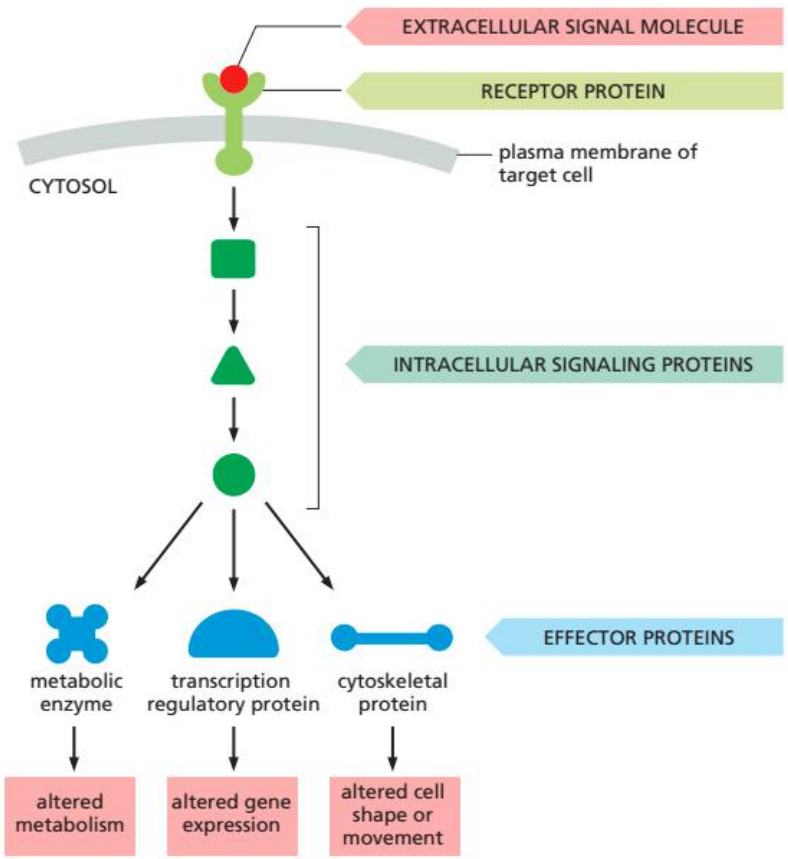
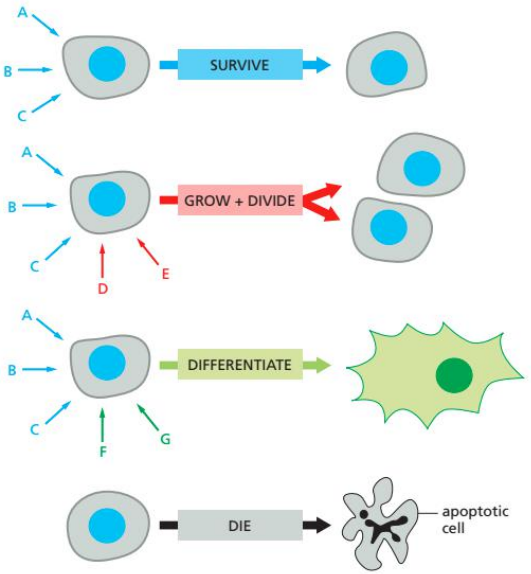
Cell membranes and cell interactions

Cell-cell communication

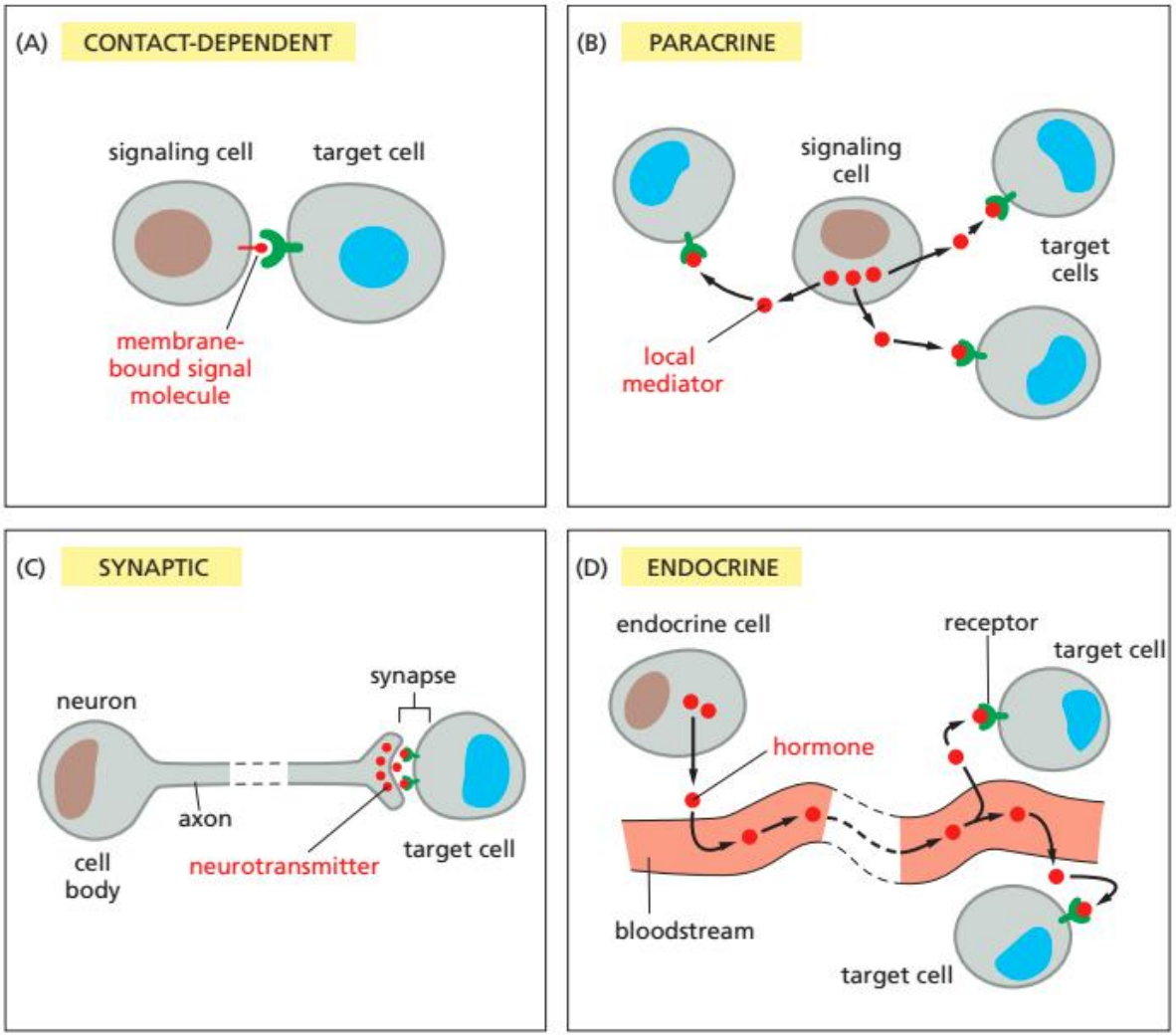


When things change, cell respond! Every cell, monitors its intracellular and extracellular environment, processes the information it gathers, and responds accordingly. (homeostasis).

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

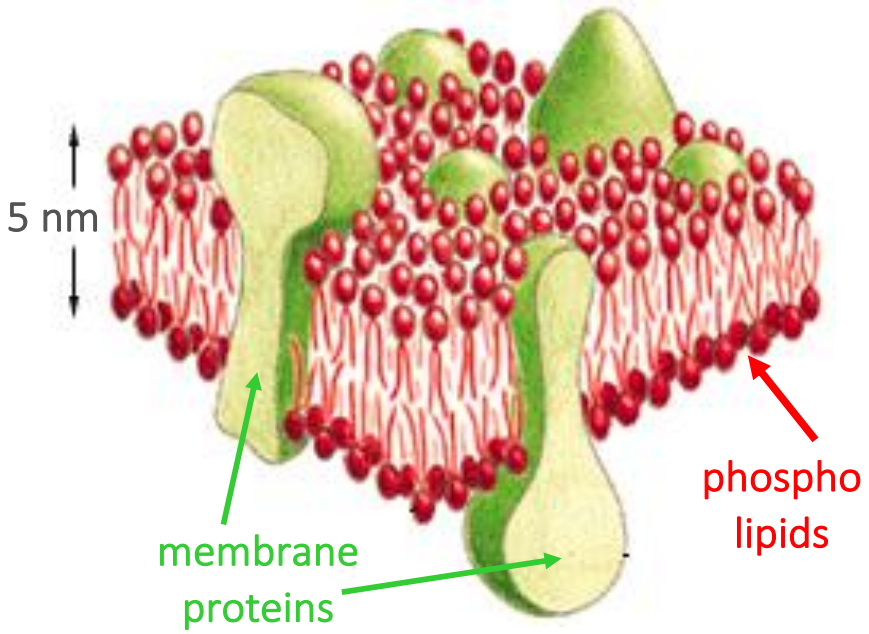
Cell-cell communication over large distances occurs mainly through nerve cells, or ***neurons***, which typically extend long, branching processes (***axons***) that enable them to contact target cells far away, where the processes terminate at the specialized sites of signal transmission known as ***chemical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

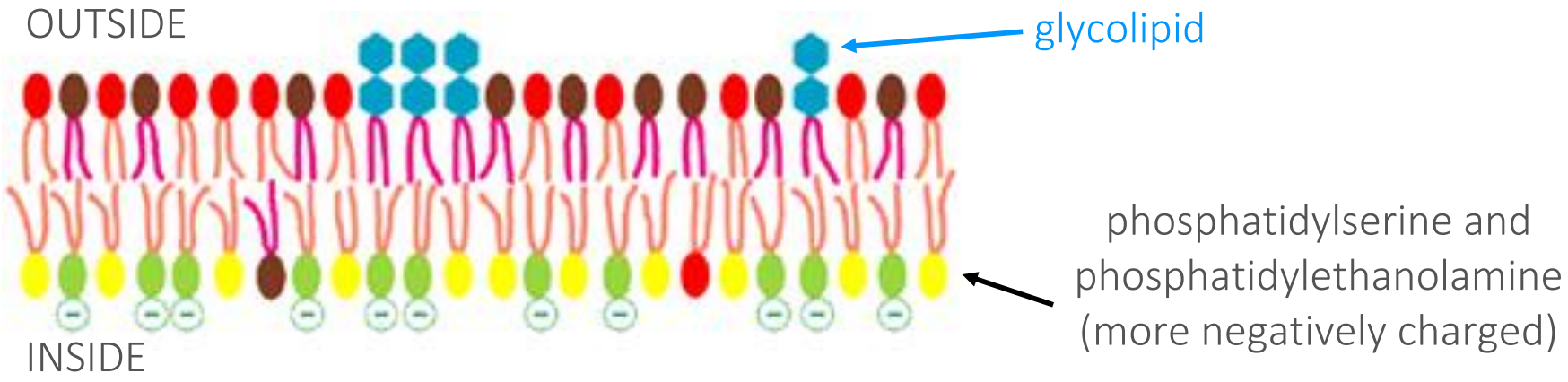
When a neuron is activated by stimuli from other nerve cells, it sends electrical impulses (***action potentials***) rapidly along its axon; when the impulse reaches the synapse at the end of the axon, it ***triggers secretion of a chemical signa***l that acts as a ***neurotransmitter.*** The tightly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

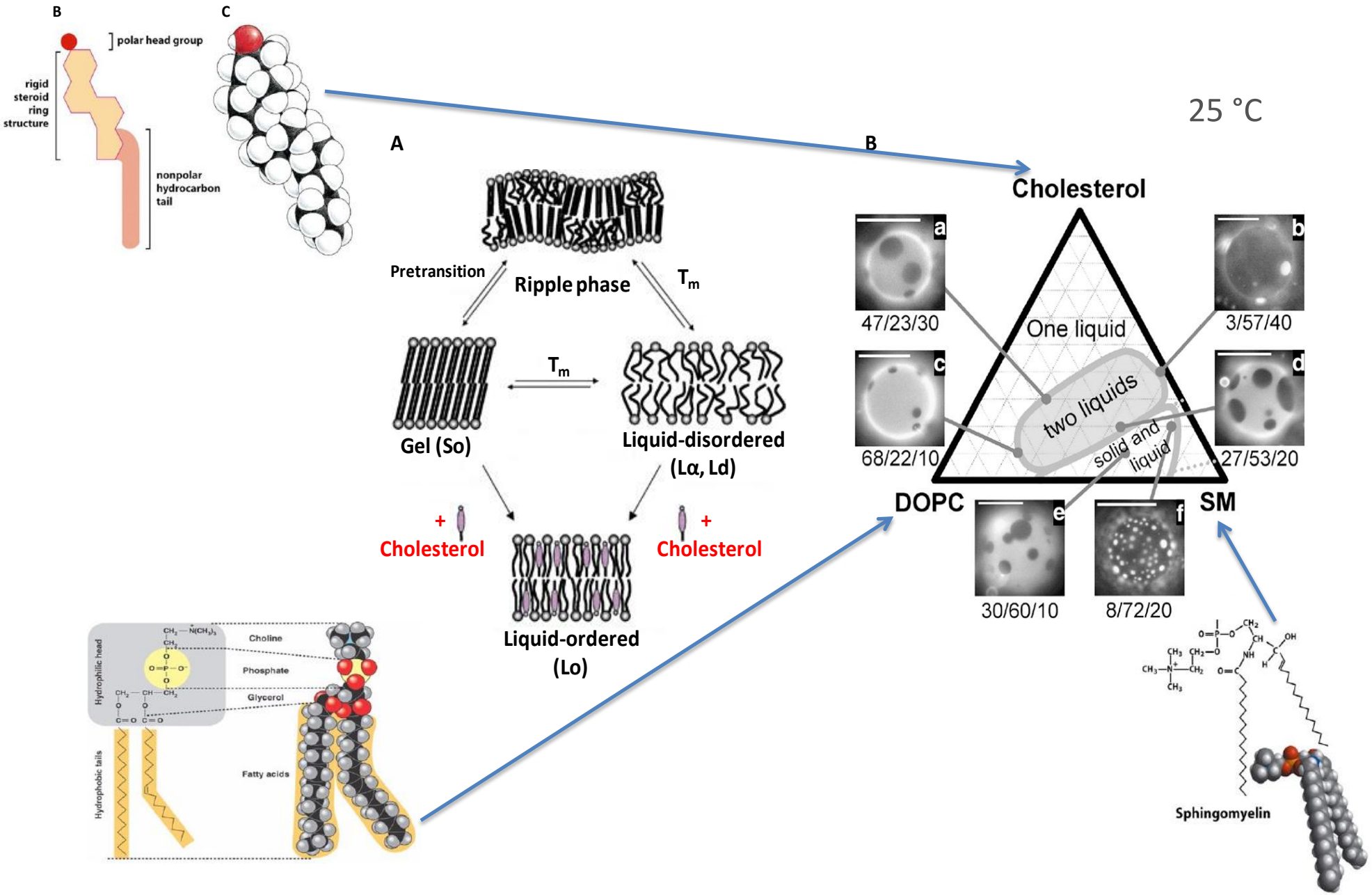
Cell membranes

- 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



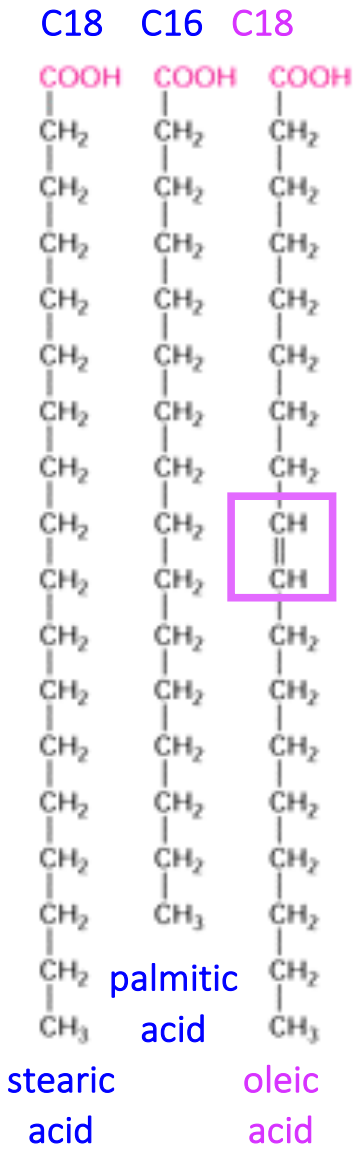


Cell membrane: an optimized 2D fluid system



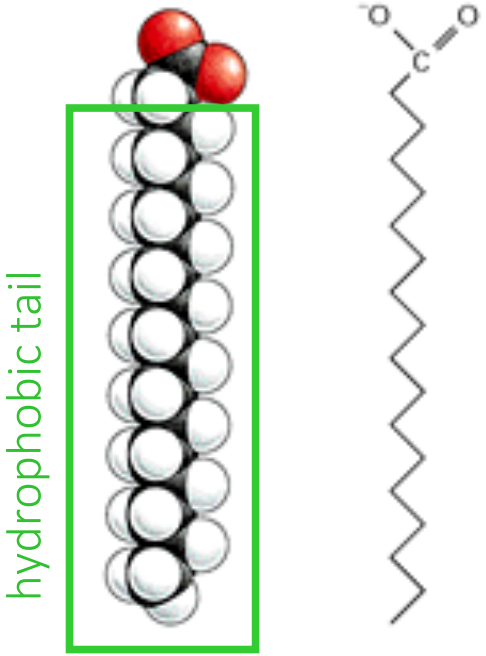
Fatty acids

Carboxylic acids with long hydrocarbon chains (12-24 $-CH_2-$ units)

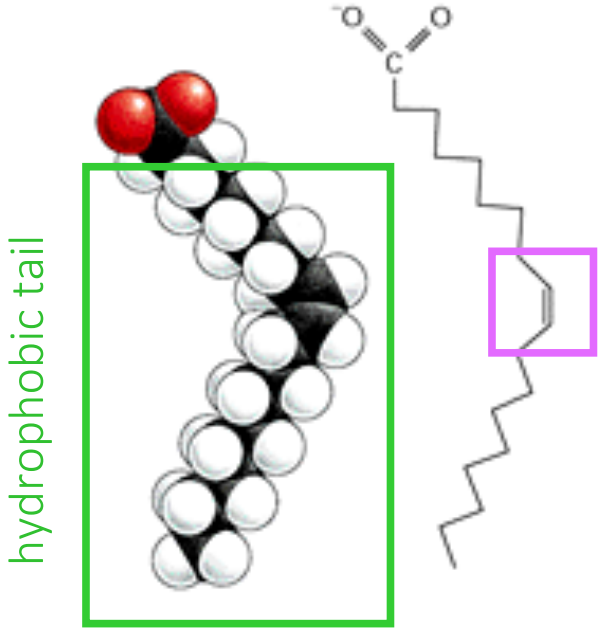


Some have one or more double bonds and are called unsaturated. The double bond is rigid and creates a kink in the chain; the rest of the chain is free to rotate

Stearic acid - saturated



Oleic acid - unsaturated



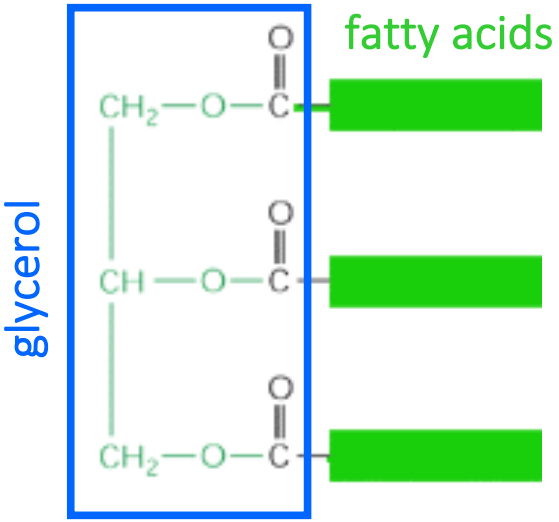
Fatty acids are used as E storage

To ensure a continuous supply of fuel for oxidative metabolism, animal cells store glucose in the form of glycogen and fatty acids in the form of fats.

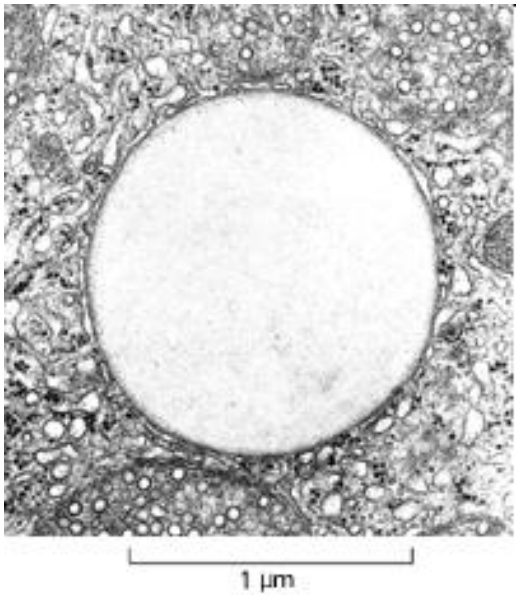
A fat molecule is composed of three molecules of fatty acid linked to glycerol: triacylglycerols (*triglycerides*).

Fat is a far more important storage form than glycogen, because its oxidation releases more than six times as much energy.

Triglycerides have no charge and are virtually insoluble in water, coalescing into droplets in the cytosol of adipose cells.

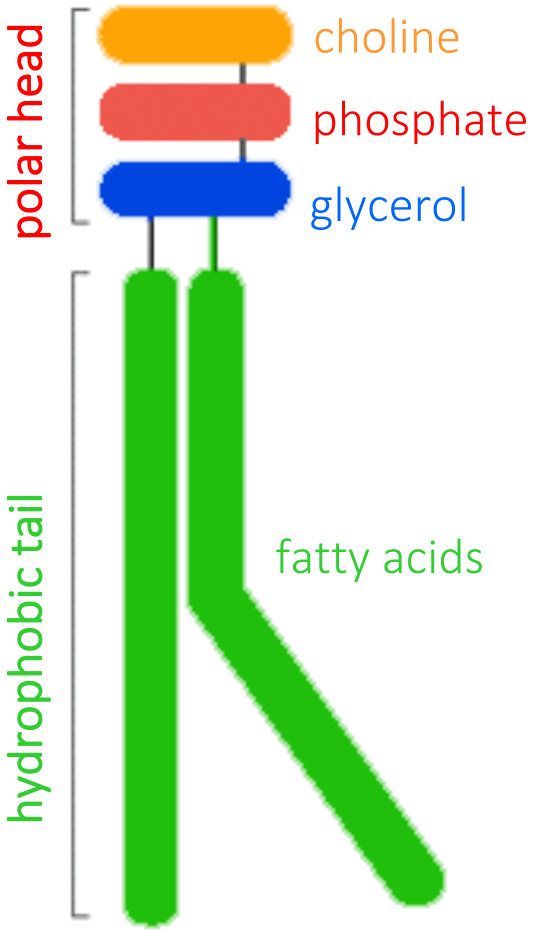


fat droplet



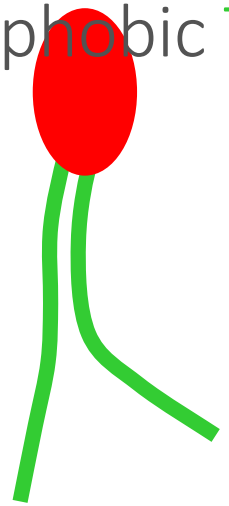
Phospholipids

In phospholipids, two of the OH groups of glycerol are linked to fatty acids, while the third is linked to a phosphate group, which can be further linked to a polar group such as choline, serine, inositol, etc...



Very asymmetric molecule:

- hydrophilic HEAD
- hydrophobic TAIL



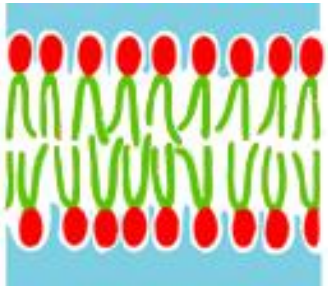
Phospholipids and membranes

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.

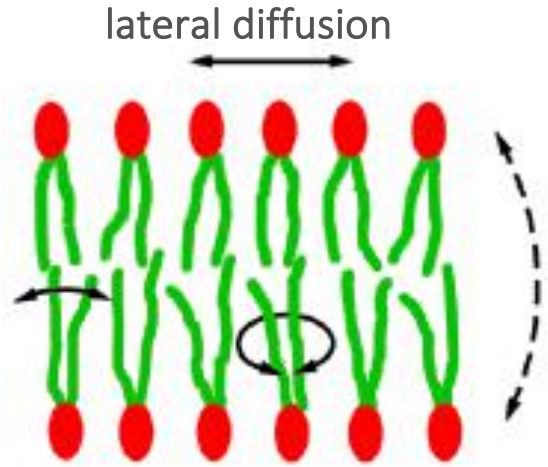
Cellular membranes are essentially made up by phospholipid bilayers.

micelle

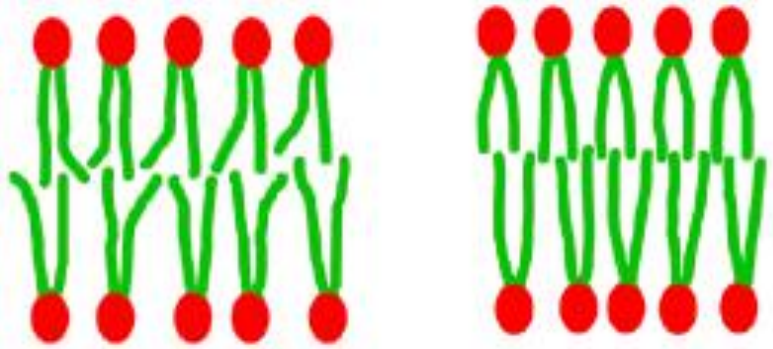


lipid bilayer

Phospholipid mobility



Saturated vs unsaturated lipids

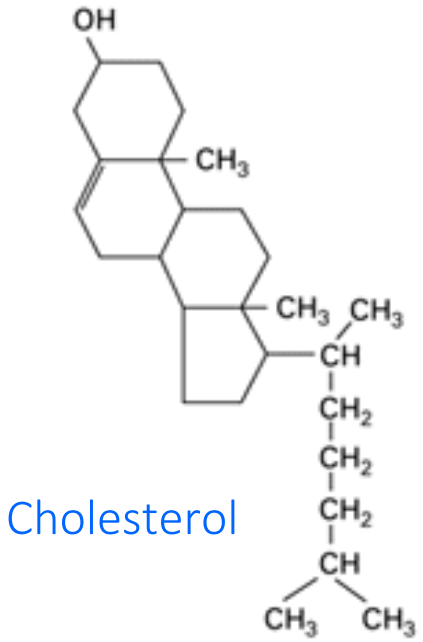


unsaturated, more difficult to pack, more fluid

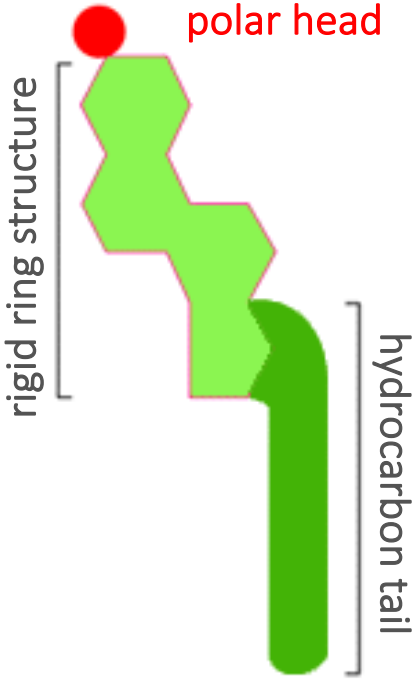
saturated, easier to pack, less fluid

Cholesterol and steroids

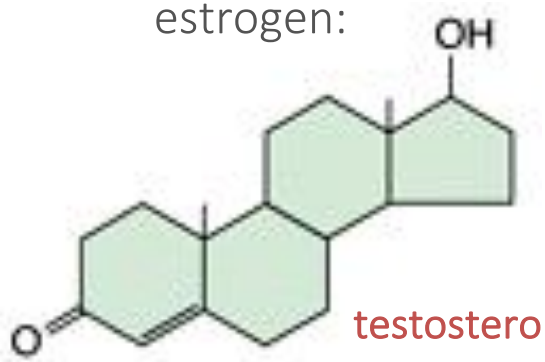
Steroids (such as cholesterol) have a rigid structure made up by 4 rings.



Cholesterol

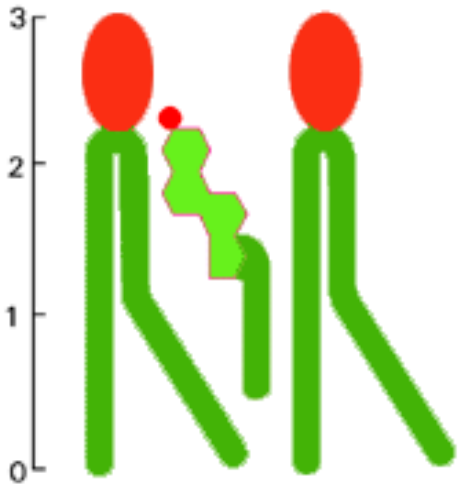


Other important steroid are the sex hormones, such as testosterone and estrogen:



testosterone

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

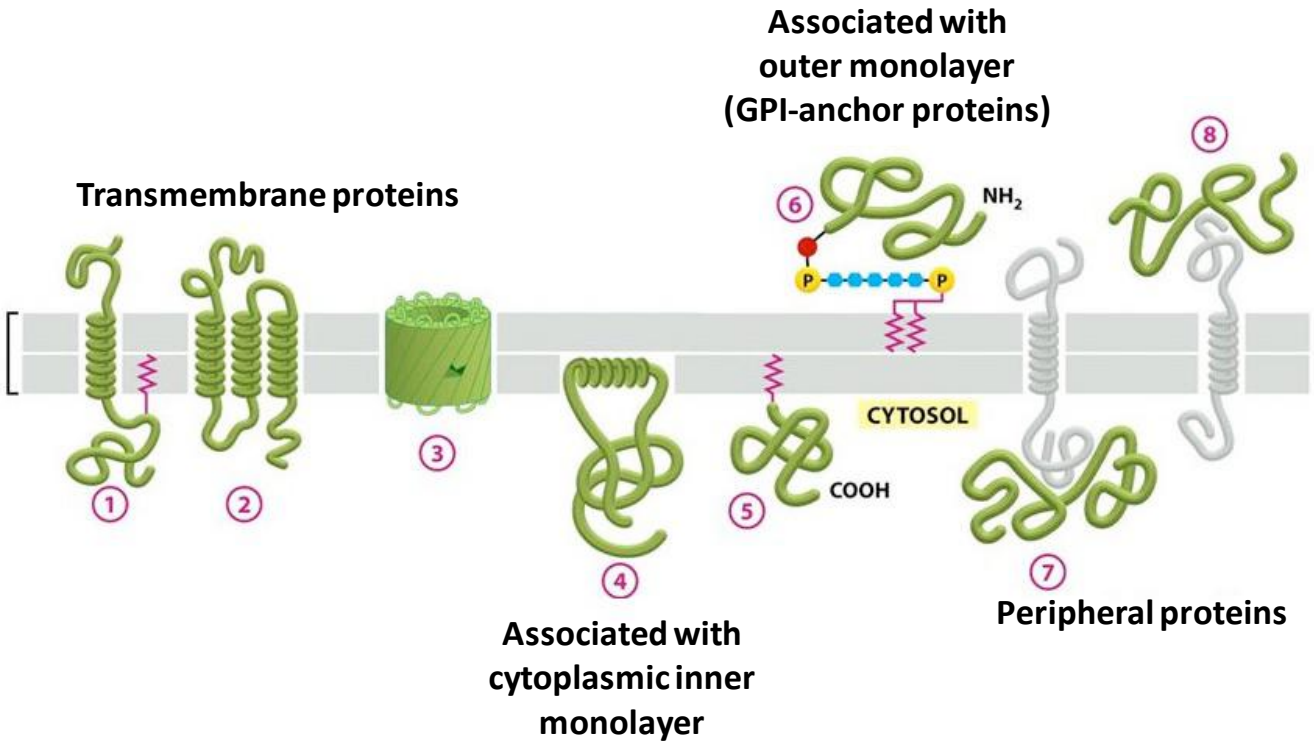


Cell membrane: an optimized 2D fluid system

Membrane fluidity depends on the type of lipid:

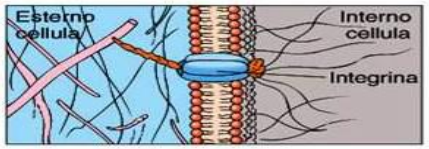
Saturated lipid are more ordered, therefore mode rigid then the **unsaturated** ones
Cholesterol is hydrophobic, but reacts with a OH^- group with the hydrophilic heads of neighbor phospholipids
Low T: chol is a spacer, keeping fluidity high
High T: chol stabilize the membrane (sealing)

Type and function of membrane proteins



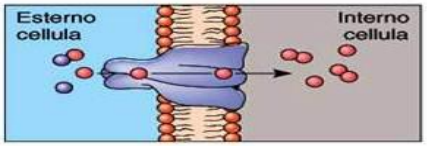
Trans-membrane proteins cross the bilayer as **(1)** a single α helix, **(2)** as multiple α helices, or **(3)** as a β barrel. Other membrane proteins are exposed at only one side of the membrane. **(4)** Some of these are anchored to the cytosolic surface by an amphipathic α helix that partitions into the cytosolic monolayer of the lipid bilayer through the hydrophobic face of the helix. **(5)** Others are 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)** many proteins are attached to the membrane only by non-covalent interactions with other membrane proteins

Type and function of **transmembrane proteins**



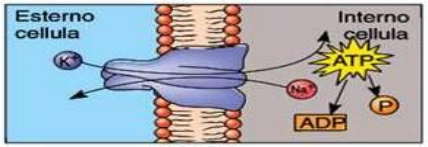
(a) Ancoraggio. Alcune proteine di membrana, per esempio le integrine, ancorano la cellula alla matrice extracellulare ed inoltre si connettono ai microfilamenti intracellulari.

Ancoraggio (integrine)



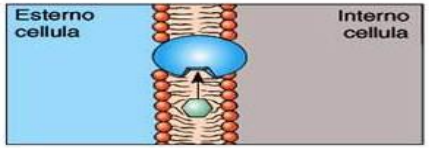
(b) Trasporto passivo. Certe proteine formano canali che permettono il passaggio selettivo di ioni o molecole.

Trasporto passivo



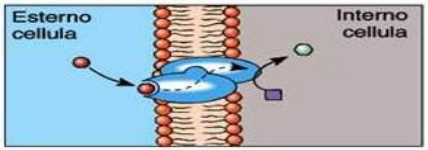
(c) Trasporto attivo. Alcune proteine di trasporto pompano i soluti attraverso la membrana, un processo che richiede un apporto di energia.

Trasporto attivo



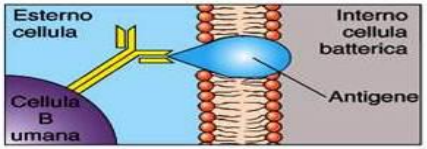
(d) Attività enzimatica. Molti enzimi legati alla membrana catalizzano reazioni che avvengono all'interno o sulla superficie della membrana.

Attività enzimatica



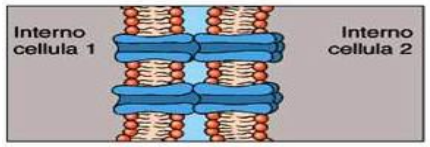
(e) Trasduzione del segnale. Alcuni recettori legano molecole segnale come gli ormoni e trasmettono l'informazione all'interno della cellula.

Attività recettoriale e trasduzione del segnale



(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.

Riconoscimento cellulare



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

Giunzione intercellulare

Passive and Active Transport

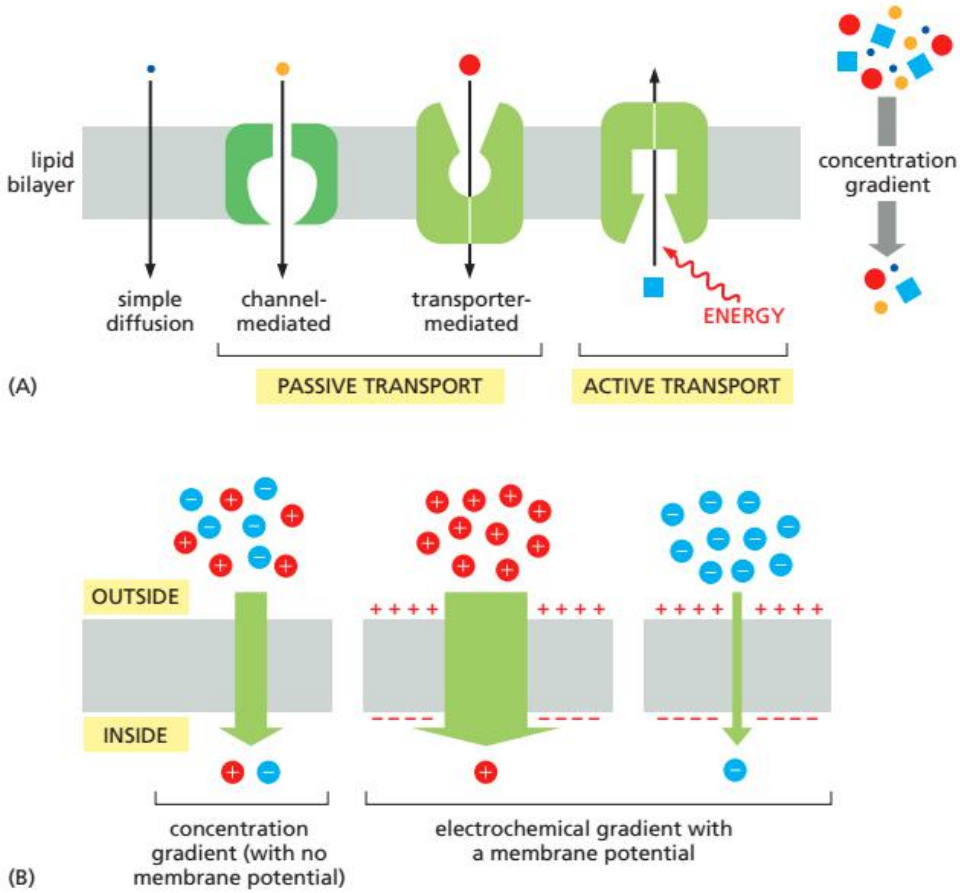


Figure 11–4 Different forms of membrane transport and the influence of the membrane. Passive transport down a concentration gradient (or an electrochemical gradient—see B below) occurs spontaneously, by diffusion, either through the lipid bilayer directly or through channels or passive transporters. 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 electrical potential

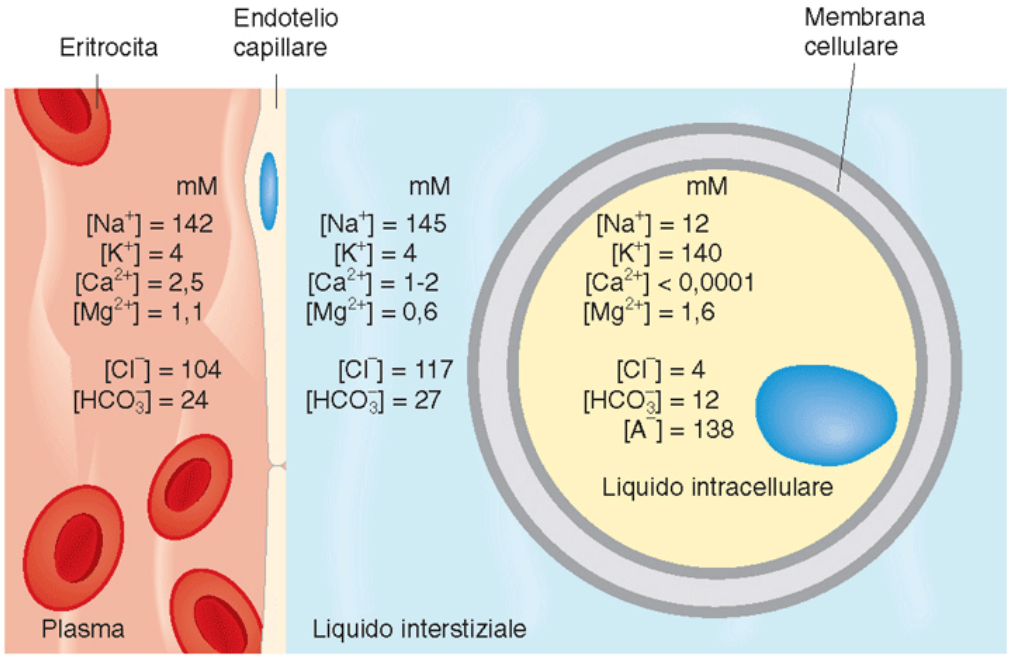


TABLE 11–1 A Comparison of Inorganic Ion Concentrations Inside and Outside a Typical Mammalian Cell*

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.

