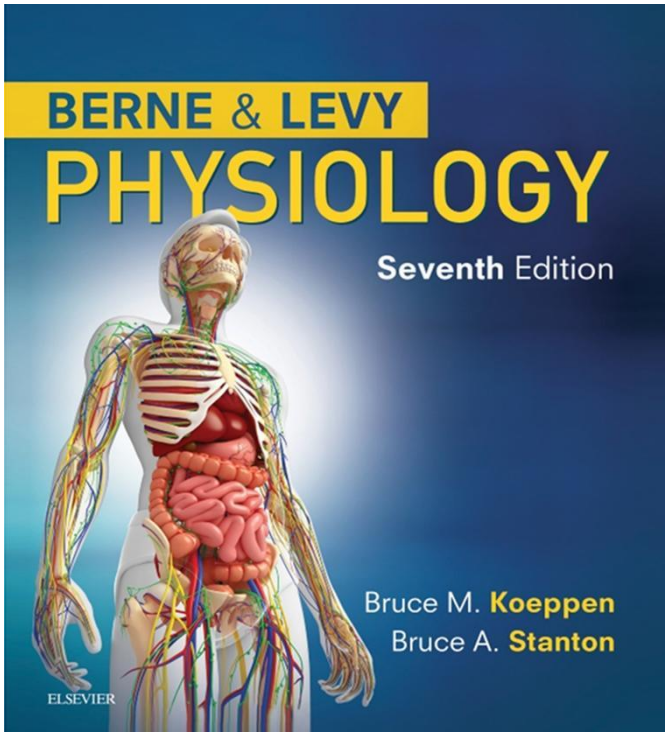
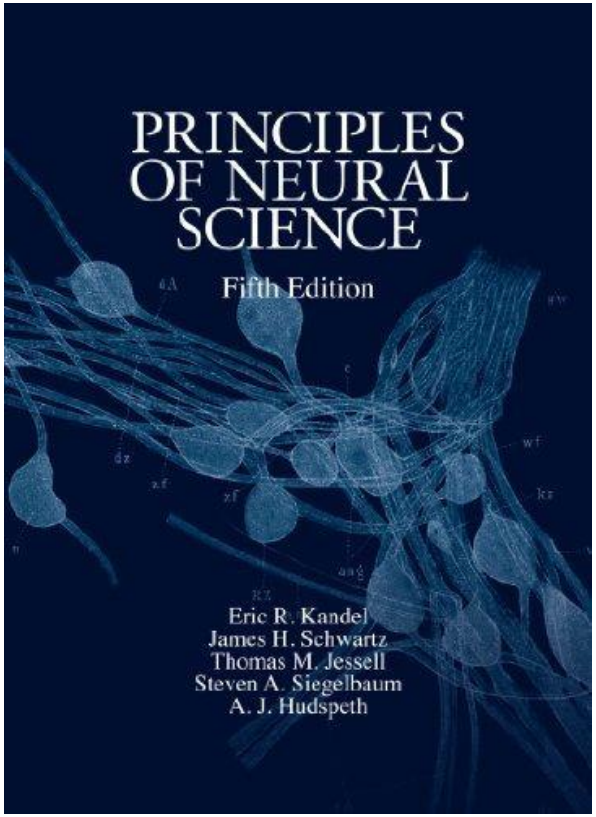
Membrane and Action Potentials

