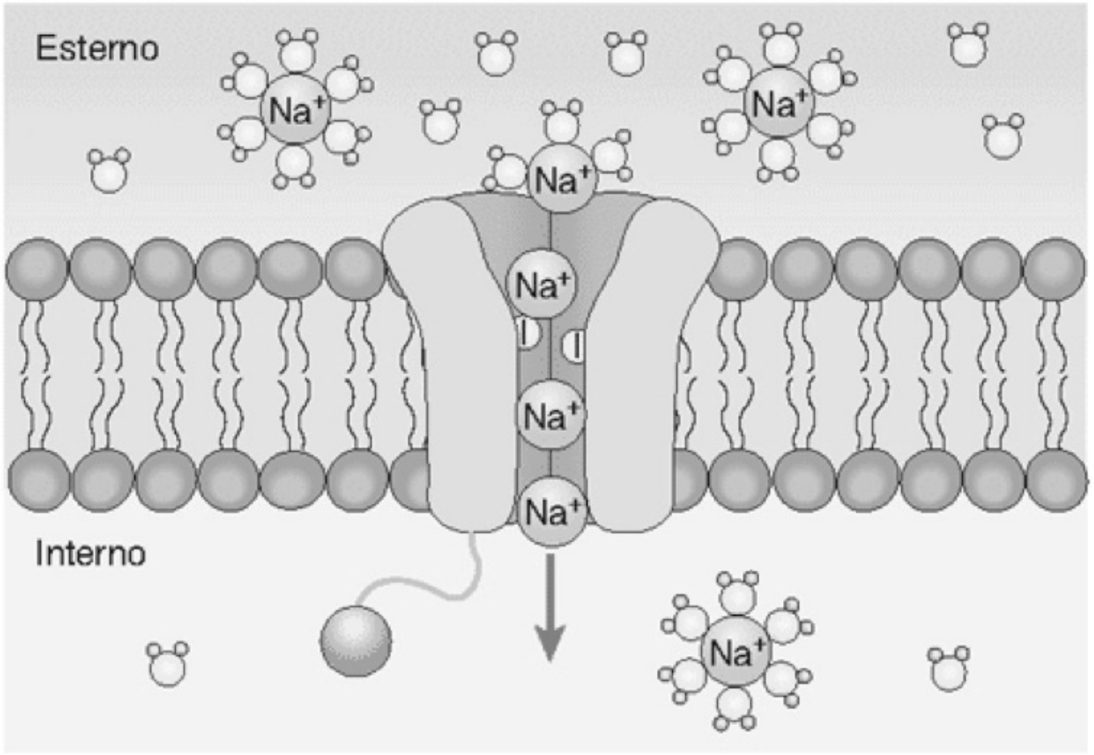
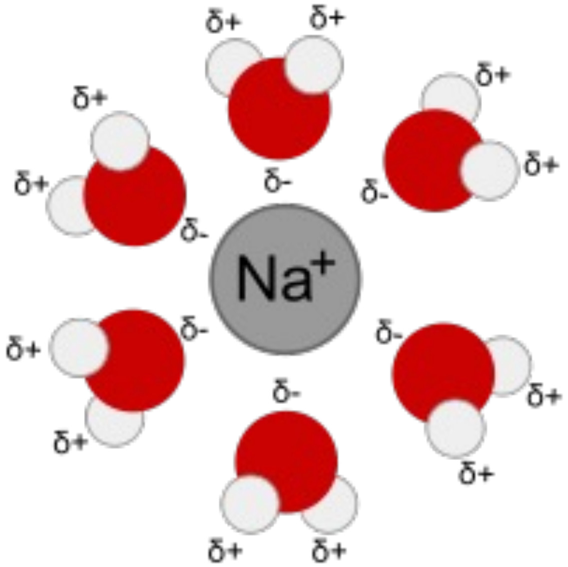


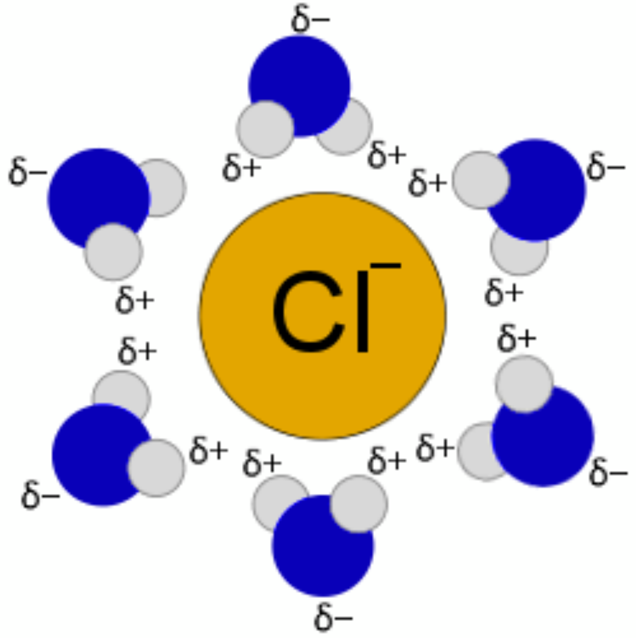
Figura 1.11 Modello di canale del Na^+. Gli ioni Na^+ extracellulari spinti dal loro gradiente elettrochimico diffondono attraverso il canale aperto. Prima perdono le molecole di idratazione, poi si legano in successione alle cariche negative disposte sulle pareti interne del poro. Il movimento "in fila indiana" verso l'interno è imposto dall'alta concentrazione esterna di ioni Na^+.

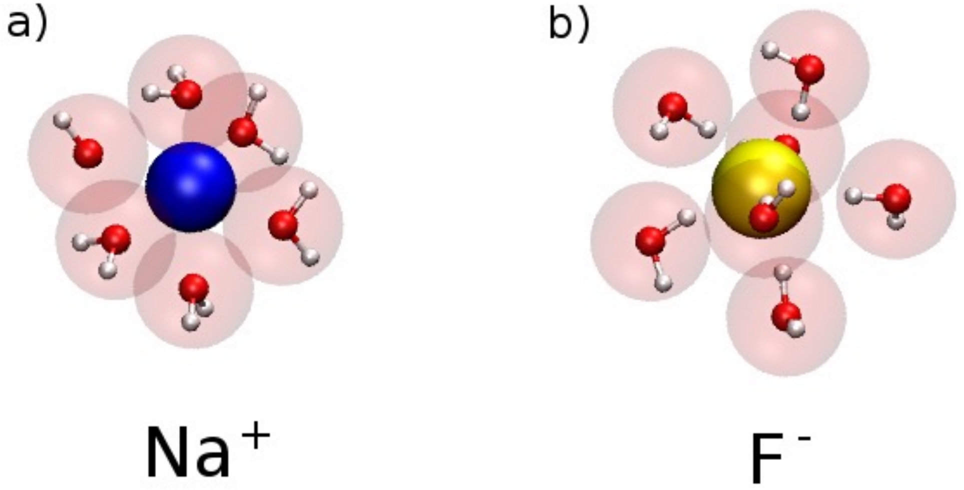
Solvation shells

A **solvation shell** is the solvent interface of any chemical compound or biomolecule that constitutes the solute. When the solvent is water it is often referred to as a **hydration shell** or **hydration sphere**.

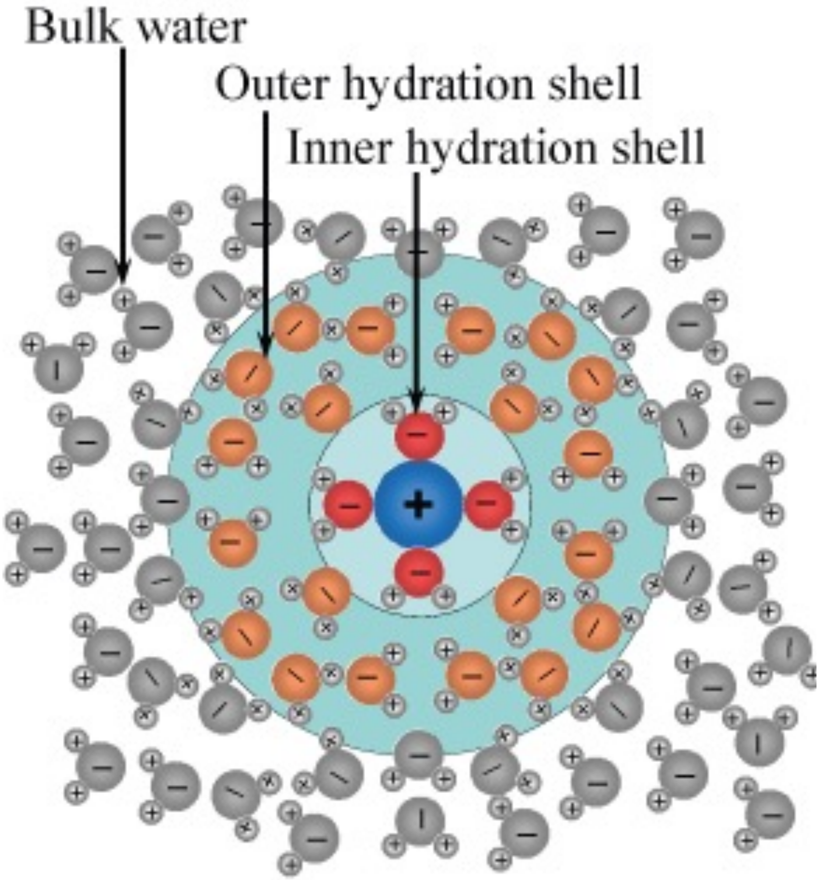
For example, if the latter were a cation, the electronegative oxygen atom of the water molecule would be attracted electrostatically to the positive charge on the metal ion. The result is a solvation shell of water molecules that surround the ion.