Passive Transport Is driven by concentration gradient

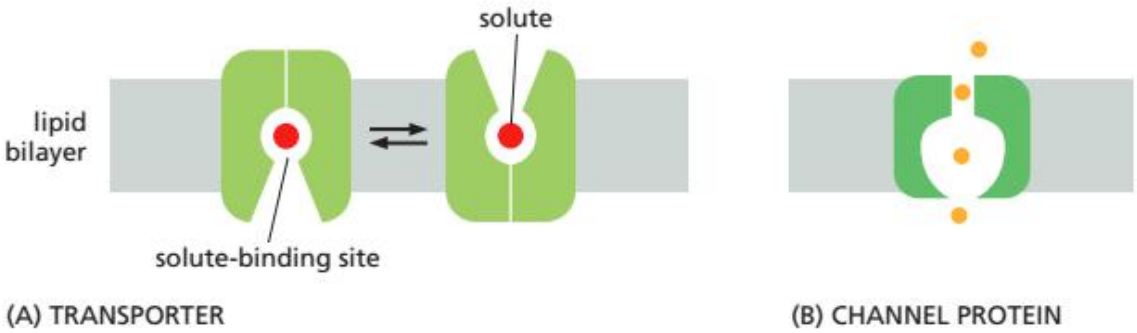


Figure 11–3 Transporters and channel proteins. (A) A transporter alternates between two conformations, so that the solute-binding site is sequentially accessible on one side of the bilayer and then on the other. (B) In contrast, a channel protein forms a pore across the bilayer through which specific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

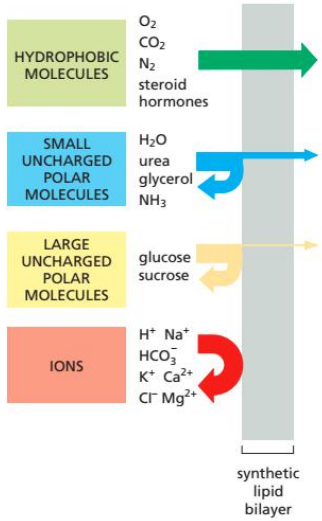
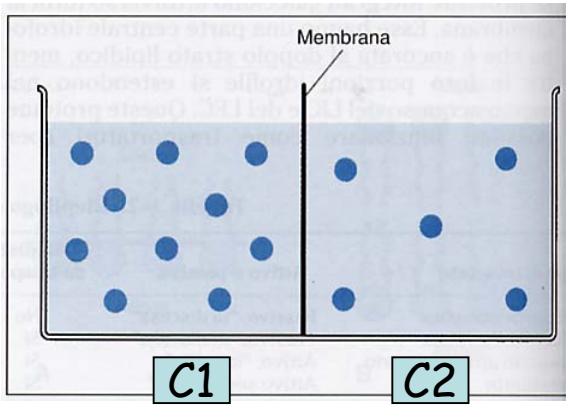


Figure 11–1 The relative permeability of a synthetic lipid bilayer to different classes of molecules. The smaller the molecule and, more importantly, the less strongly it associates with water, the more rapidly the molecule diffuses across the bilayer.

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

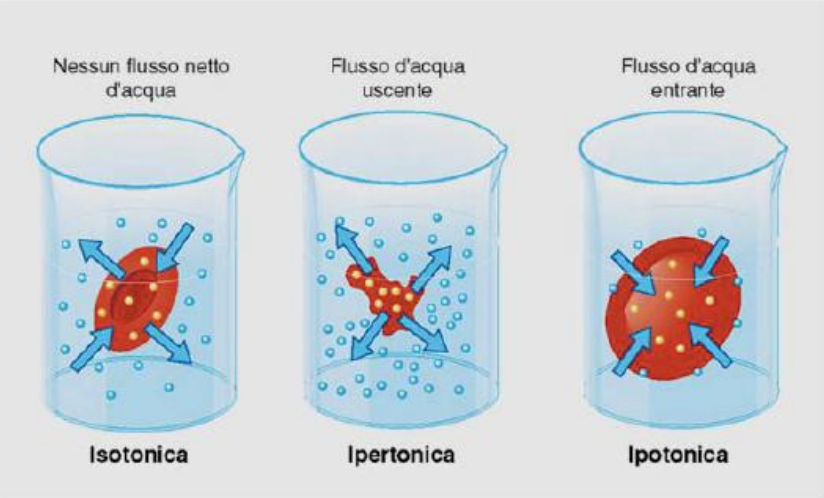
$$dm/dt = D \times A/d \times (c1-c2)$$

Fick low
m = mass
t= time

The Permeability P is defined as D/d :

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

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



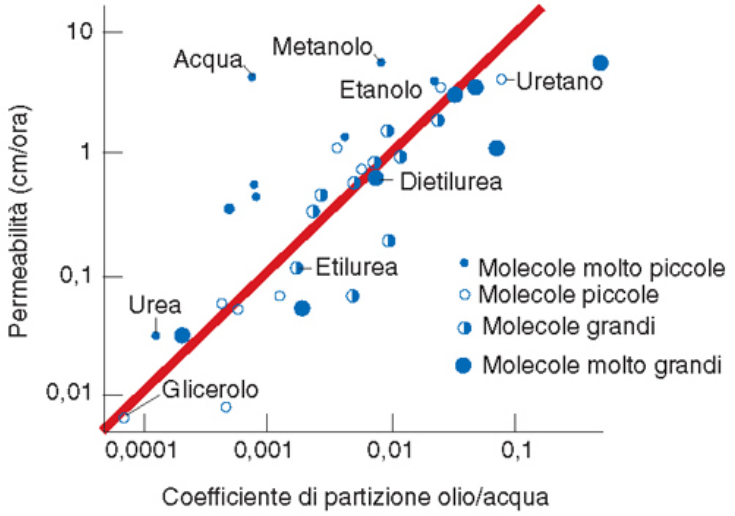
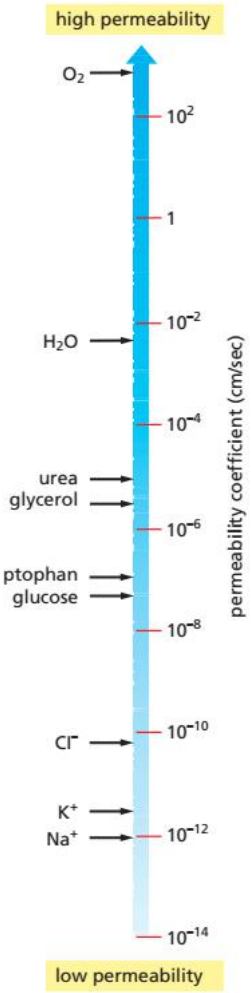


Figura 1.9 Relazione lineare tra coefficiente di partizione olio/acqua e permeabilità di membrana. Si noti come la permeabilità non dipenda dalla dimensione delle molecole. Due molecole piccole come glicerolo e uretano hanno permeabilità molto diverse perché i loro coefficienti di partizione differiscono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



Passive Transport through Channels

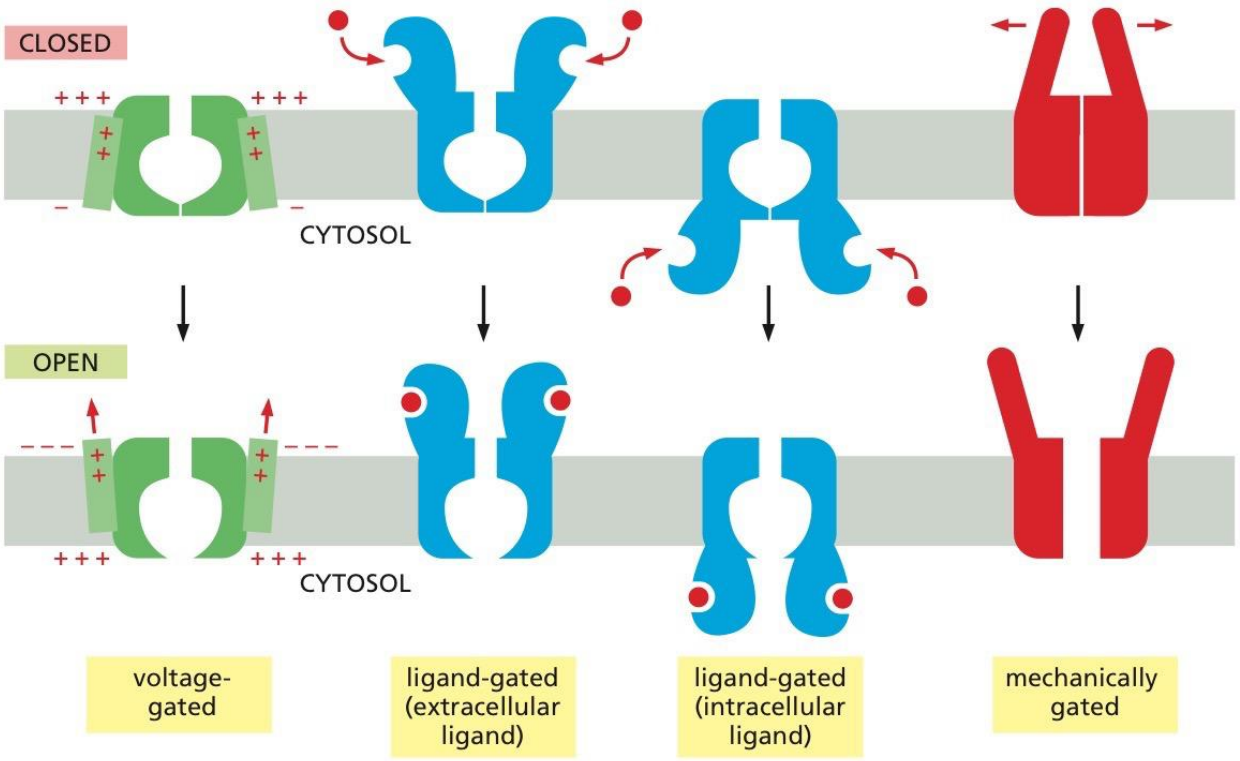


Figure 11–22 The gating of ion channels. This schematic drawing shows several kinds of stimuli that open ion channels. Mechanically gated channels often have cytoplasmic extensions (not shown) that link the channel to the cytoskeleton.

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

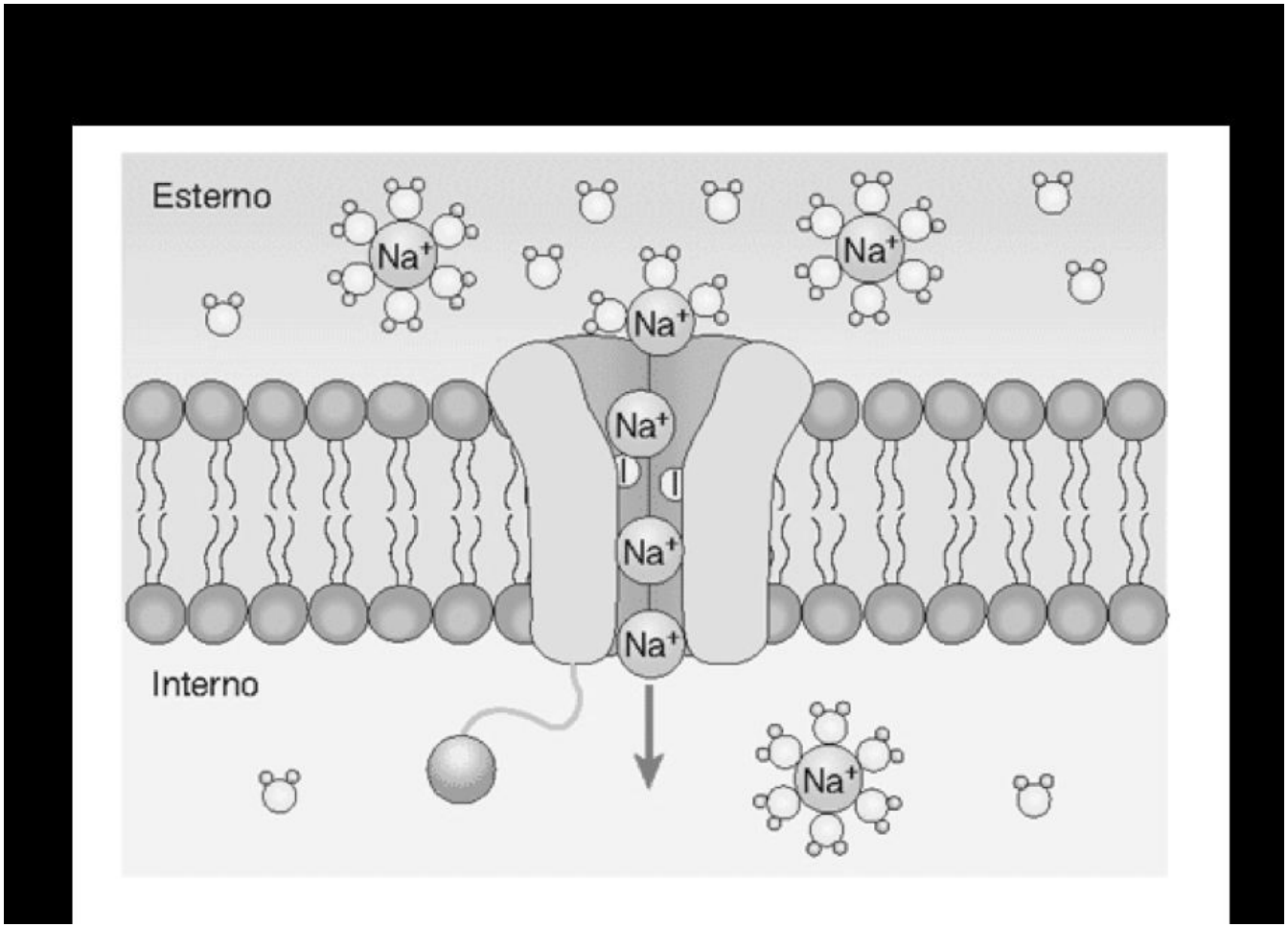
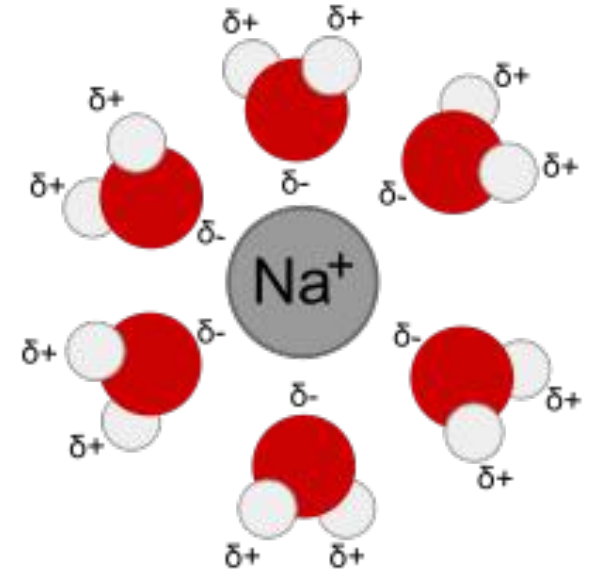


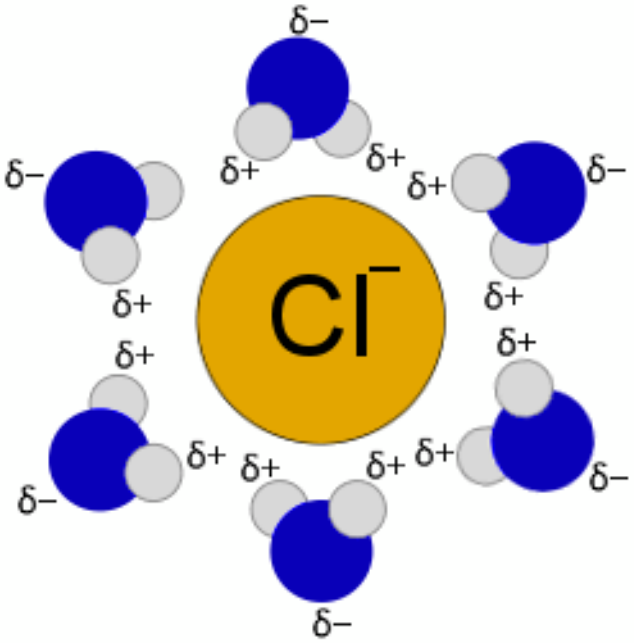
Figura 1.11 Modello di canale del Na^+. Gli ioni Na^+ extracellulari spinti dal loro gradiente elettrochimico diffondono attraverso il canale aperto. Prima perdono le molecole di idratazione, poi si legano in successione alle cariche negative disposte sulle pareti interne del poro. Il movimento "in fila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

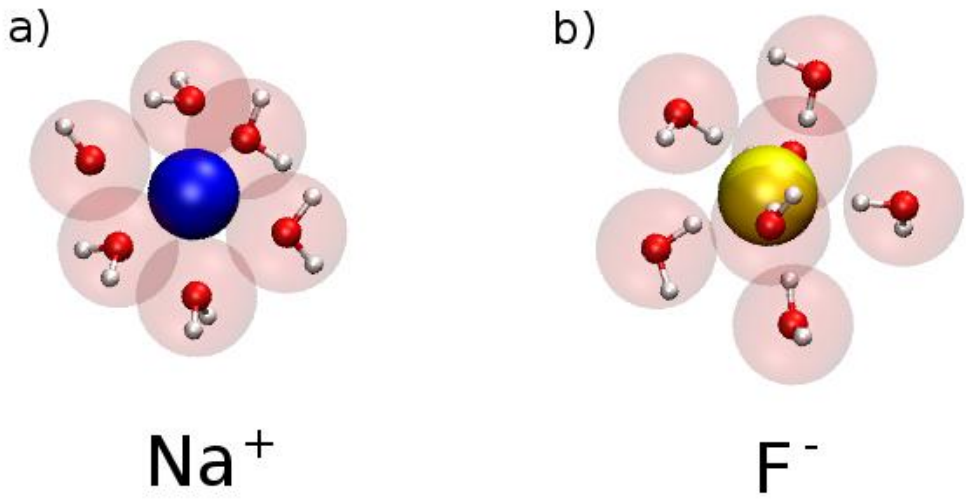
Solvation shells

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**.

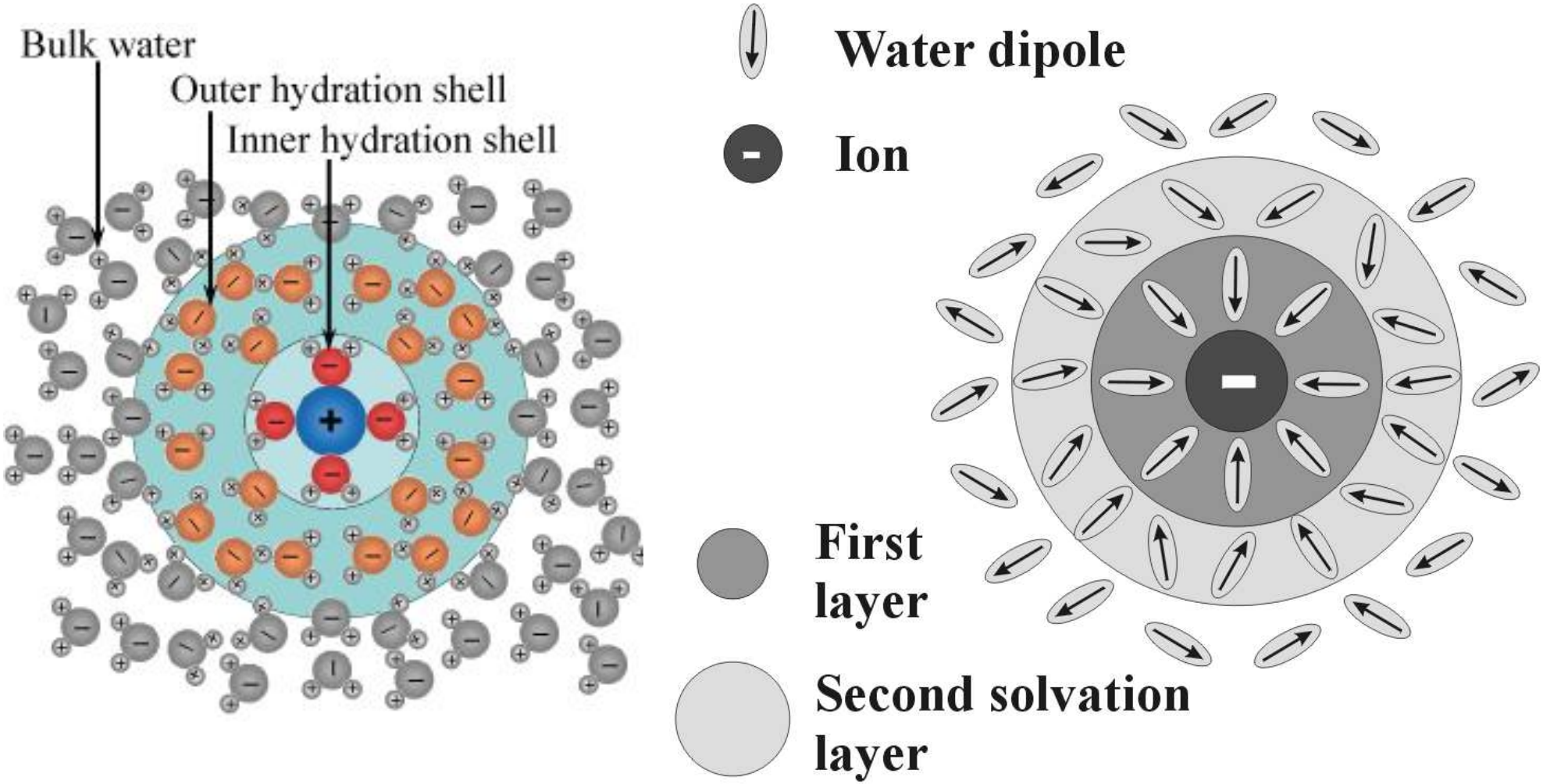
For example, if the latter were a cation, the electronegative oxygen atom of the water molecule would be attracted electrostatically to the positive charge on the metal ion. The result is a solvation shell of water molecules that surround the ion.





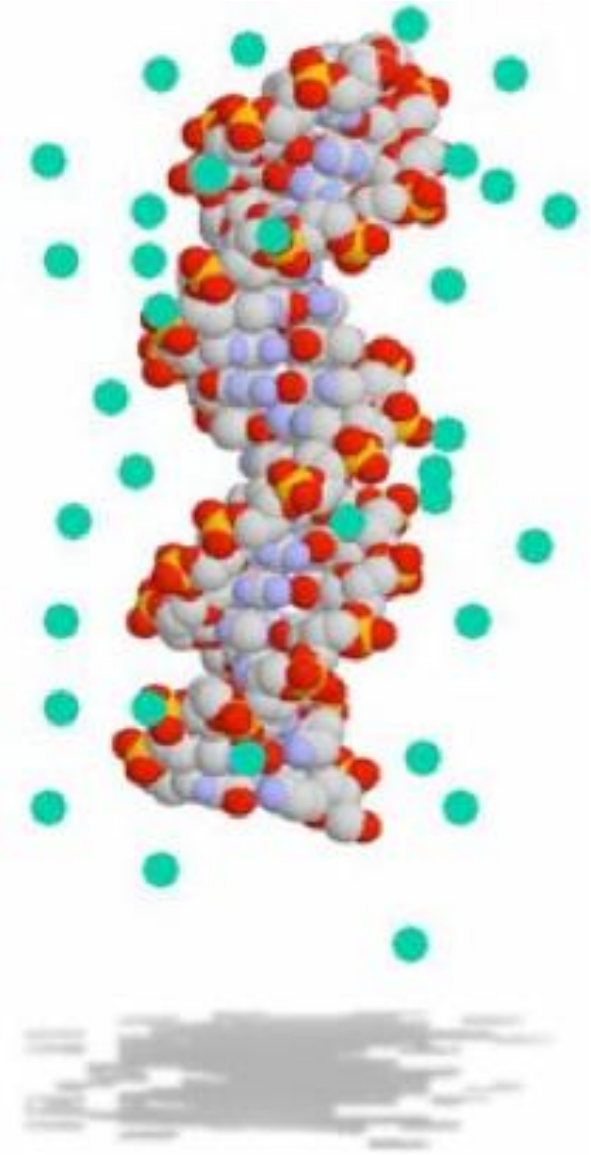


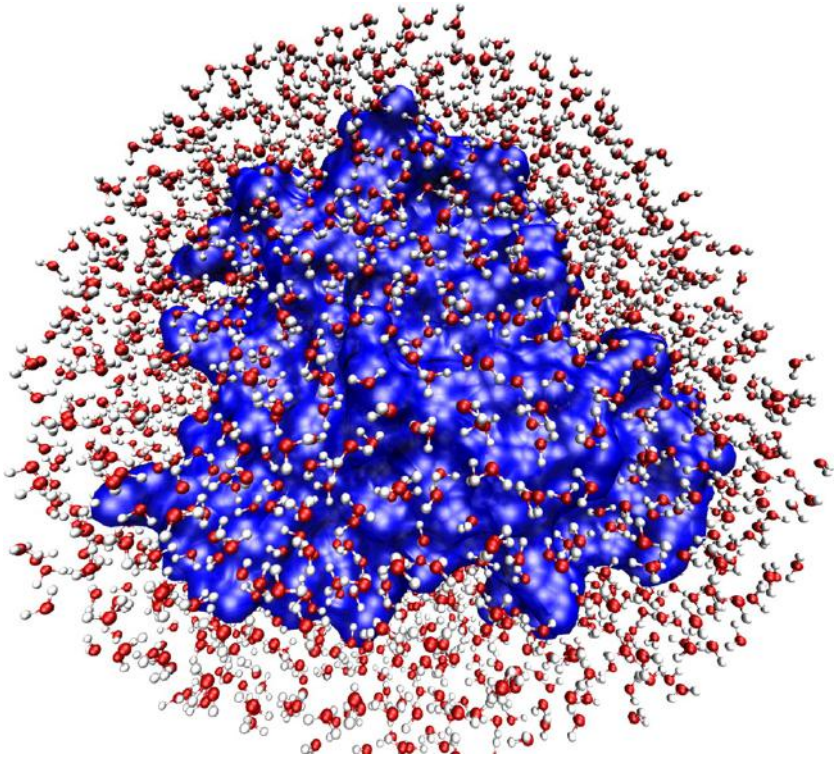
Solvation/hydration shells



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

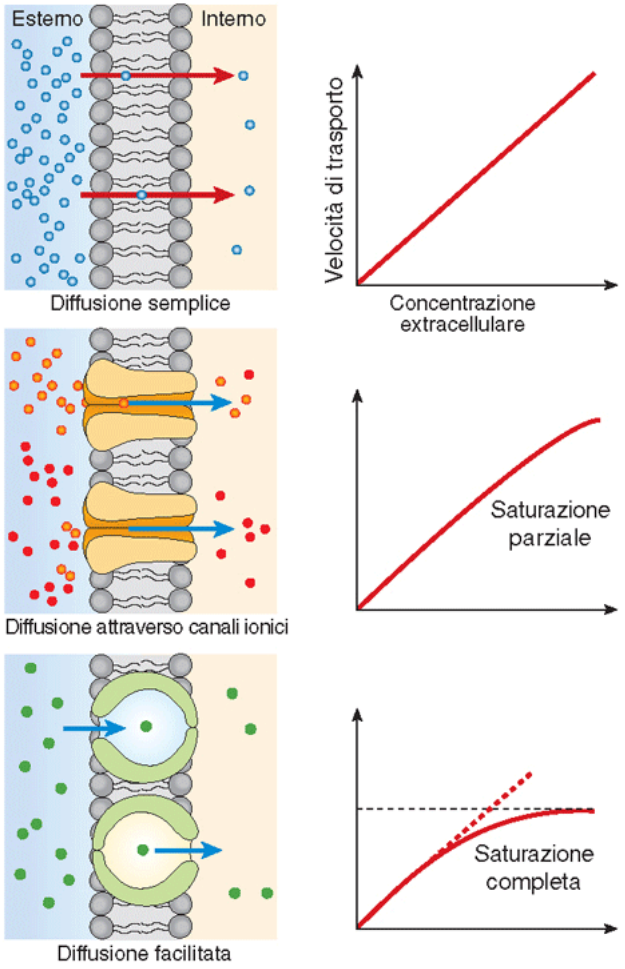


Figura 1.10 Relazione tra permeabilità (velocità di trasporto attraverso la membrana) e la concentrazione di soluti nel liquido extracellulare. Nel caso della diffusione passiva la relazione è lineare. Nel caso della diffusione facilitata (carrier) o attraverso canali ionici, la relazione è invece lineare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

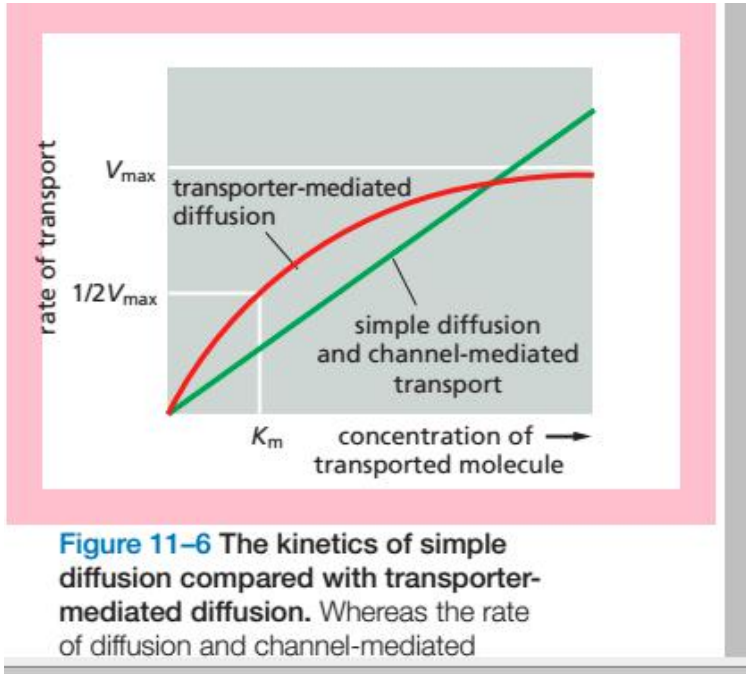


Figure 11–6 The kinetics of simple diffusion compared with transporter-mediated diffusion. Whereas the rate of diffusion and channel-mediated

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

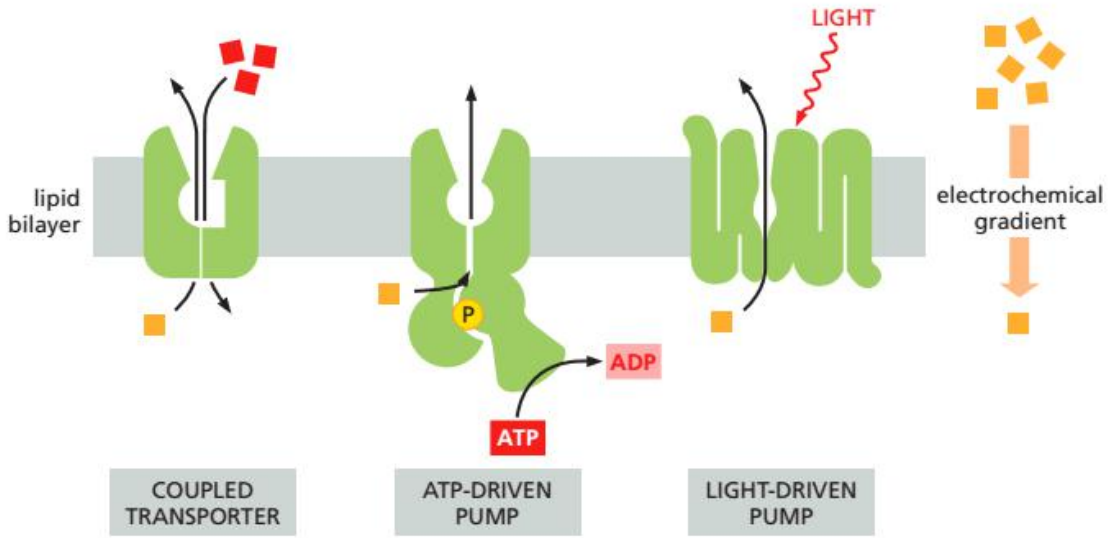
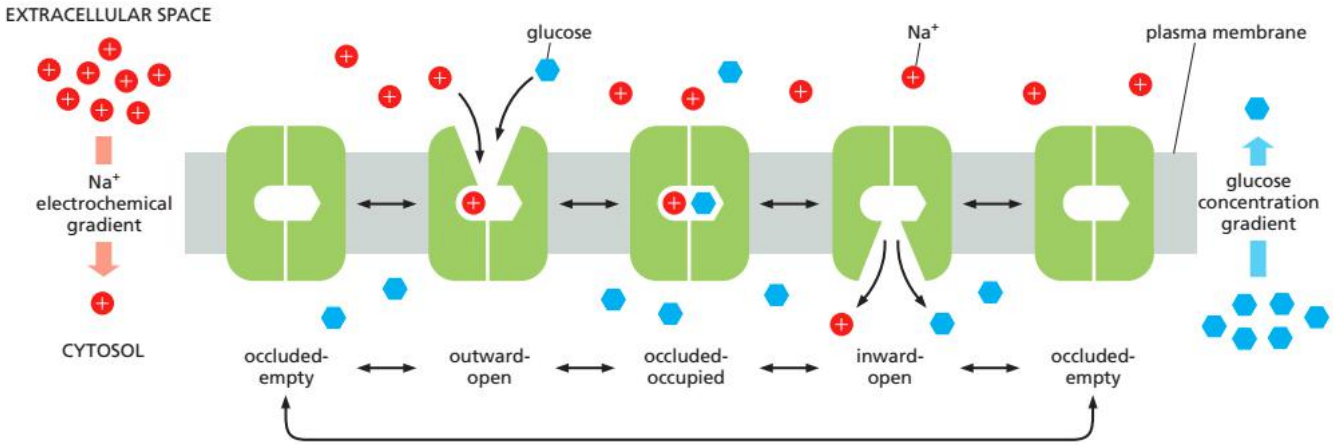


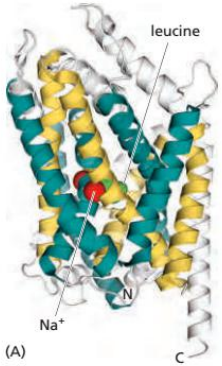
Figure 11–7 Three ways of driving active transport. The actively transported molecule is shown in *orange*, and the energy source is shown in *red*. Redox driven active transport is discussed in Chapter 14 (see Figures 14–18 and 14–19).

- 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

co-transporters





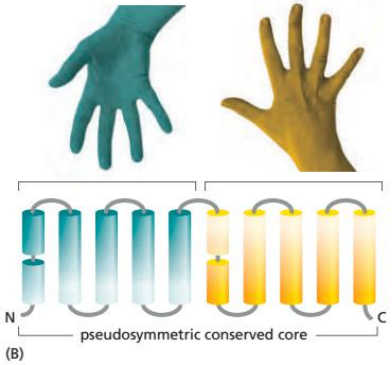
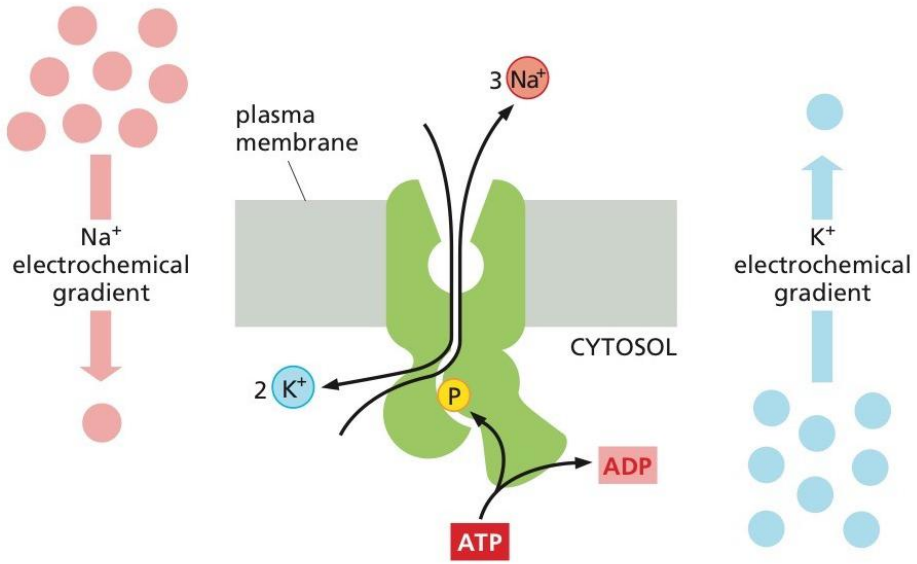


Figure 11–9 Mechanism of glucose transport fueled by a Na^+ gradient. As in the model shown in Figure 11–5, the transporter alternates between inward-open and outward-open states via an occluded intermediate state. Binding of Na^+ and glucose is cooperative—that is, the binding of either solute increases the protein's affinity for the other. Since the Na^+ concentration is much higher in the extracellular space than in the cytosol, glucose is more likely to bind to the transporter in the outward-facing state. The transition to the occluded state occurs only when both Na^+ and glucose are bound; their precise interactions in the solute-binding sites slightly stabilize the occluded state and thereby make this transition energetically favorable. Stochastic fluctuations caused by thermal energy drive the transporter randomly into the inward-open or outward-open conformation. If it opens outwardly, nothing is achieved, and the process starts all over. However, whenever it opens inwardly, Na^+ dissociates quickly in the low-Na^+-concentration environment of the cytosol. Glucose dissociation is likewise enhanced when Na^+ is lost, because of cooperativity in binding of the two solutes. The overall result is the net transport of both Na^+ and glucose into the cell. Because the occluded state is not formed when only one of the solutes is bound, the transporter switches conformation only when it is fully occupied or fully empty, thereby assuring strict coupling of the transport of Na^+ and glucose.