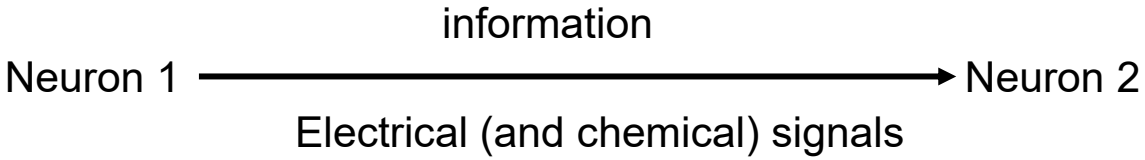


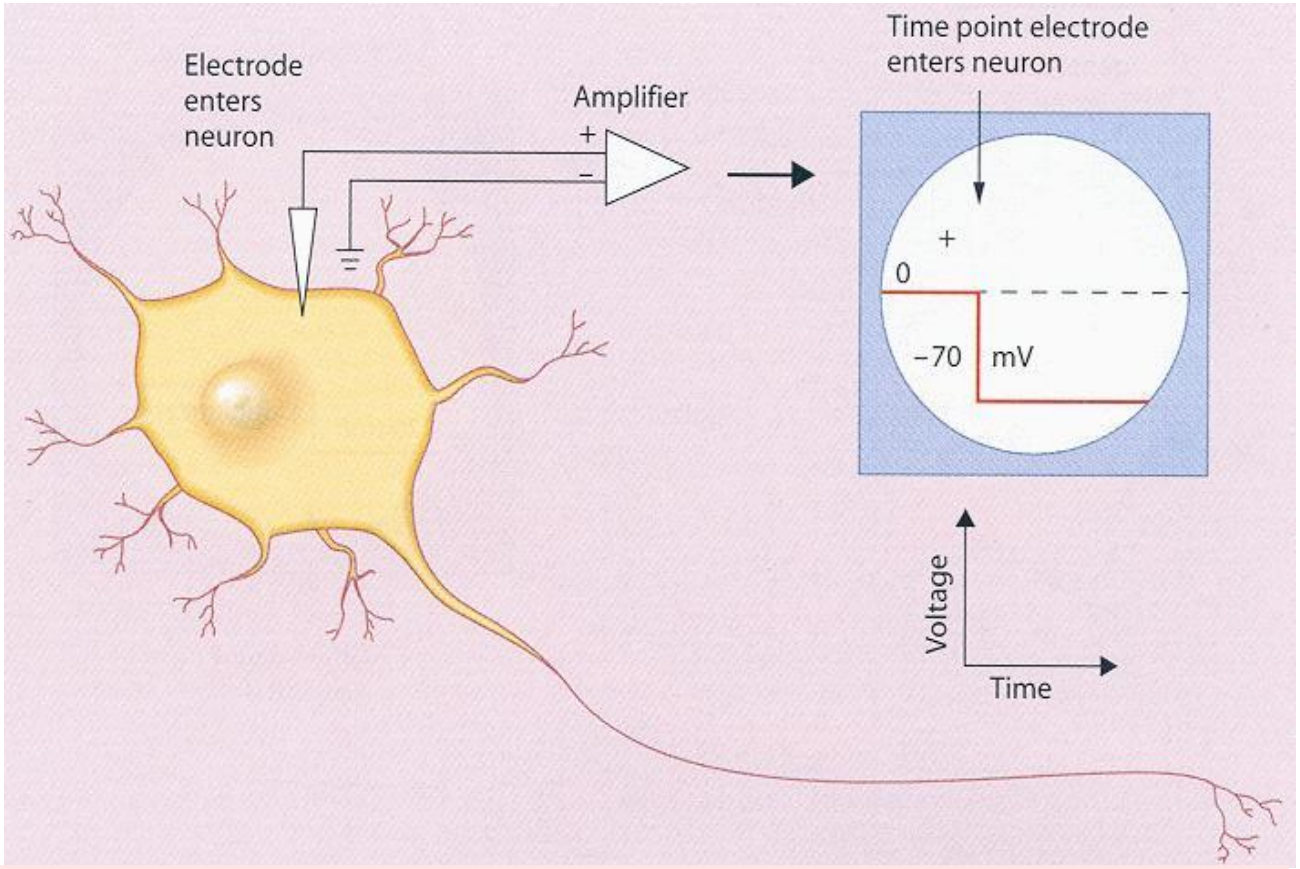
Chapters 1 and 5



Chapters 6 and 7

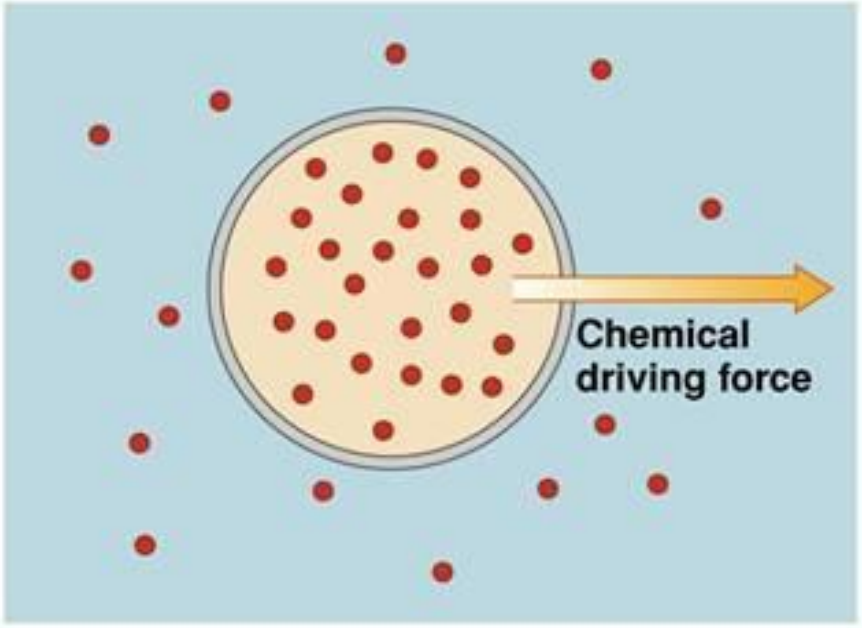
Electro-chemical properties of cells are important





Resting membrane potential varies according to types of cells

Skeletal muscle cells:	**−95 mV**
Smooth muscle cells:	**−50 mV**
Neurons:	**−70 mV**
Erythrocytes:	**−12 mV**



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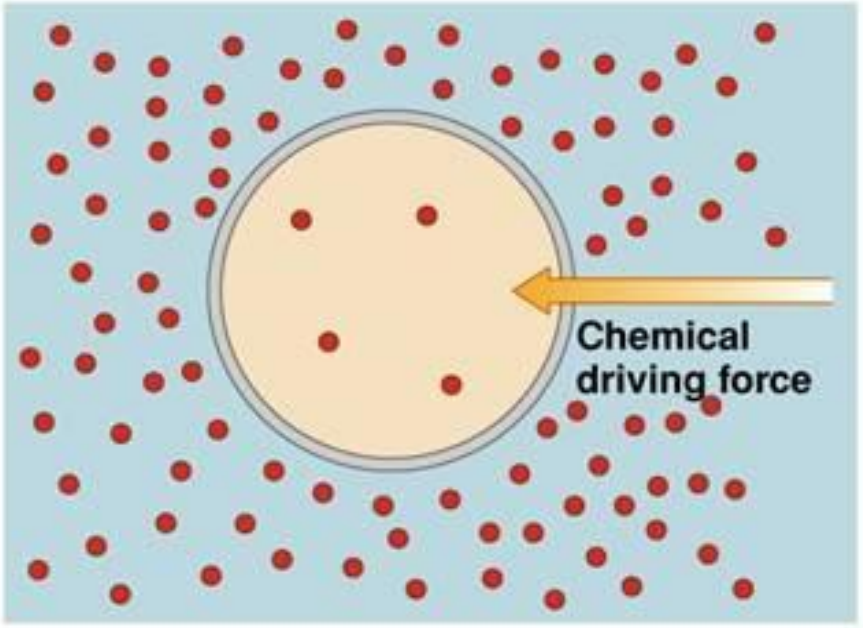

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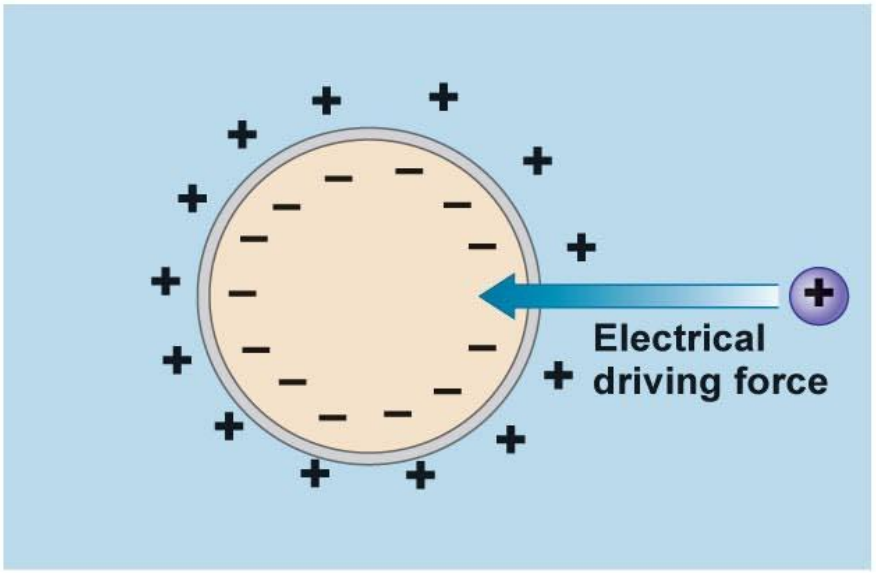
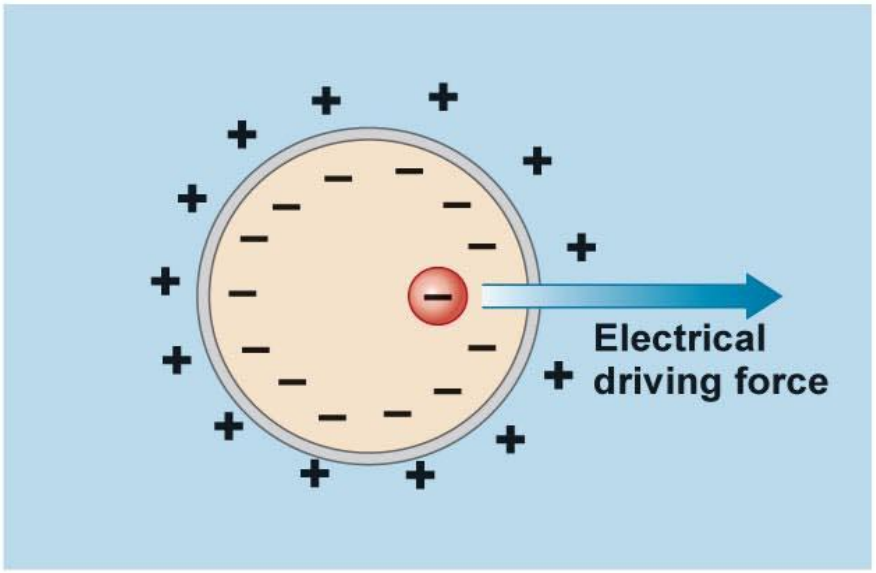