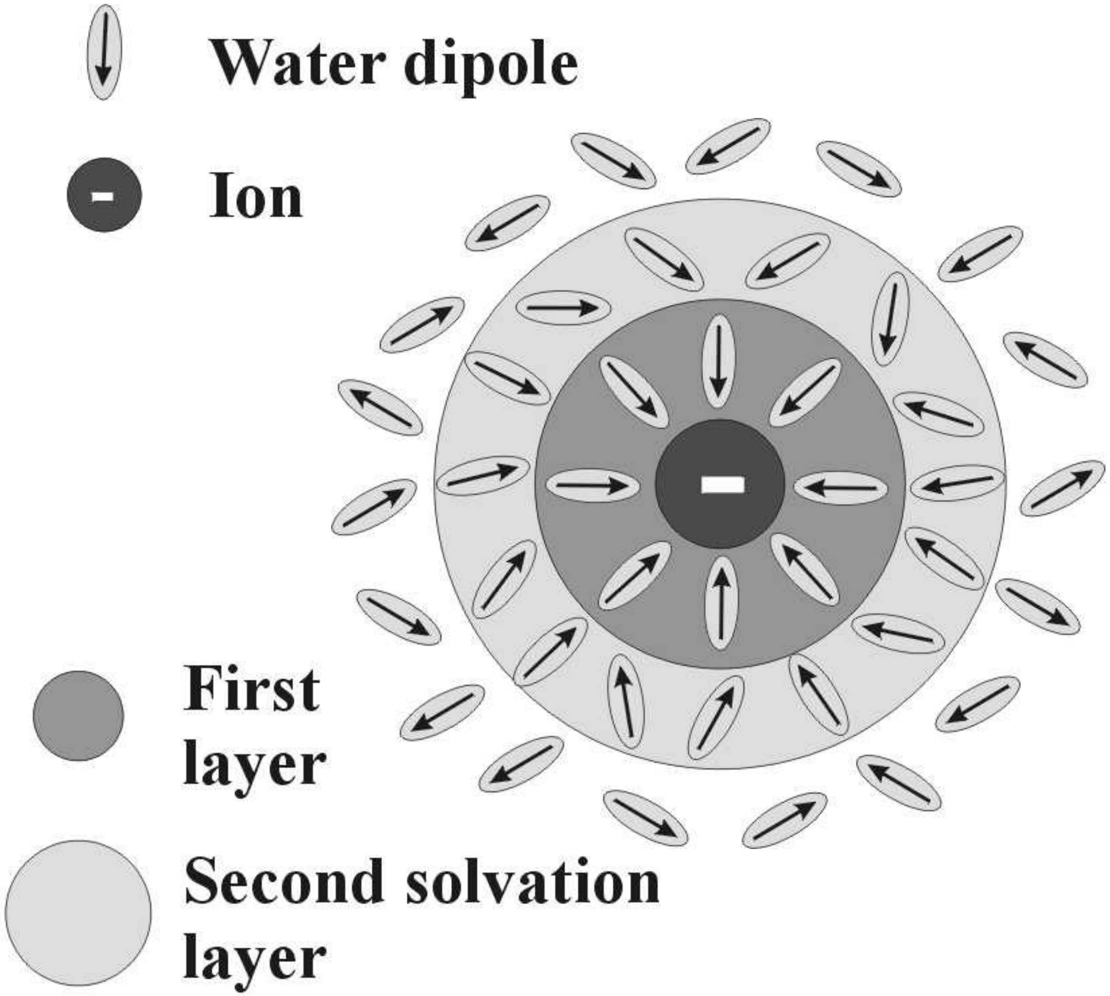






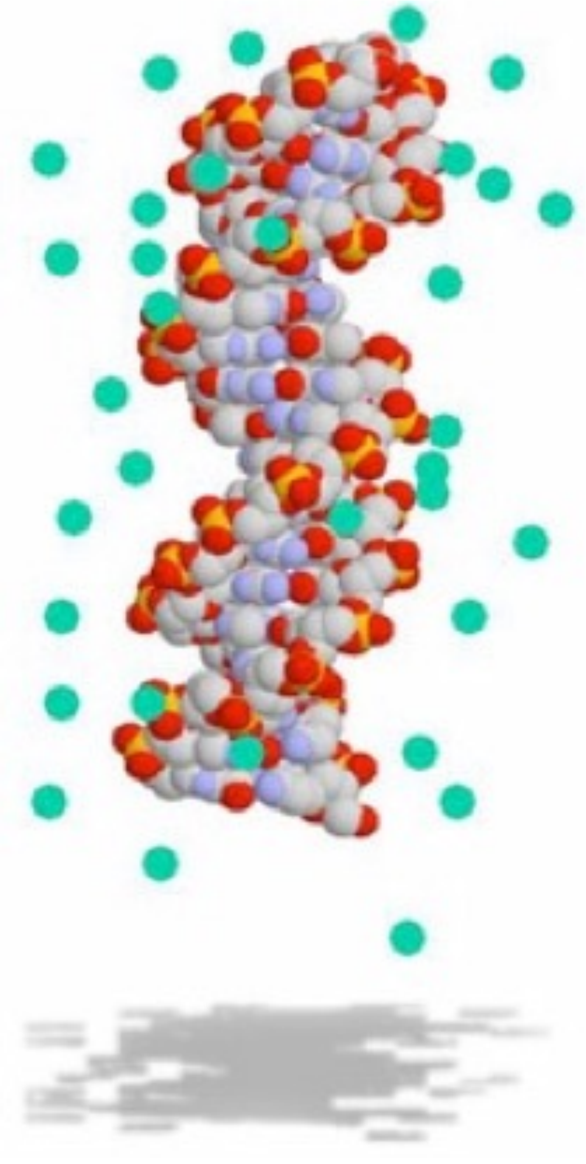
Solvation/hydration shells

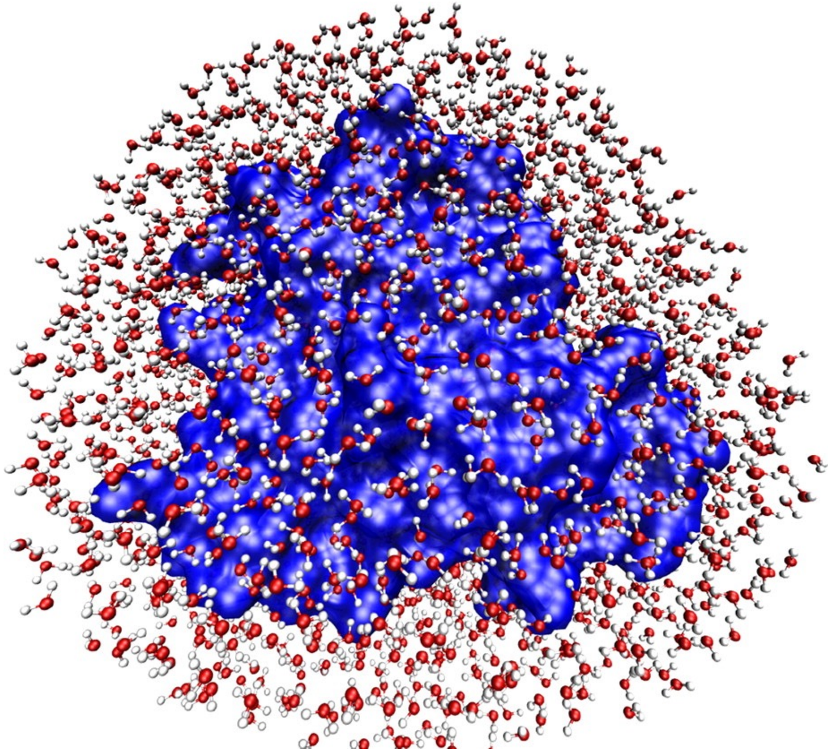




The hydration/solvation shell can be several molecules thick, dependent upon the charge of the ion, its distribution and spatial dimensions. The rearrangement also extend to several layer before reaching again the conditions of bulk solution.

Solvation/hydration shells in biomolecules





The hydration shell (also sometimes called hydration layer) that forms around biomolecules is of particular importance in biochemistry. This interaction of the protein surface with the surrounding water is often referred to as protein hydration and is fundamental to the activity of the biomolecules.