Neurotransmitters (released by nerve cells to signal at synapses) are taken up again by Na + symporters after their release. These neurotransmitter transporters are important drug targets: stimulants, such as cocaine and antidepressants, inhibit them and thereby prolong signaling by the neurotransmitters, which are not cleared efficiently.

Active Transport Is Mediated by Transporters Coupled to an Energy Source

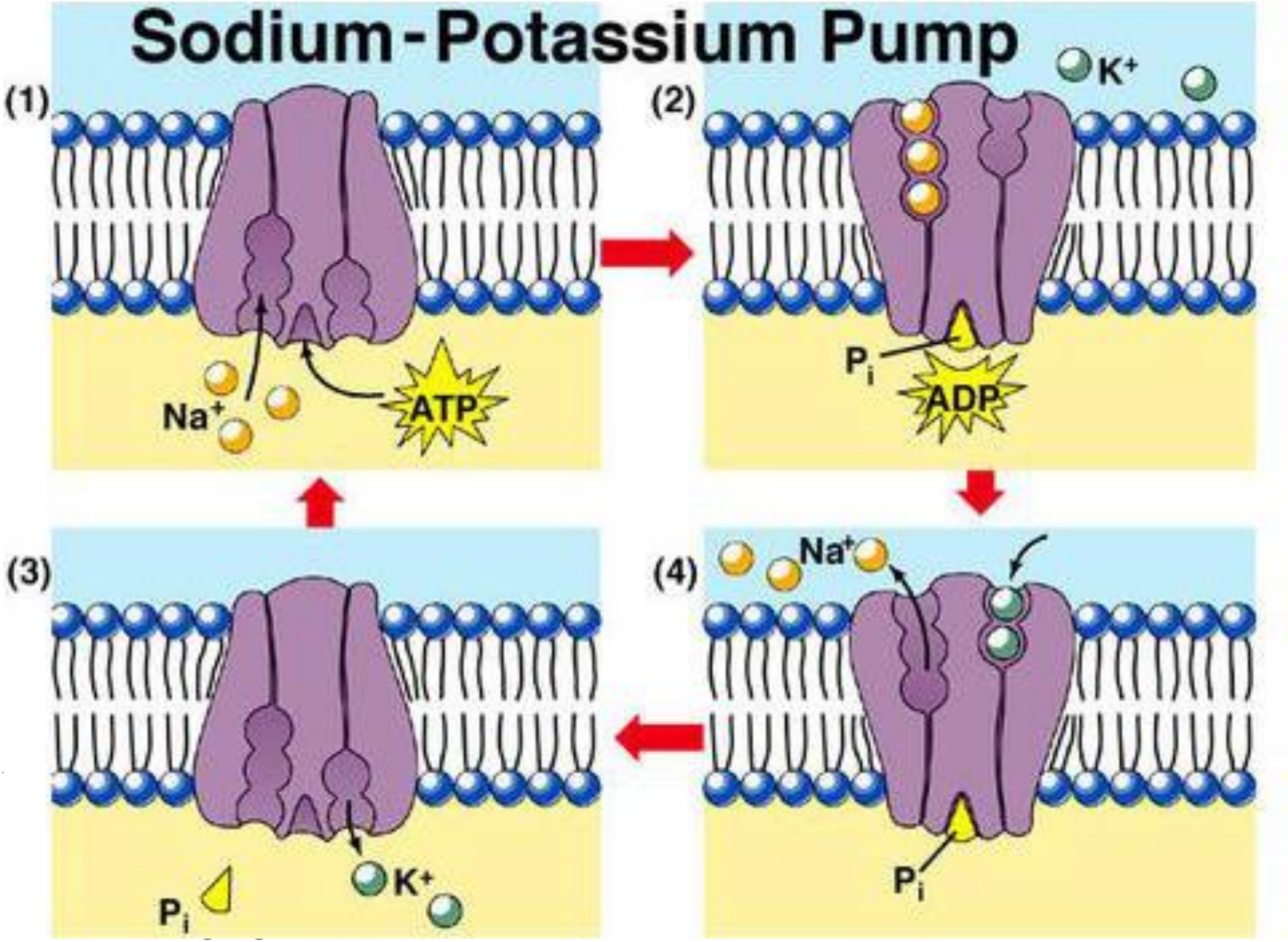
The concentration of K + is typically 10–30 times higher inside cells than outside, whereas the reverse is true of Na +



Na^+- K^+ ATPase

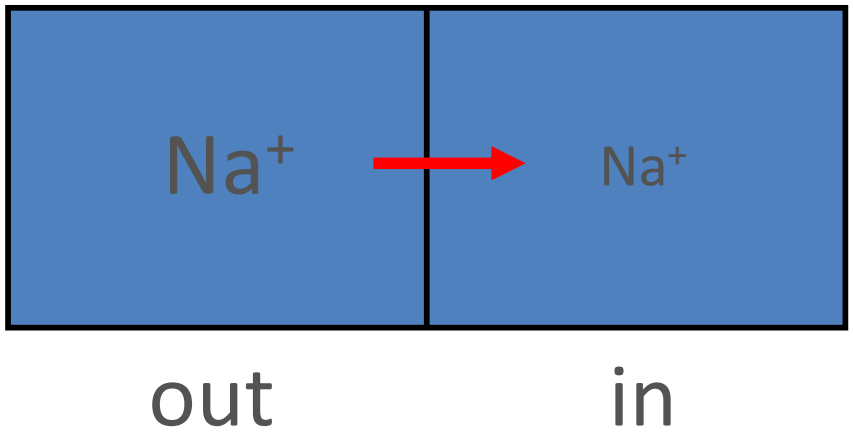
P-type pumps are structurally and functionally related multipass transmembrane proteins. They are called "P-type" because they phosphorylate themselves during the pumping cycle. For each ATP hydrolized, it pumps 3 Na^+ out and 2 K^+ in

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.

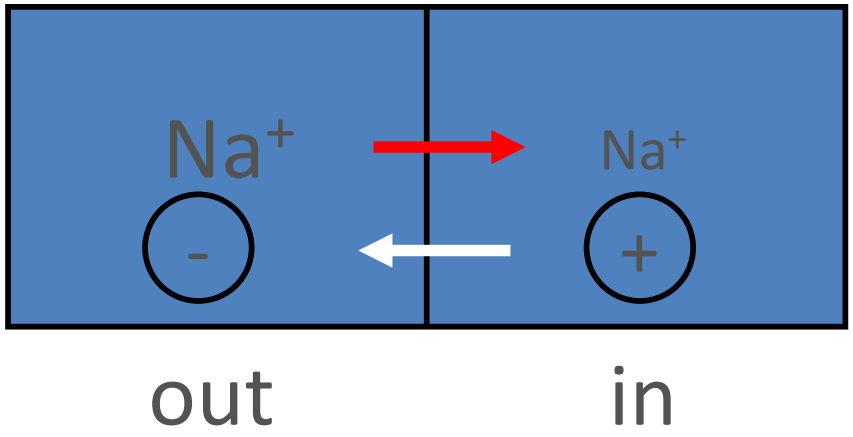

Sodium-Potassium Pump
(1)
Na+
ATP
(2)
K+
Pi
ADP
(3)
Pi
K+
(4)
Na+
Pi

Membrane potential

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

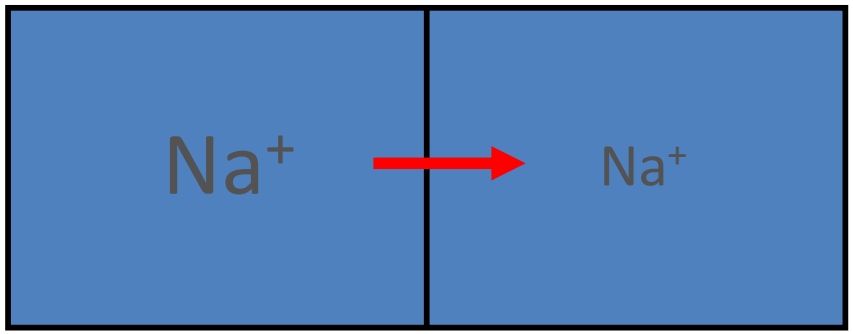


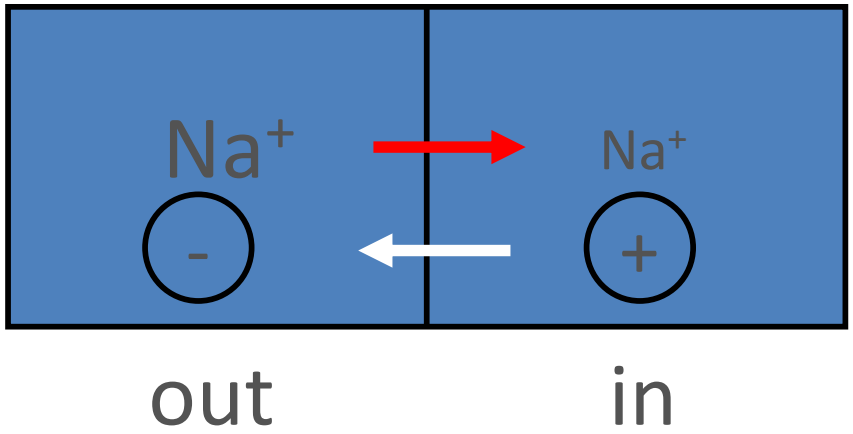
Chemical gradient



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 J mol^{-1} K^{-1})
- T = the absolute temperature (K)
- F = Faraday's constant (9.6×10^4 J V^{-1} 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,

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

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+

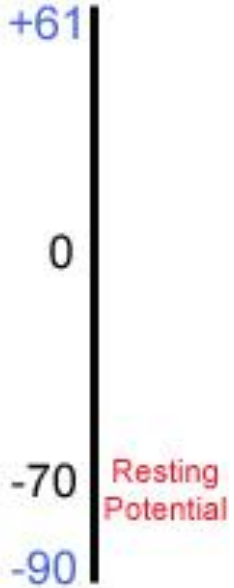
$$E = 61 \log \left[\frac{\text{Conc Na+ out (150 mM)}}{\text{Conc Na+ in (15 mM)}}\right]$$

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

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^+

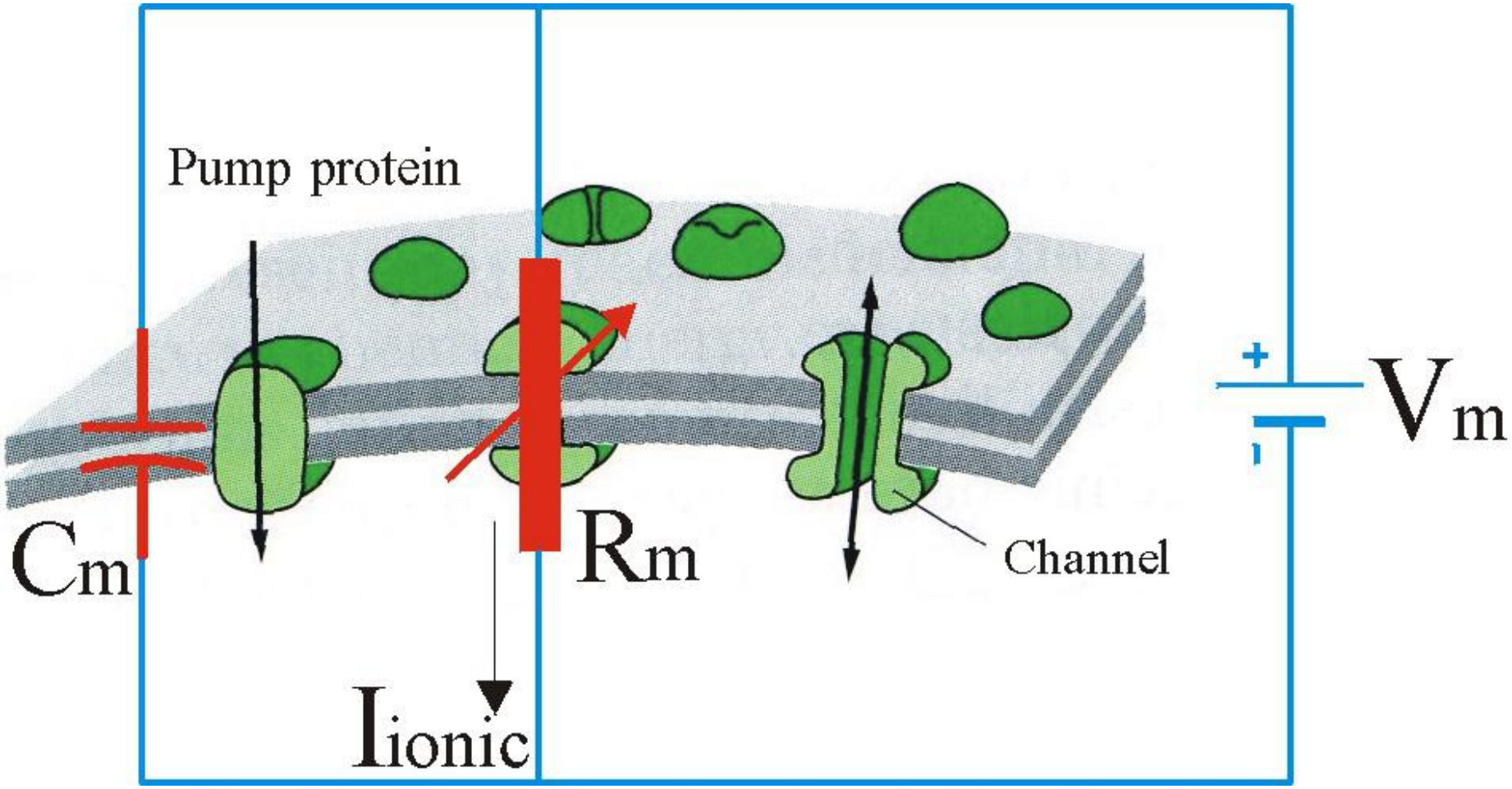
$$E_m = \frac{RT}{F} \ln\left(\frac{\rho_K[K^+]_o + \rho_{Na}[Na^+]_o + \rho_{Cl}[Cl^-]_i}{\rho_K[K^+]_i + \rho_{Na}[Na^+]_i + \rho_{Cl}[Cl^-]_o}\right)$$

then,

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

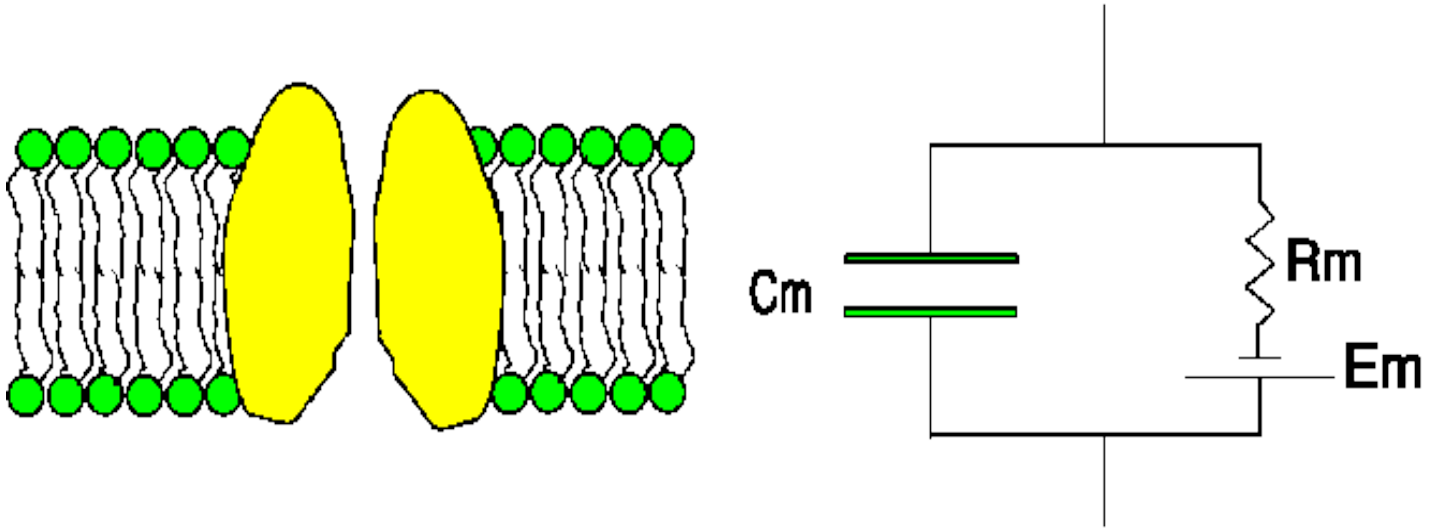
Goldman Equation

Membrane potential electrical model

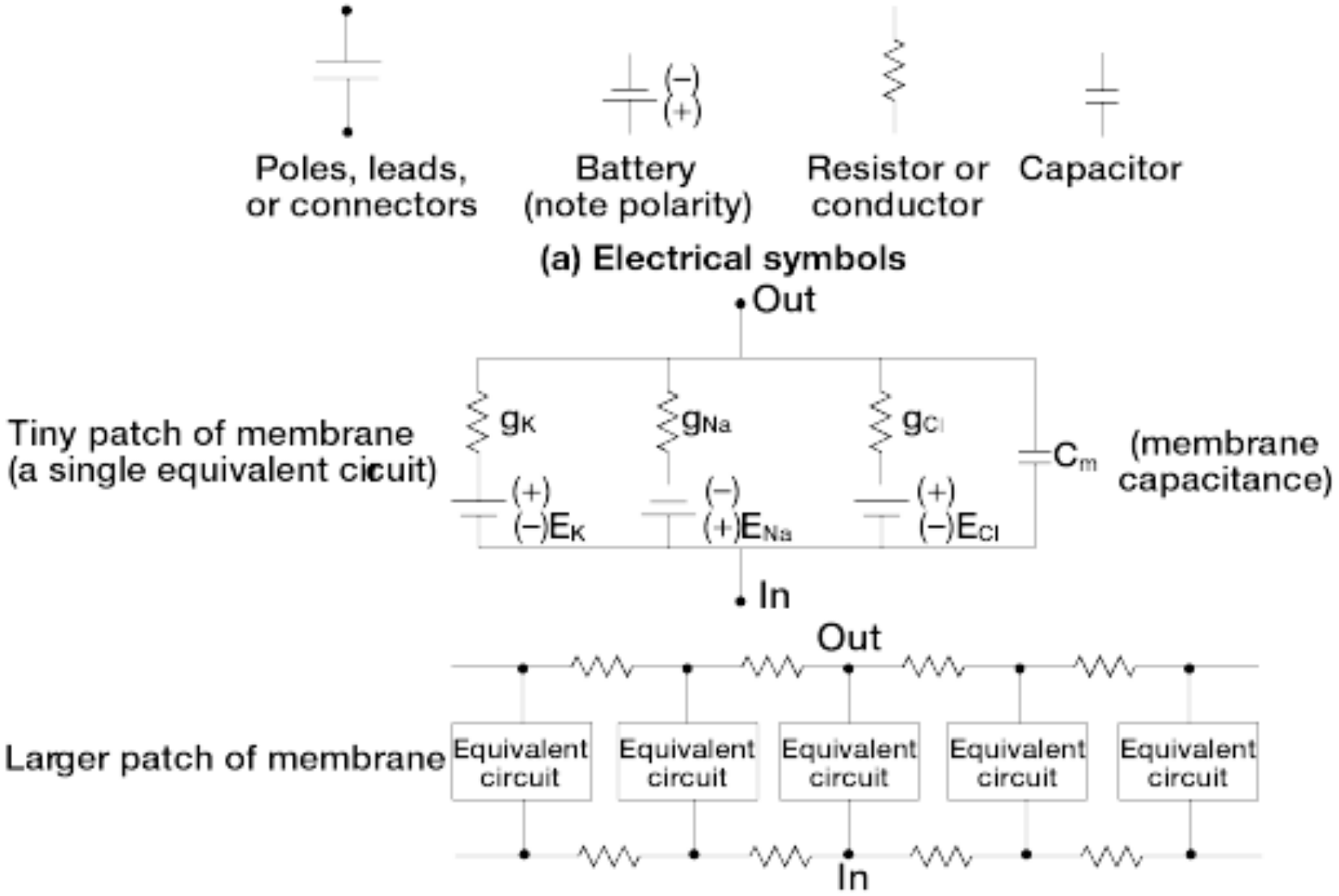


The resting potential is the equivalent of a battery

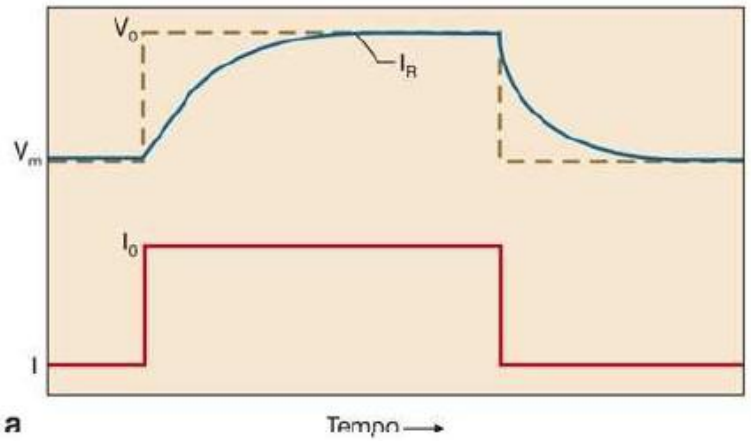
Membrane potential electrical model



The Equivalent Circuit



Membrane potential electrical model

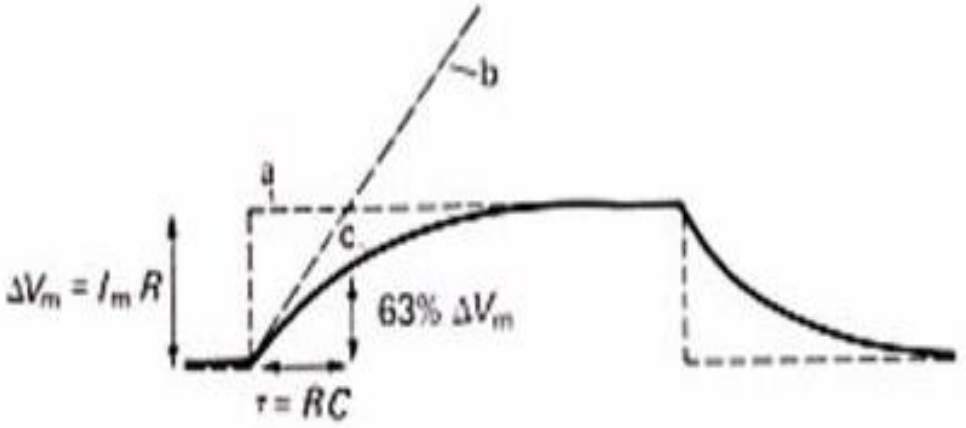


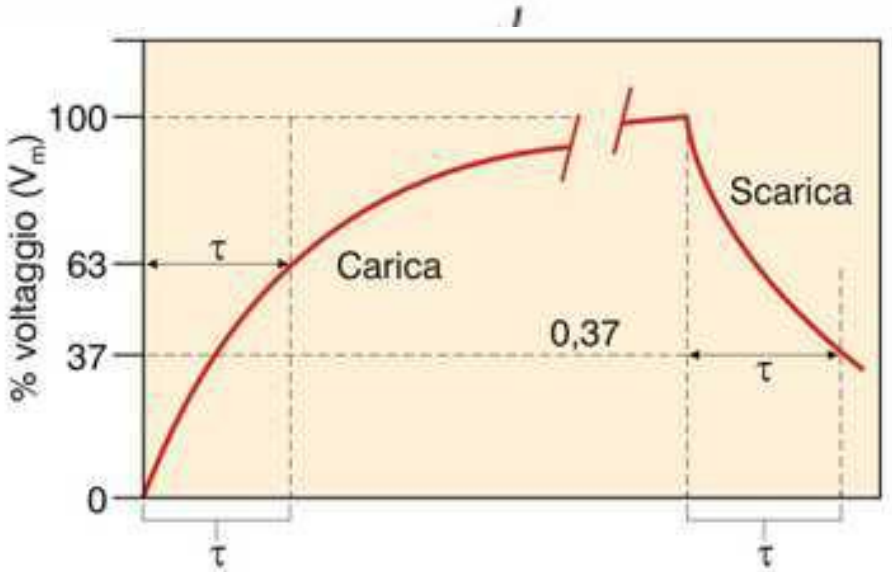
- Le proprietà del circuito RC di membrana determinano ampiezza ed andamento temporale delle variazioni del potenziale causate da flussi di correnti che attraversano la membrana grazie ai canali ionici.
- Spiegano alcune caratteristiche delle risposte neuronali.

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 $V=I_rR$.





Membrane potential electrical model

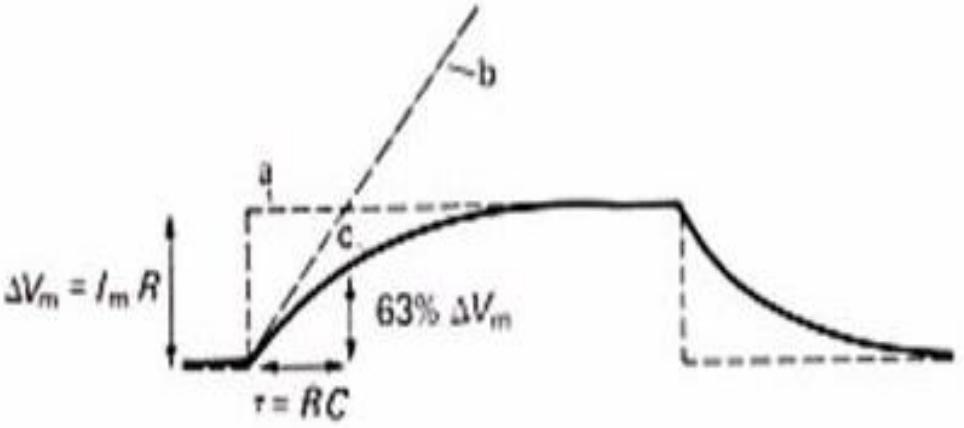
Stimolata da un passaggio di corrente la membrana risponde con una variazione del potenziale in modo proporzionale al valore di resistenza e capacità. Quando la corrente è iniettata essa comincia a fluire attraverso la capacità che tende a caricarsi. La fase di crescita del potenziale è data da: $V=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

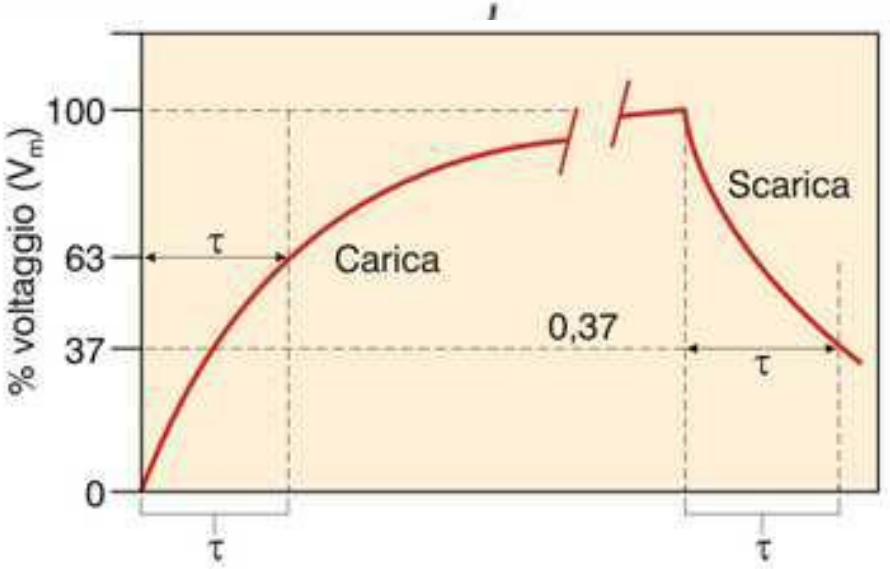
La costante di tempo ($t = \mathbf{R_M C_M}$) è il tempo necessario perché Vm
aumenti o diminuisca fino a raggiungere o perdere il 63% del suo valore
finale. Per valori di Rm compresi tra 10 e 10.000 Wcm2 e Cm = 1mF/cm2
la costante di tempo delle cellule eccitabili varia da 10 ms a 10 ms.

In un neurone la risposta a correnti sotto soglia dipende da:

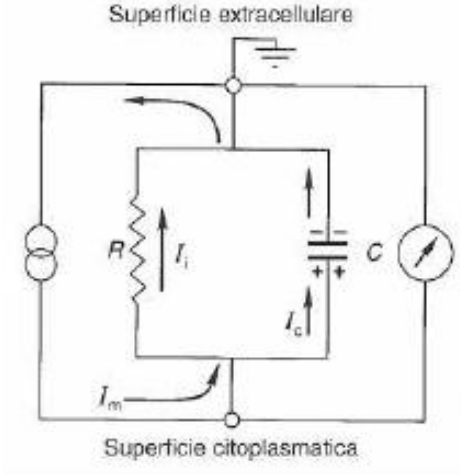
R_M: determina il valore di **Vm** che si raggiunge quando uno stimolo viene applicato per tempi lunghi.

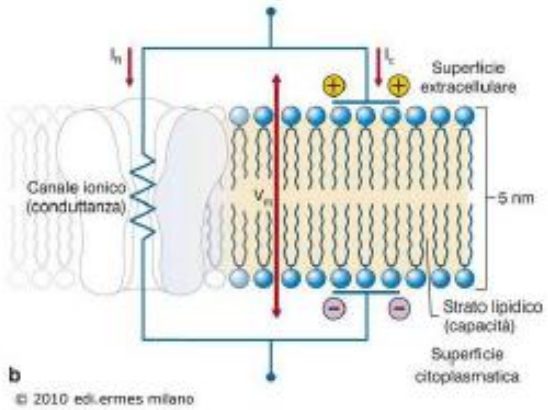
C_M: rallenta il raggiungimento del livello di **Vm** e il ritorno al valore di riposo, in base al prodotto **$R_M C_M$**

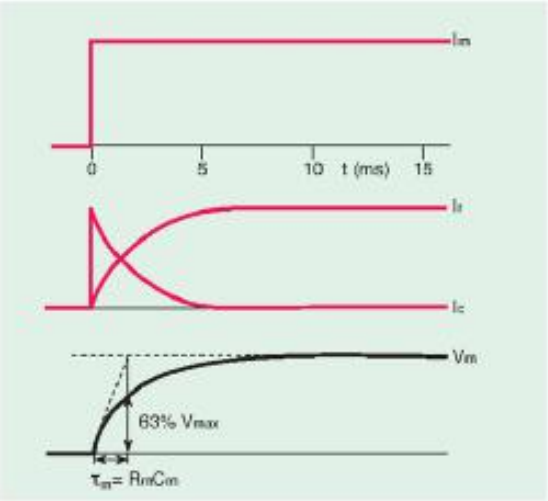




Equivalente Elettrico della membrana (Capacità e Resistenza in parallelo)







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).

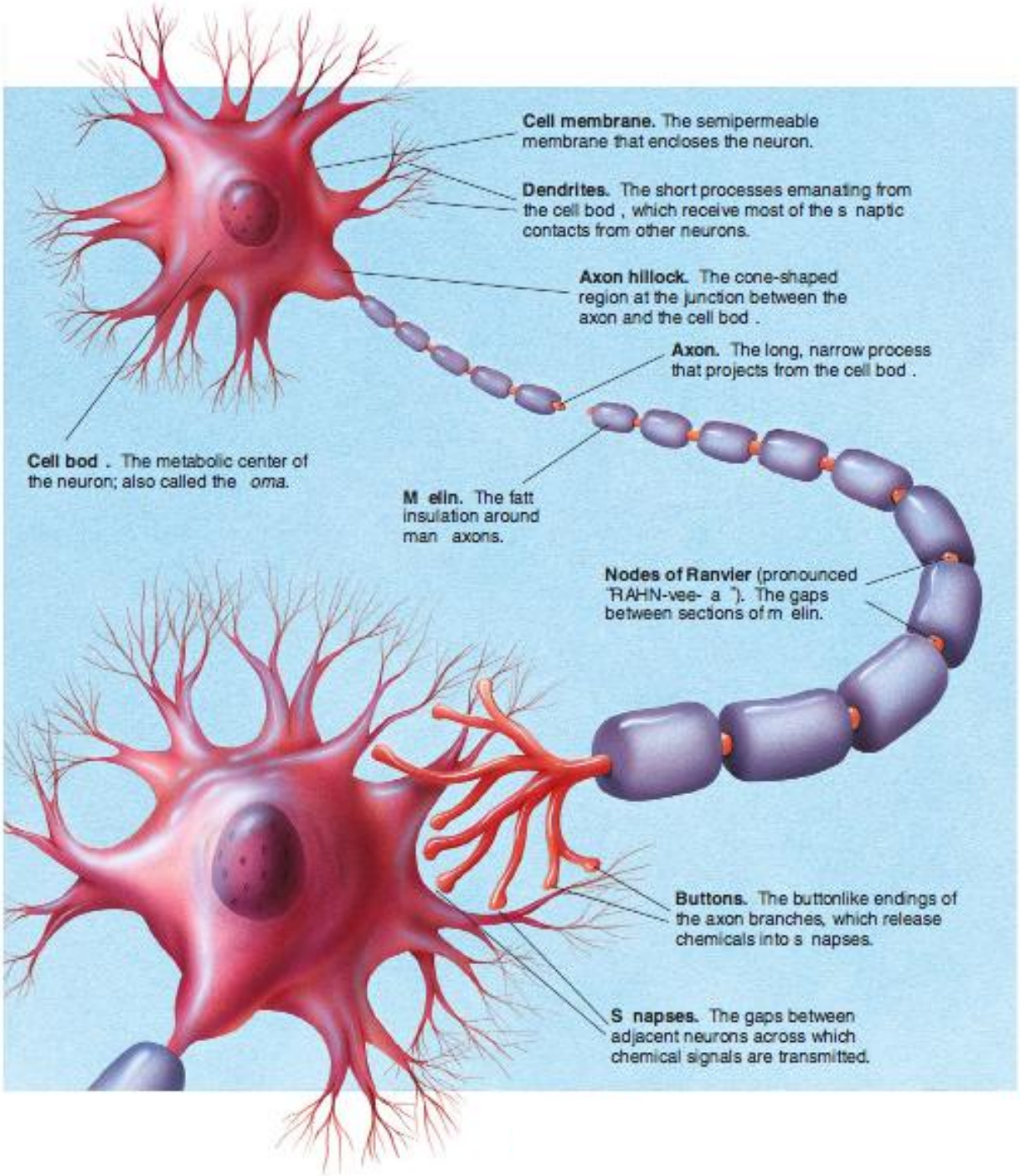
2) Man mano che Vm si modifica, gli ioni cominciano ad attraversare i canali (R), aumenta Ii.

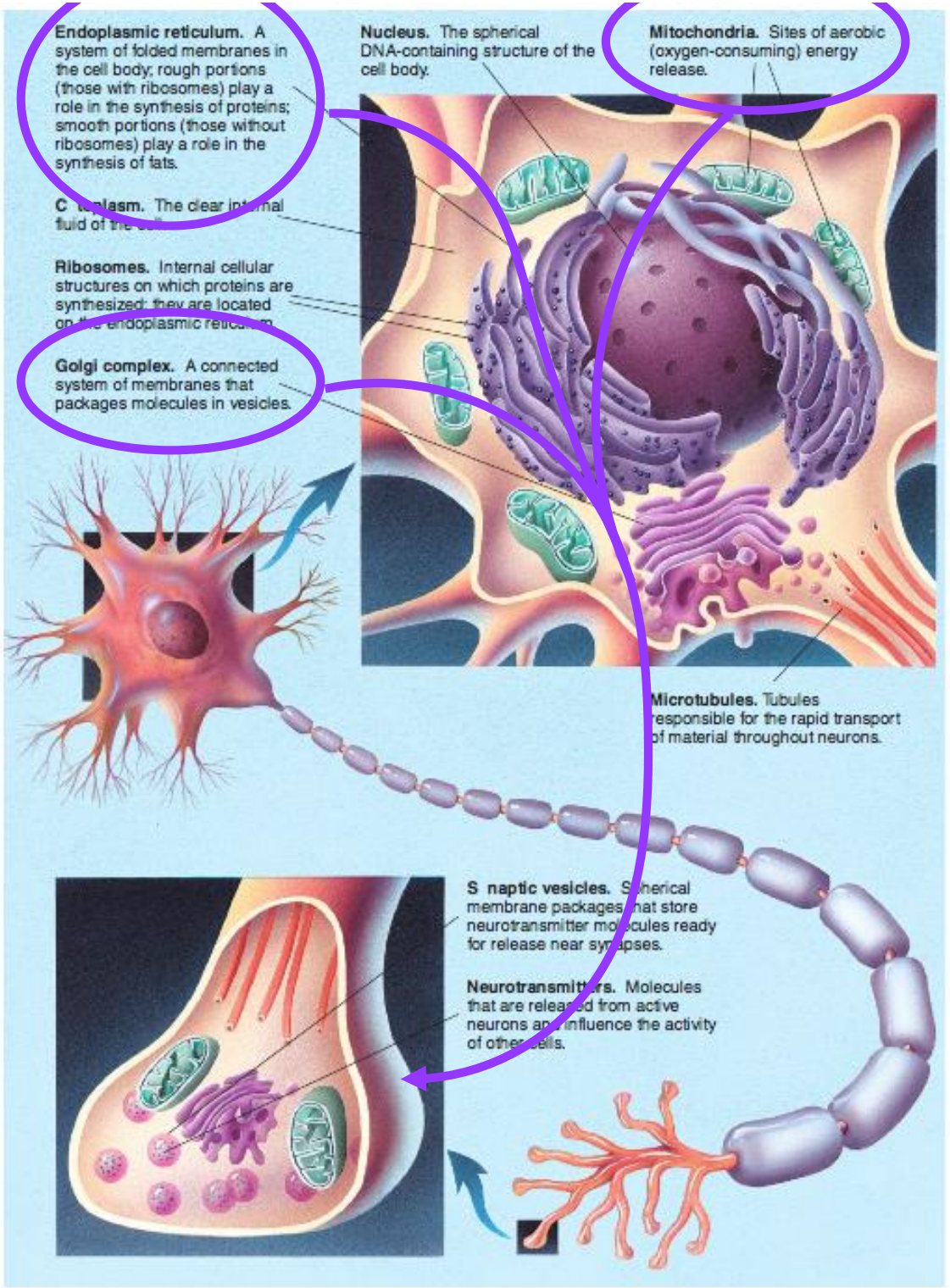
3) Quando il condensatore è carico, tutta la corrente applicata attraversa la R.