(a)



(b)

https://www.youtube.com/watch?v=VDUX5nN43ck

The Chemical Potential (μ(chem)).

For a substance X, with no electric charge, and concentration [X], the Chemical Potential is

$$\mu(chem)\ X = RT \ln [X]$$

If X is a solute in the intracellular (int) and extracellular (ext) compartments:

$$\mu(chem)Xint = RT \ln [X]int \quad AND \quad \mu(chem)Xext = RT \ln [X]ext$$

$$\Delta\mu X(chem) = \mu(chem)Xint - \mu(chem)Xext$$

$$\Delta\mu X(chem) = RT \ln [X]int - RT \ln [X]ext = RT \ln ([X]int / [X]ext)$$

Similarly, The Electric Potential (μ(el)) of a charged solutes is

$$\mu(el)\ X = F\ zX(V\ local)$$

$$\mu(el)Xint = F\ zX\ [V]int \quad AND \quad \mu(el)X\ ext = F\ zX\ [V]ext$$

$$\Delta\mu(el)X = F\ zX\ (Vint - Vext)$$

R = Gas constant = 8.314 J/(mol K); T = Temperature in K; Z_x = valence of charged molecules (Na^+ is 1, Ca^{++} is 2); F = Faraday constant = electric charge per mole of electrons = 96485.332 C mol−1

$$\Delta\mu\,(\text{electrochemical})X = \Delta\mu(\text{chem})X + \Delta\mu(\text{el})X$$

$$\Delta\mu(\text{electrochemical})X = RT\ \ln([X]int / [X]ext) + F\ zX\ (Vint - Vext)$$

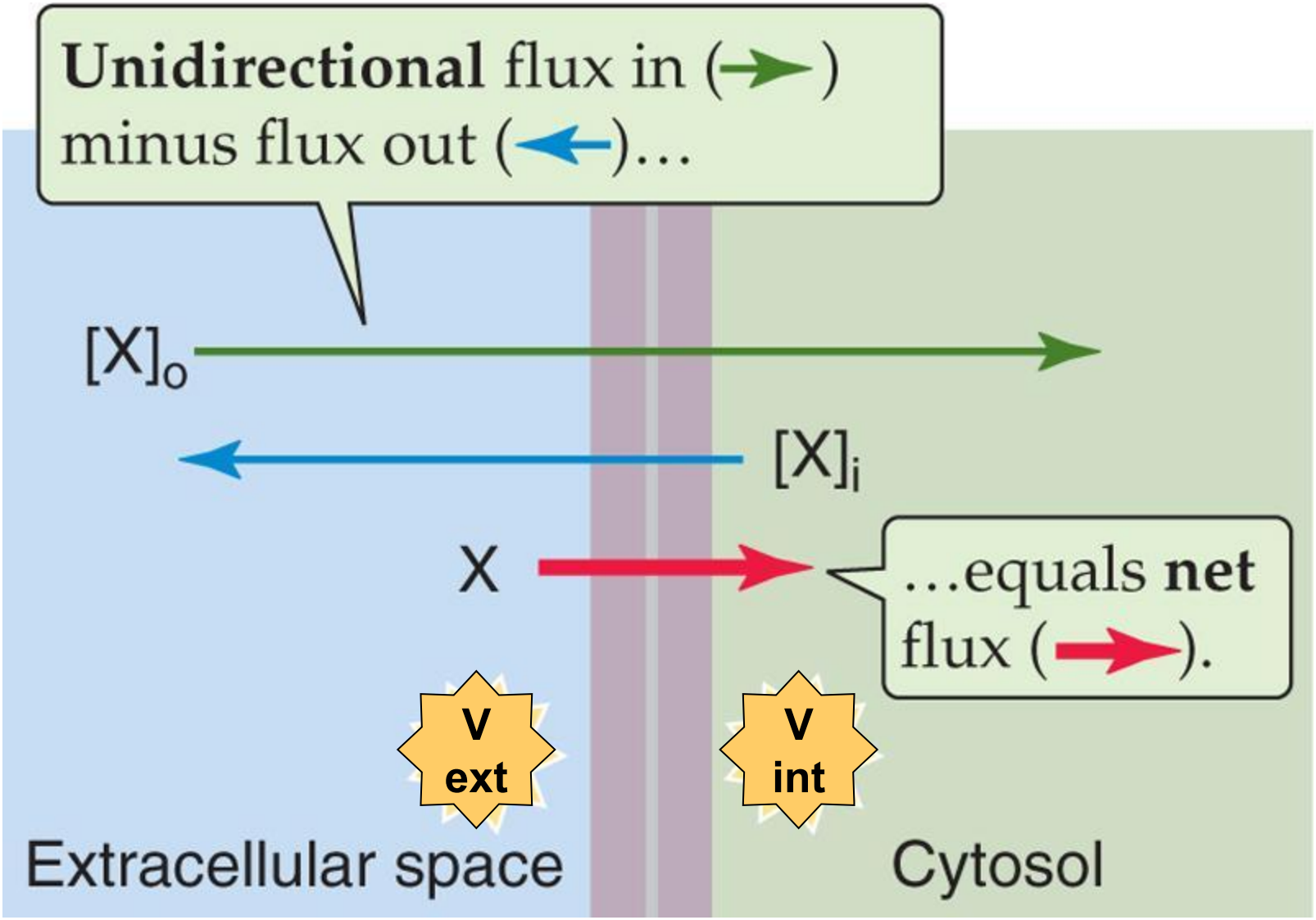
At the equilibrium, $\Delta\mu(\text{electrochemical})X = 0$ ->

$$RT\ \ln([X]int / [X]ext) + F\ zX\ (Vint - Vext) = 0$$

IF (Vint-Vext) = ΔV = VmX (potential difference between the inside and the outside of the membrane generated by X), Then:

$$VmX = -\ (RT / zX\ F)\ \ln([X]int / [X]ext) = 2.3026\ (RT/\ zX\ F)\ \text{Log}\ ([X]ext/[X]int)$$