Passive Transport through Channels/Transporters

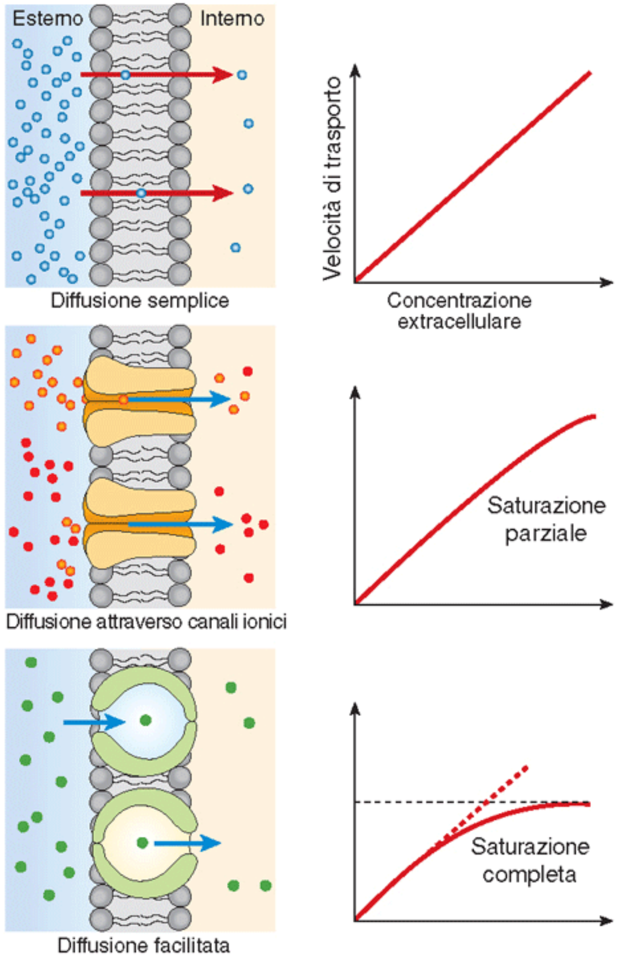


Figura 1.10 Relazione tra permeabilità (velocità di trasporto attraverso la membrana) e la concentrazione di soluti nel liquido extracellulare. Nel caso della diffusione passiva la relazione è lineare. Nel caso della diffusione facilitata (carrier) o attraverso canali ionici, la relazione è invece lineare a basse concentrazioni per poi saturare in maniera diversa ad alte concentrazioni.

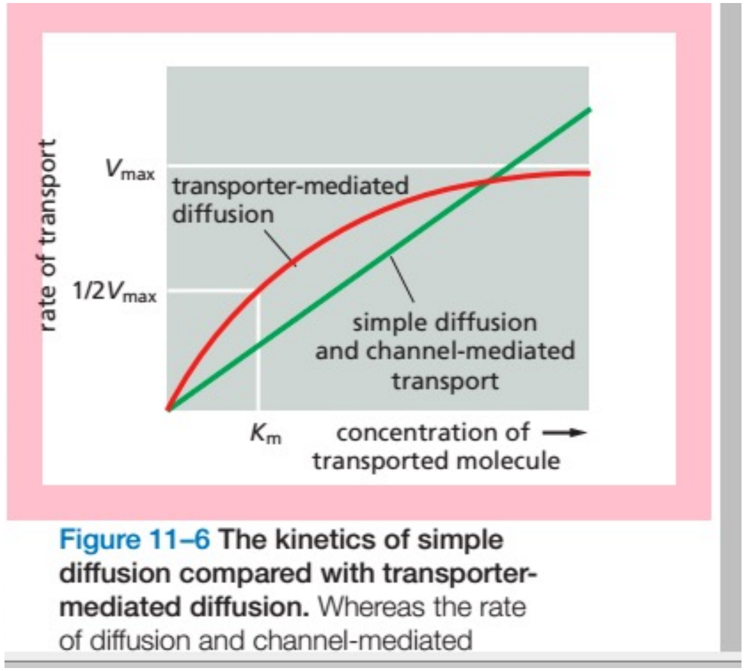


Figure 11–6 The kinetics of simple diffusion compared with transporter-mediated diffusion. Whereas the rate of diffusion and channel-mediated

As for enzymes, V_{max} (V for velocity), is characteristic of the specific carrier. V_{max} measures the rate at which the carrier can flip between its conformational states.
Each transporter has a characteristic affinity for its solute, the K_m of the reaction, equal to the concentration of solute when the transport rate is half its maximum value

Active Transport Is Mediated by Transporters Coupled to an Energy Source

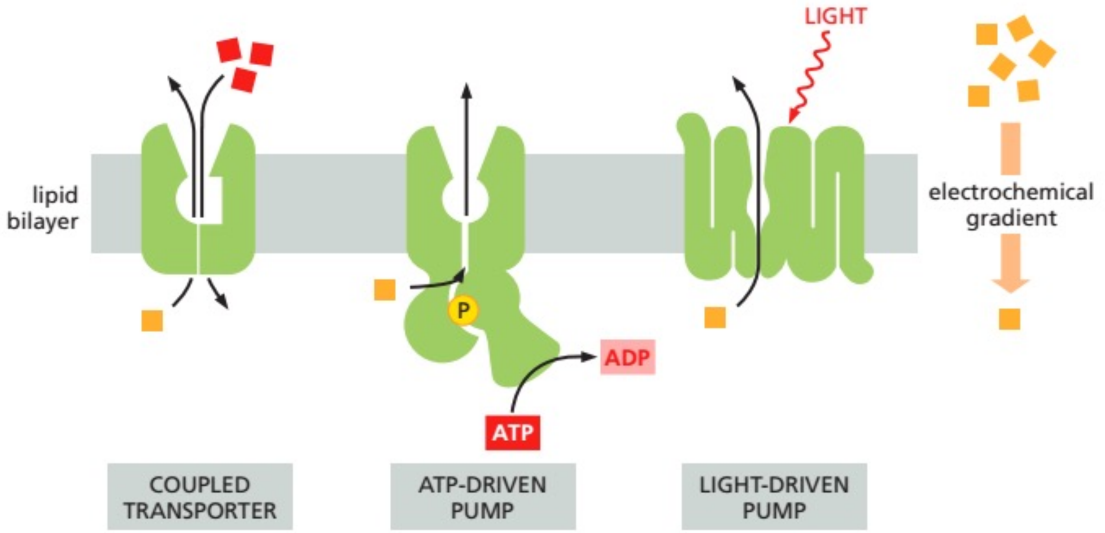
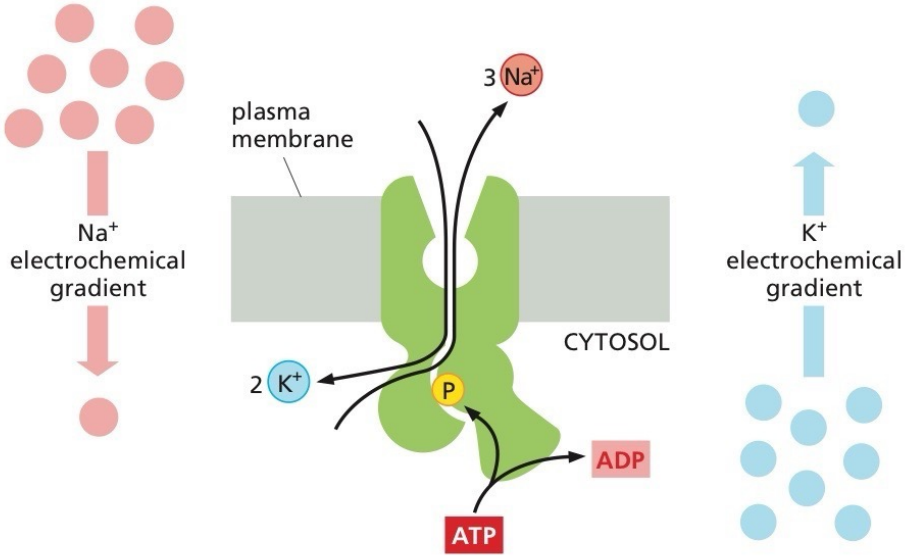


Figure 11–7 Three ways of driving active transport. The actively transported molecule is shown in *orange*, and the energy source is shown in *red*. Redox driven active transport is discussed in Chapter 14 (see Figures 14–18 and 14–19).

- 1. Coupled transporters harness the energy stored in concentration gradients to couple the uphill transport of one solute across the membrane to the downhill transport of another.
- 2. ATP-driven pumps couple uphill transport to the hydrolysis of ATP.
- 3. Light- or redox-driven pumps, which are known in bacteria, archaea, mitochondria, and chloroplasts, couple uphill transport to an input of energy from light, as with bacteriorhodopsin, or from a redox reaction, as with cytochrome c oxidase