$\Delta V_m = i \cdot R$

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

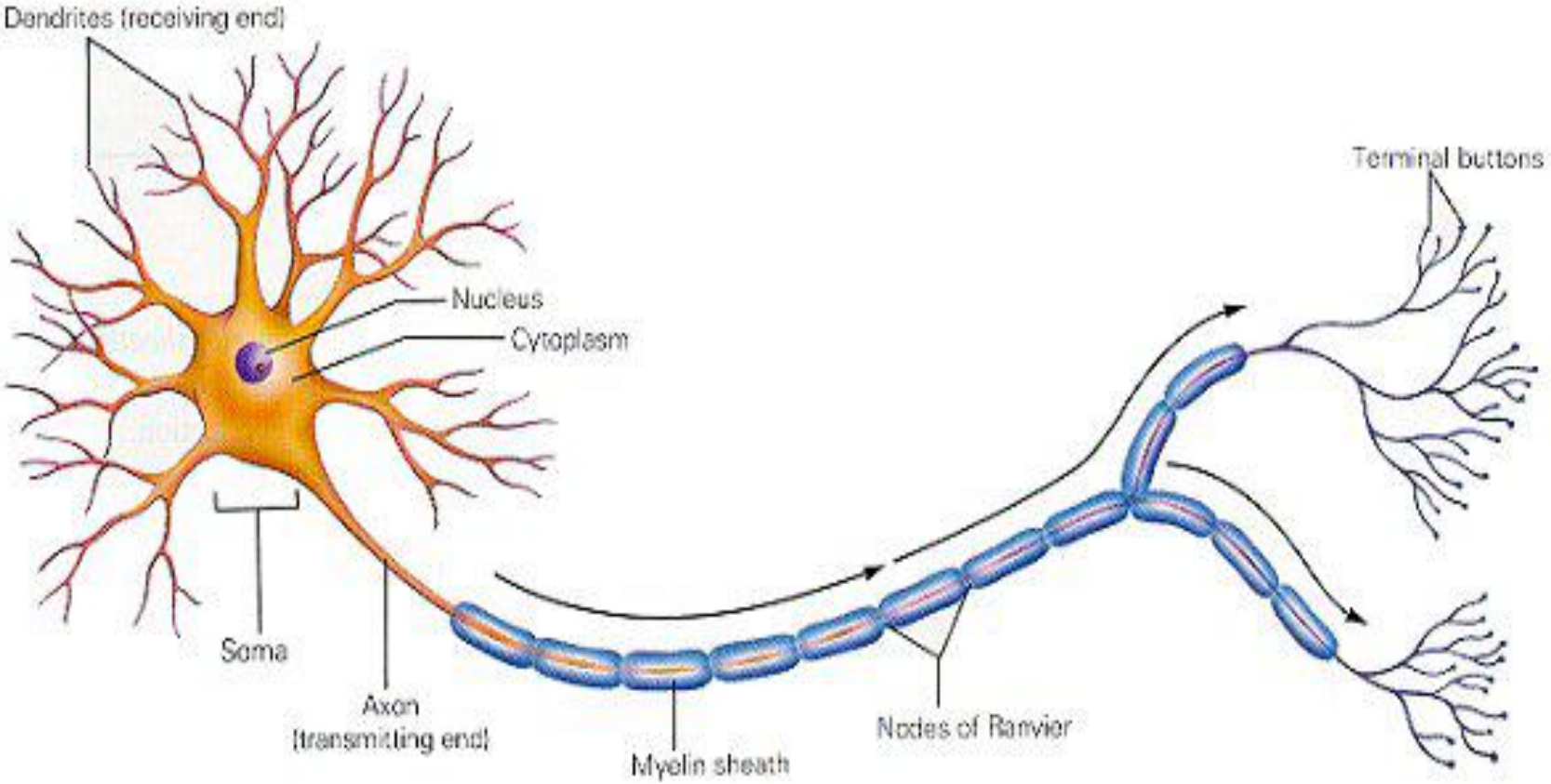
An introduction to CNS Cells

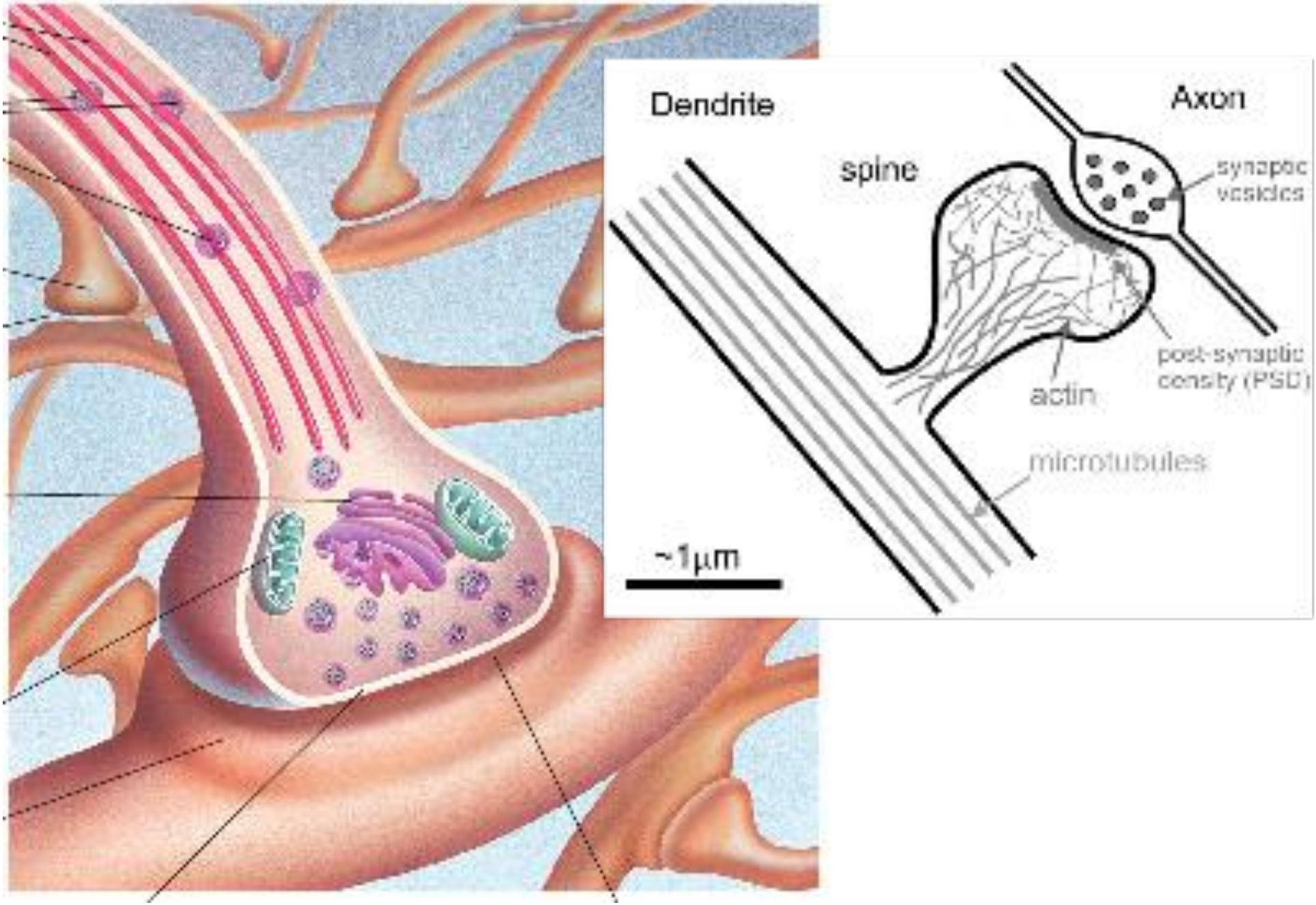



Endoplasmic reticulum. A system of folded membranes in the cell body; rough portions (those with ribosomes) play a role in the synthesis of proteins; smooth portions (those without ribosomes) play a role in the synthesis of fats.
Nucleus. The spherical DNA-containing structure of the cell body.
Mitochondria. Sites of aerobic (oxygen-consuming) energy release.
Ribosomes. Internal cellular structures on which proteins are synthesized; they are located
Golgi complex. A connected system of membranes that packages molecules in vesicles.
Microtubules. Tubules responsible for the rapid transport of material throughout neurons.
Neurotransmitters. Molecules that are released from active neurons and influence the activity of other cells.

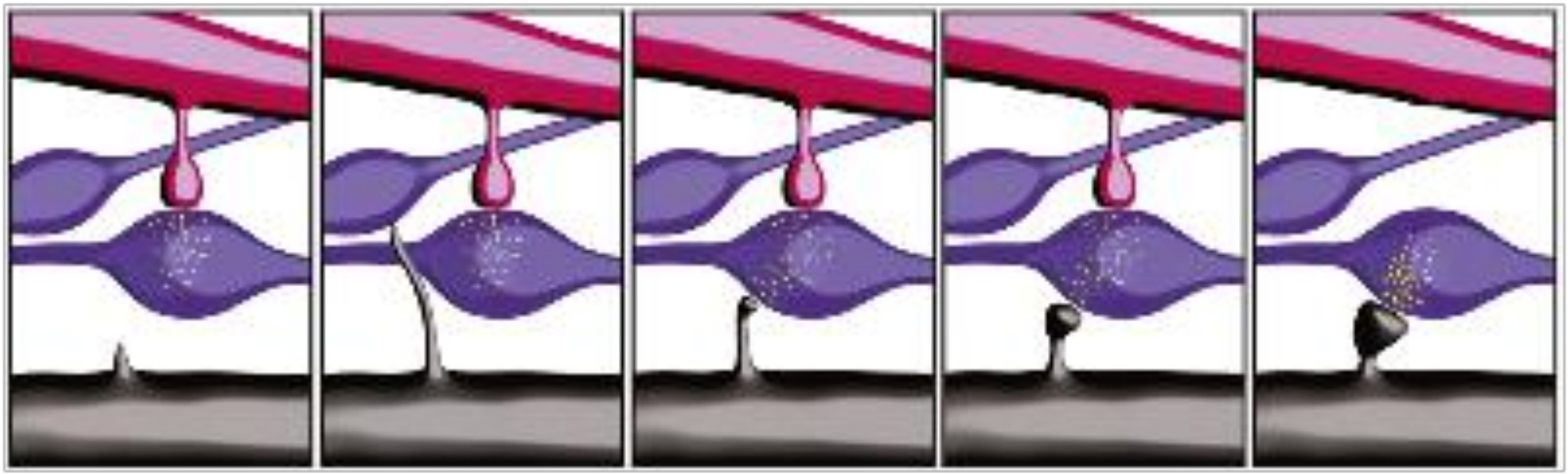
The Major Structures of the Neuron

The neuron receives nerve impulses through its dendrites. It then sends the nerve impulses through its axon to the terminal buttons where neurotransmitters are released to stimulate other neurons.

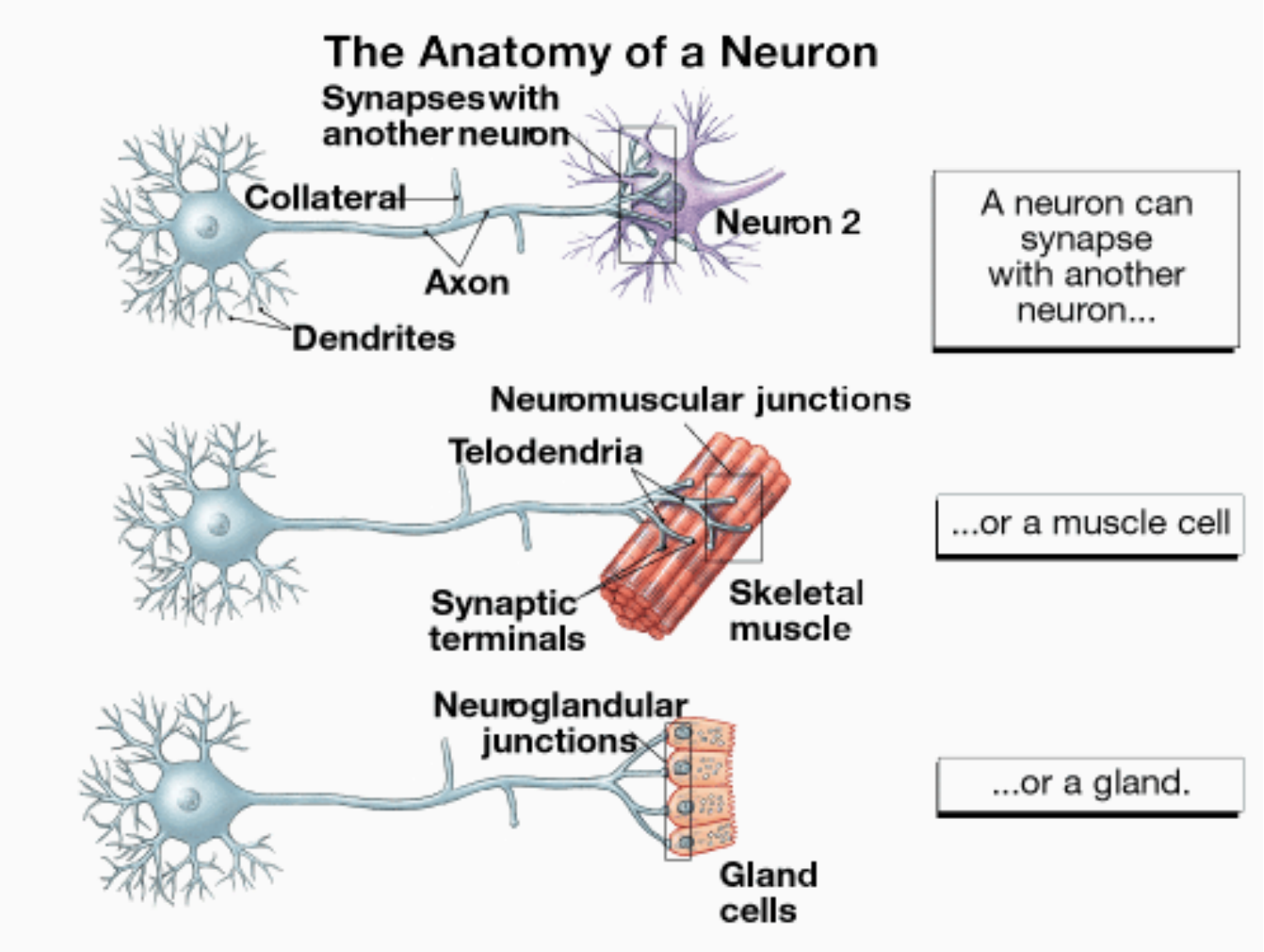


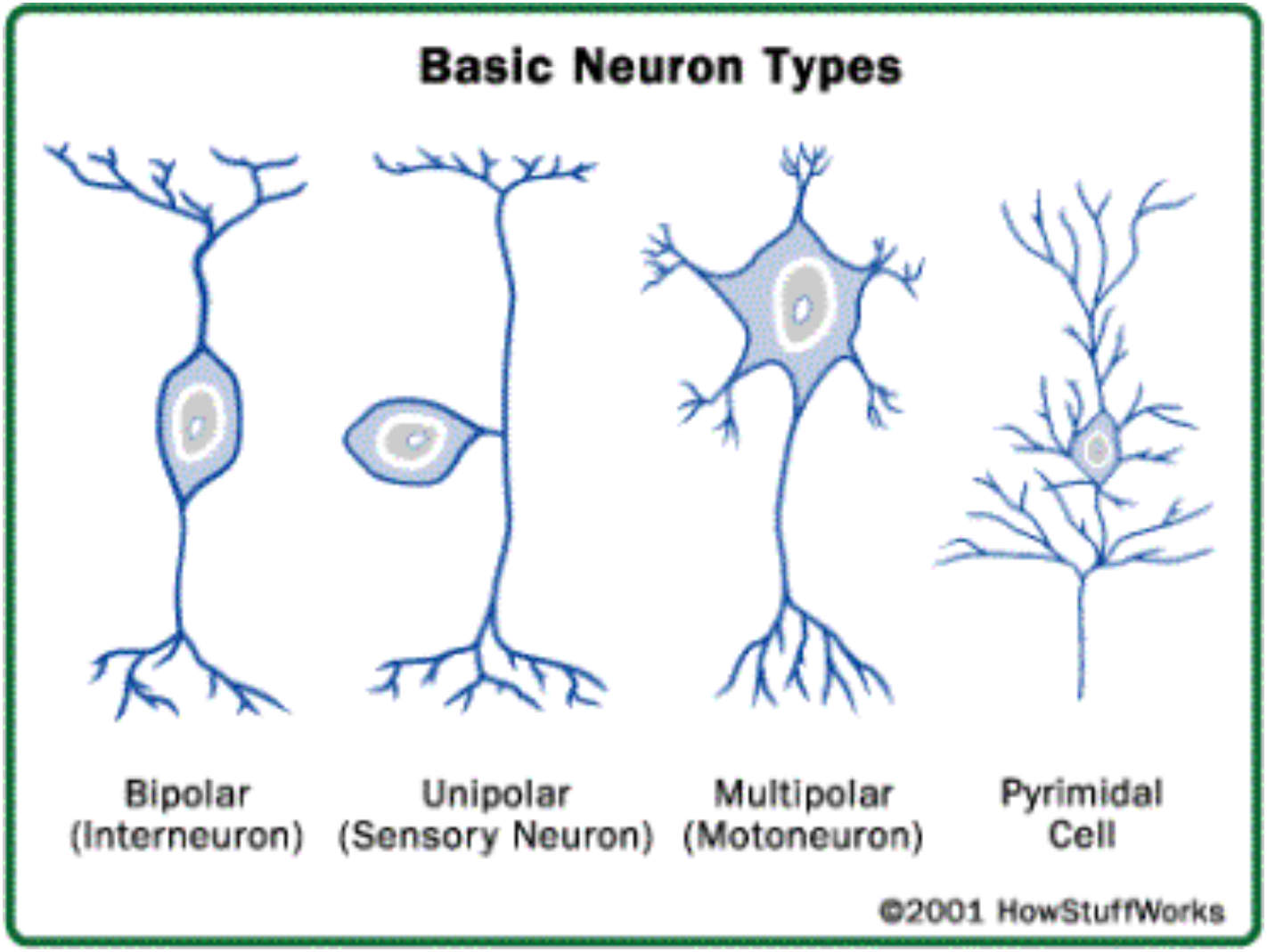


1000-10000 synapses per neuron!



Un neurone può contrarre sinapsi con:




Basic Neuron Types
Bipolar (Interneuron)
Unipolar (Sensory Neuron)
Multipolar (Motoneuron)
Pyrimidal Cell
©2001 HowStuffWorks

Resting potential

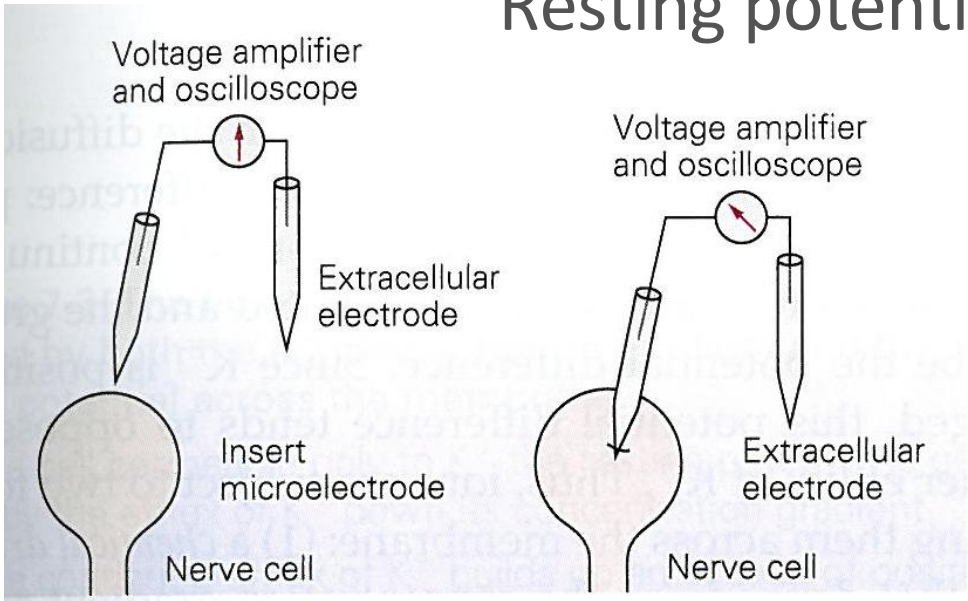


Figure 7-2A The recording setup.

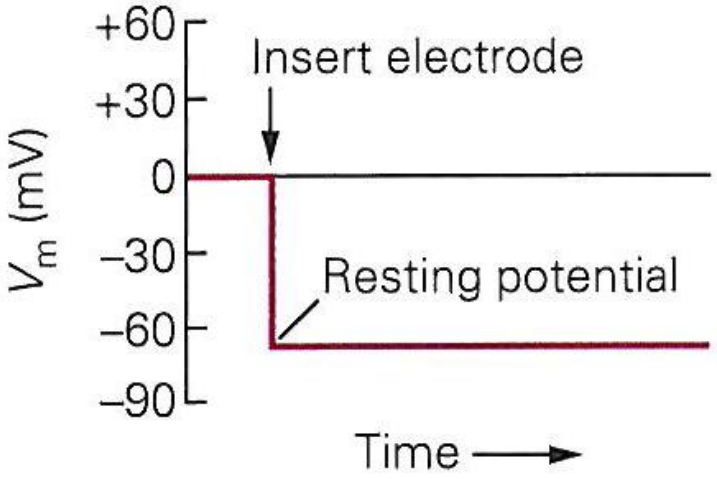
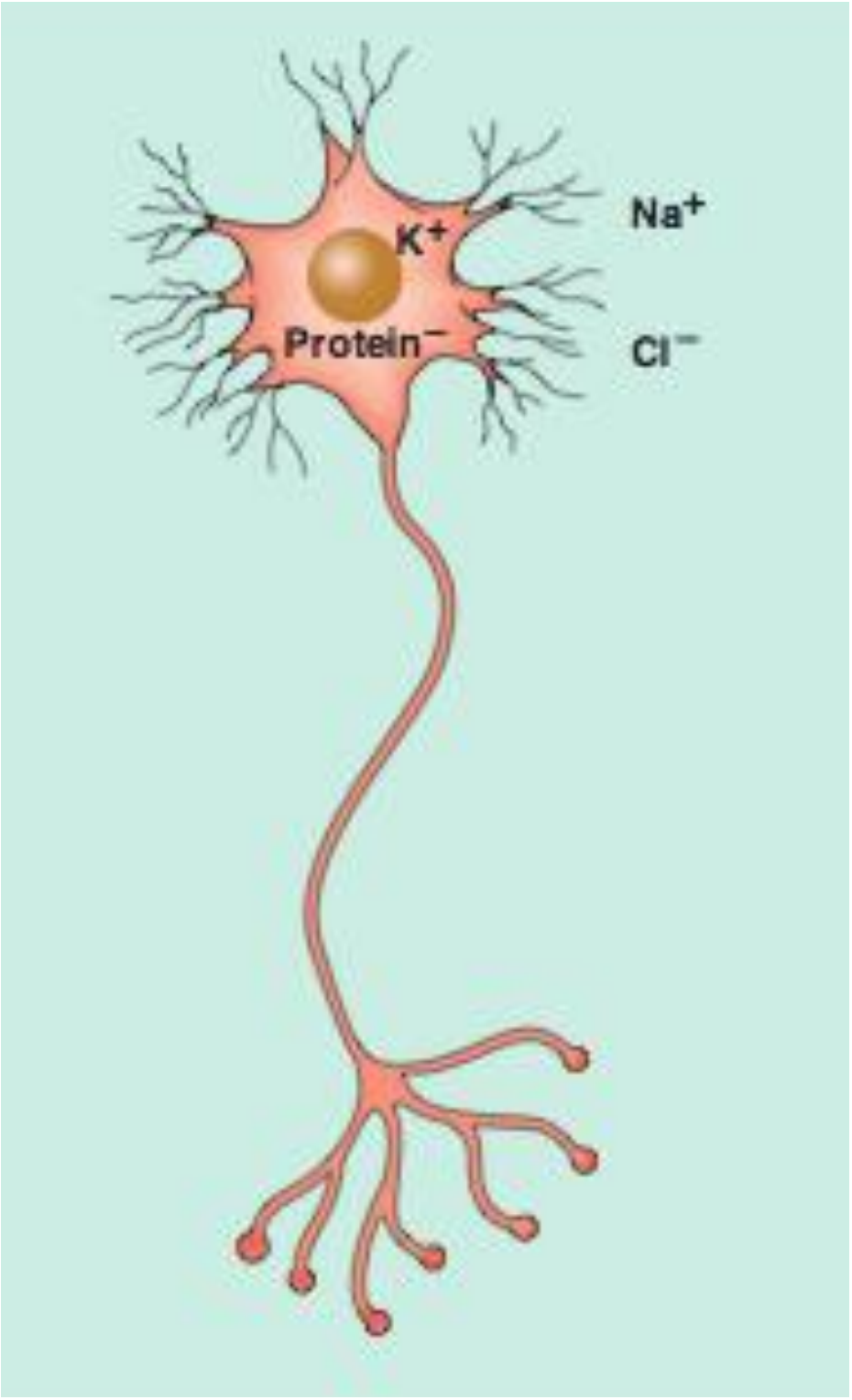
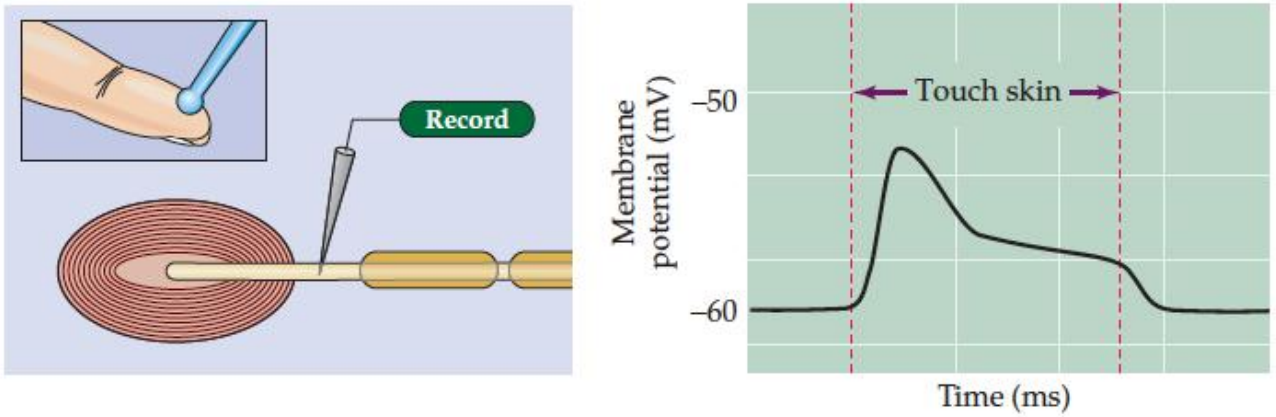


Figure 7-2B Oscilloscope display.

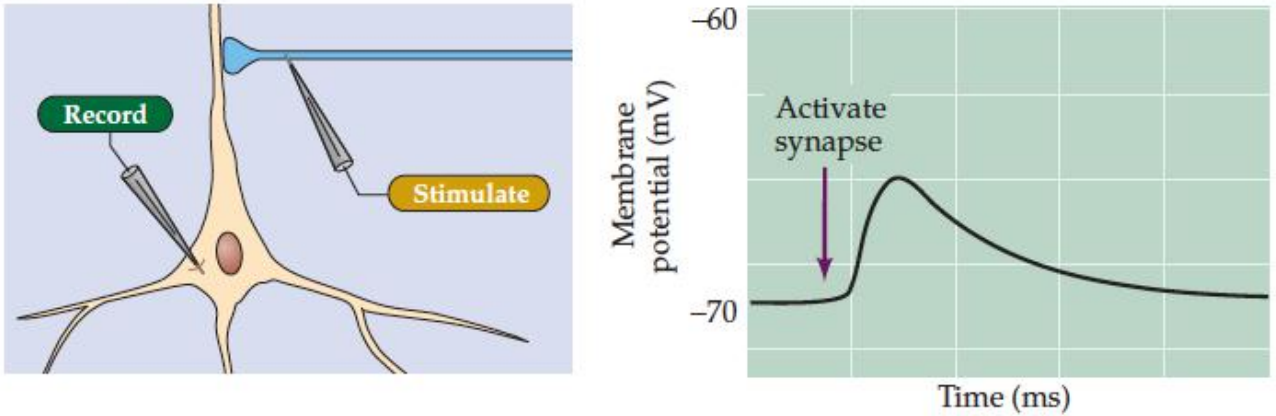


Stimuli

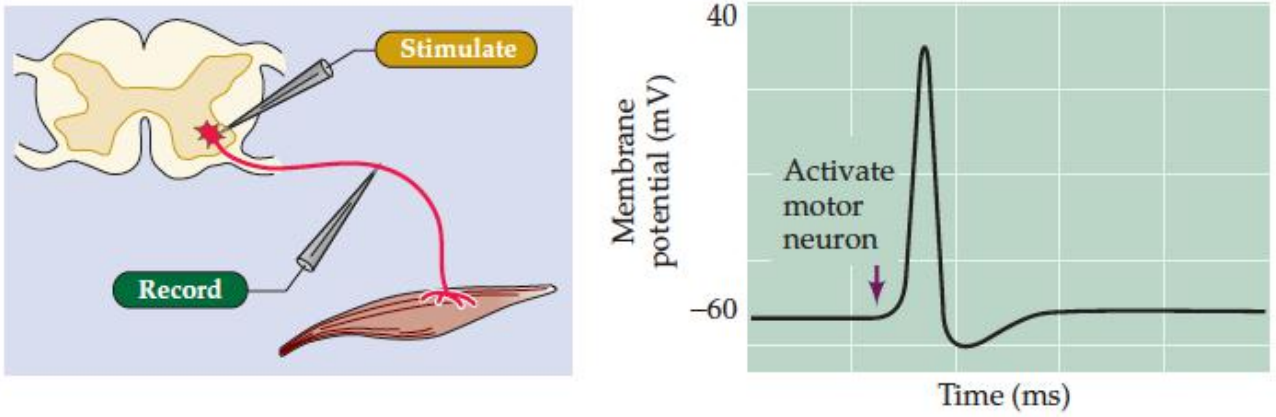
(A) Receptor potential



(B) Synaptic potential



(C) Action potential



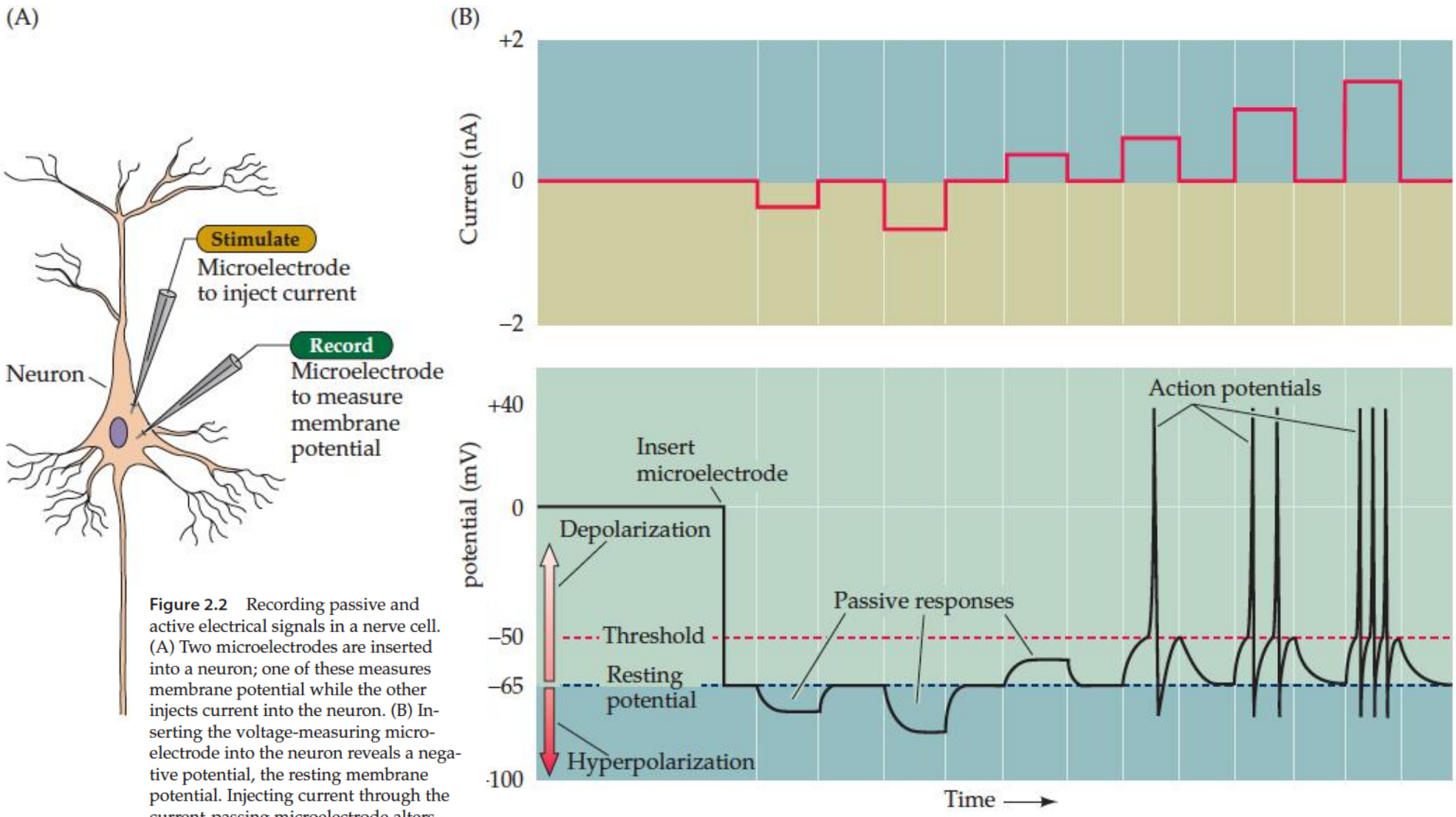


Figure 2.2 Recording passive and active electrical signals in a nerve cell. (A) Two microelectrodes are inserted into a neuron; one of these measures membrane potential while the other injects current into the neuron. (B) Inserting the voltage-measuring microelectrode into the neuron reveals a negative potential, the resting membrane potential. Injecting current through the current-passing microelectrode alters the neuronal membrane potential. Hyperpolarizing current pulses produce only passive changes in the membrane potential. While small depolarizing currents also elict only passive responses, depolarizations that cause the membrane potential to meet or exceed threshold additionally evoke action potentials. Action potentials are active responses in the sense that they are generated by changes in the permeability of the neuronal membrane.

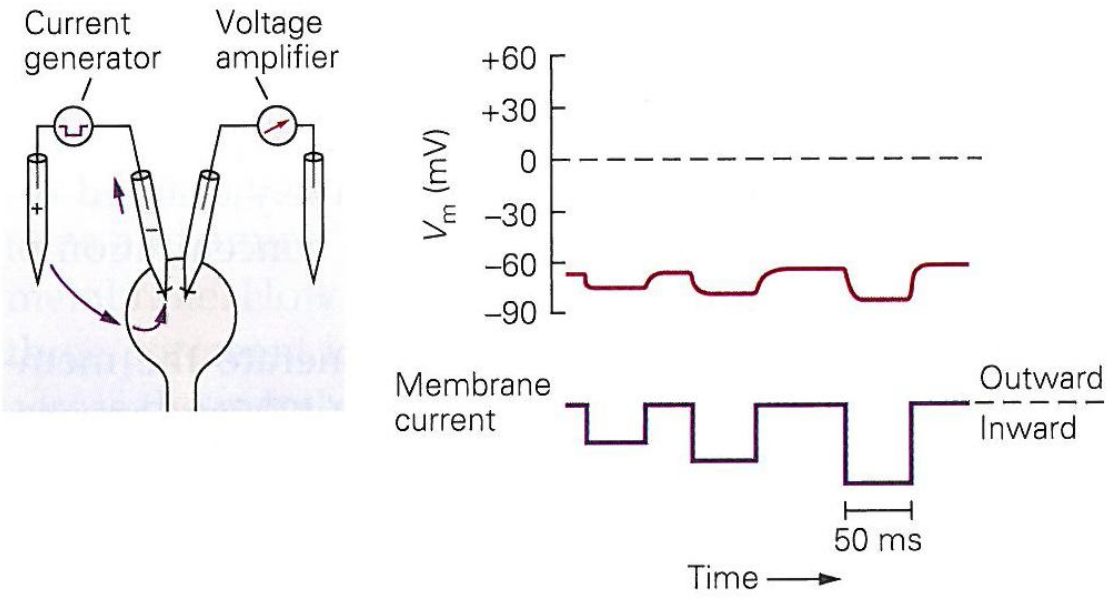


Figure 7-2D Hyperpolarization.