This is the **Nernst equation**



$$\Delta V\ (Vm) = (V_{int} - V_{ext})$$

$$VmX = - (RT / zX F) \ln ([X]int / [X]ext)$$

$F = 96485{,}337$ Coulombs (C)/mol

$R = 8{,}314\ J\ K^{-1}\ mol^{-1}$

Nernst equation can be simplified by using log instead of ln

([log X = ln X / ln 10]) -> log X = ln X / 2,303 -> ln X = 2,303 log X

and by using actual parameters.

at 20°C

$$VmX = - [(8{,}31)\ (293{,}15) / (zX)\ (96485{,}34)]\ [(2{,}303)]\ \log ([X]int / [X]ext)$$

$$VmX = - (58{,}1 / zX) \log ([X[int / [X]ext)$$

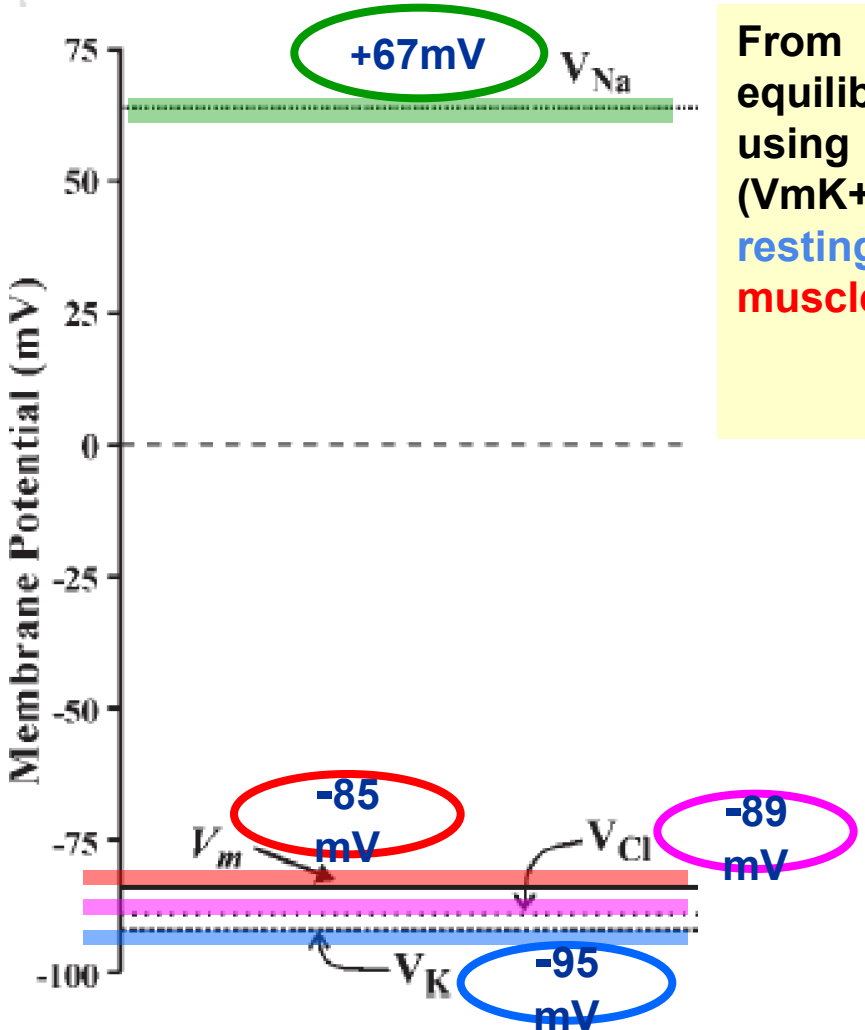
at 37°C

$$VmX = - (61{,}5 / zX) \log ([X]int / [X]ext)$$

at 29,5°C

$$VmX = - (60 / zX) \log ([X]int / [X]ext)$$

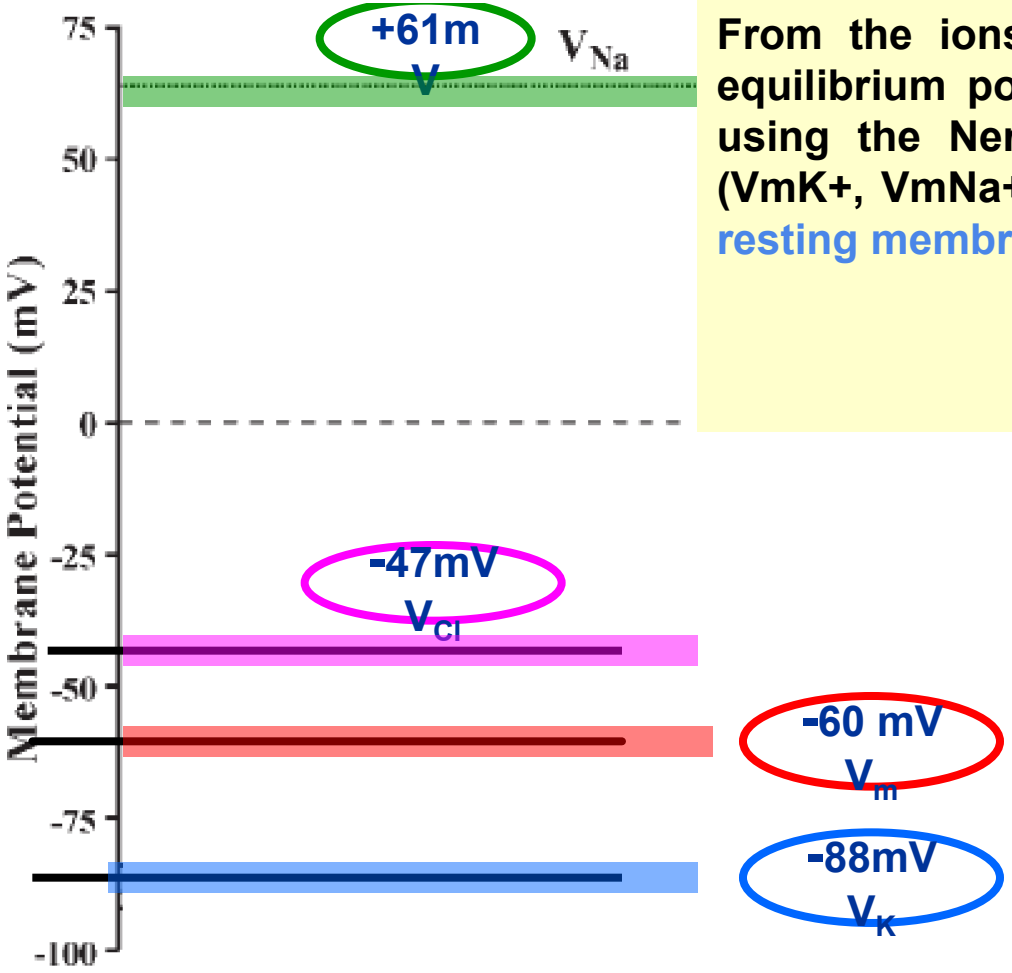
Ion (X)	$[X]_{out}$ (mM)	$[X]_{in}$ (mM)	$[X]_{out}/[X]_{in}$	V_x* (mV)
		Skeletal muscle		
K^+	4.5	155	0.026	-95
Na^+	145	12	12	+67
Ca^{2+}	1.0	10^{-4}	10,000	+123
Cl^-	116	4.2	29	-89
HCO_3^-	24	12	2	-19