Active Transport Is Mediated by Transporters Coupled to an Energy Source

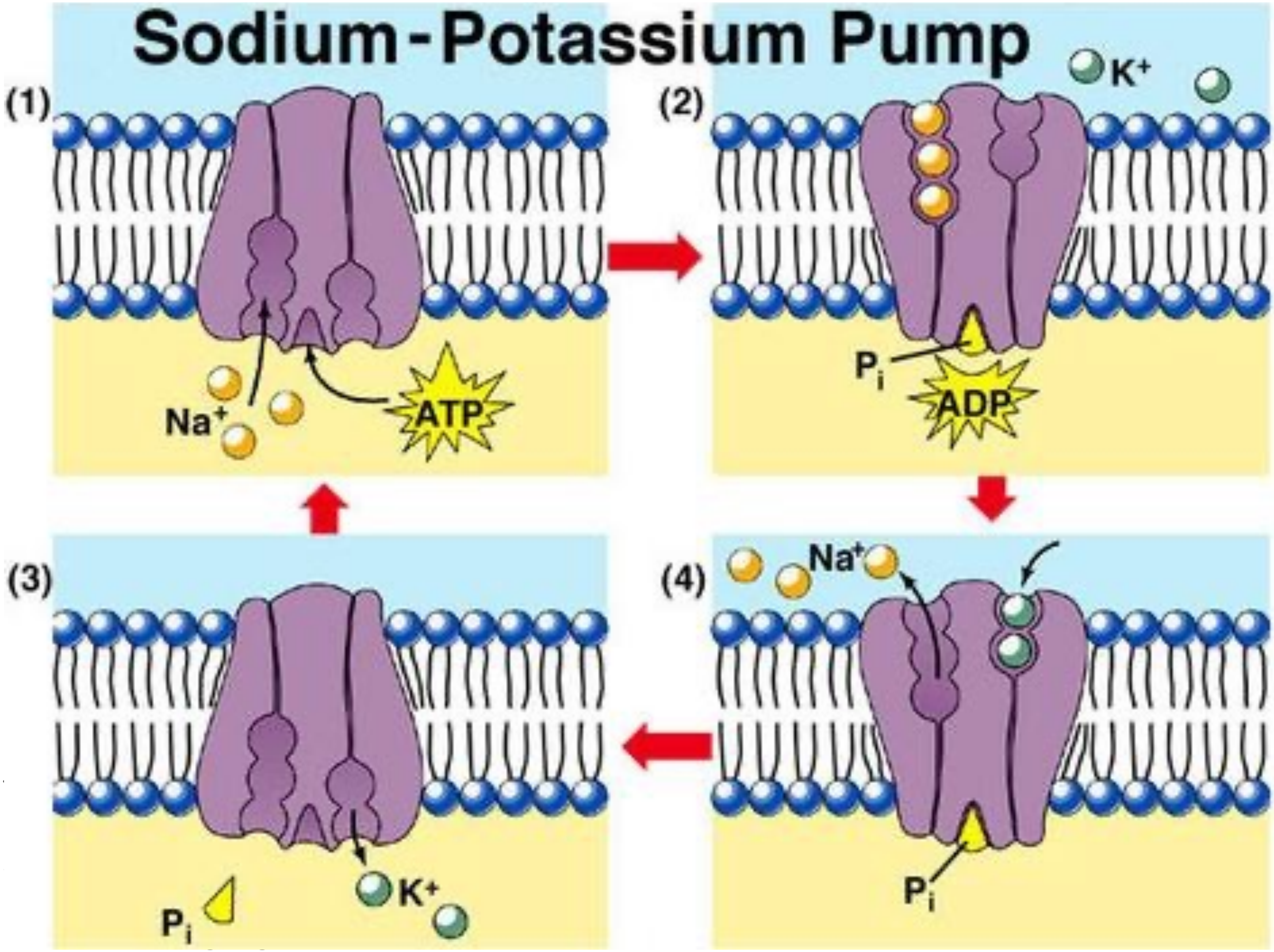
The concentration of K + is typically 10–30 times higher inside cells than outside, whereas the reverse is true of Na +



Na^+- K^+ ATPase

P-type pumps are structurally and functionally related multipass transmembrane proteins. They are called “P-type” because they phosphorylate themselves during the pumping cycle. For each ATP hydrolized, it pumps 3 Na^+ out and 2 K^+ in

This pump drives the transport of most nutrients into animal cells and also has a crucial role in regulating cytosolic pH. The pump consumes about 1/3 of the entire cell energy and even more in nerve cells.
Since it drives three positively charged ions out of the cell for every two it pumps in, it is electrogenic: it drives a net electric current across the membrane, **tending to create an electrical potential,** with the cell’s inside being negative relative to the outside.



Sodium-Potassium Pump

d,

Membrane potential

membranes act as capacitors maintaining a potential difference between oppositely charged surfaces composed mainly of phospholipids with proteins embedded in them.

A typical value of the capacitance per unit area C/A is about 1µF/cm2.
This relates to the membrane's **dielectric constant κ** via the following equation:

$$\frac{C}{A} = \frac{\kappa \varepsilon_0}{d}$$

where $\varepsilon_0 = 8.85 \times 10^{-12}\ C^2/Nm^2$, giving a value of κ ∼=10, which is greater than κ ∼=3 for phospholipids above, resulting from the active presence of proteins.

Membrane potential

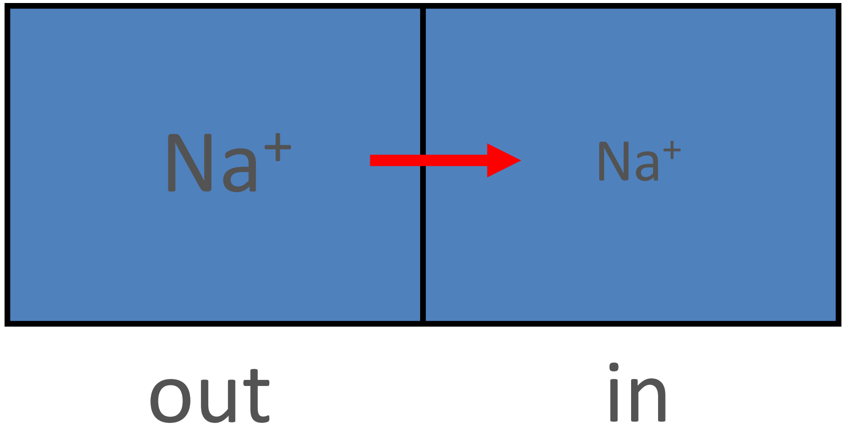
The cellular membrane is much more permeable to potassium ions (more potassium channel!) than sodium ions (the intercellular fluid contains primarily sodium chloride) in the normal resting state, which results in an outward flow of potassium ions, and the **voltage inside the cell is −85 mV**.
This voltage is called **the resting potential of the cell**.

If the cell is stimulated by mechanical, chemical, or electrical means, sodium ions diffuse more readily into the cell since the stimulus changes the permeability of the cellular membrane.
The inward diffusion of a small amount of sodium ions increases the interior voltage to +60 mV (145 mV net voltage difference!), which is known as the **action potential** of the cell.

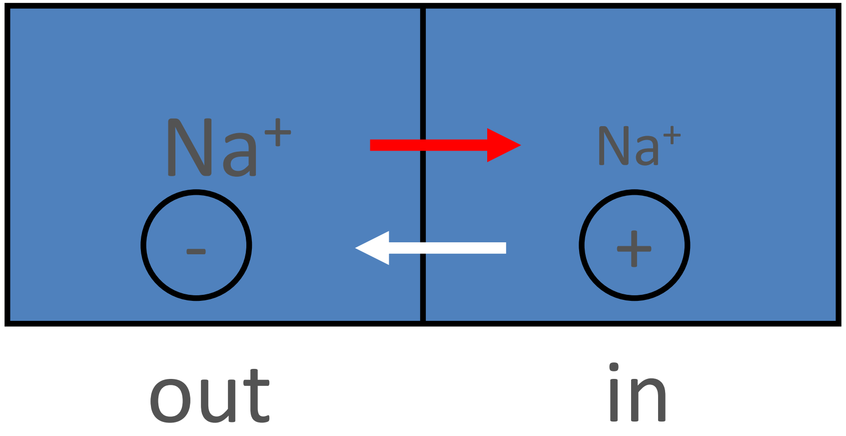
The membrane again changes its permeability once the cell has achieved its action potential, and potassium ions then readily diffuse outward so the cell returns to its resting potential.

Membrane potential

The overall membrane potential is the result of the action of voltage-gated K^+ and Na^+ pumps and of Na^+ K^+ ATPase