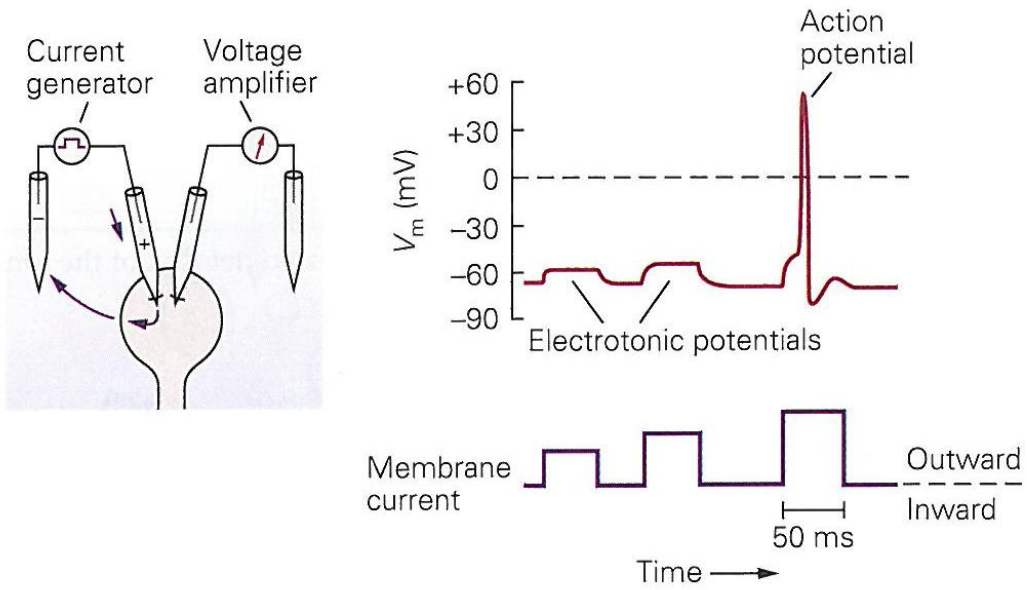
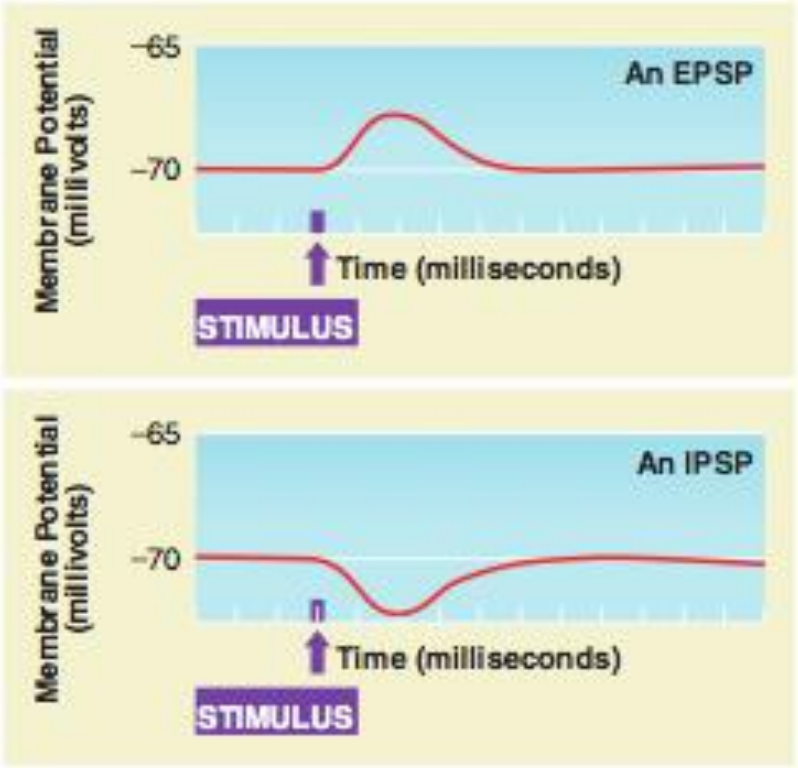


Figure 7-2C Depolarization.



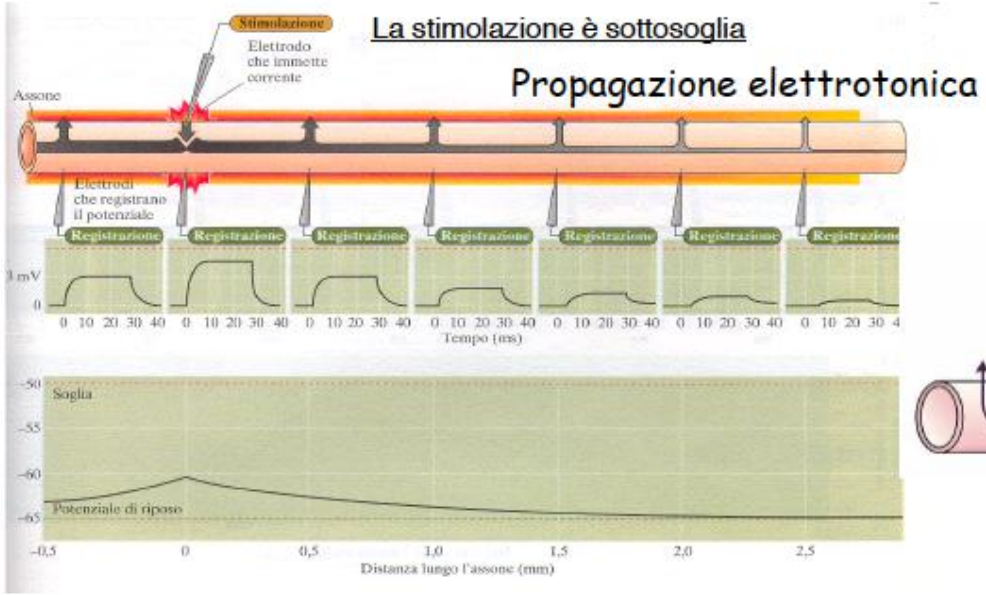
Come può il potenziale di membrana cambiare e poi tornare al suo valore di *riposo*?
Na+ K+ pumps!

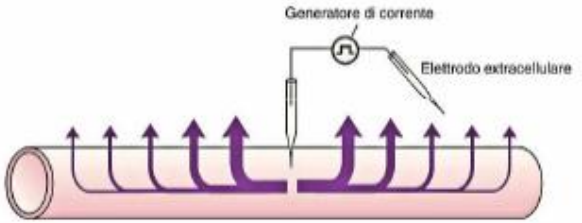
Electrotonic Propagation

(predominant in dendrites and soma)

Membrane depolarizations spread passively quickly but only along short distances

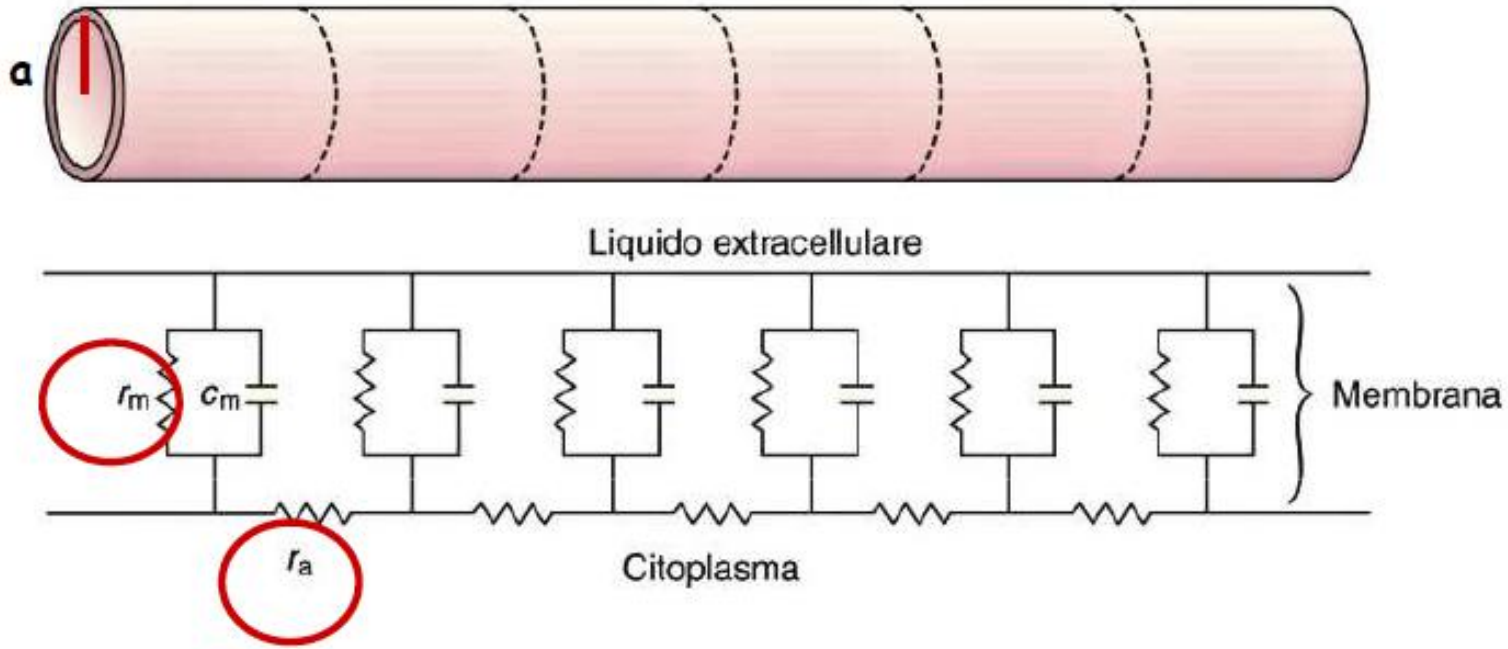
Un potenziale sotto soglia nato in un punto diminuisce di ampiezza man mano che è condotto lungo l'assone o i dendriti di un neurone (**conduzione elettrotonica**). La resistenza di membrana (r_m) e dell'assone (r_a) influenzano l'efficienza con cui vengono condotti i segnali elettrici.





La corrente applicata in un punto si propaga lungo l'assone ma in parte viene persa attraverso la r_m. Questo determina attenuazione del segnale man mano che ci si allontana dal punto di stimolazione.

Sia r_a che r_m dipendono dal diametro del conduttore



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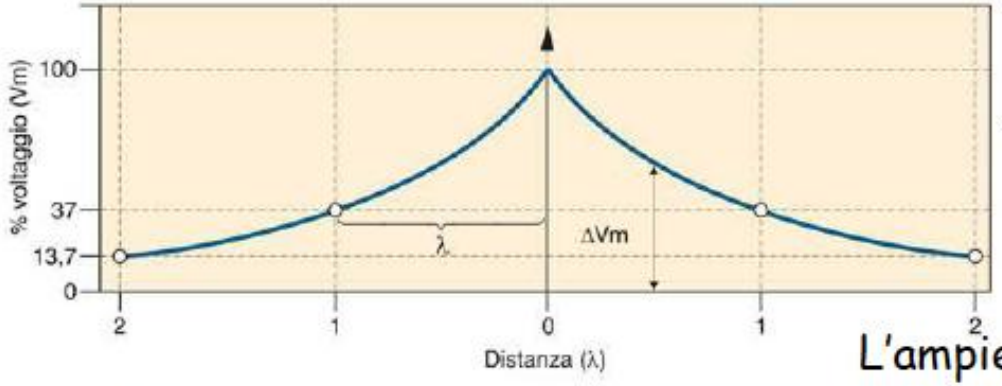
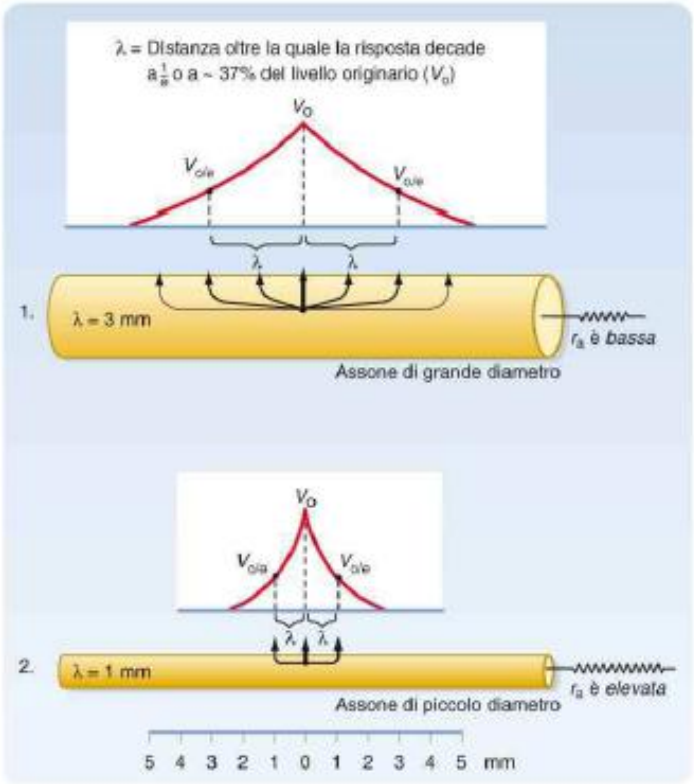
Electrotonic Propagation



$$\Delta V(x) = \Delta V_0 e^{-\frac{x}{\lambda}}$$

$$\lambda = \sqrt{\frac{r_m}{r_a}}$$



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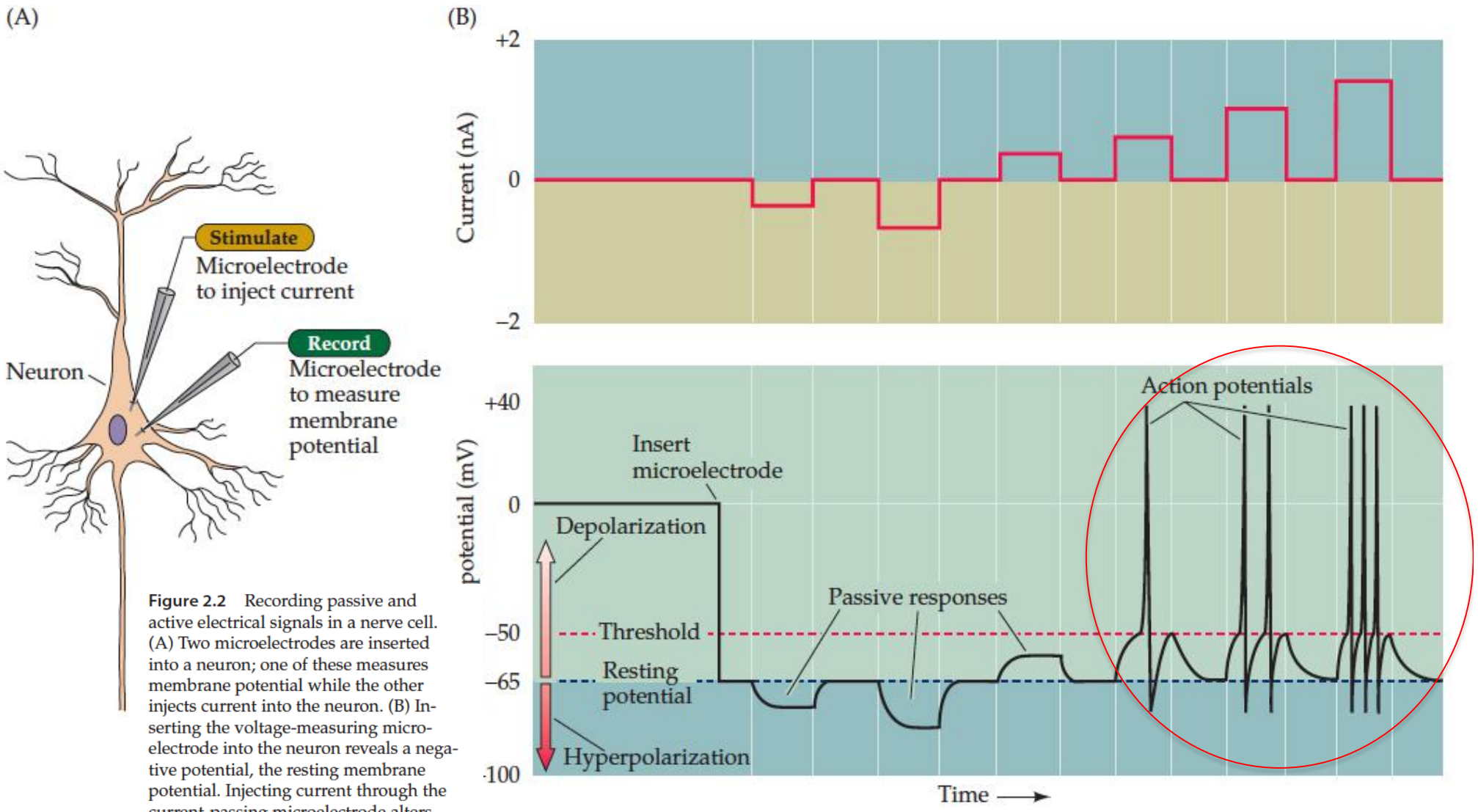
λ aumenta con il diametro (d) della fibra (il rapporto r_m/r_a è correlato al raggio, $\lambda \propto \sqrt{d}$)

Maggiore è λ migliori sono le proprietà del cavo conduttore.

λ: ~1 mm (assoni)
~150-200 μm (dendriti)



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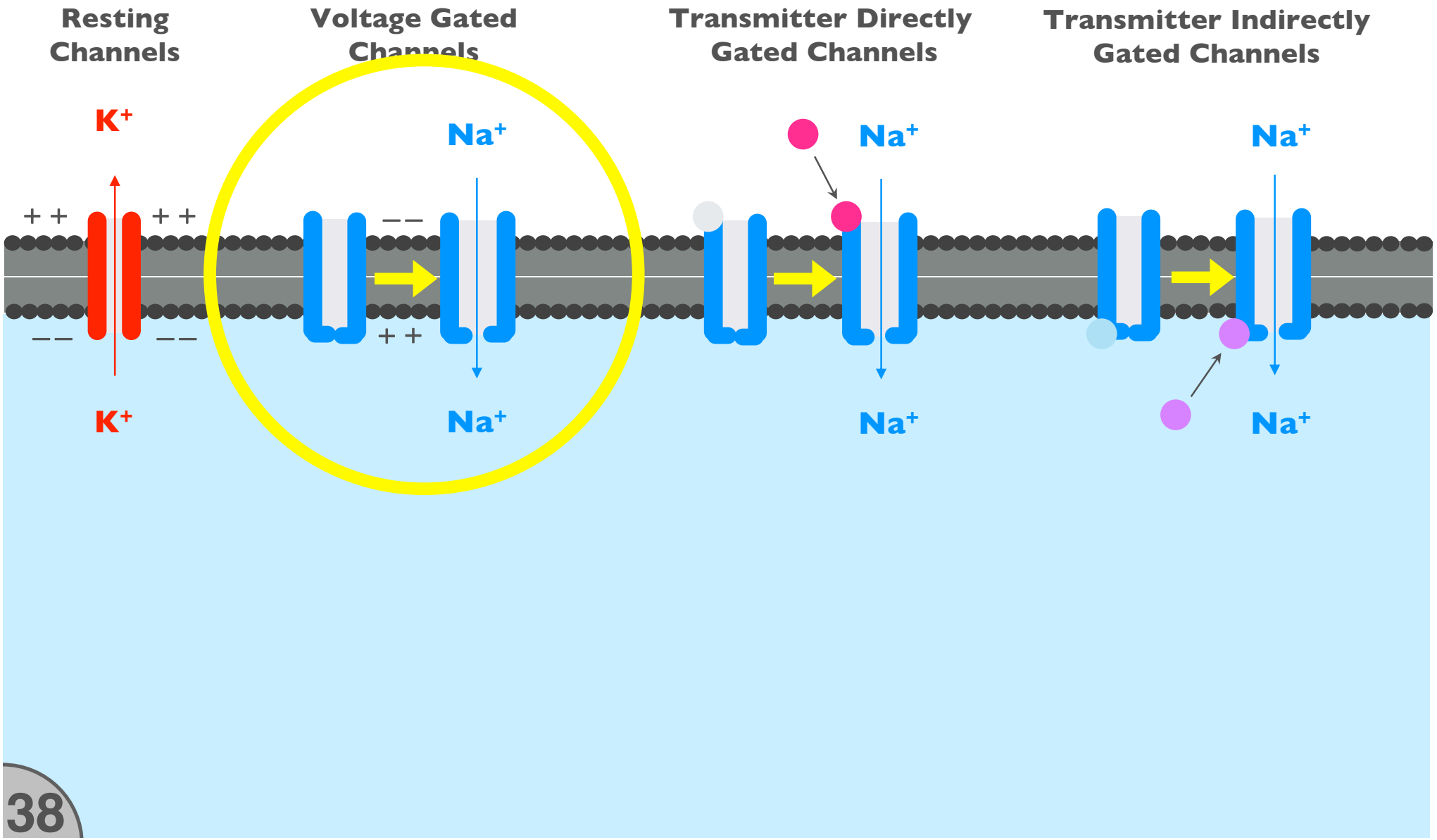
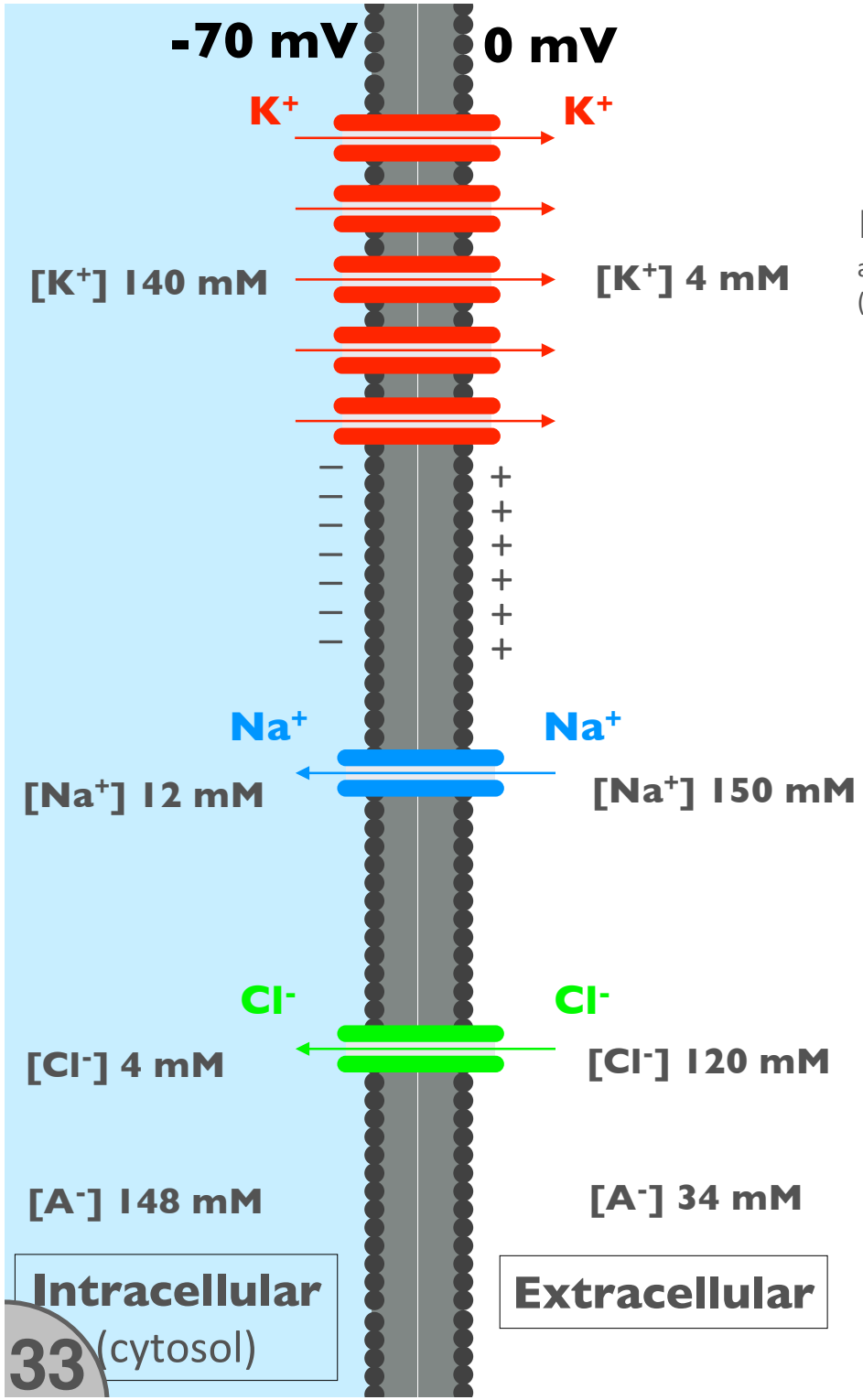
Action Potential Propagation

(predominant in the axon starting from 50 µm far from axonal hillock)





Gradiente di concentrazione
Pressione elettrostatica

From Goldman–Hodgkin–Katz voltage equation

allows one to calculate the voltage at which the net current through passive pathways (that is, ion channels) is zero

$E_{Cl-} \simeq$ -70 mV (equilibrium at RP!)

$E_{K+} \simeq$ -90 mV (20 mV of driving out force)

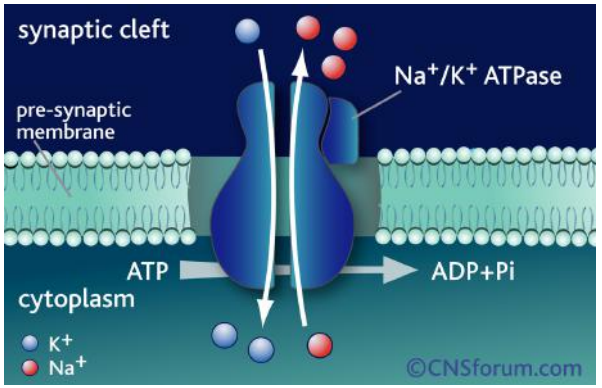
$E_{Na+} \simeq$ +50 mV (120 mV of driving in force!!!)

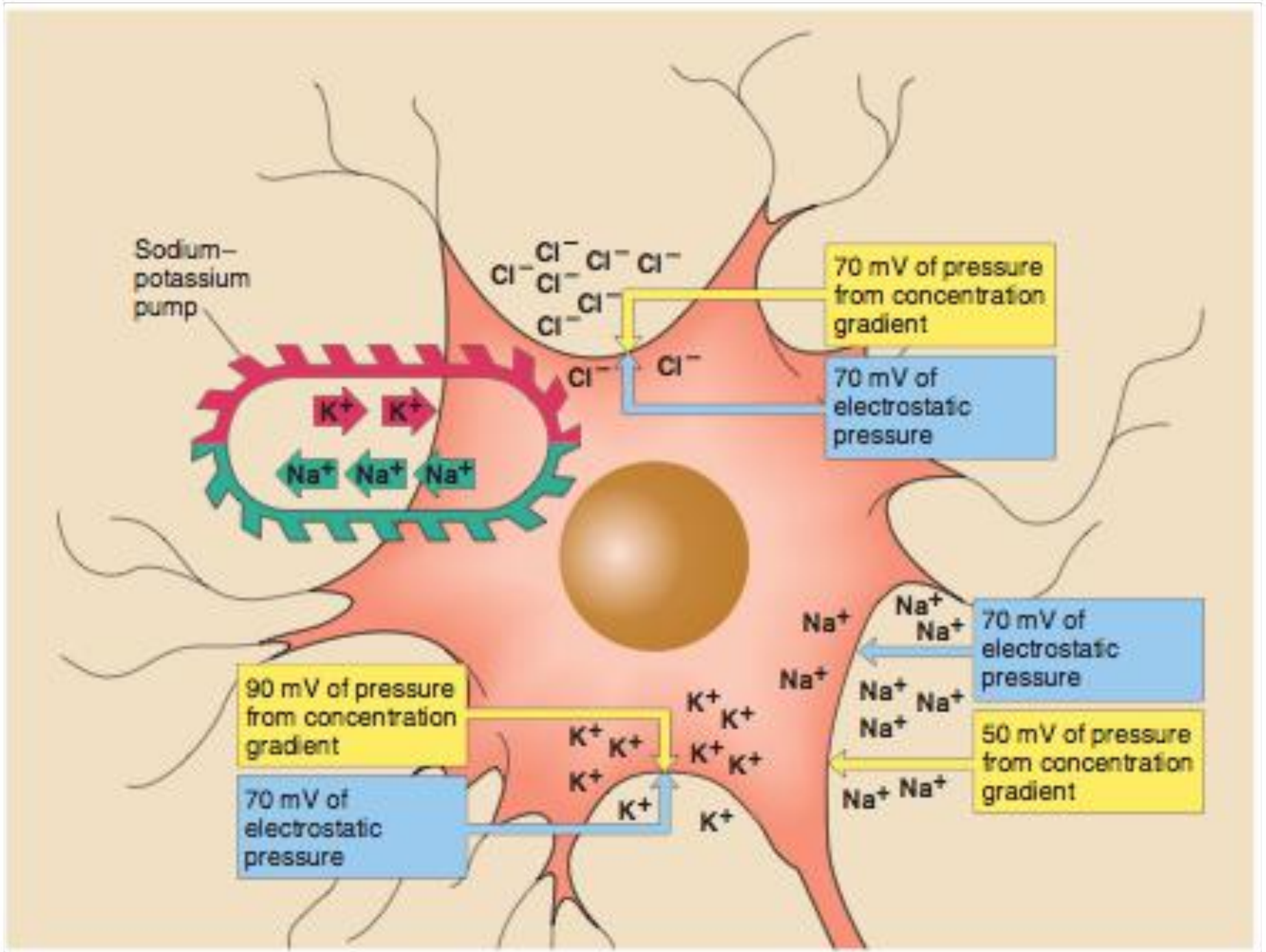
Permeabilità della membrana cellulare:

p_{Na^+} molto bassa
p_{K^+} bassa
p_{Cl^-} bassa
p_{A^-} praticamente zero

An ACTIVE mechanism is necessary!!!

The Na^+/K^+ Pump




Sodium–
potassium
pump
Cl⁻
70 mV of pressure
from concentration
gradient
70 mV of
electrostatic
pressure
K⁺
Na⁺
90 mV of pressure
from concentration
gradient
70 mV of
electrostatic
pressure
70 mV of
electrostatic
pressure
50 mV of pressure
from concentration
gradient

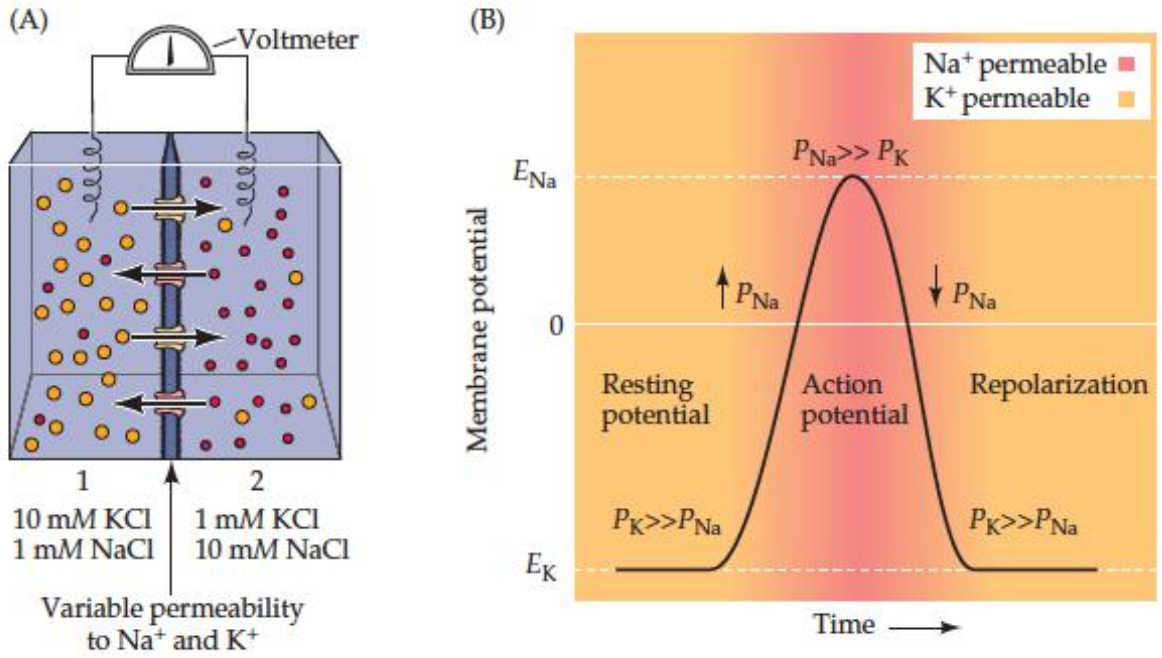
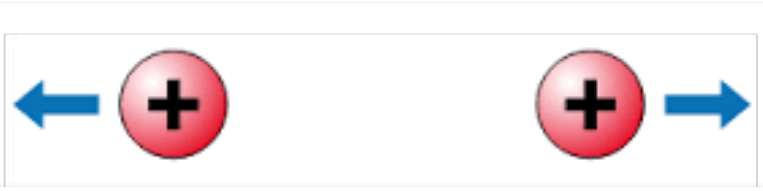
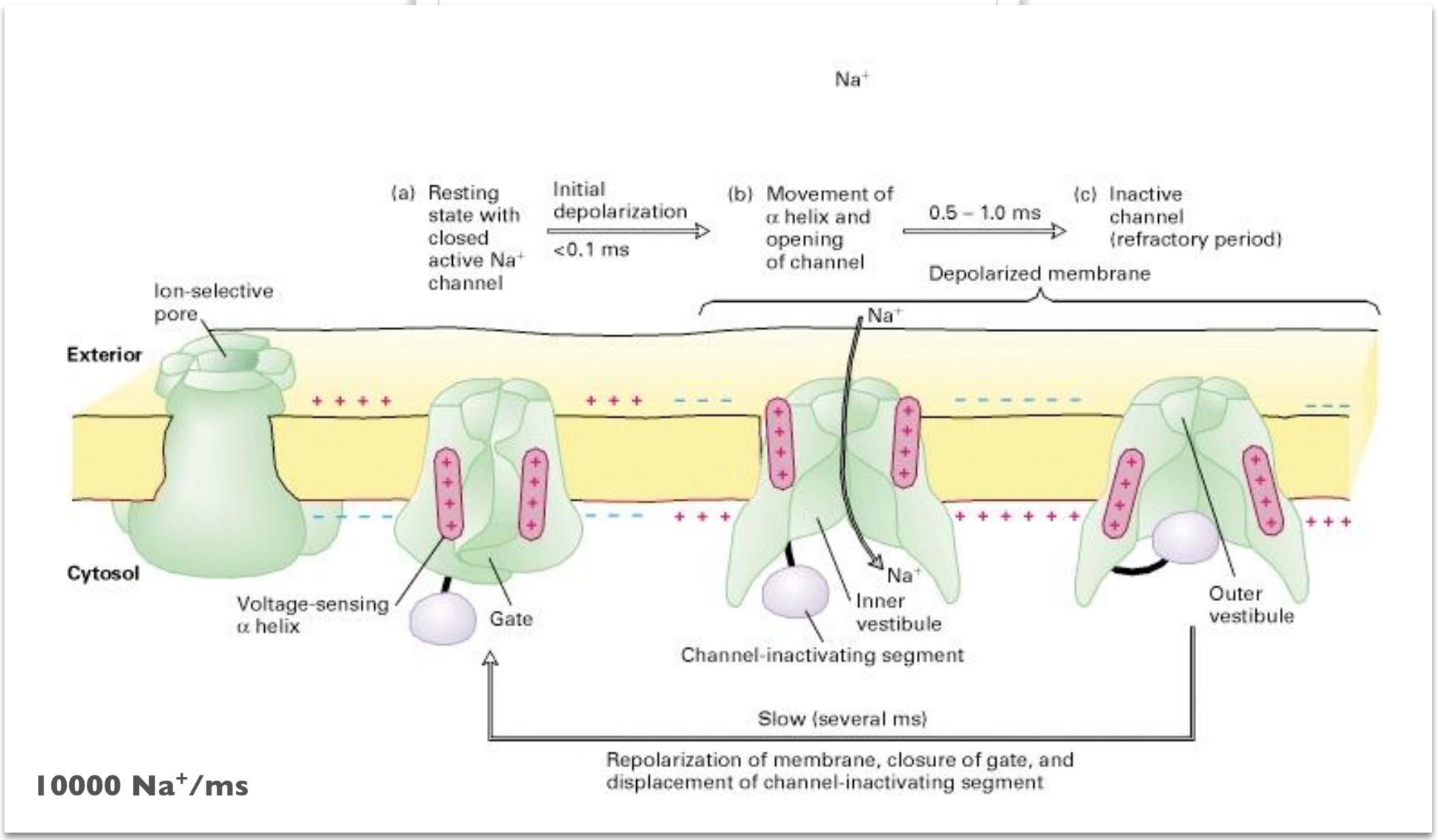


Figure 2.6 Resting and action potentials entail permeabilities to different ions. (A) Hypothetical situation in which a membrane variably permeable to Na^+ (red) and K^+ (yellow) separates two compartments that contain both ions. For simplicity, Cl^- ions are not shown in the diagram. (B) Schematic representation of the membrane ionic permeabilities associated with resting and action potentials. At rest, neuronal membranes are more permeable to K^+ (yellow) than to Na^+ (red); accordingly, the resting membrane potential is negative and approaches the equilibrium potential for K^+, E_K. During an action potential, the membrane becomes very permeable to Na^+ (red); thus the membrane potential becomes positive and approaches the equilibrium potential for Na^+, E_{Na}. The rise in Na^+ permeability is transient, however, so that the membrane again becomes primarily permeable to K^+ (yellow), causing the potential to return to its negative resting value. Notice that at the equilibrium potential for a given ion, there is no net flux of that ion across the membrane.