From the ions concentration here reported, the equilibrium potential (VmX) can be calculated by using the Nernst Equation for each of the ion (VmK+, VmNa+, VmCl-) involved in generating the resting membrane potential (Vm) of the skeletal muscle cell.

Compared to other excitable cells, skeletal muscle has unusually high Cl- conductance, accounting for up to 85% of all membrane conductance at rest. *(EC Aromataris, GY Rychkov, 2006)*

Ion (X)	$[X]_{out}$ (mM)	$[X]_{in}$ (mM)	$[X]_{out}/[X]_{in}$	V_x* (mV)
		Other cell		
K^+	4.5	120	0.038	-88
Na^+	145.4	15	9.67	+61
Ca^{2+}	1.0	10^{-4}	10,000	+123
Cl^-	116	20	5.8	-47
HCO_3^-	24	15	1.6	-13



From the ions concentration here reported, the equilibrium potential (VmX) can be calculated by using the Nernst Equation for each of the ion (VmK+, VmNa+, VmCl-) involved in generating the resting membrane potential (Vm)

Intracellular and extracellular concentrations and Nernst equilibrium potential values for a few ions of physiological importance (Neuron). Vr = -70mV

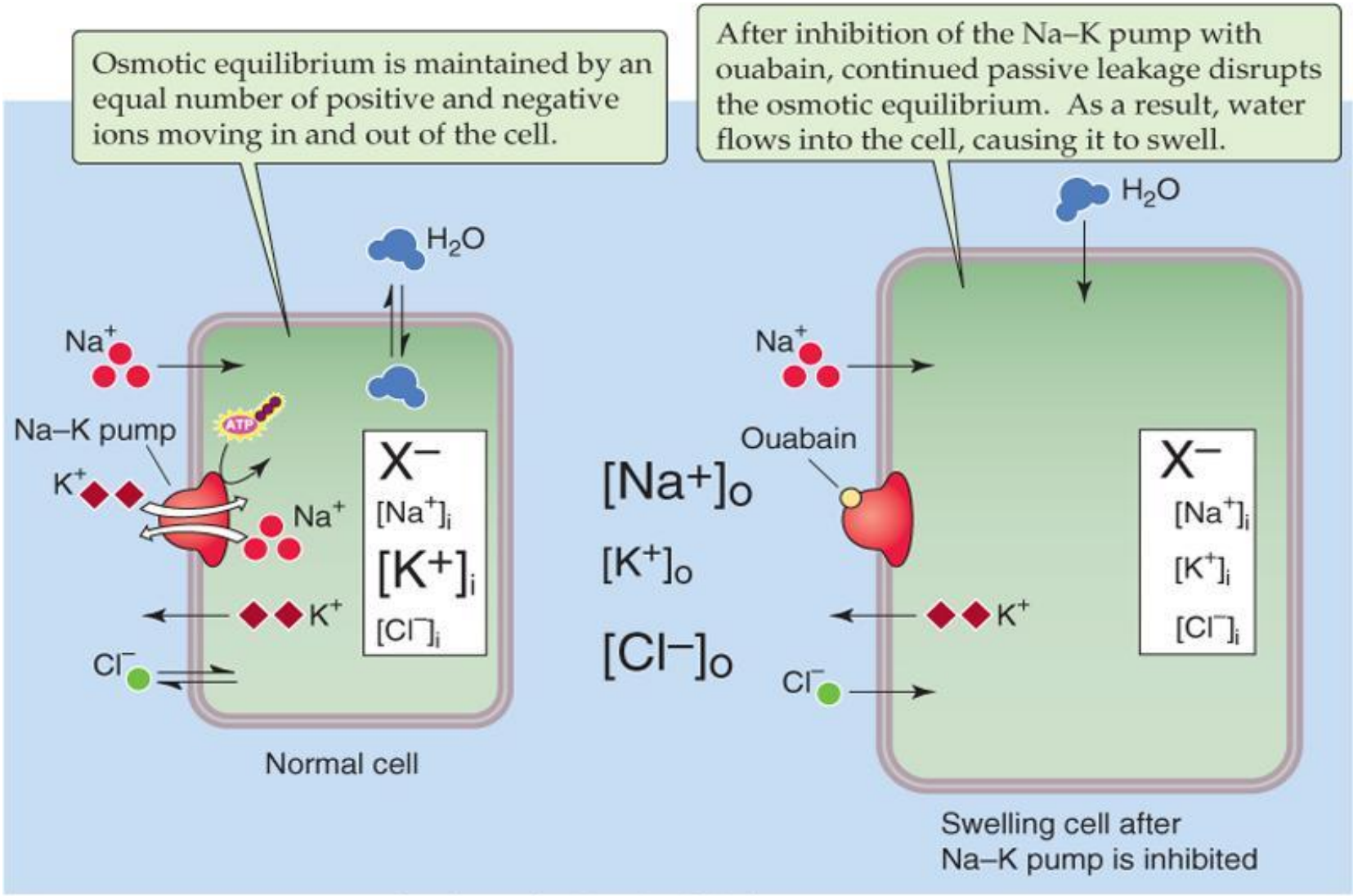
Ionic Species	Intracellular Concentration	Extracellular Concentration	Equilibrium Potential
Sodium (Na^+)	15 mM	145 mM	V_{Na} = +60.60 mV
Potassium (K^+)	150 mM	4 mM	V_K = −96.81 mV
Calcium (Ca^{2+})	70 nM	2 mM	V_{Ca} = +137.04 mV
Hydrogen ion (proton, H^+)	63 nM (pH 7.2)	40 nM (pH 7.4)	V_H = −12.13 mV
Magnesium (Mg^{2+})	0.5 mM	1 mM	V_{Mg} = +9.26 mV
Chloride (Cl^-)	10 mM	110 mM	V_{Cl} = −64.05 mV
Bicarbonate (HCO_3^-)	15 mM	24 mM	V_{HCO3-} = −12.55 mV

What is the origin of the membrane resting (its cause)?