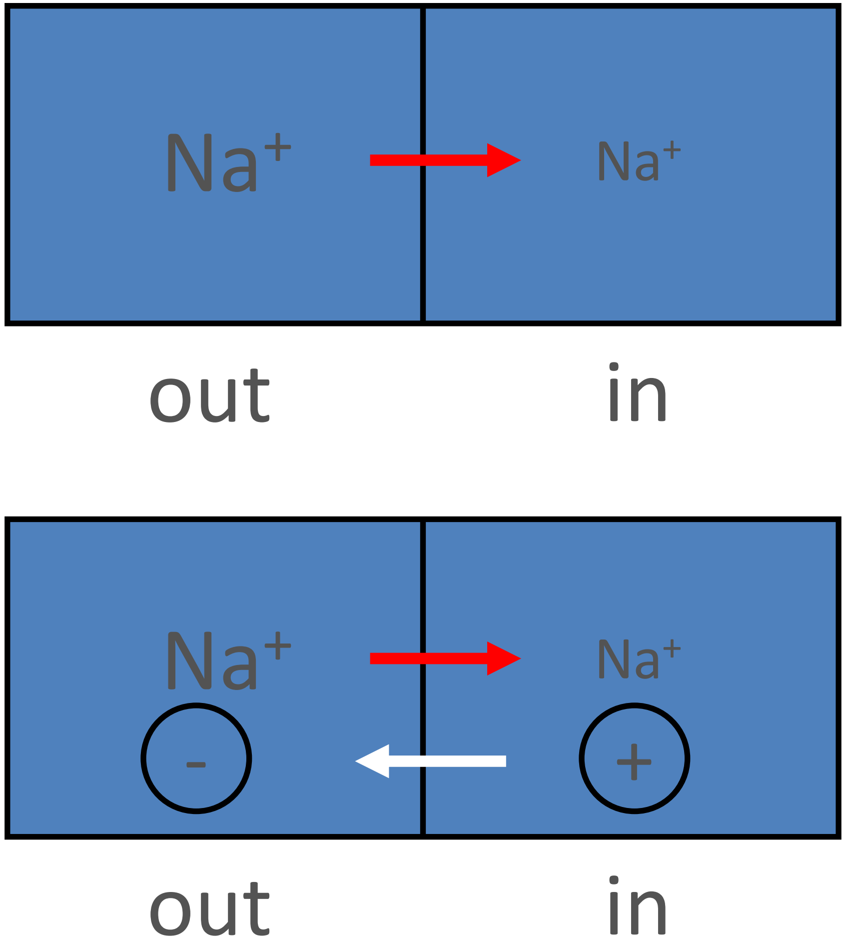


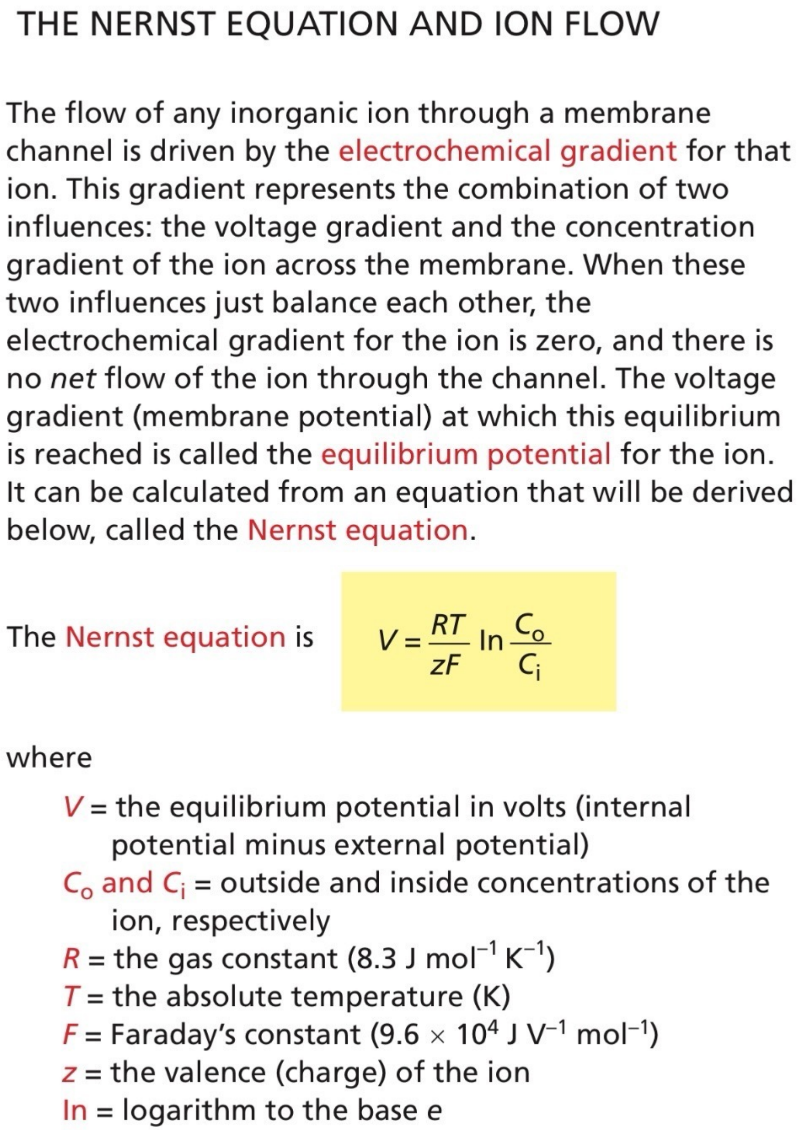
Chemical gradient



Electrochemical gradient

Membrane potential





THE NERNST EQUATION AND ION FLOW

The flow of any inorganic ion through a membrane channel is driven by the electrochemical gradient for that ion. This gradient represents the combination of two influences: the voltage gradient and the concentration gradient of the ion across the membrane. When these two influences just balance each other, the electrochemical gradient for the ion is zero, and there is no *net* flow of the ion through the channel. The voltage gradient (membrane potential) at which this equilibrium is reached is called the equilibrium potential for the ion. It can be calculated from an equation that will be derived below, called the Nernst equation.

The Nernst equation is

$$V = \frac{RT}{zF} \ln \frac{C_o}{C_i}$$

where

V = the equilibrium potential in volts (internal potential minus external potential)

C_o and C_i = outside and inside concentrations of the ion, respectively

R = the gas constant ($8.3 \text{ J mol}^{-1} \text{ K}^{-1}$)

T = the absolute temperature (K)

F = Faraday's constant ($9.6 \times 10^4 \text{ J V}^{-1} \text{ mol}^{-1}$)

z = the valence (charge) of the ion

ln = logarithm to the base e

A molecule in solution (a solute) tends to move from a region of high concentration to a region of low concentration simply due to the random movement of molecules, which results in their equilibrium. Consequently, movement down a concentration gradient is accompanied by a favorable free-energy change ($\Delta G < 0$), whereas movement up a concentration gradient is accompanied by an unfavorable free-energy change ($\Delta G > 0$). (Free energy is introduced in Chapter 2 and discussed in the context of redox reactions in Panel 14–1, p. 765.)

The free-energy change per mole of solute moved across the plasma membrane (ΔG_{conc}) is equal to $-RT \ln C_o / C_i$.

If the solute is an ion, moving it into a cell across a membrane whose inside is at a voltage V relative to the outside will cause an additional free-energy change (per mole of solute moved) of $\Delta G_{volt} = zFV$.

At the point where the concentration and voltage gradients just balance,

$$\Delta G_{conc} + \Delta G_{volt} = 0$$

and the ion distribution is at equilibrium across the membrane.

Thus,

$$zFV - RT \ \ln \frac{C_o}{C_i} = 0$$

and, therefore,

$$V = \frac{RT}{zF} \ln \frac{C_o}{C_i}$$

or, using the constant that converts natural logarithms to base 10,

$$V = 2.3 \frac{RT}{zF} \log_{10} \frac{C_o}{C_i}$$

For a univalent cation,

$$2.3 \frac{RT}{F} = 58 \text{ mV at } 20°\text{C} \quad \text{and} \quad 61.5 \text{ mV at } 37°\text{C}.$$

Thus, for such an ion at 37°C,

$$V = +\,61.5 \text{ mV for } C_o / C_i = 10,$$

whereas

$$V = 0 \text{ for } C_o / C_i = 1.$$

The K^+ equilibrium potential (V_K), for example, is

$$61.5 \log_{10}([K^+]_o / [K^+]_i) \text{ millivolts}$$

(–89 mV for a typical cell, where $[K^+]_o = 5$ mM
and $[K^+]_i = 140$ mM).

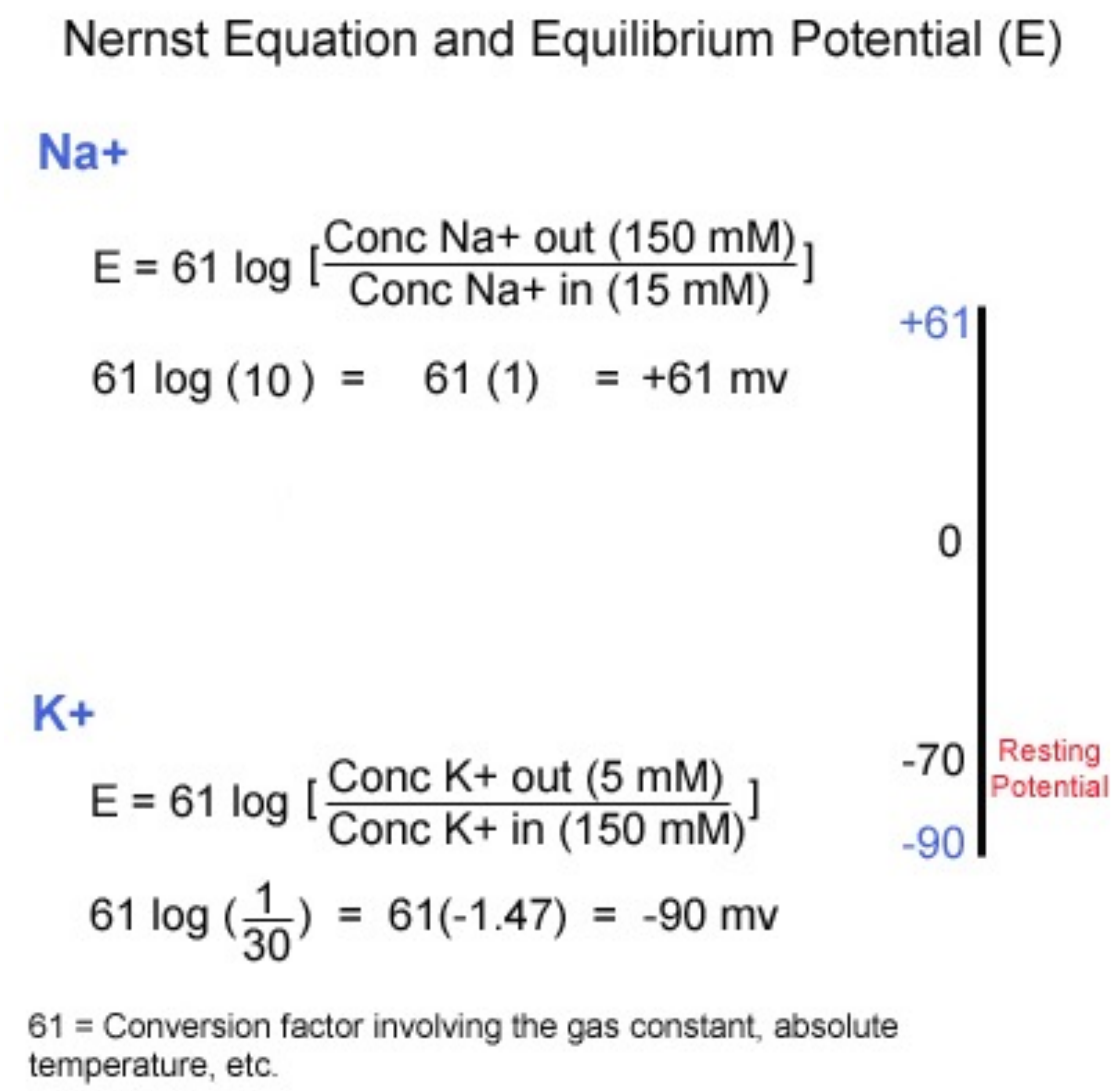
At V_K, there is no net flow of K^+ across the membrane.