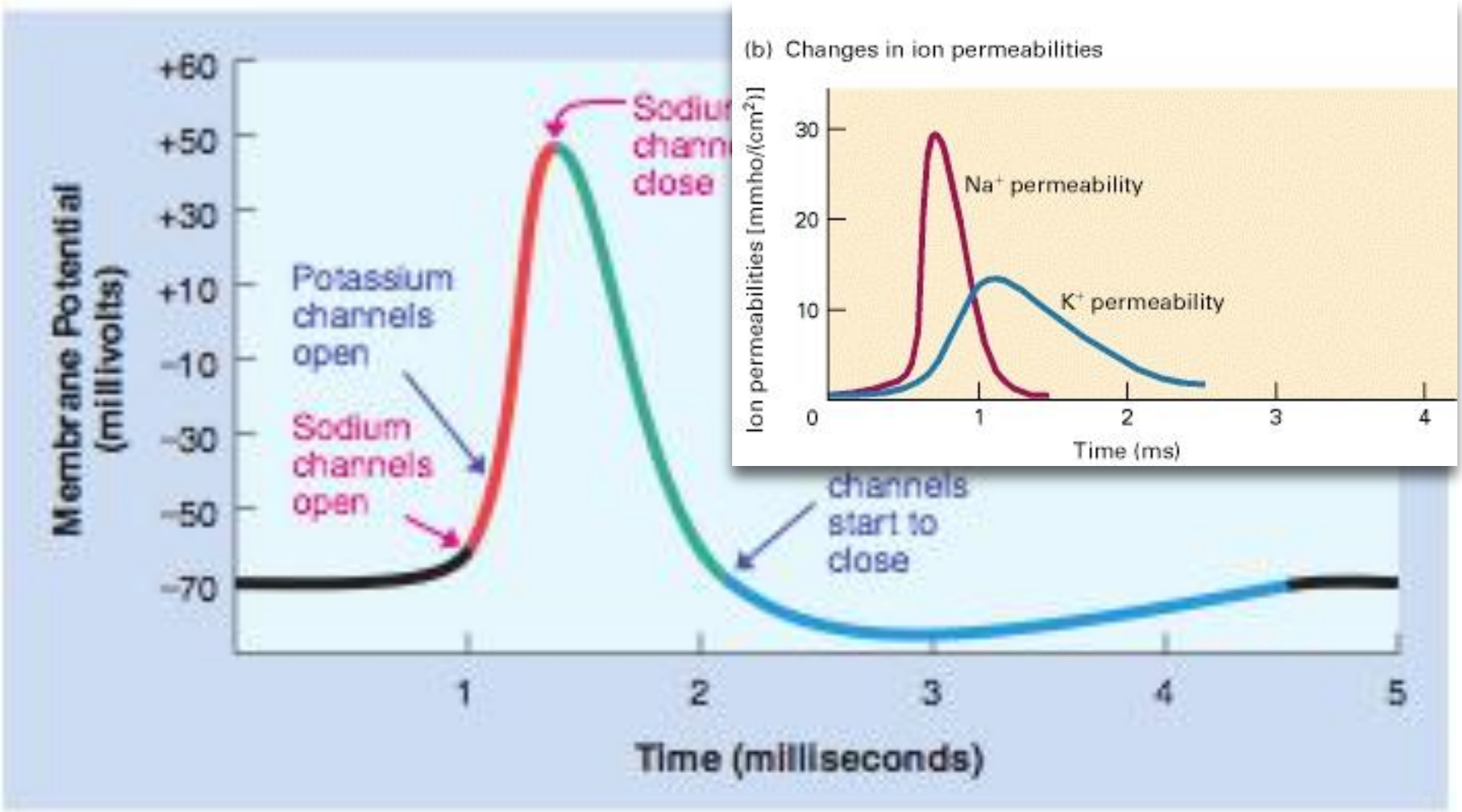

Na+
(a) Resting state with closed active Na+ channel
Initial depolarization
<0.1 ms
(b) Movement of α helix and opening of channel
0.5 – 1.0 ms
(c) Inactive channel (refractory period)
Depolarized membrane
Ion-selective pore
Exterior
Cytosol
Na+
Na+
Voltage-sensing α helix
Gate
Inner vestibule
Channel-inactivating segment
Outer vestibule
Slow (several ms)
Repolarization of membrane, closure of gate, and displacement of channel-inactivating segment

10000 Na^+/ms

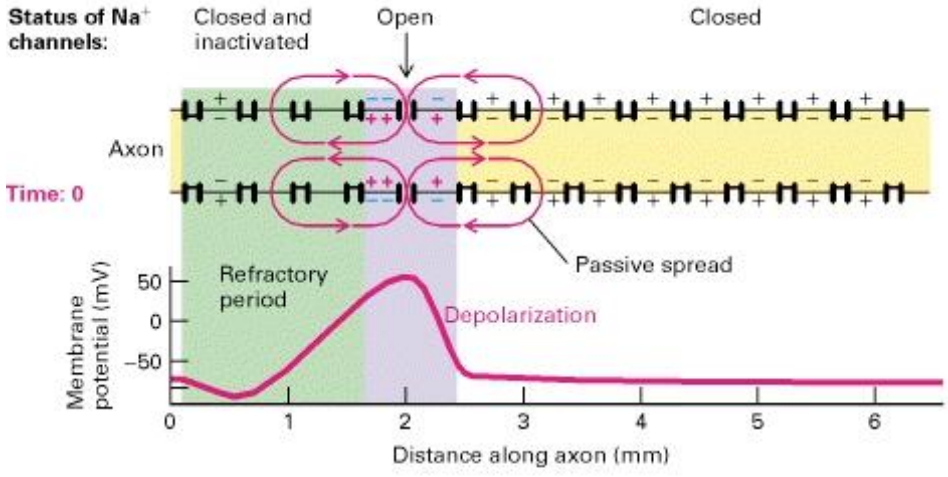
Action Potential Propagation

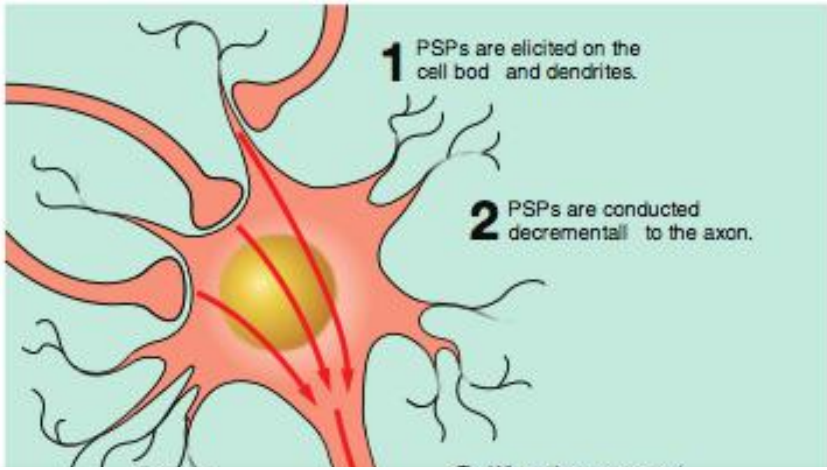
(predominant in the axon starting from 50 µm far from axonal hillock)

Voltage-Gated Cation Channels Generate Action Potentials (slow but propagate for longer distances)



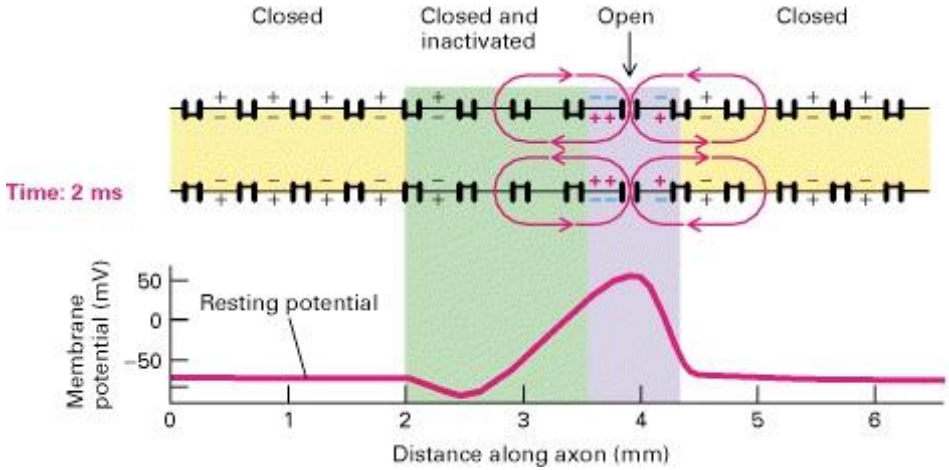
https://www.youtube.com/watch?v=oa6rvUJlg7o

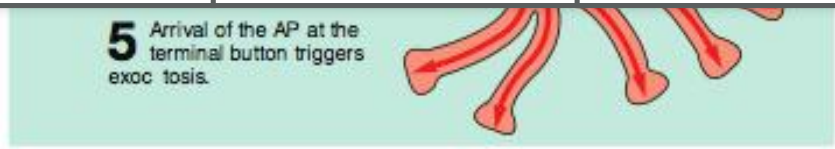




Alcune importanti differenze tra le due forme di conduzione:

Propagazione Elettrotonica	Passiva	Veloce	Brevi distanze	Bidirezionali	Integrabile nello spazio e nel tempo	L'ampiezza conta	La frequenza non conta#
Potenziali di Azione	Attiva	Lenta*	Lunghe distanze*	Monodirezionali	Tutto o Niente	L'ampiezza non conta (tutto o niente)	La frequenza conta!





Absolute refractory period (1-2 ms)

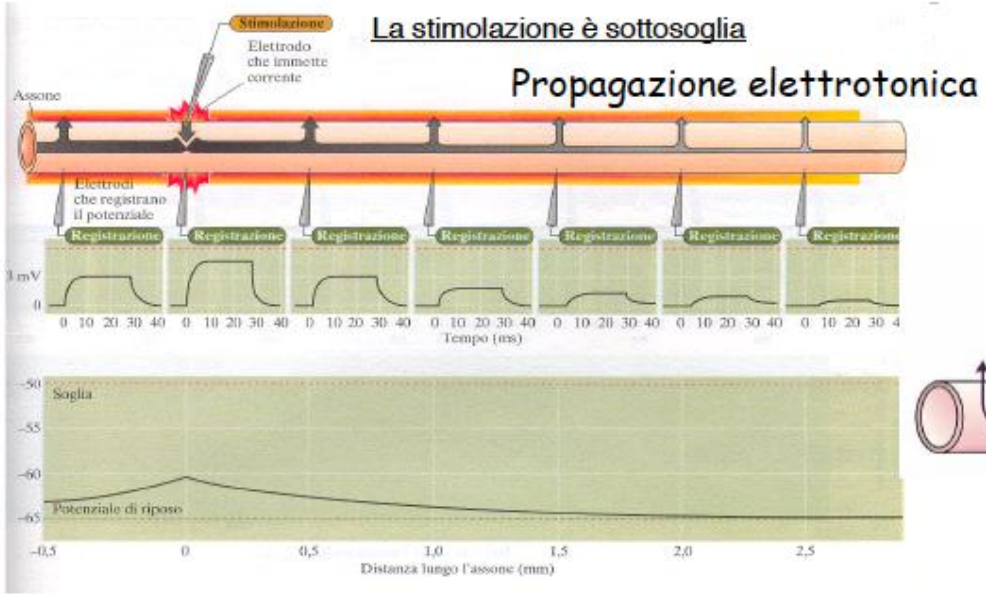
Relative refractory period
(hyperdepolarization)
Fundamental for frequency codification of signal intensity

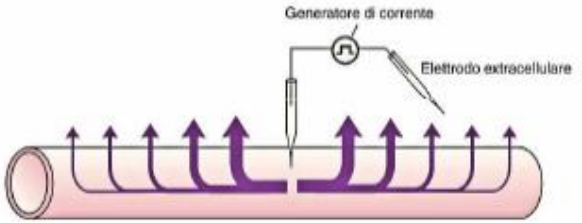
Electrotonic Propagation

(predominant in dendrites and soma)

Membrane depolarizations spread passively quickly but only along short distances

Un potenziale sotto soglia nato in un punto diminuisce di ampiezza man mano che è condotto lungo l'assone o i dendriti di un neurone (**conduzione elettrotonica**). La resistenza di membrana (r_m) e dell'assone (r_a) influenzano l'efficienza con cui vengono condotti i segnali elettrici.





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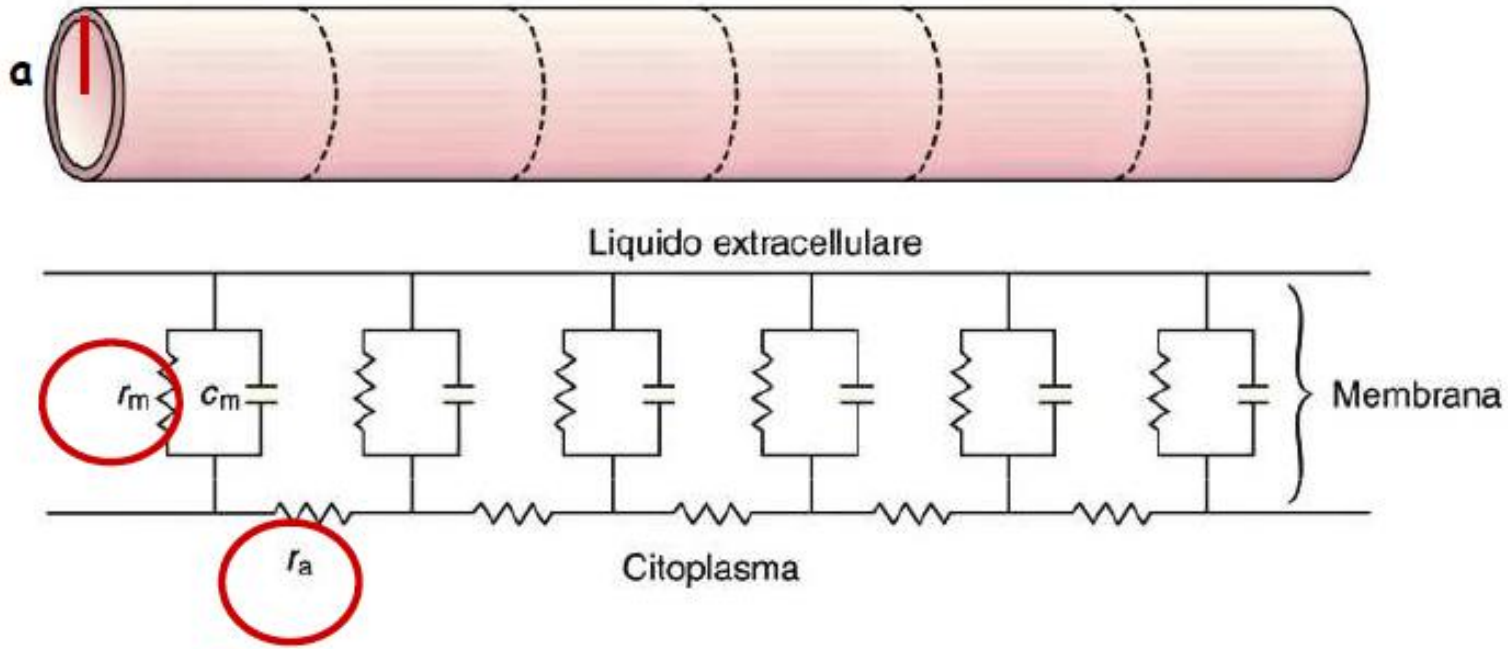
Sia r_a che r_m dipendono dal diametro del conduttore



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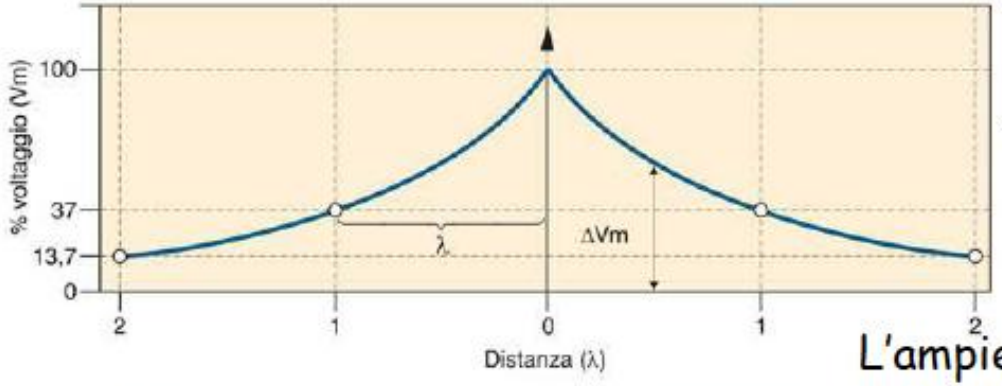
Electrotonic Propagation



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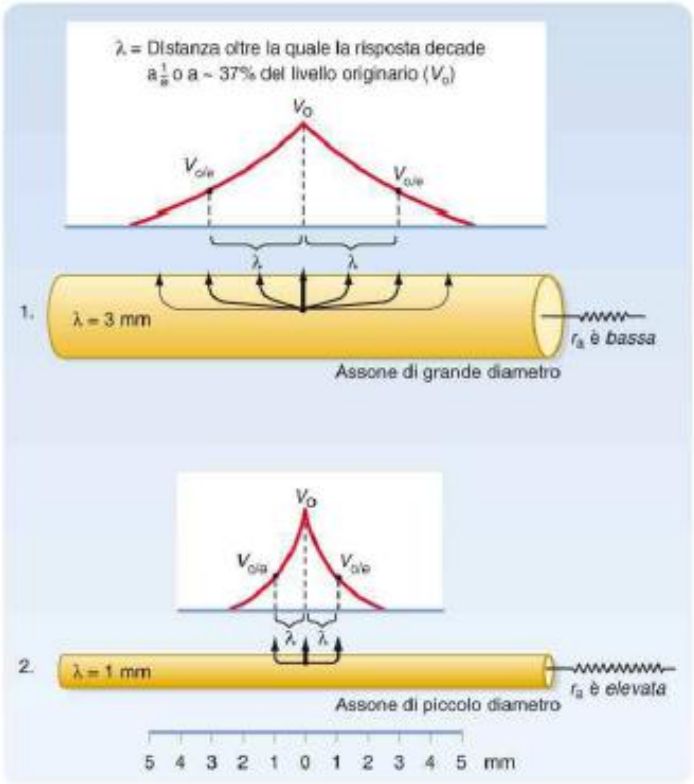

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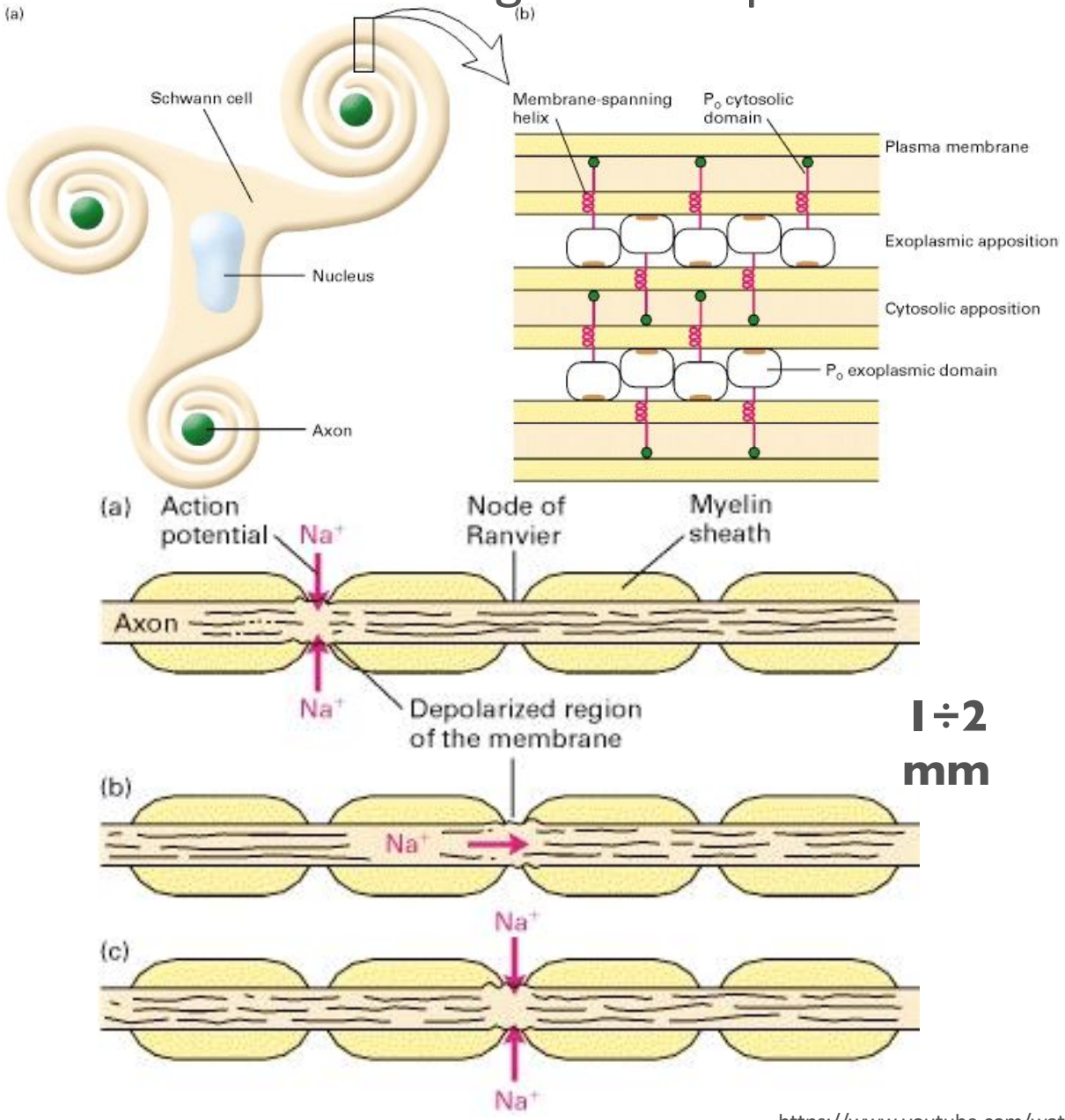
λ: ~1 mm (assoni)
~150-200 μm (dendriti)

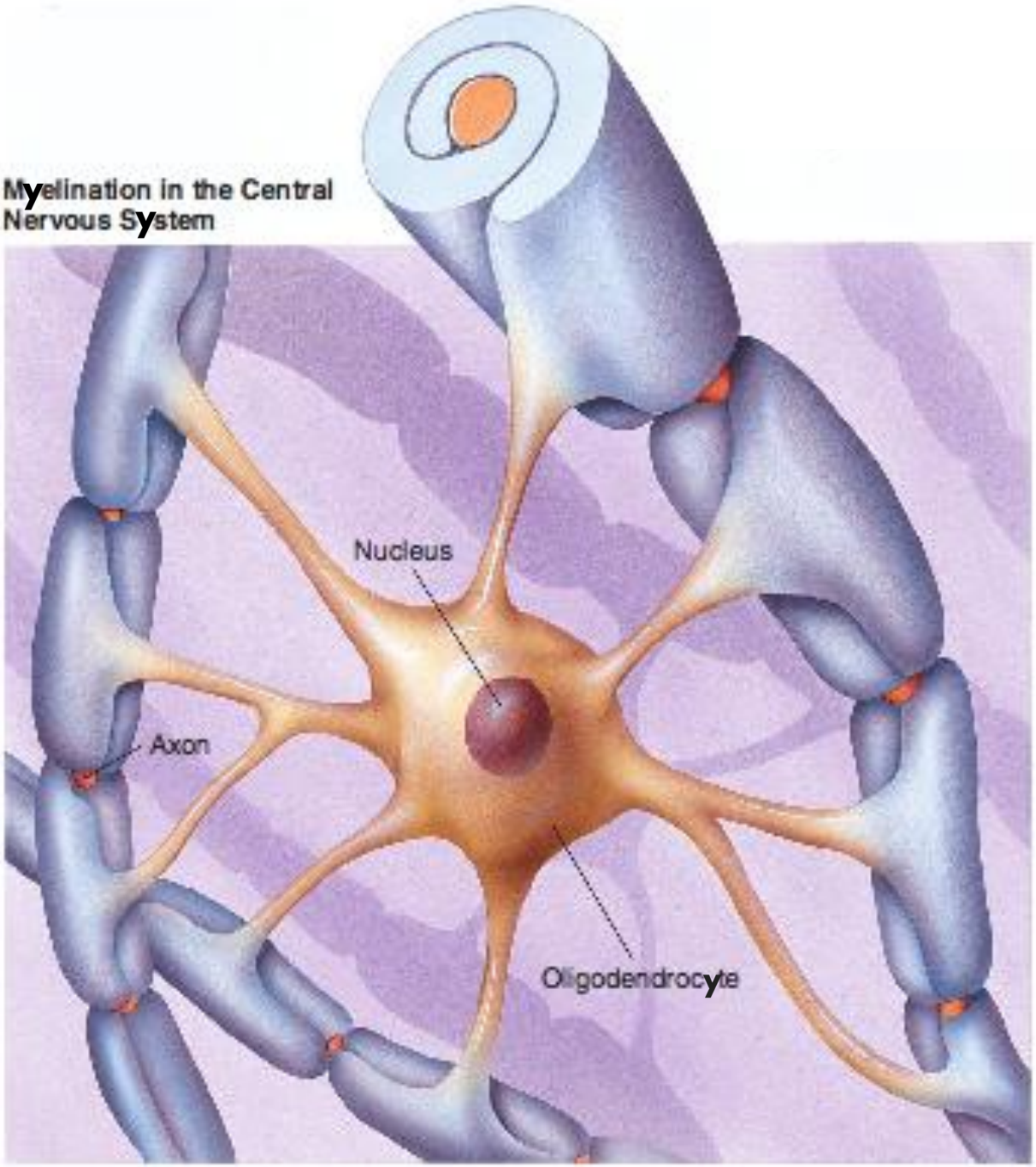
“Saltatory” Propagation

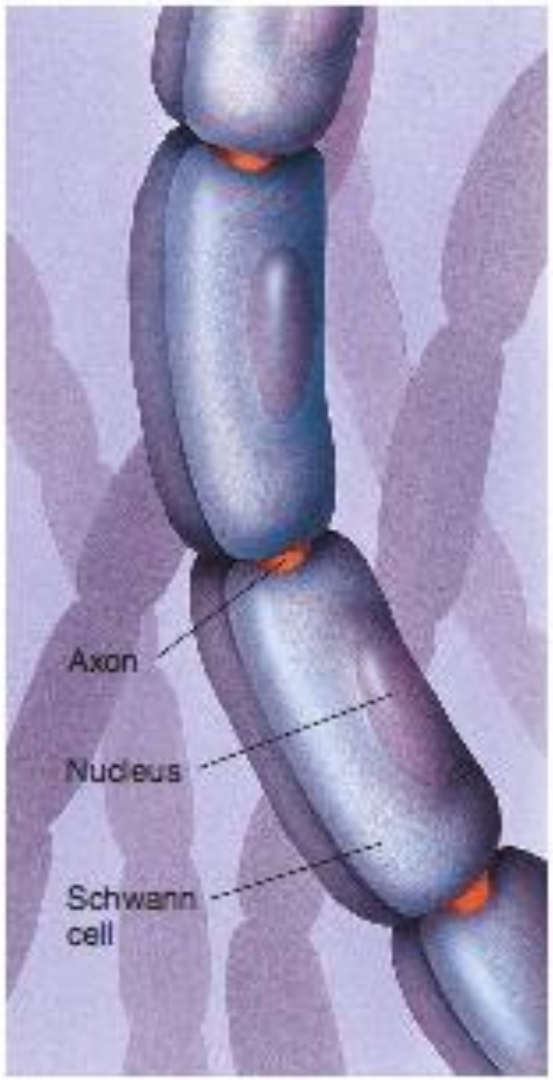
(predominant in the axon starting from 50 µm far from axonal hillock)