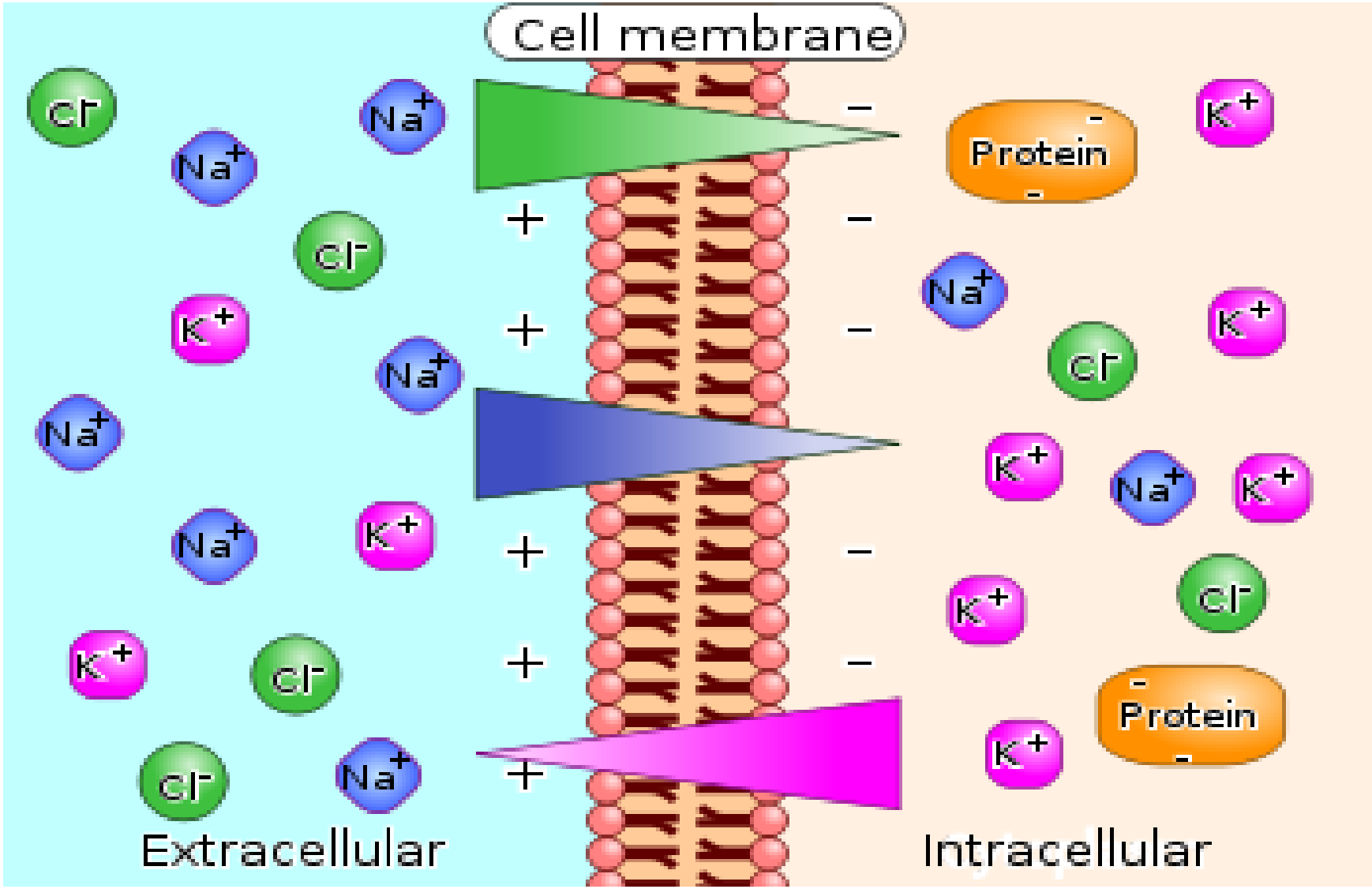
1) The electrogenic effect of the Na^+/K^+ pump (3 Na^+ out / per 2 K^+ in).

2) The Donnan effect.

3) The asymmetric distribution of ions across the membrane (selective permeability of the mb – K+ leak channels)