Similarly, when the membrane potential has a value of

$$61.5 \log_{10}([Na^+]_o / [Na^+]_i),$$

the Na^+ equilibrium potential (V_{Na}),
there is no net flow of Na^+.

Membrane potential



Nernst Equation and Equilibrium Potential (E)

Na+

$$E = 61 \log \left[\frac{\text{Conc Na+ out (150 mM)}}{\text{Conc Na+ in (15 mM)}}\right]$$

$$61 \log (10) = 61 (1) = +61 \text{ mv}$$

K+

$$E = 61 \log \left[\frac{\text{Conc K+ out (5 mM)}}{\text{Conc K+ in (150 mM)}}\right]$$

$$61 \log \left(\frac{1}{30}\right) = 61(-1.47) = -90 \text{ mv}$$

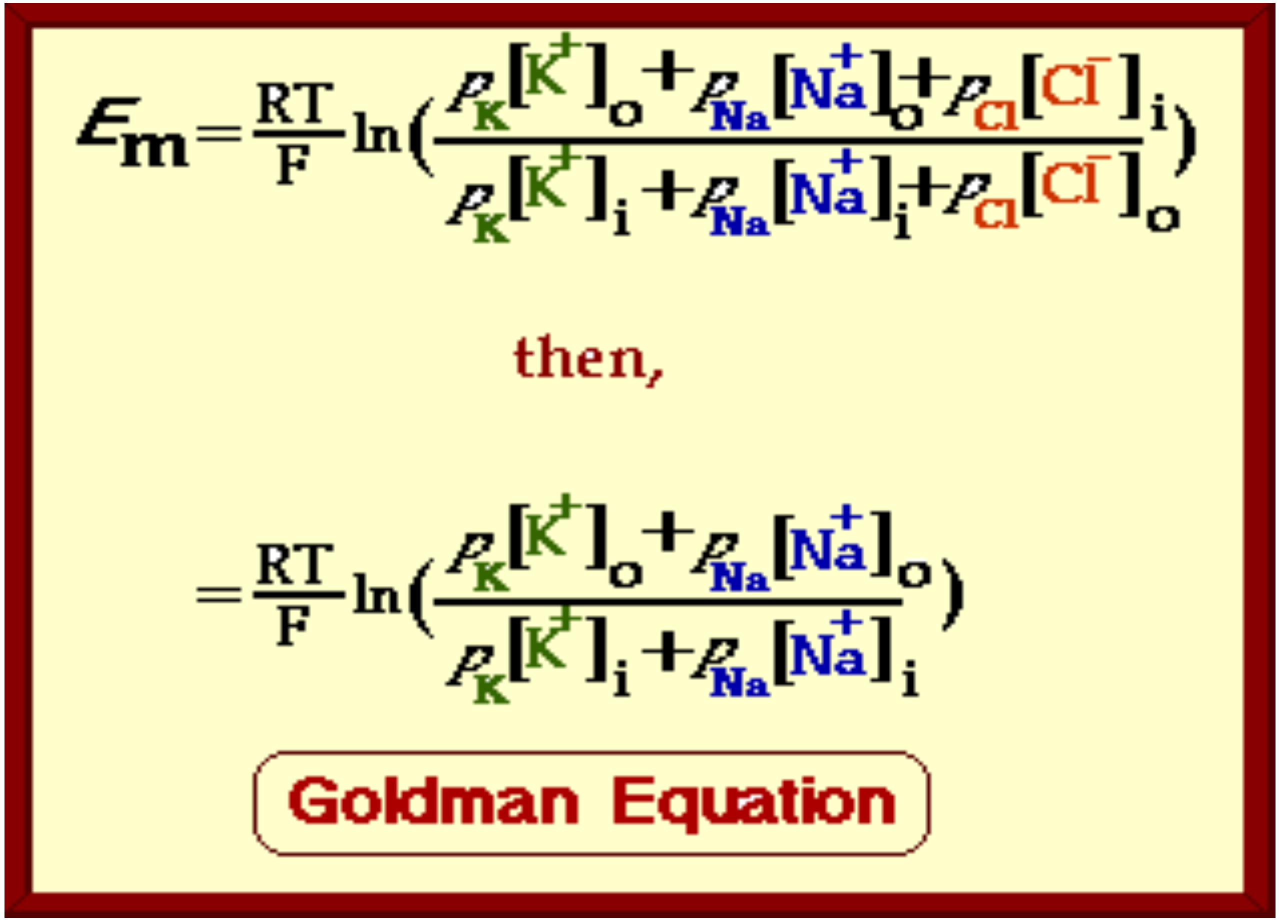
61 = Conversion factor involving the gas constant, absolute temperature, etc.

Membrane potential

Ion	Typical Internal Concentration (mM)	Typical External Concentration (mM)	Nernst Potential (mV)
Na^+	12	145	+67
K^+	155	4	-98
Ca^{2+}	10^{-4}	1.5	+129
Cl^-	4	120	-90

Membrane potential

Indeed, also membrane permeability plays a big role: Na^+ and K^+ permeability ratio is 1/100
Therefore the membrane resting potential is similar to the one of K^+



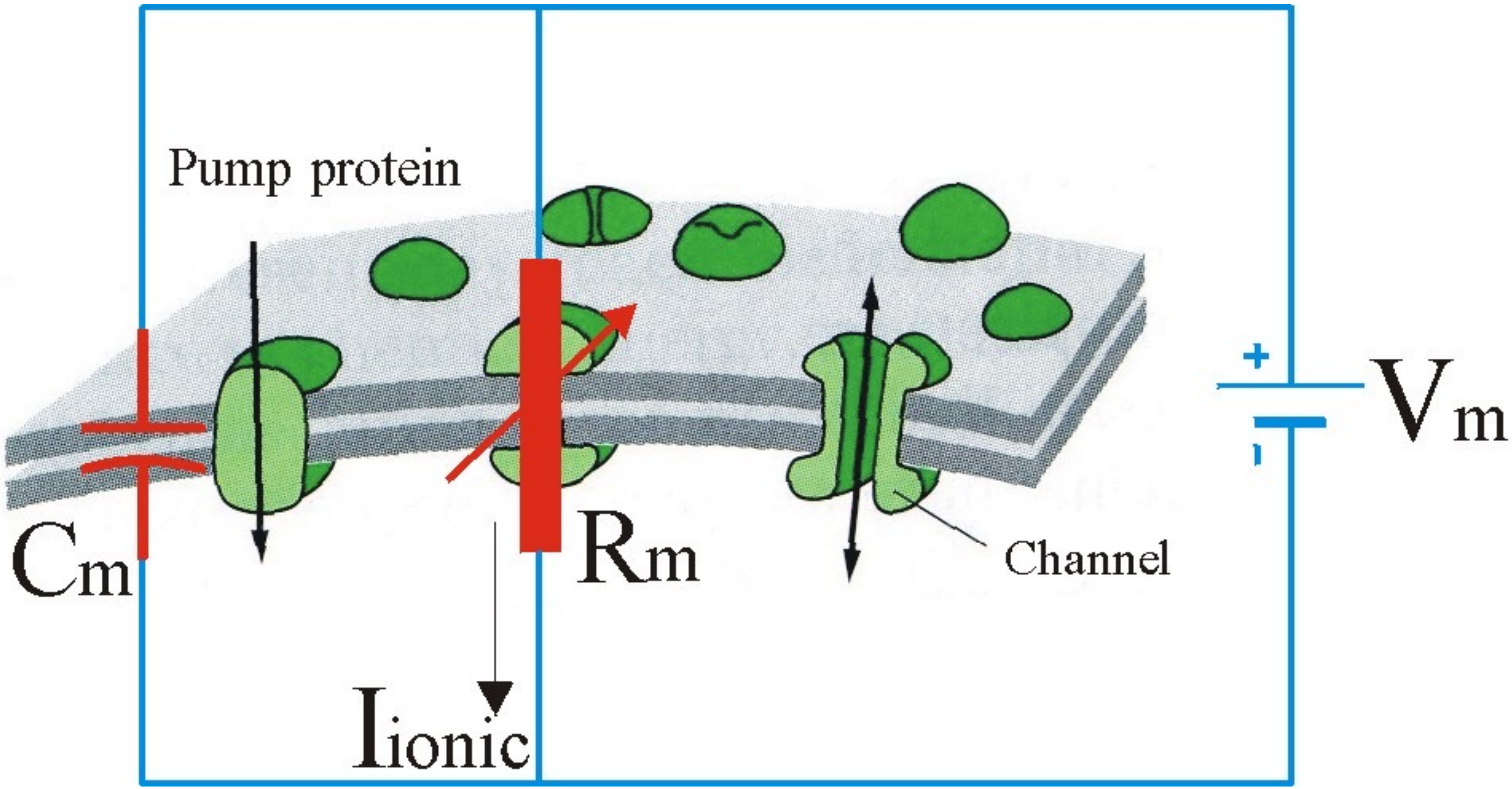
$$E_m = \frac{RT}{F} \ln\left(\frac{P_K[K^+]_o + P_{Na}[Na^+]_o + P_{Cl}[Cl^-]_i}{P_K[K^+]_i + P_{Na}[Na^+]_i + P_{Cl}[Cl^-]_o}\right)$$