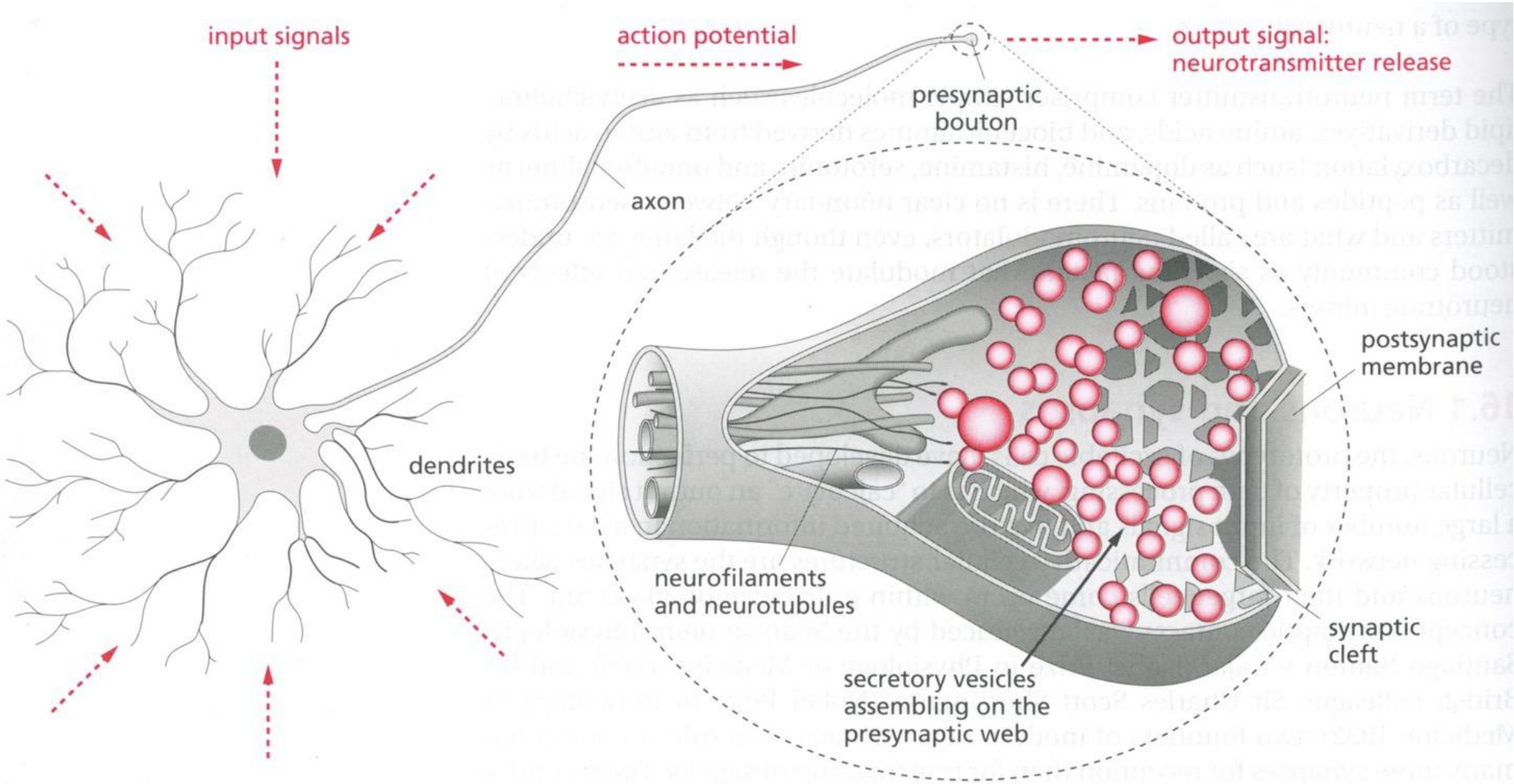
1÷2 mm

https://www.youtube.com/watch?v=oa6rvUJlg7o

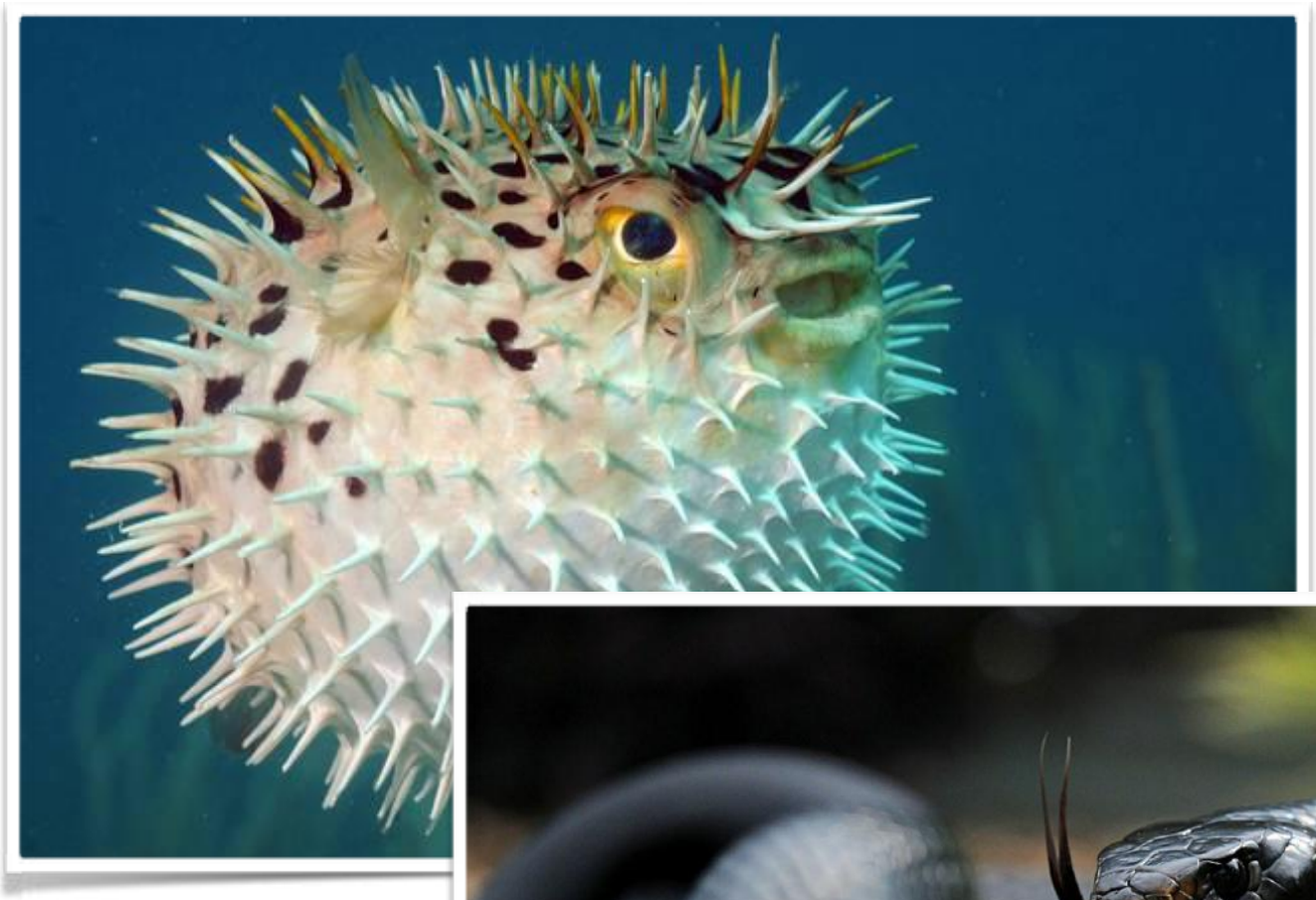

Myelination in the Central Nervous System
Nucleus
Axon
Oligodendrocyte


Myelination in the Peripheral Nervous System
Axon
Nucleus
Schwann cell

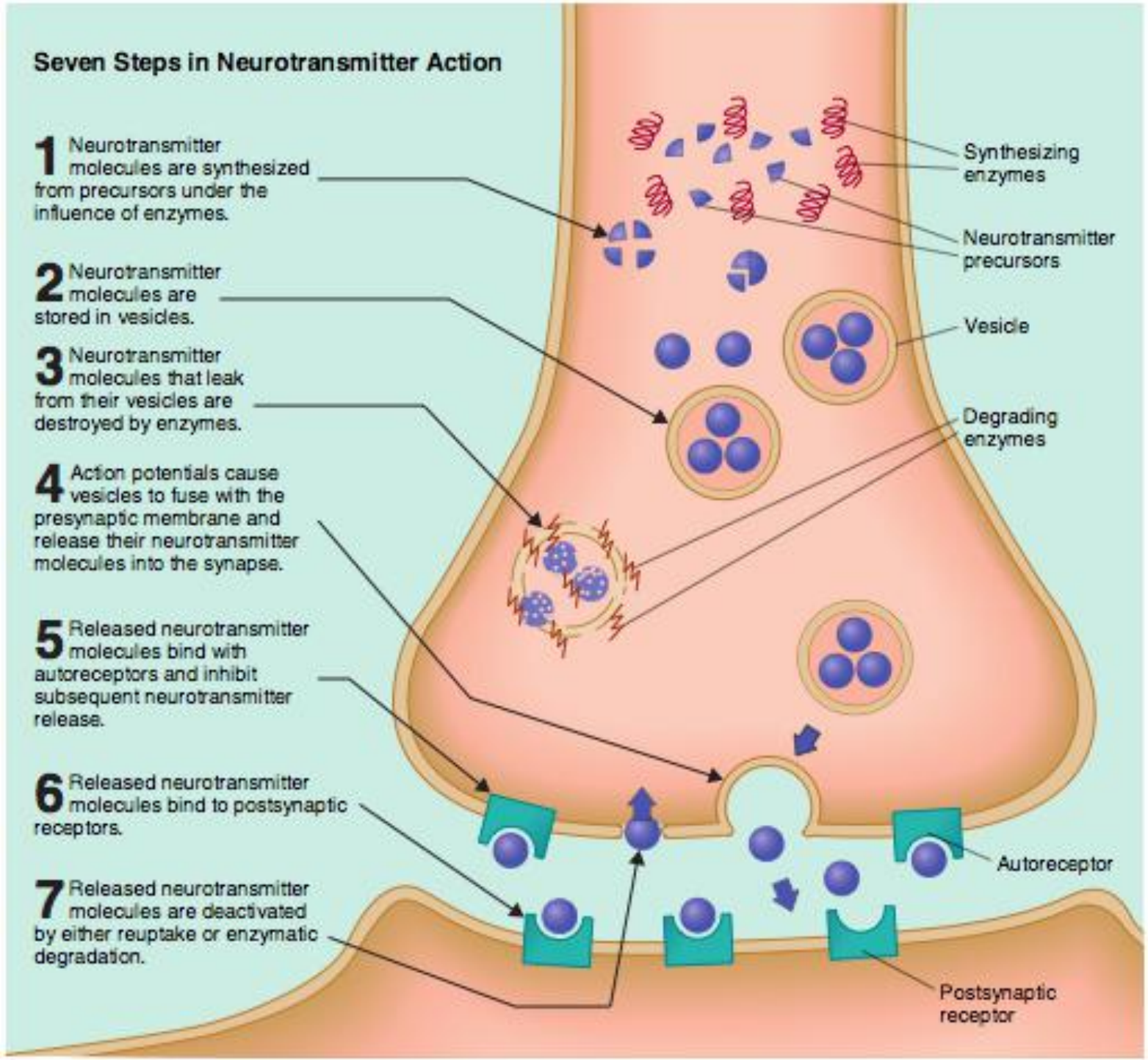
Chemical Synapses

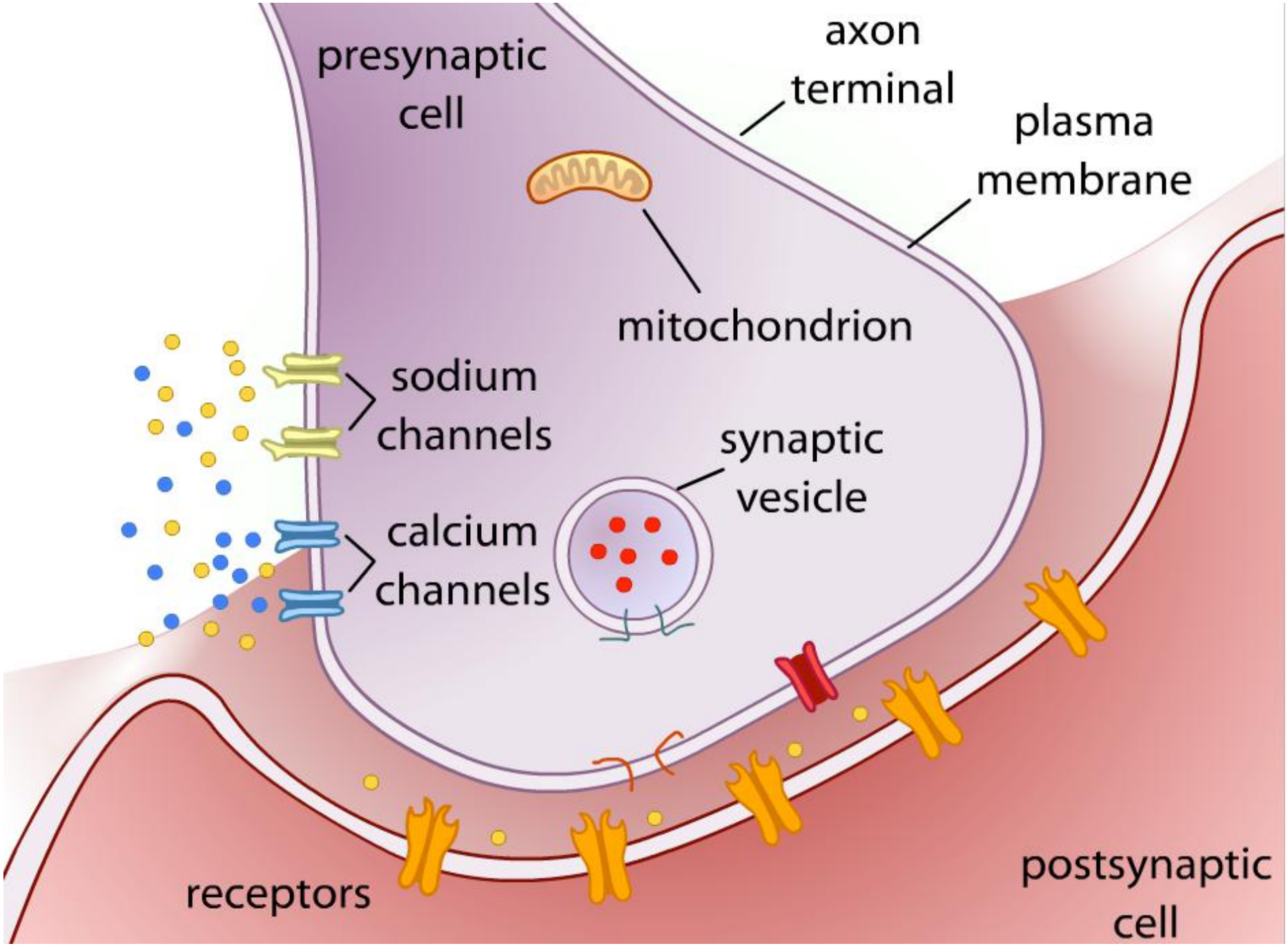


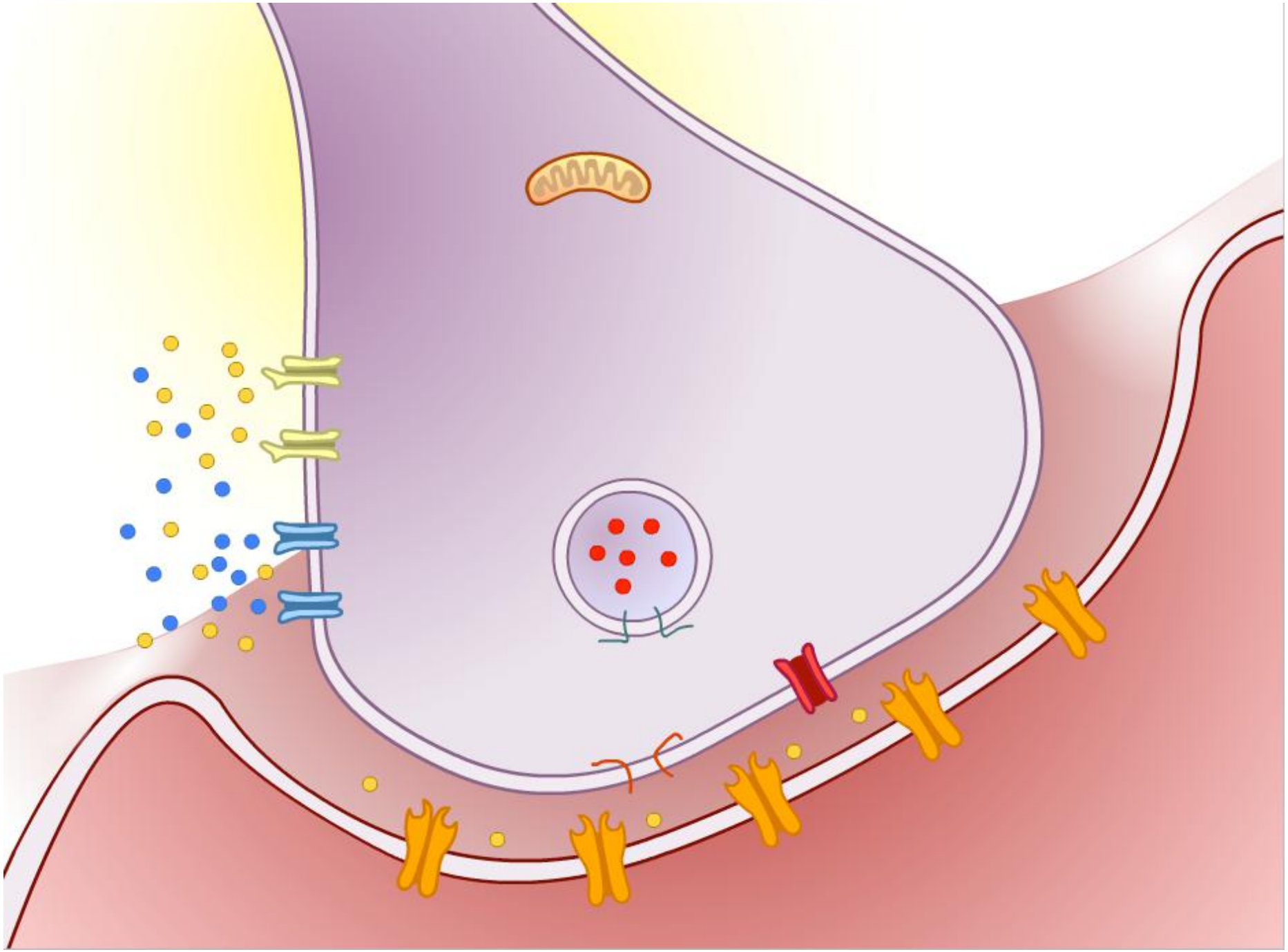
Many different synapses are present in the NS

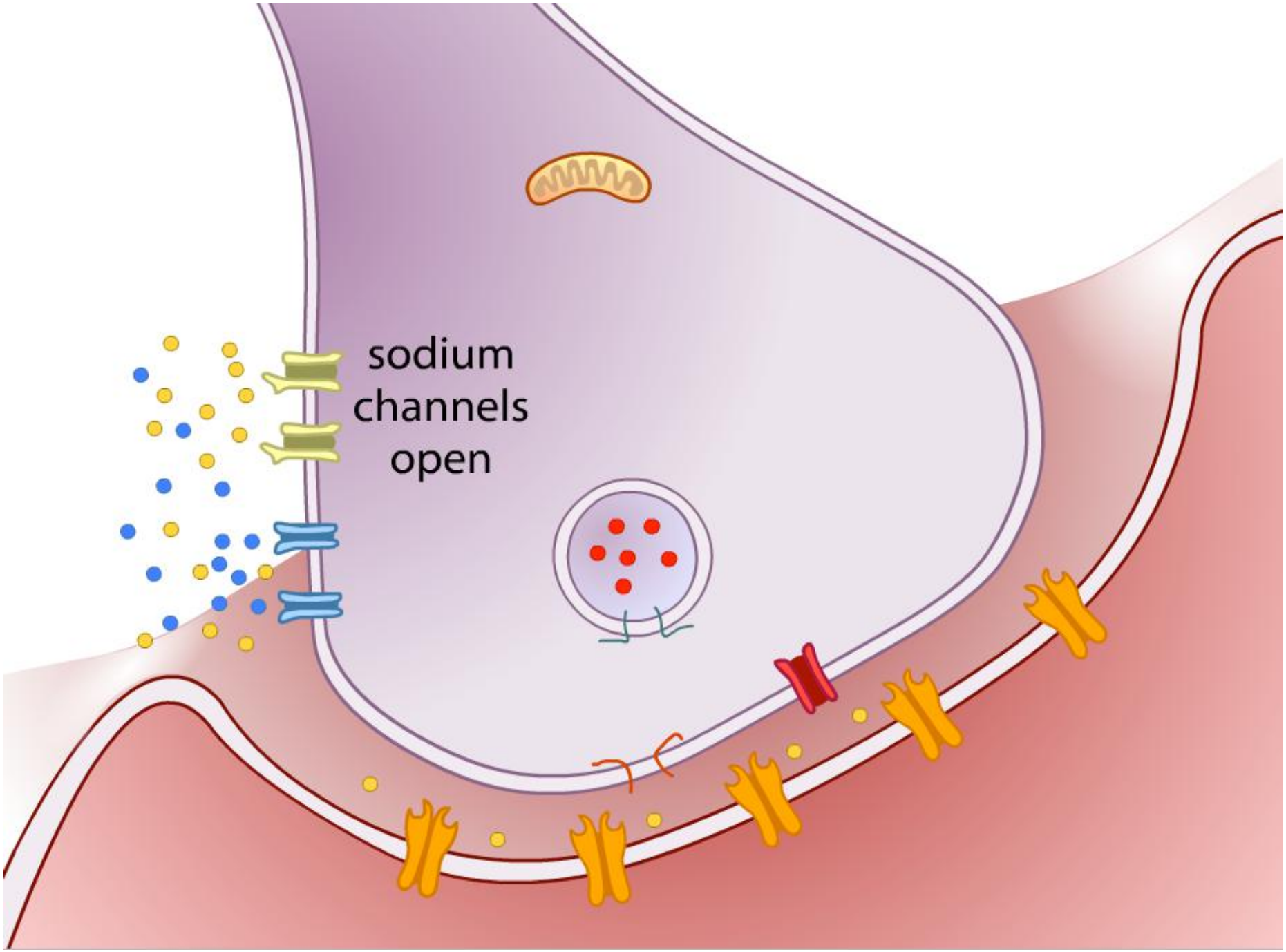


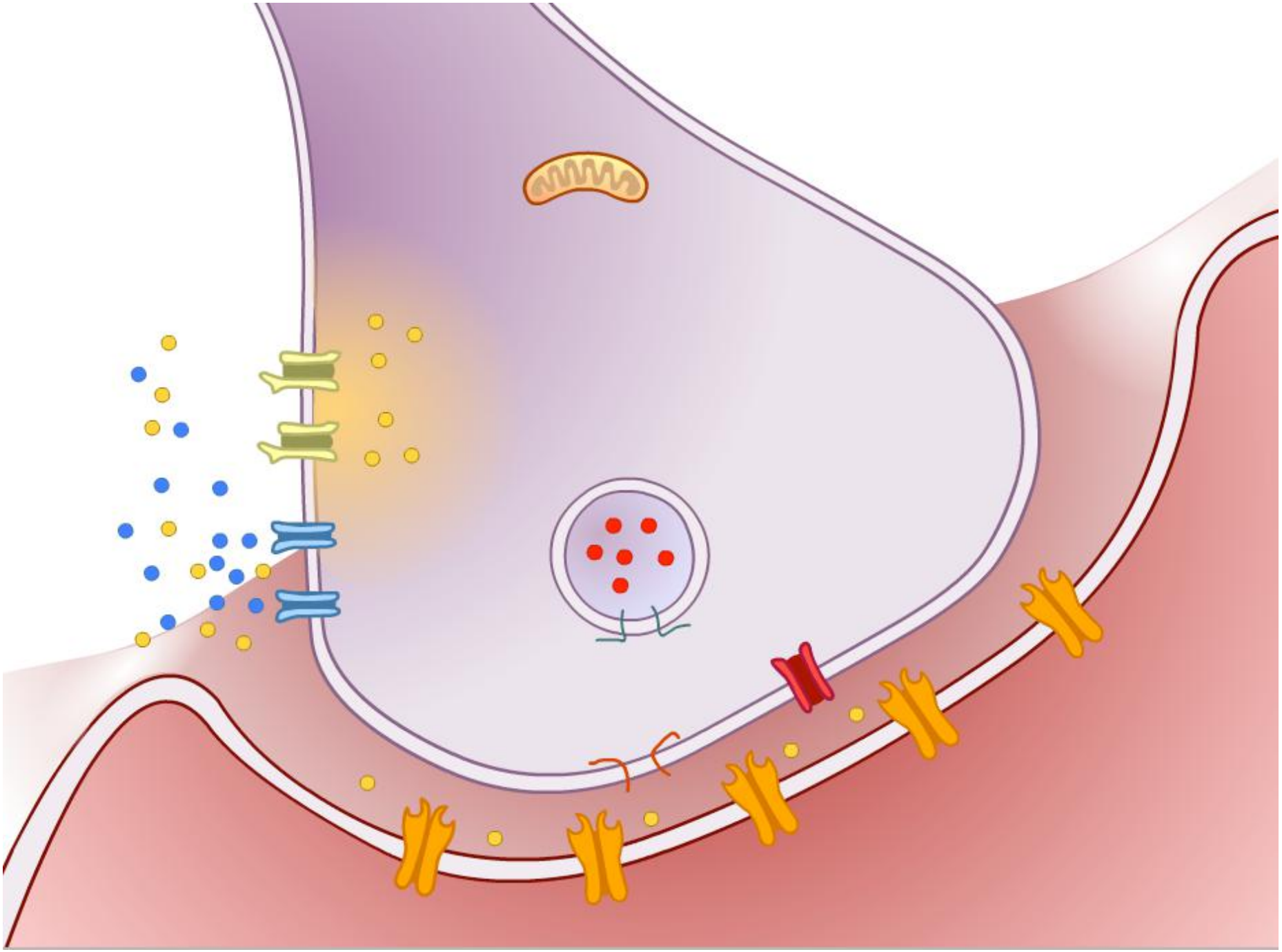
Dendrotossina (DTX)

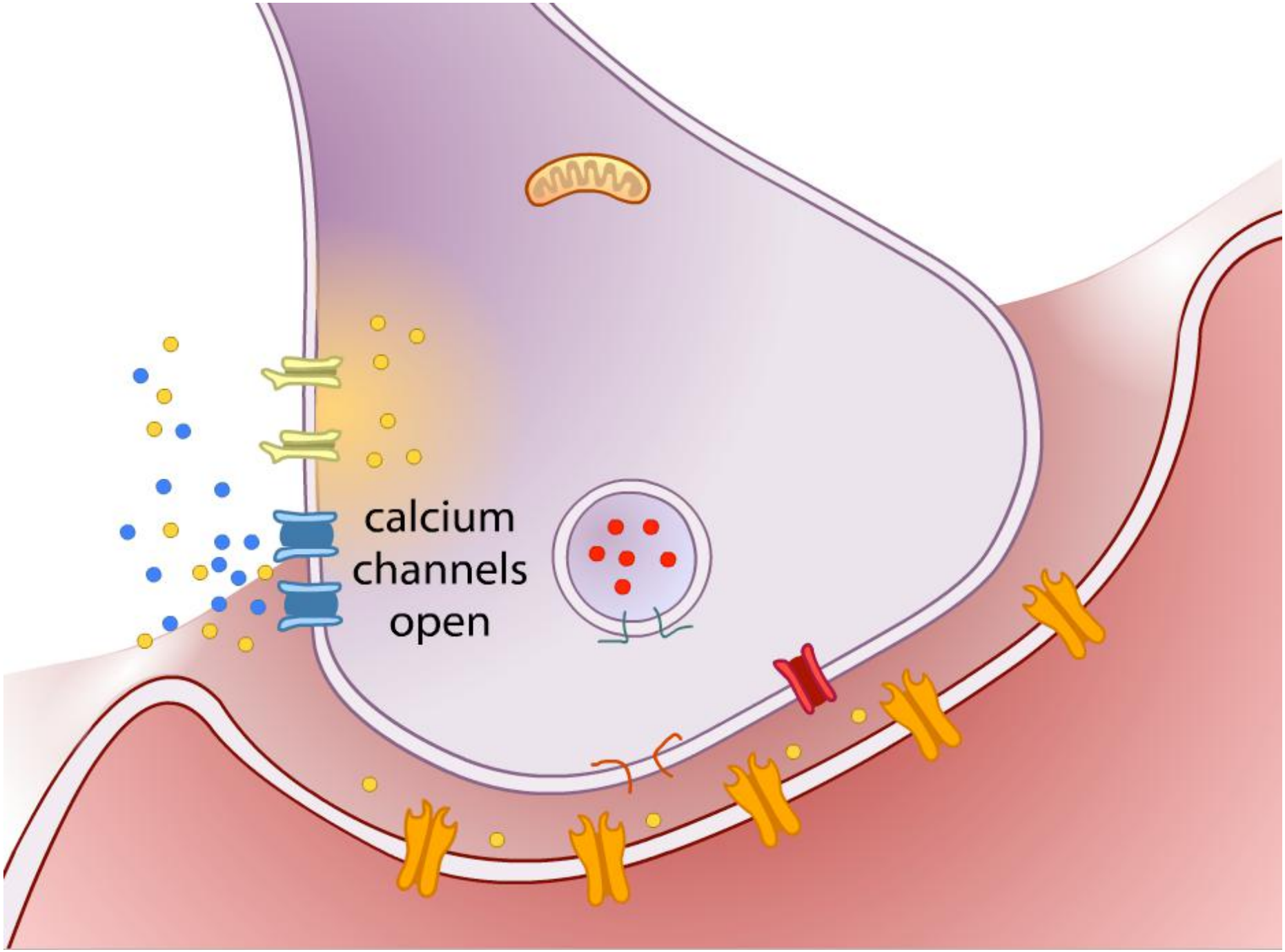

Seven Steps in Neurotransmitter Action
1 Neurotransmitter molecules are synthesized from precursors under the influence of enzymes.
2 Neurotransmitter molecules are stored in vesicles.
3 Neurotransmitter molecules that leak from their vesicles are destroyed by enzymes.
4 Action potentials cause vesicles to fuse with the presynaptic membrane and release their neurotransmitter molecules into the synapse.
5 Released neurotransmitter molecules bind with autoreceptors and inhibit subsequent neurotransmitter release.
6 Released neurotransmitter molecules bind to postsynaptic receptors.
7 Released neurotransmitter molecules are deactivated by either reuptake or enzymatic degradation.
Synthesizing enzymes
Neurotransmitter precursors
Vesicle
Degrading enzymes
Autoreceptor
Postsynaptic receptor

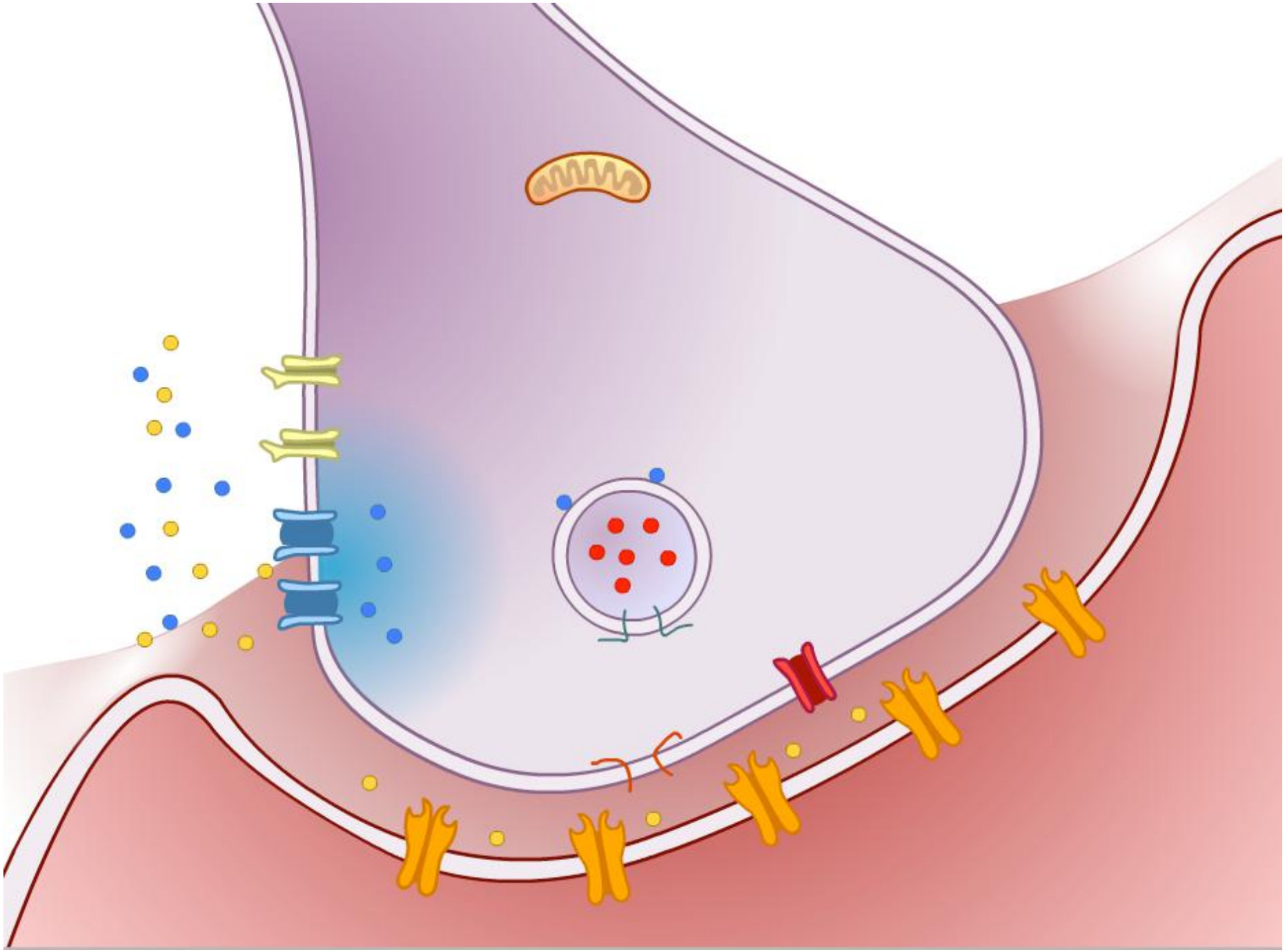

presynaptic cell
axon terminal
plasma membrane
mitochondrion
sodium channels
synaptic vesicle
calcium channels
receptors
postsynaptic cell