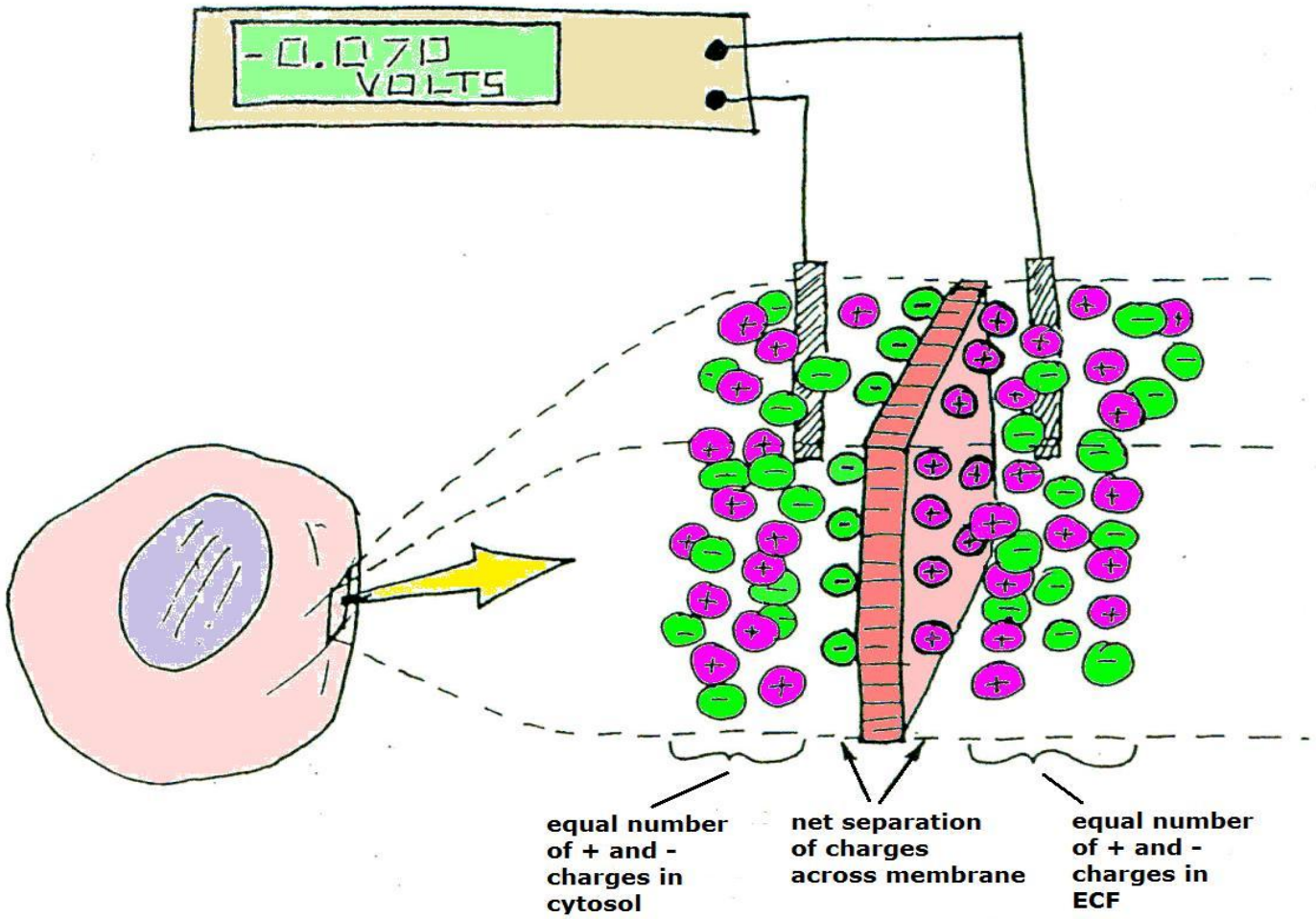


1) A blockade of the Na^+/K^+ pump will induce a 4-5 mV change in the membrane resting potential.



2) The Donnan effect is negligible for excitable cells because Na^+ and Cl^- permeability are very low.

3) The asymmetric distribution of ions across the membrane is what better explains the origin of the membrane resting potential.



Recording mb potential (Vm)

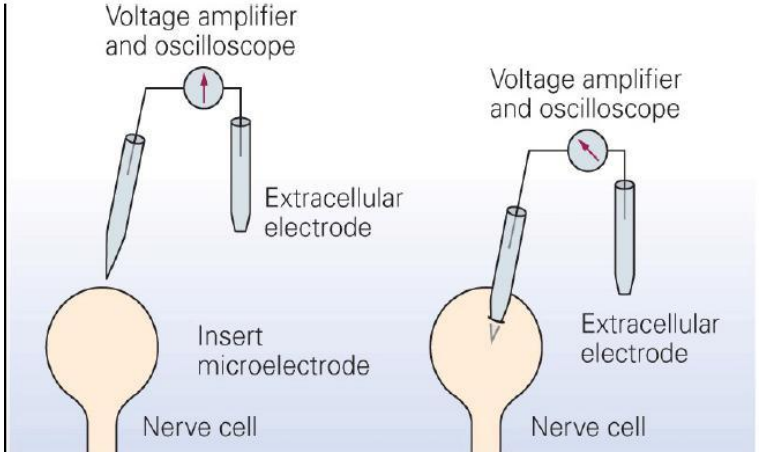


Fig. 6.2A Kandel

This is a reliable technique started to develop in late 1940s. Hodgkin, Huxley and Eccles won the Nobel prize in 1963.

Glass micropipettes filled with concentrated salt solution serve as electrodes. Wires inserted into the back ends of the pipette and connected to a voltage amplifier and oscilloscope.

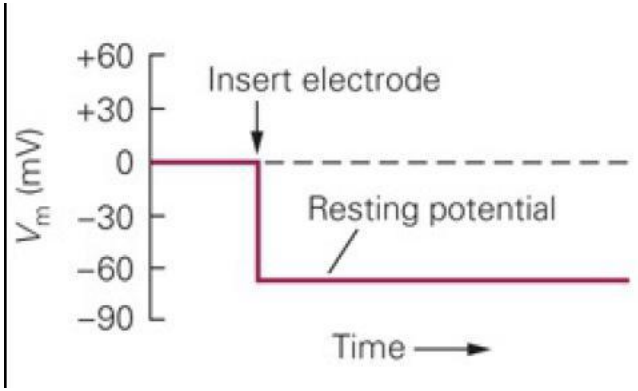


Fig. 6.2B Kandel

Intracellular recording micropipettes are filled with a solution with similar ionic composition than intracellular environment. The diameter of the micropipette tip is small (< 1 μm) and can be inserted into the cell without damaging it. Once you insert the micropipette into the cell

Neurons have a Vm near the EK^+.

This is because the membrane is more permeable to this ion compared to Na^+ and Cl^-.

The membrane of skeletal muscle cell has a higher permeability to Cl^- and Vm will approximate ECl^-

The actual Vm is the consequence of a very small excess of charges in a very narrow region nearby the membrane.

Vm is directly proportional to the number of charges separated by the lipid bilayer. Reduction in this separation is a depolarization while an increase is a hyperpolarization

Ion channels are responsible for changes in Vm. These channels can be subdivided in 2 major classes: passive and active ion channels.

Passive channels are always open and keep the Vm steady in the absence of any signal (Vr)

Active channels can open or close in response to different triggers: ligand, mechanical stretching of the mb or changes in Vm (depolarization).

Changes in Vm that do not lead to the opening of gated ion channels are passive responses termed ***electrotonic potentials***. Hyperpolarizing potentials and small depolarizations are almost always electrotonic potentials.

Vr is the result of the passive flux of individual ions through several passive ion channels. No single ion species is distributed equally across the 2 sides of a neuron mb. Na and Cl are most abundant outside while K and anions inside.