then,

$$= \frac{RT}{F} \ln\left(\frac{P_K[K^+]_o + P_{Na}[Na^+]_o}{P_K[K^+]_i + P_{Na}[Na^+]_i}\right)$$

Goldman Equation

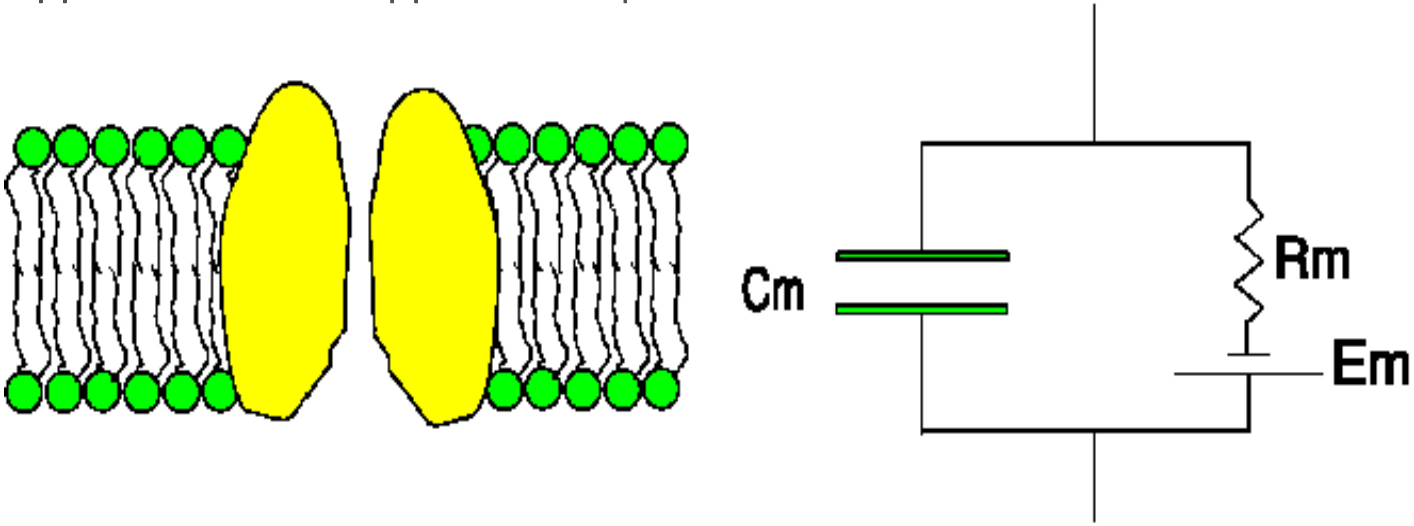
Membrane potential electrical model



The resting potential is the equivalent of a battery

Membrane potential electrical model

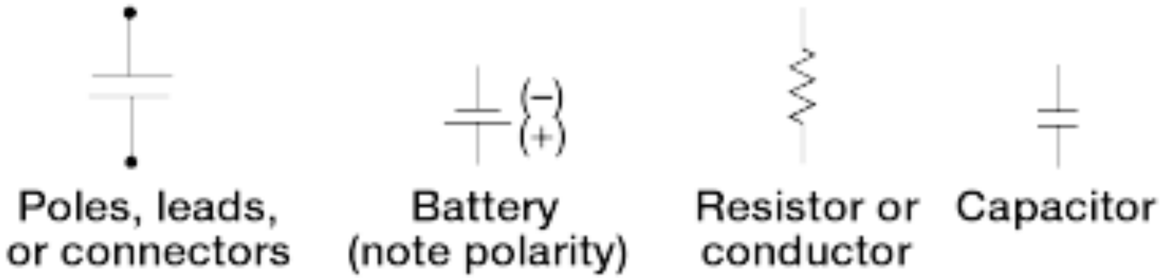
Il doppio strato lipidico, dal punto di vista elettrico si comporta come un condensatore. Le due piastre conduttrici sono rappresentate dal mezzo intracellulare e da quello extracellulare. Il dielettrico isolante è rappresentato dal doppio strato lipidico.



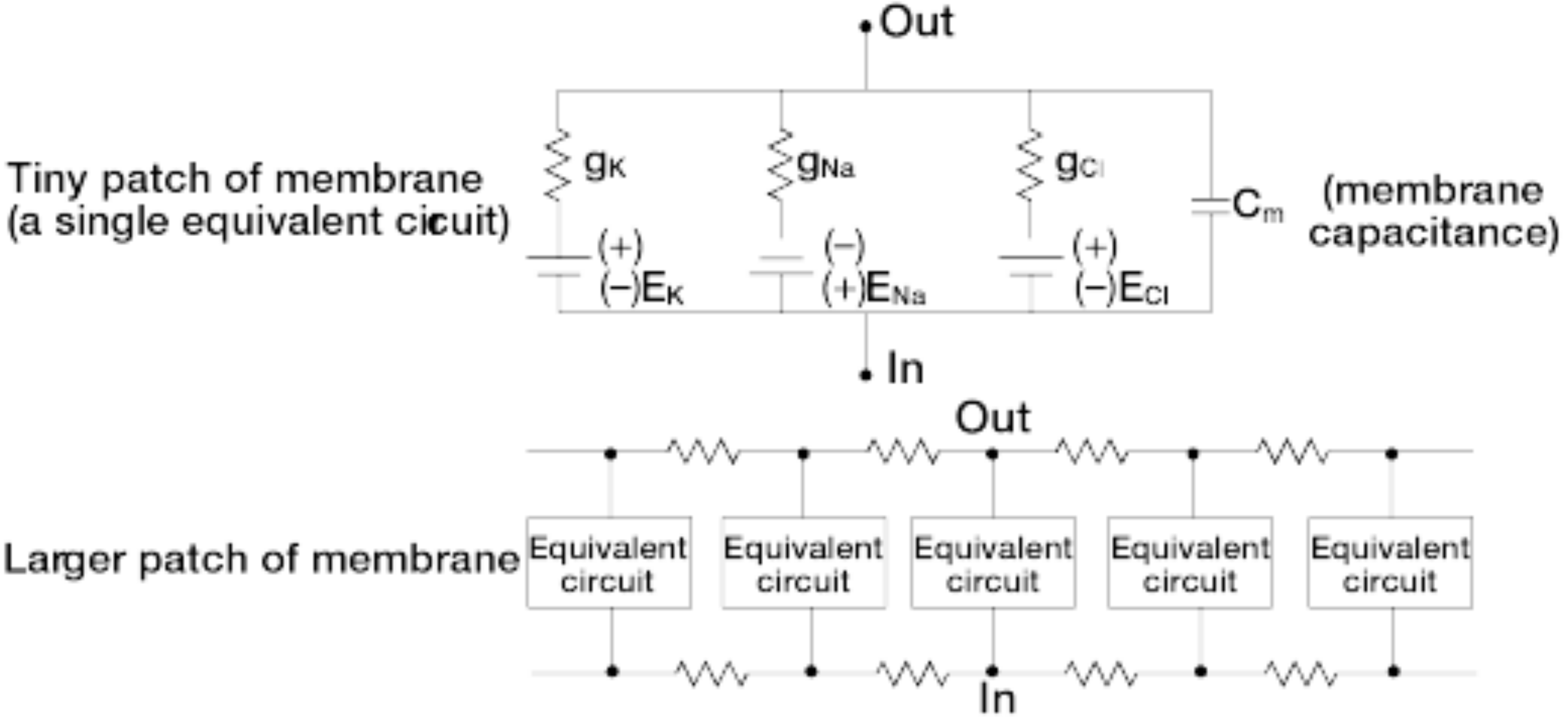
$C= \varepsilon A / d$ *A* area della membrana; *d* spessore della membrana