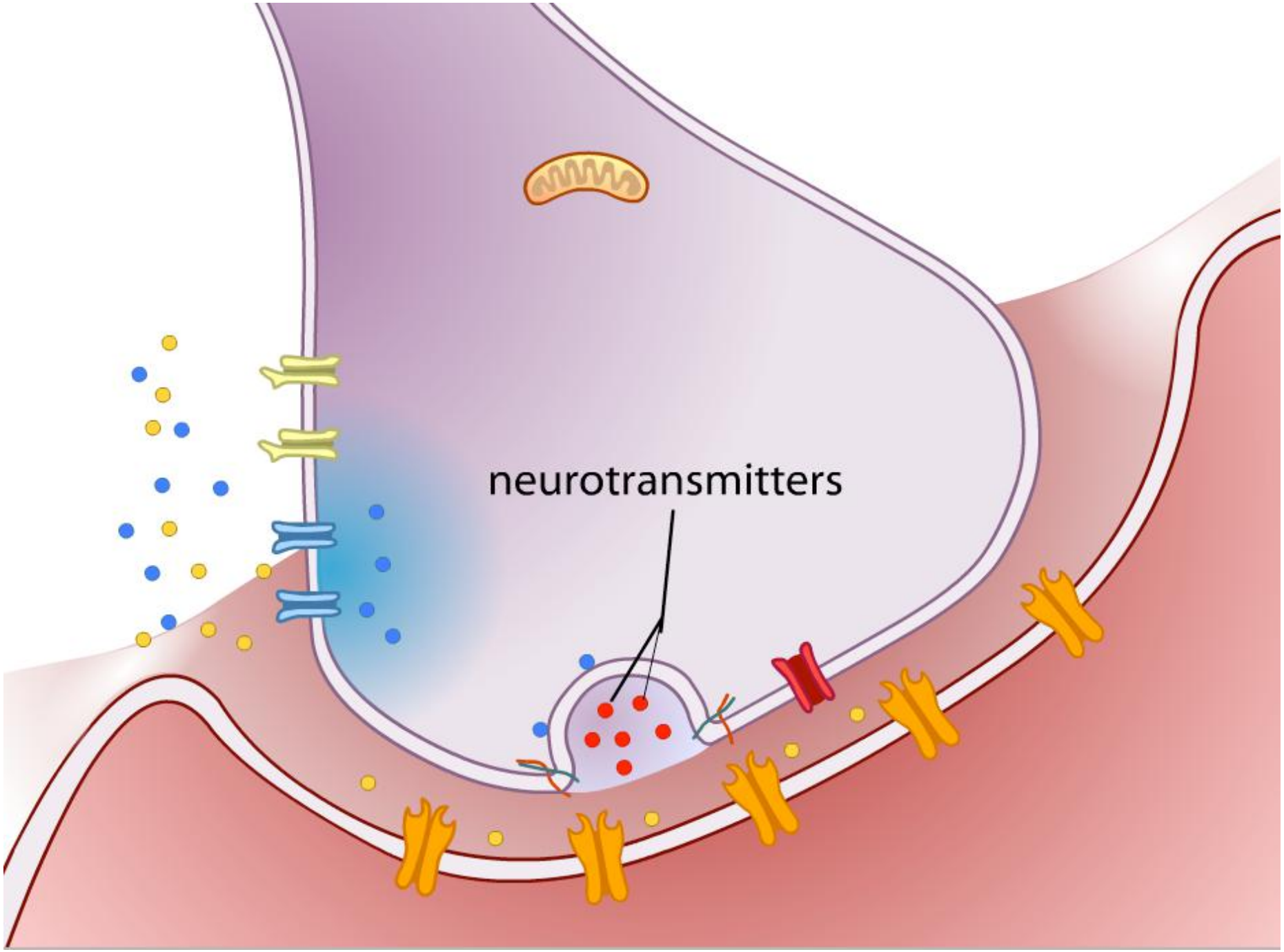


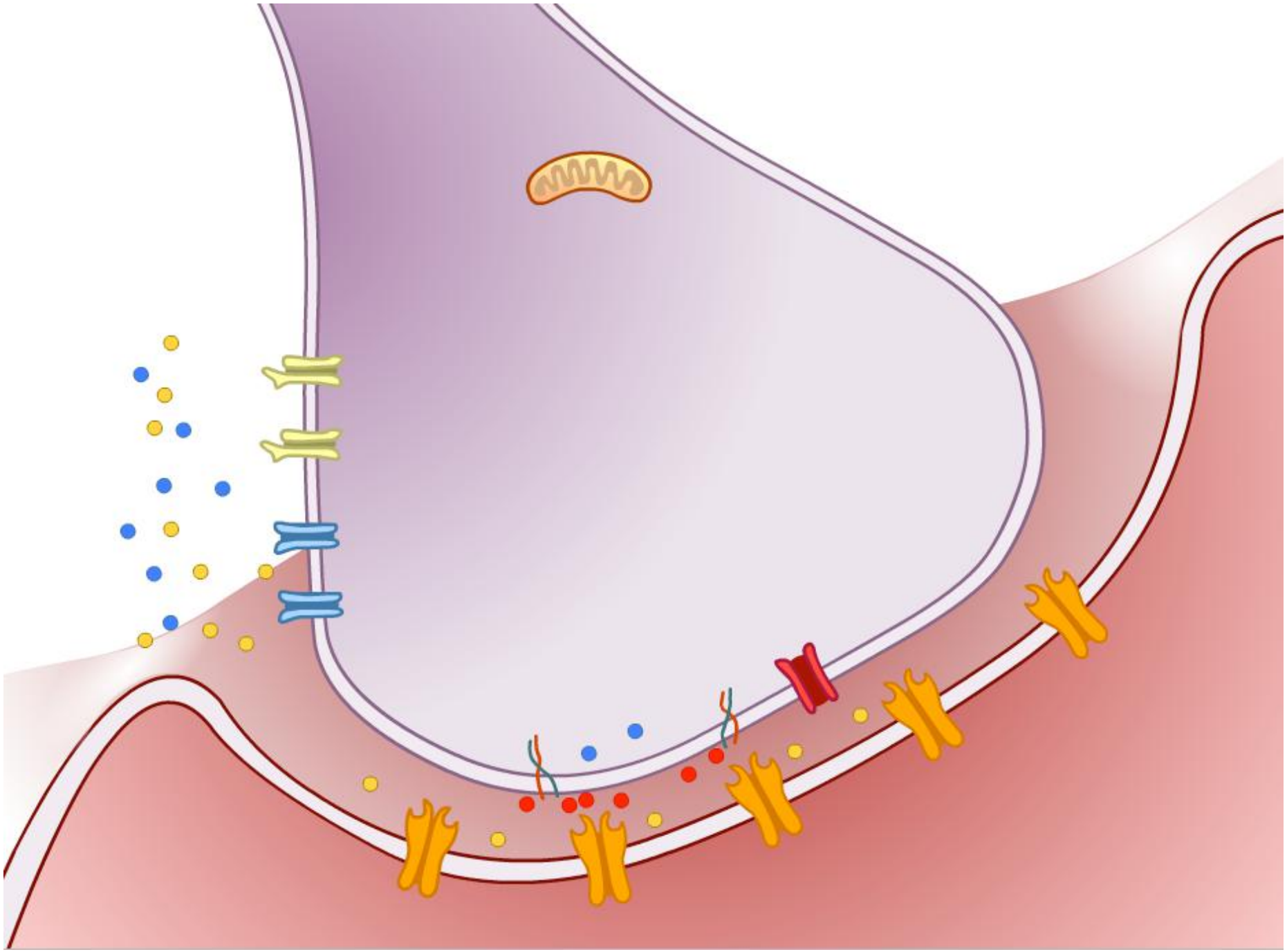

sodium
channels
open

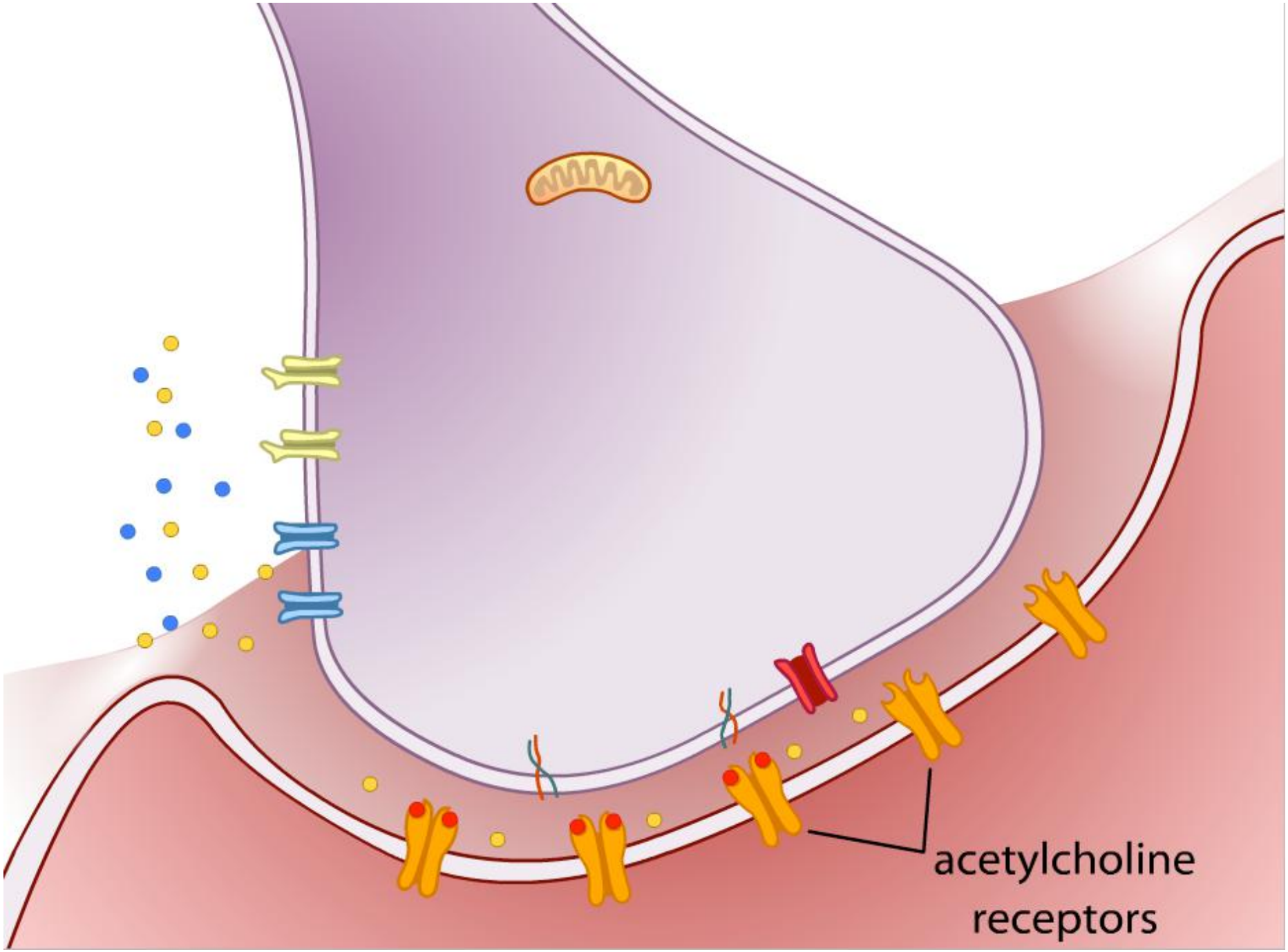


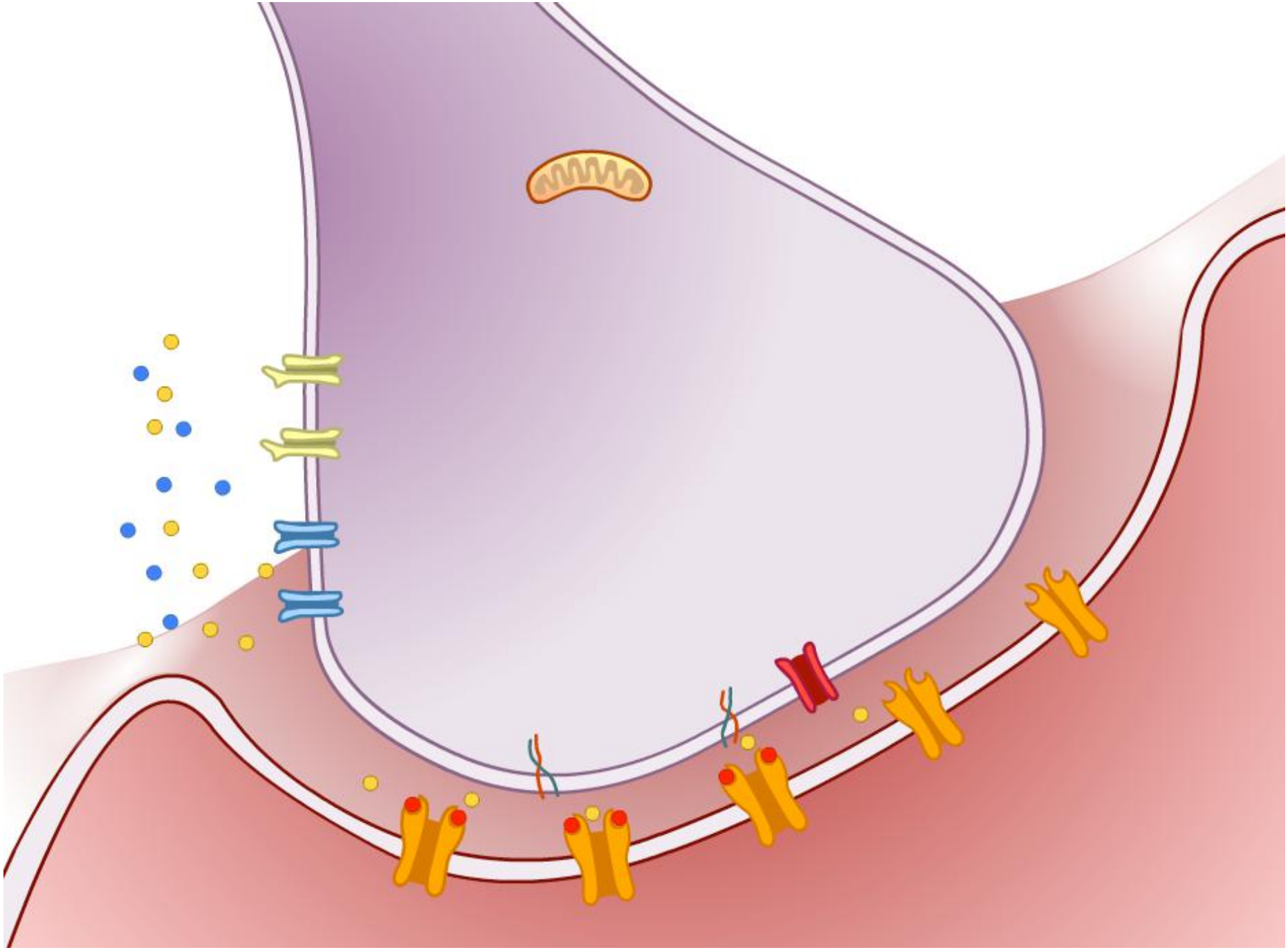

calcium
channels
open

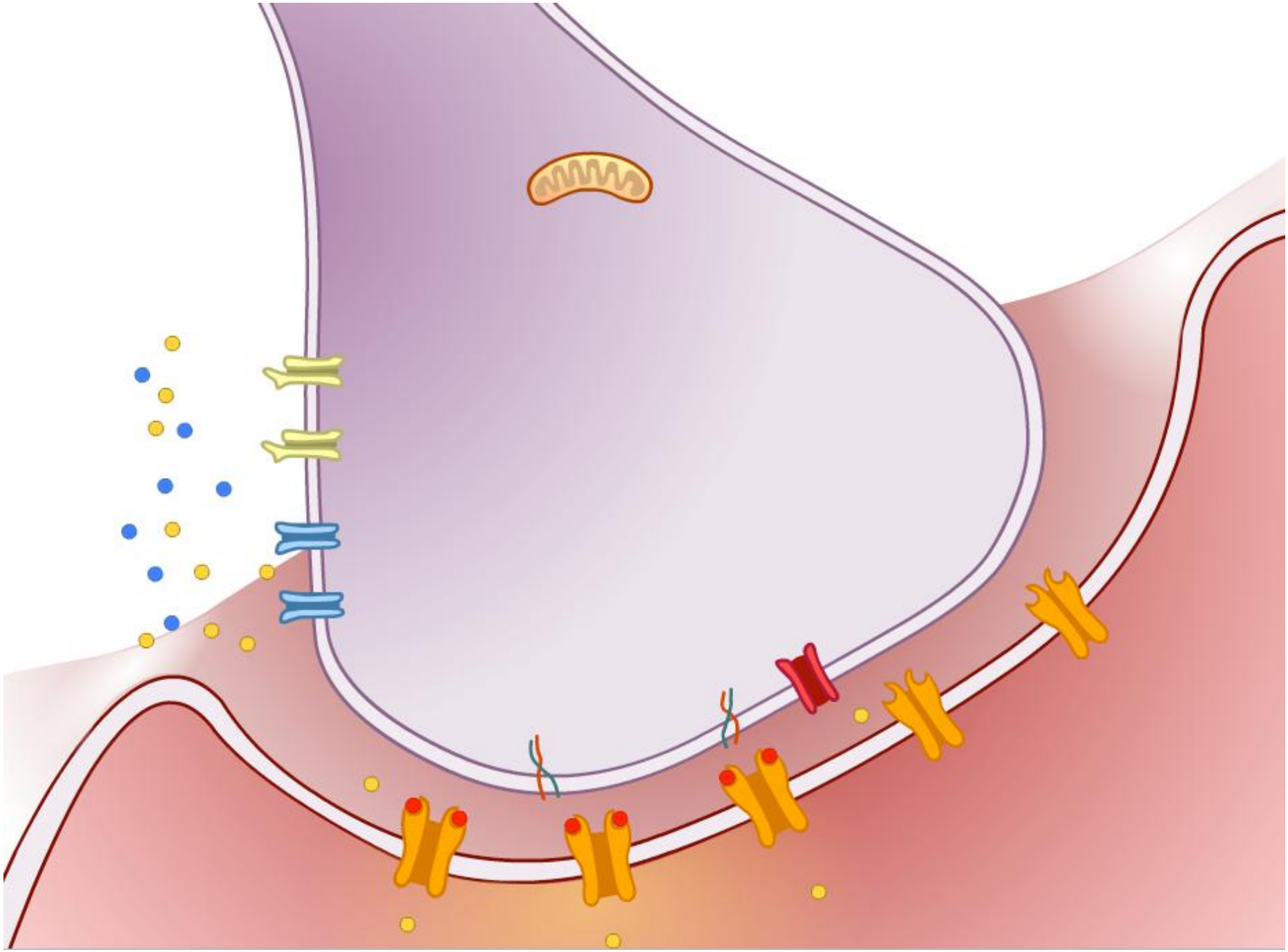


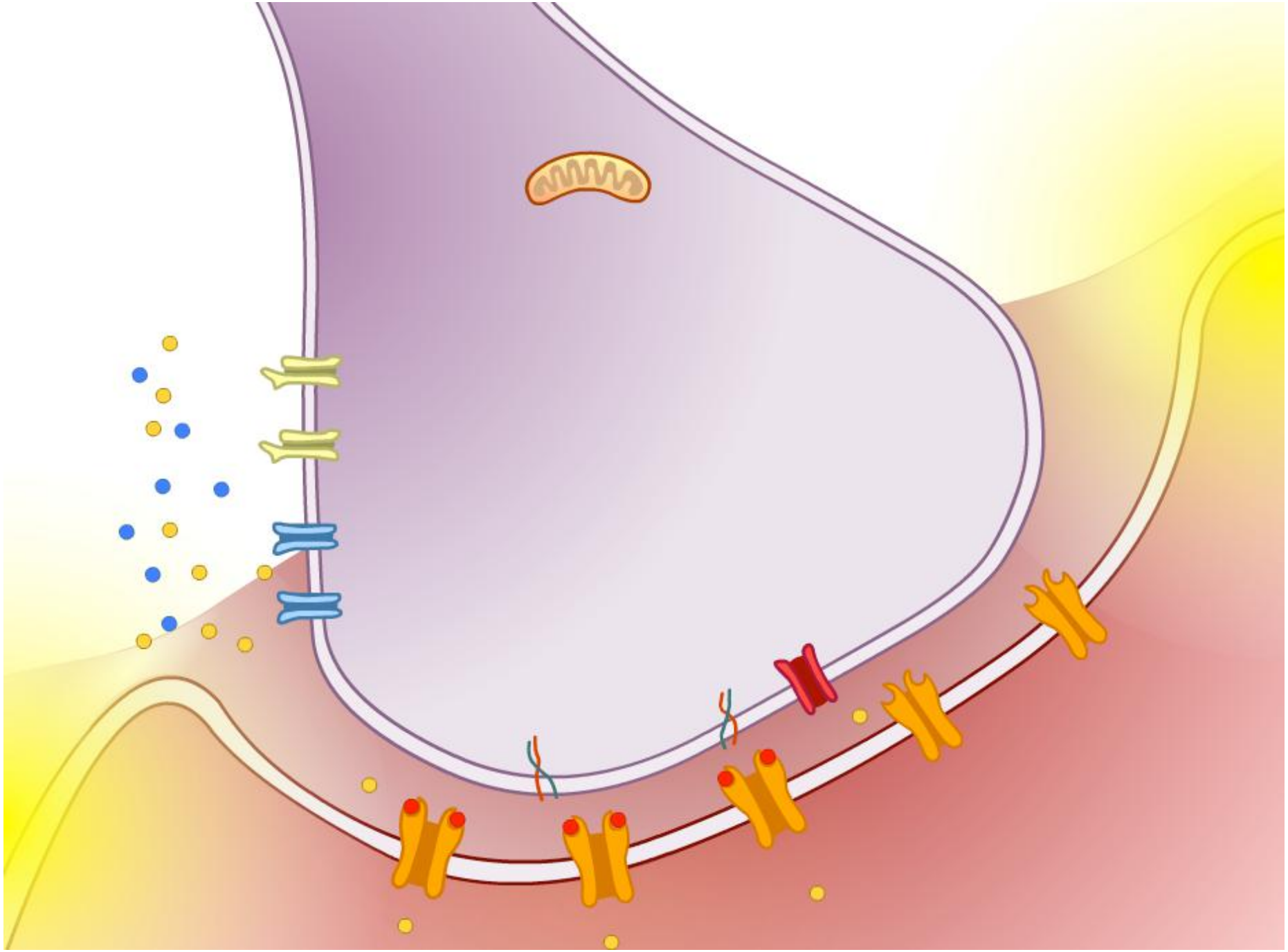

neurotransmitters

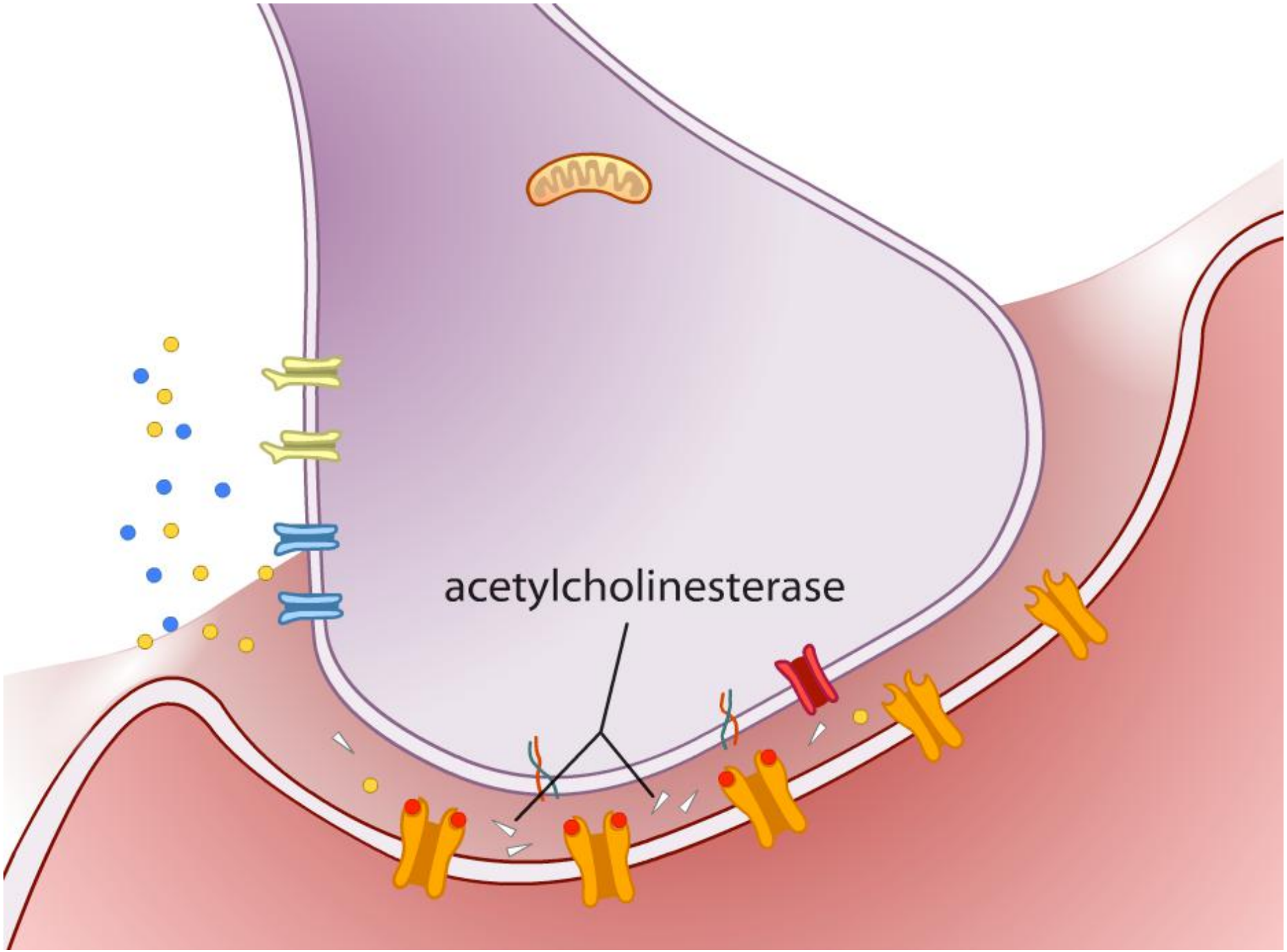


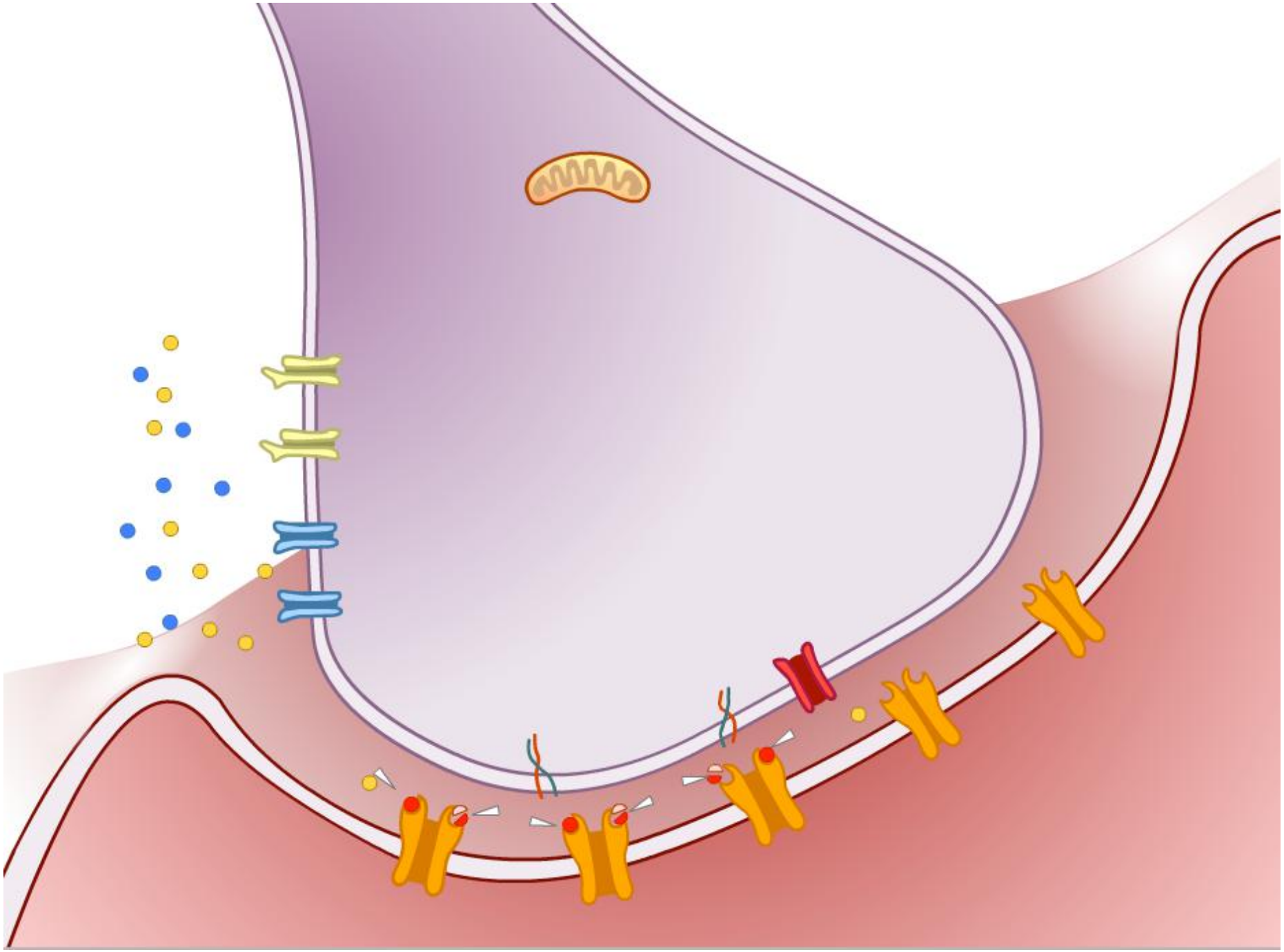

acetylcholine
receptors

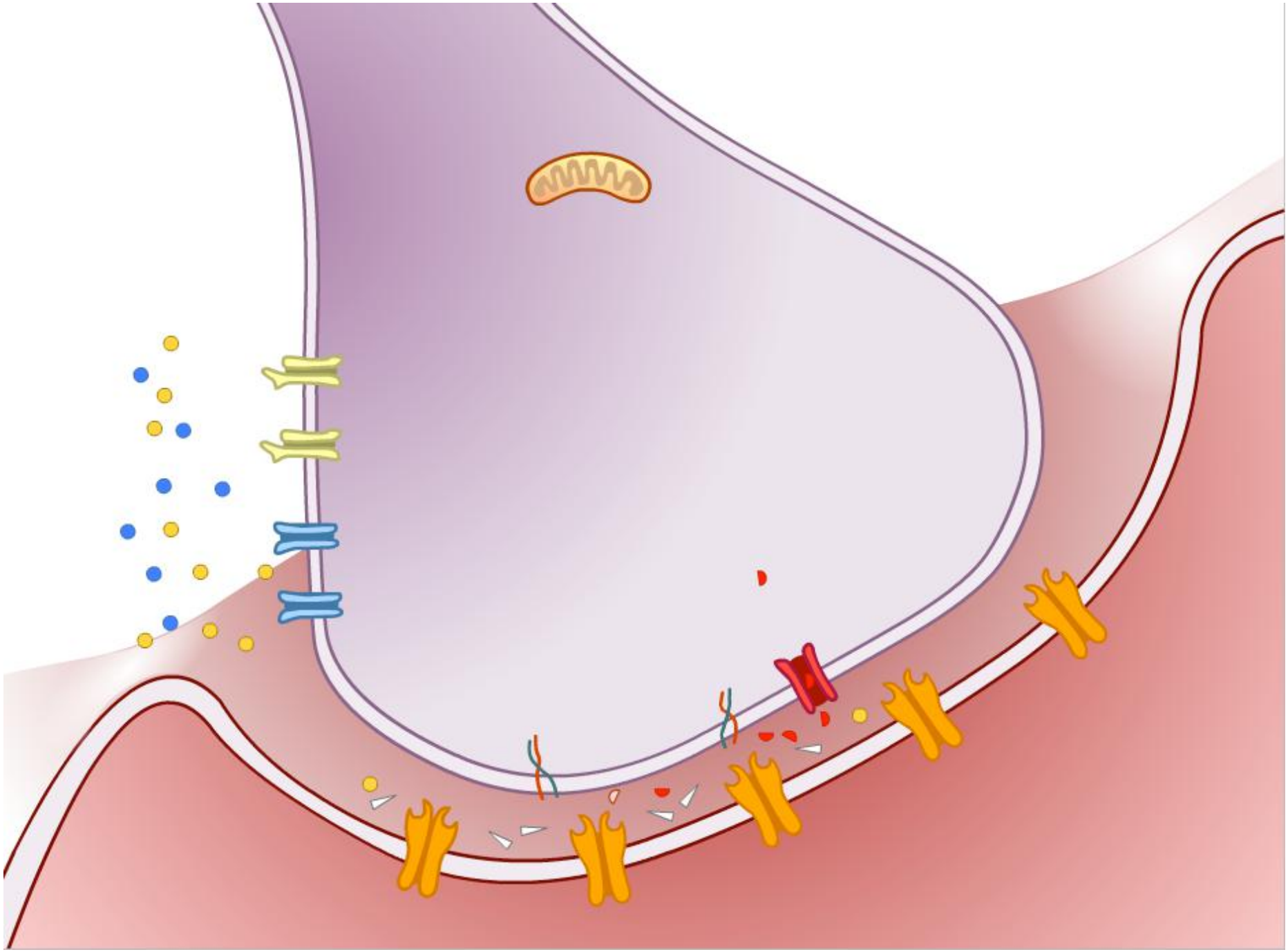


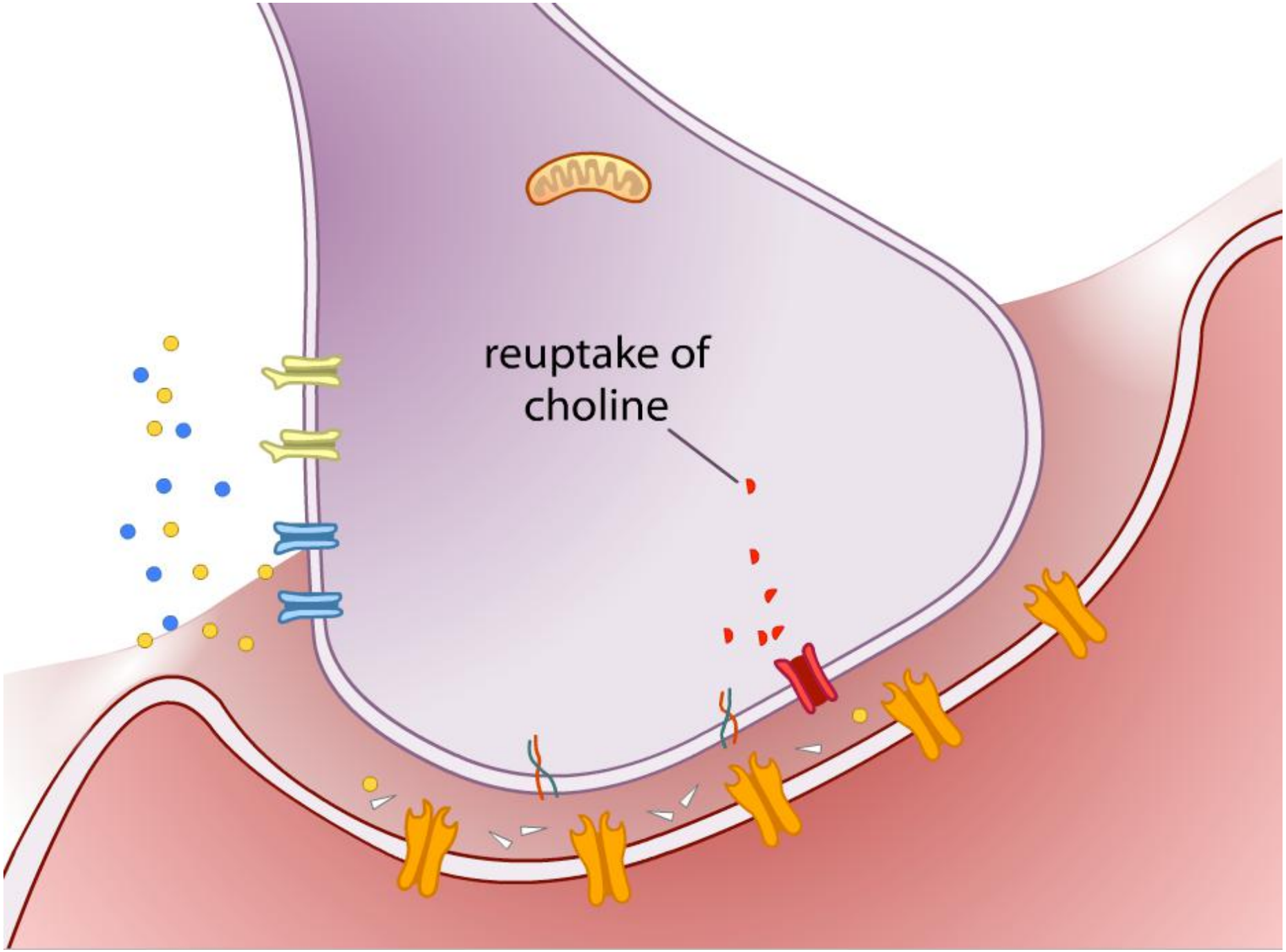


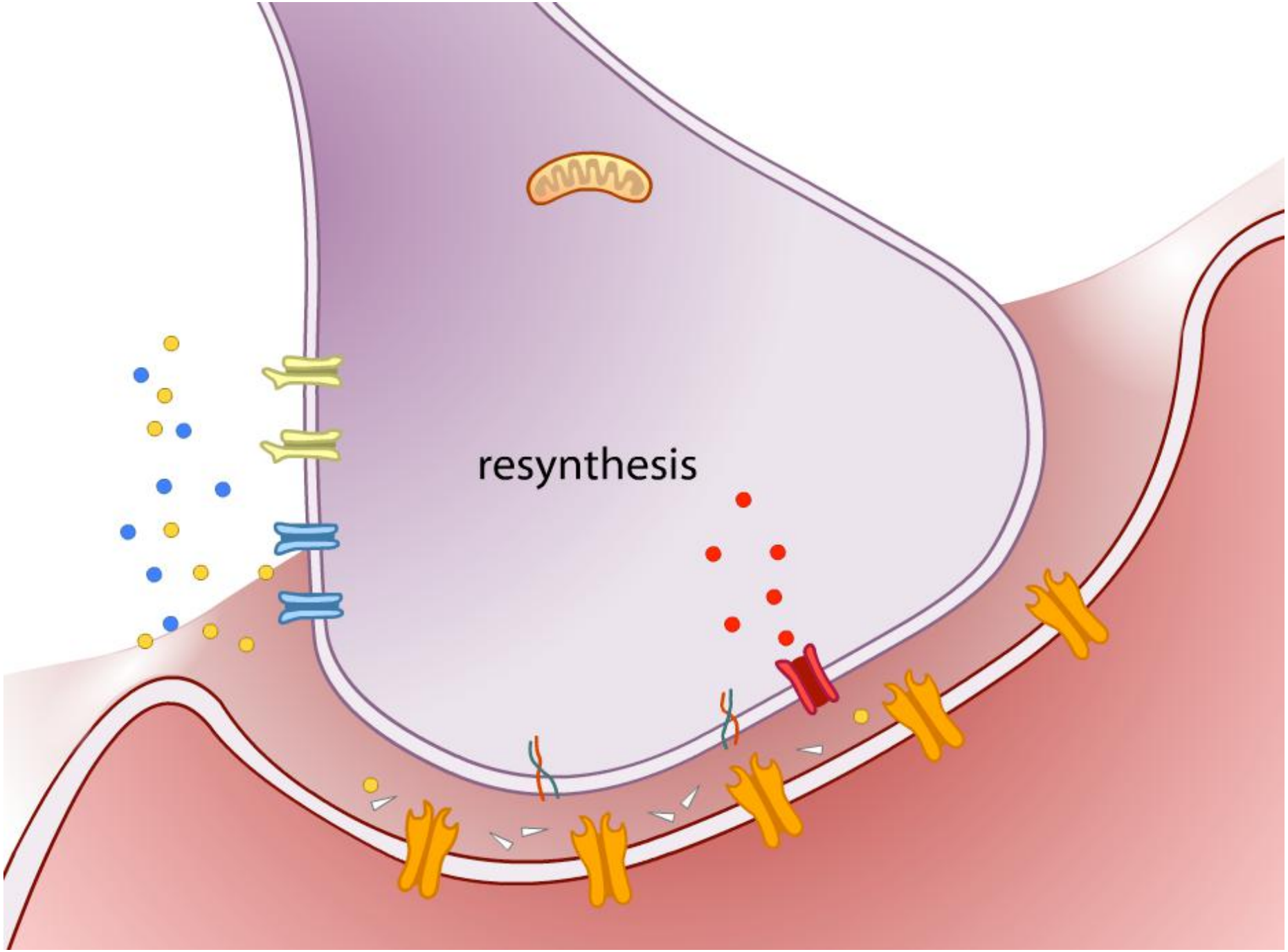


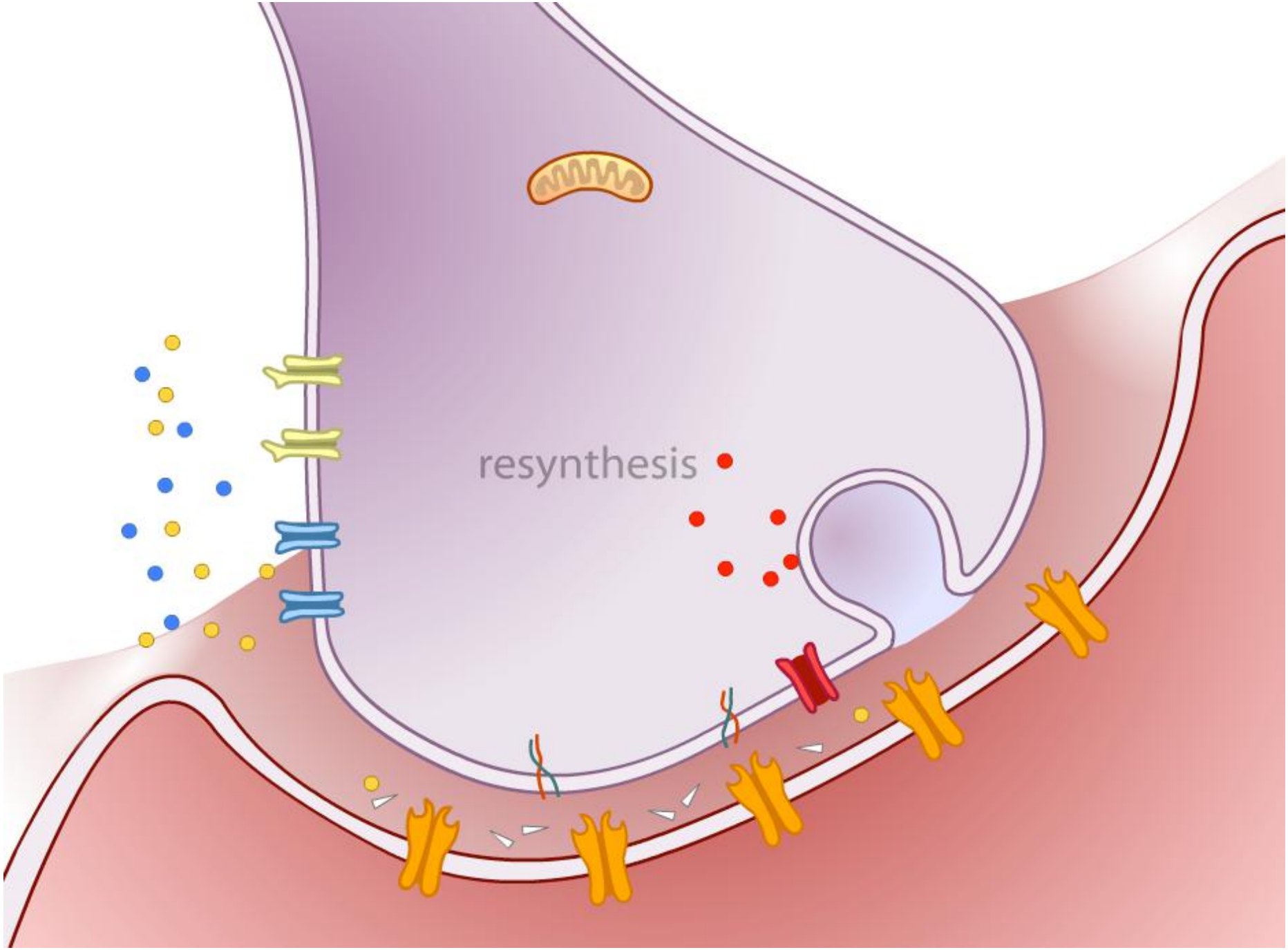

acetylcholinesterase

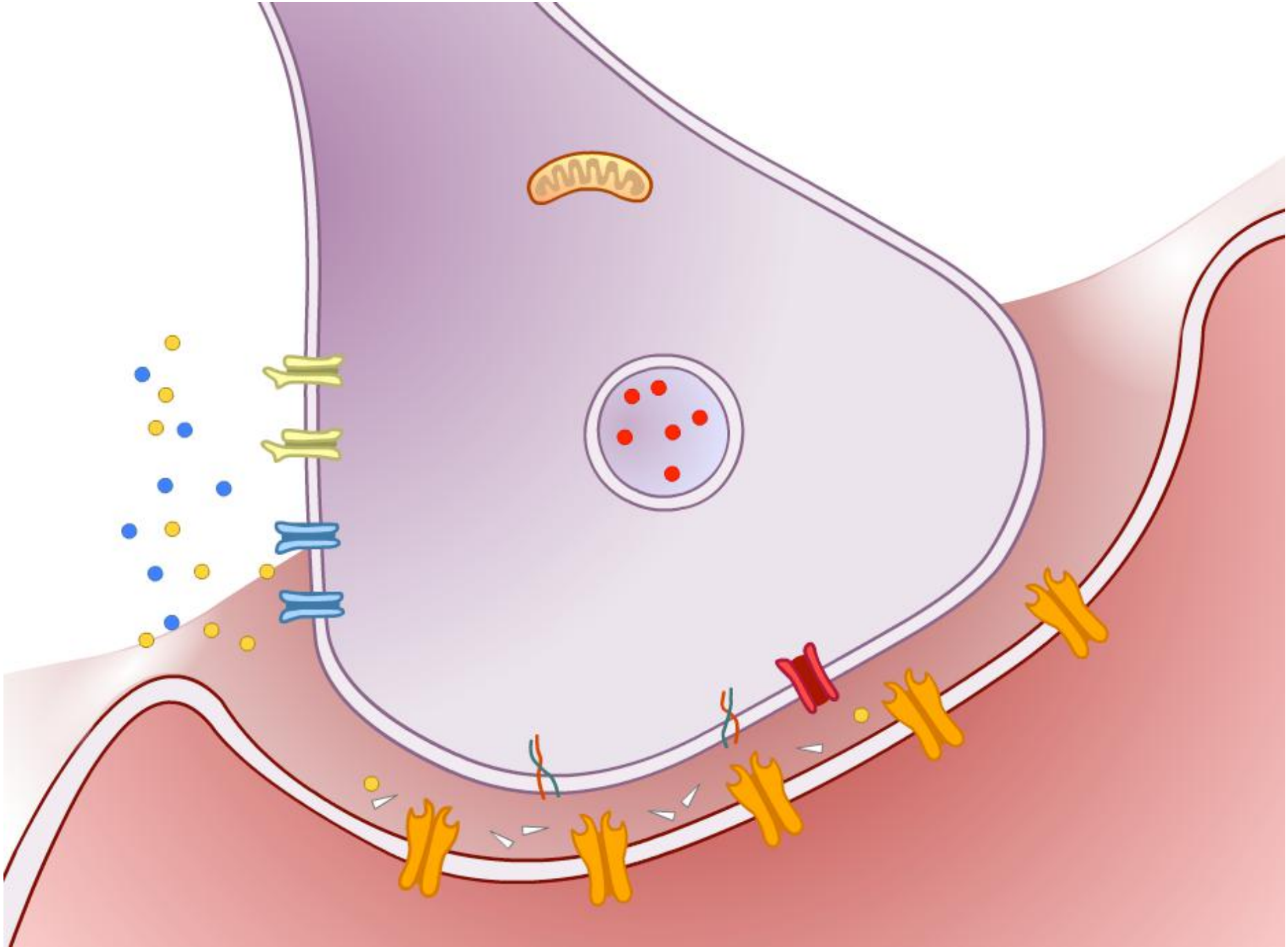


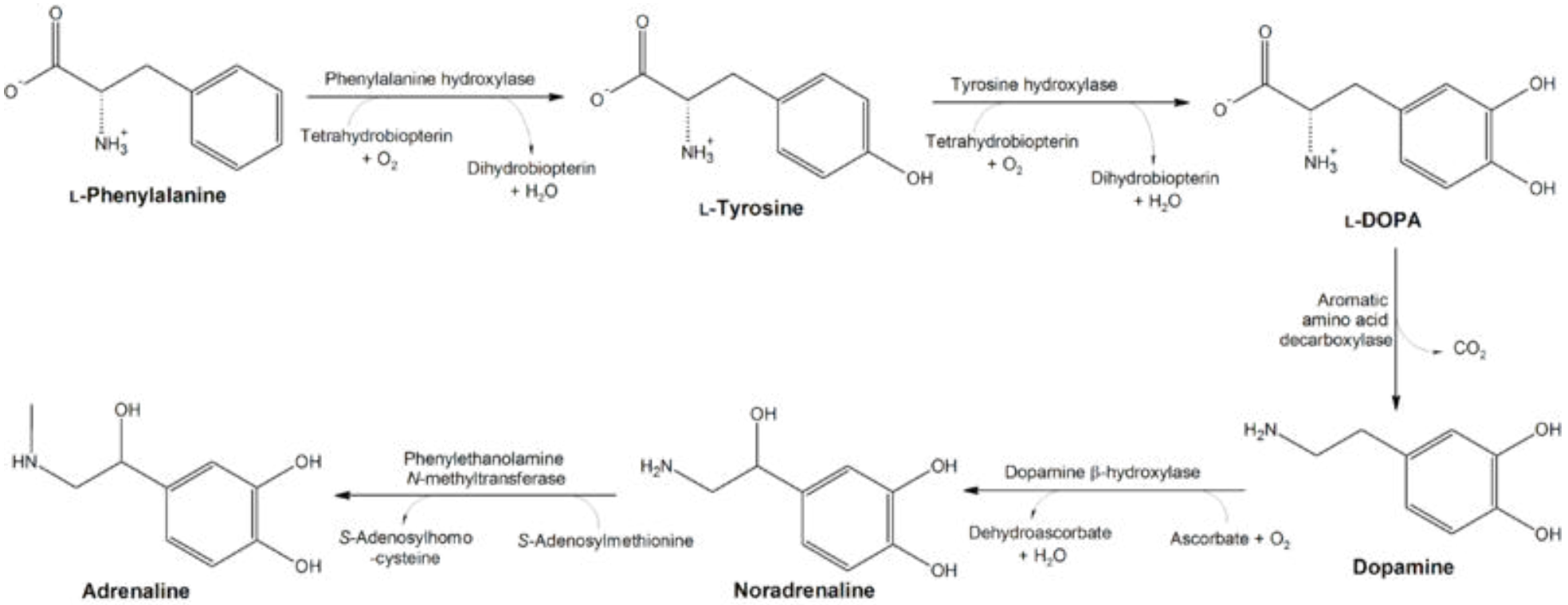



reuptake of
choline


resynthesis


resynthesis




L-Phenylalanine
Phenylalanine hydroxylase
Tetrahydrobiopterin + O_2
Dihydrobiopterin + H_2O
L-Tyrosine
Tyrosine hydroxylase
Tetrahydrobiopterin + O_2
Dihydrobiopterin + H_2O
L-DOPA
Aromatic amino acid decarboxylase
CO_2
Dopamine
Dopamine β-hydroxylase
Dehydroascorbate + H_2O
Ascorbate + O_2
Noradrenaline
Phenylethanolamine N-methyltransferase
S-Adenosylhomo -cysteine
S-Adenosylmethionine
Adrenaline

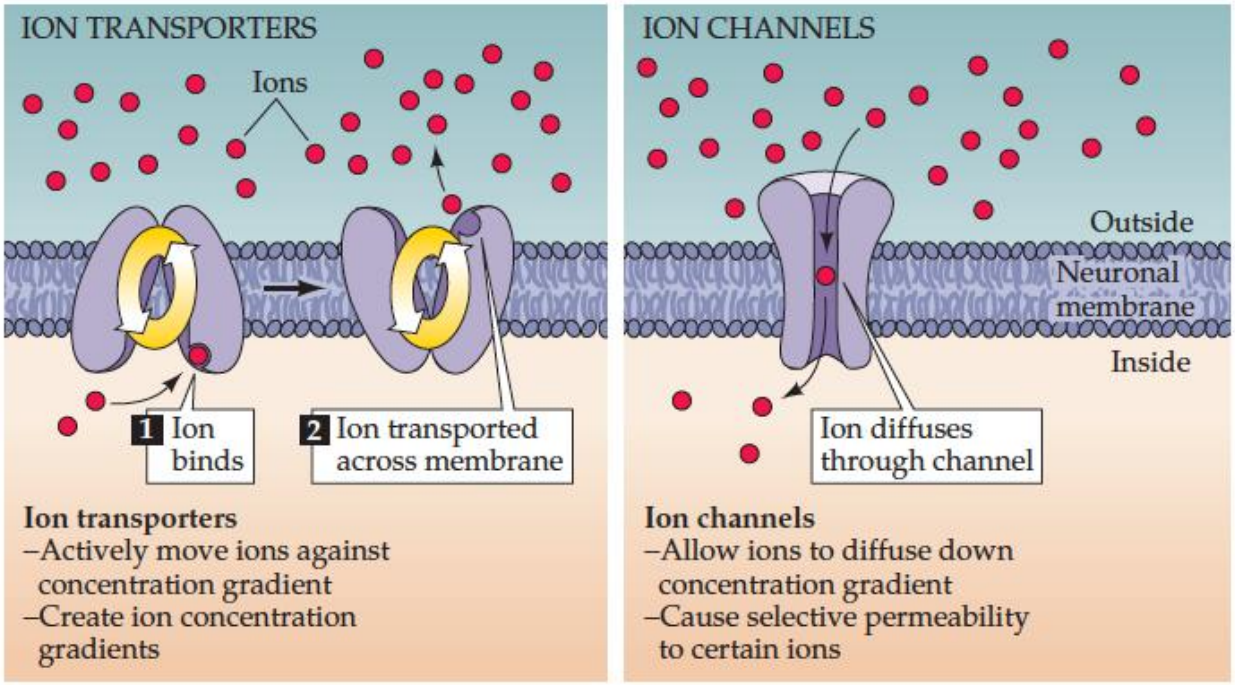


Figure 2.3 Ion transporters and ion channels are responsible for ionic movements across neuronal membranes. Transporters create ion concentration differences by actively transporting ions against their chemical gradients. Channels take advantage of these concentration gradients, allowing selected ions to move, via diffusion, down their chemical gradients.