$C_m= C /A = \varepsilon / d$ $d=50$ Å $C_m=2\mu F/cm^2$

The Equivalent Circuit

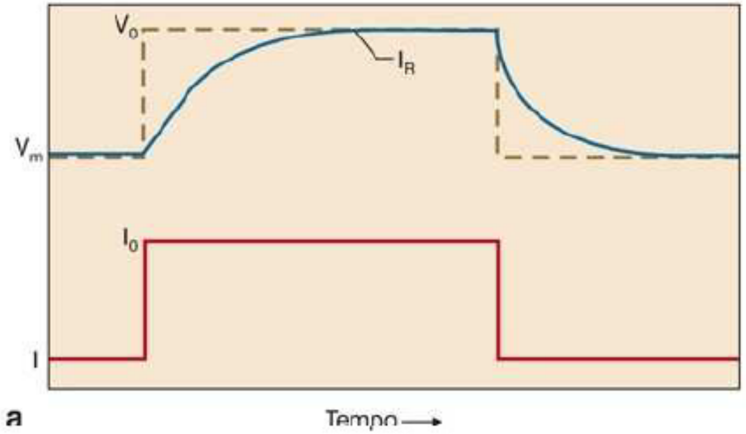


(a) Electrical symbols



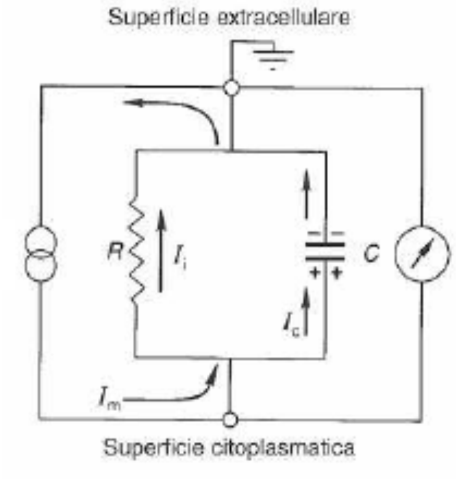
(b) The equivalent circuit for a resting cell membrane

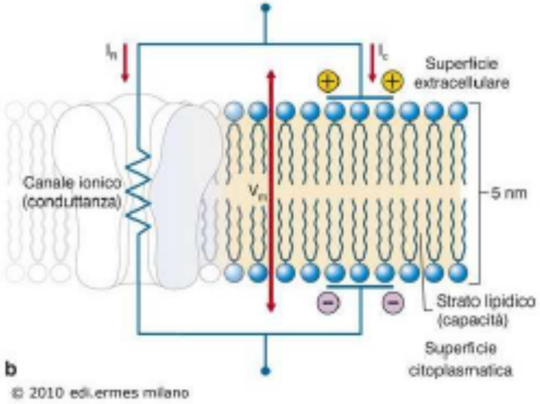
Membrane potential electrical model

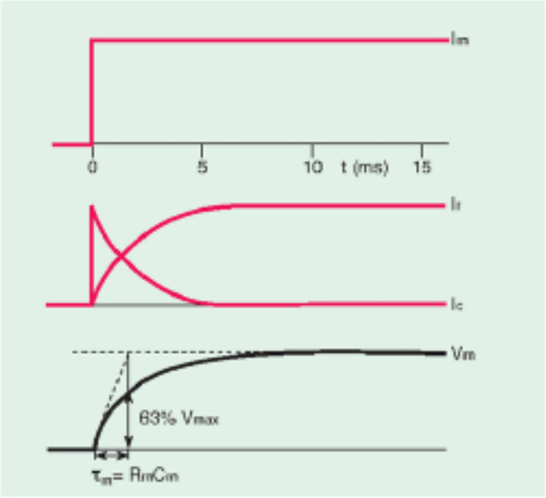


- Le proprietà del circuito RC di membrana determinano ampiezza ed andamento temporale delle variazioni del potenziale causate da flussi di correnti che attraversano la membrana grazie ai canali ionici.
- Spiegano alcune caratteristiche delle risposte neuronali.

Equivalente Elettrico della membrana (Capacità e Resistenza in parallelo)







La corrente I_m che attraversa la membrana in seguito all'applicazione di uno stimolo si divide in due componenti: I_c (corrente capacitiva: flusso di ioni che fa variare la carica sulla capacità di membrana, I_i (I_r, corrente ionica: flusso di ioni attraverso i canali ionici, R).

Quando si applica uno stimolo si verificherà:

1) La corrente che attraversa la membrana va a caricare il condensatore (varia la carica, Vm).

2) Man mano che Vm si modifica, gli ioni cominciano ad attraversare i canali (R), aumenta Ii.

3) Quando il condensatore è carico, tutta la corrente applicata attraversa la R.

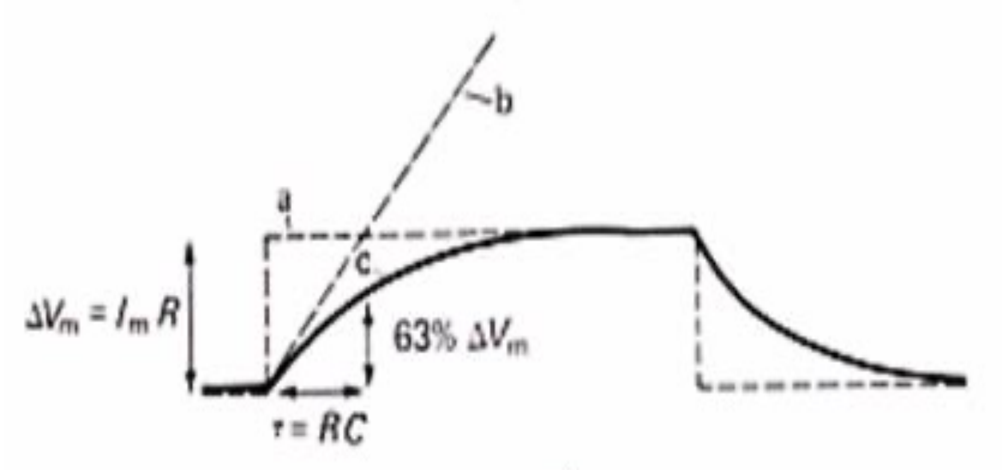
$\Delta V_m = i \cdot R$

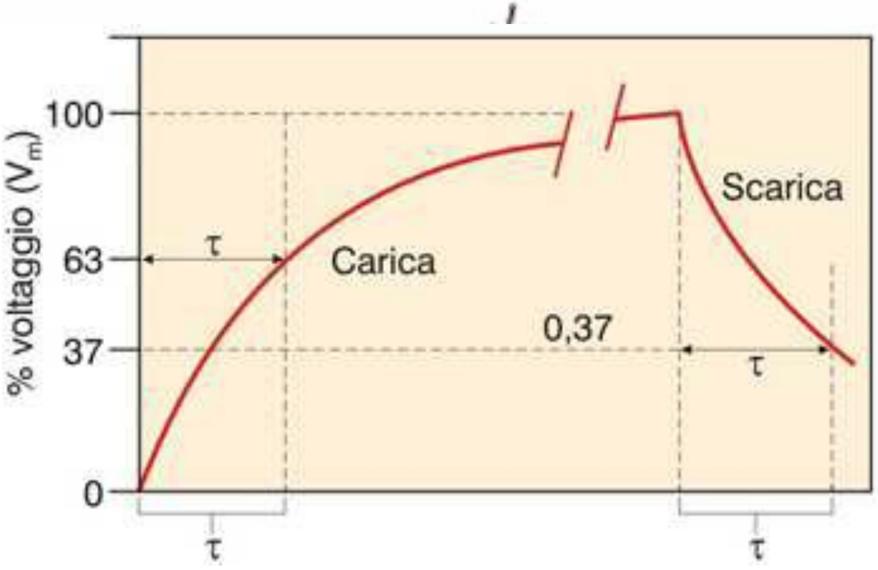
4) Alla fine dell'impulso, la corrente generata dalla scarica del condensatore passerà attraverso R, determinando un lento ritorno del Vm al valore iniziale.

Membrane potential electrical model

Stimolata da un passaggio di corrente la membrana risponde con una variazione del potenziale in modo proporzionale al valore di resistenza e capacità. Quando la corrente è iniettata essa comincia a fluire attraverso la capacità che tende a caricarsi. La fase di crescita del potenziale è data da: $V = iR\,(1 - e^{-t/\tau})$ dove $\tau = RC$. Quando $t = RC$ allora $V_t = 63\% V_0$.

RC si definisce costante tempo della membrana. Quando sono trascorse diverse costanti tempo, il potenziale approssima un asintoto e tutta la corrente fluisce attraverso la resistenza ($I_c = 0$ perché $I_c = dQ/dt = CdV/dt$) con un valore che sarà proporzionale alla legge di Ohm $V = I_r R$.





Membrane potential electrical model

Stimolata da un passaggio di corrente la membrana risponde con una variazione del potenziale in modo proporzionale al valore di resistenza e capacità. Quando la corrente è iniettata essa comincia a fluire attraverso la capacità che tende a caricarsi. La fase di crescita del potenziale è data da: $V= iR (1-e^{-t/\tau})$ dove $\tau=RC$. Quando $t=RC$ allora $V_t=63\%V_0$.

La costante di tempo (t = **$R_M C_M$**) è il tempo necessario perché Vm
aumenti o diminuisca fino a raggiungere o perdere il 63% del suo valore
finale. Per valori di Rm compresi tra 10 e 10.000 Wcm2 e Cm = 1mF/cm2
la costante di tempo delle cellule eccitabili varia da 10 ms a 10 ms.