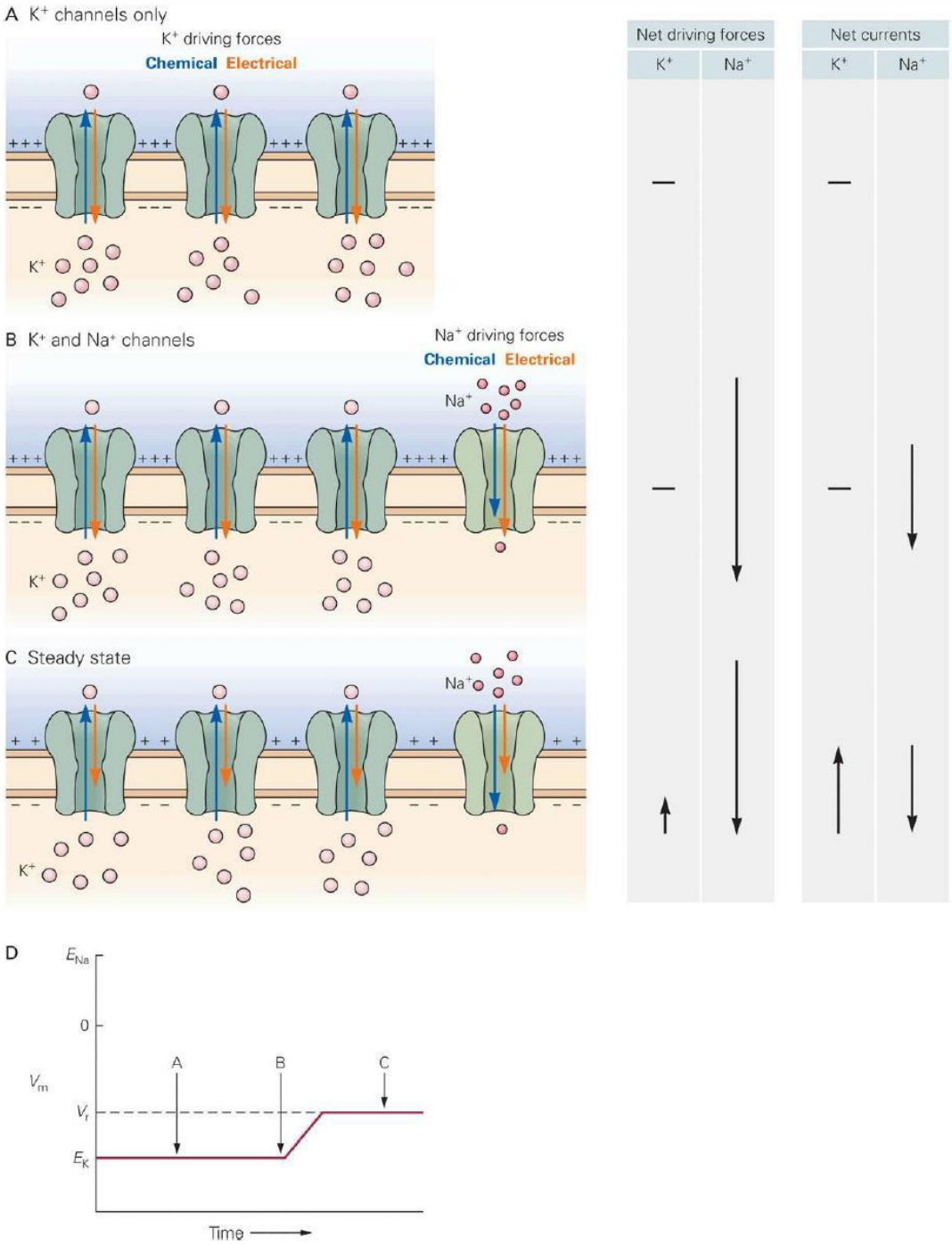


Figure 6-4 The resting potential of a cell is determined by the proportions of different types of ion channels that are open, together with Ex. Arrows represent the electrical (red) and chemical (blue) driving forces acting on Na+ or K+. Three hypothetical situations are illustrated.

A. In a resting cell in which only K+ channels are present, K+ ions are in equilibrium and Vm = Ek.
B. Adding a few Na+ channels to the resting membrane allows Na+ ions to diffuse into the cell, and this influx begins to depolarize the membrane.
C. The resting potential settles at a new level, where the influx of Na+ is balanced by the efflux of K+. In this example the aggregate conductance of the K+ channels is much greater than that of the Na+ channels because the K+ channels are more numerous. As a result, a relatively small net driving force for K+ drives a current equal and opposite to the Na+ current driven by the much larger net driving force for Na+. This is a steady-state condition, in which neither Na+ nor K+ is in equilibrium but the net flux of charge is null.
D. Membrane voltage changes during the hypothetical situations illustrated in A, B, and C.

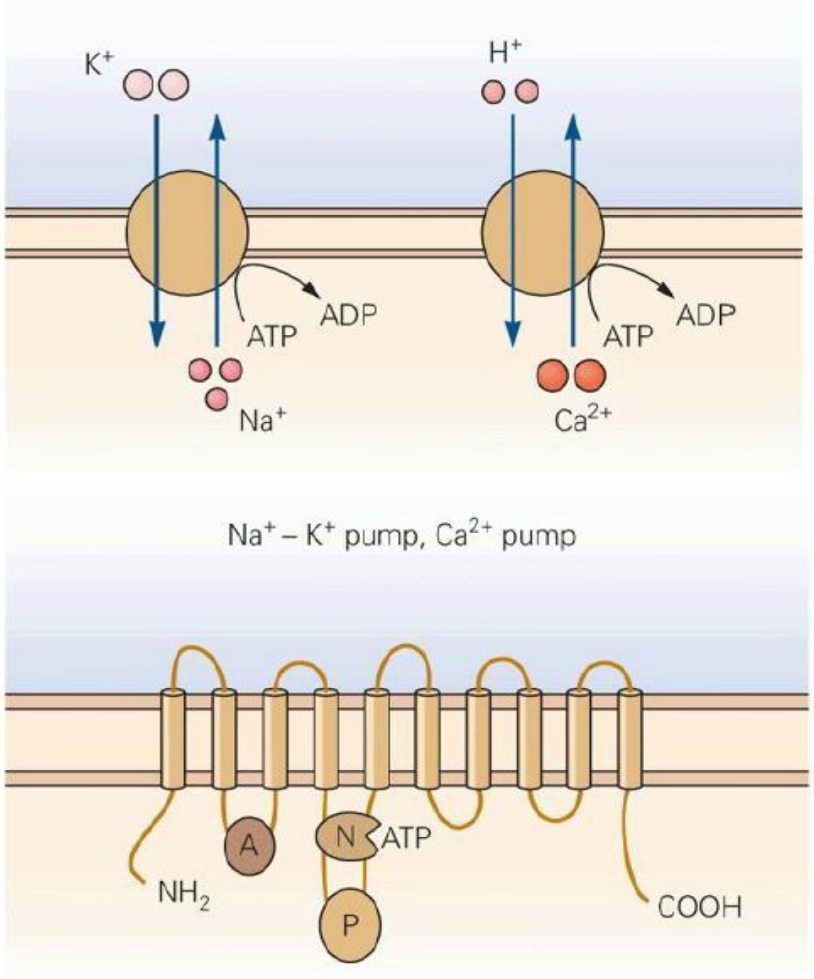
Ion flux = (electrical driving force + chemical driving force) x membrane conductance

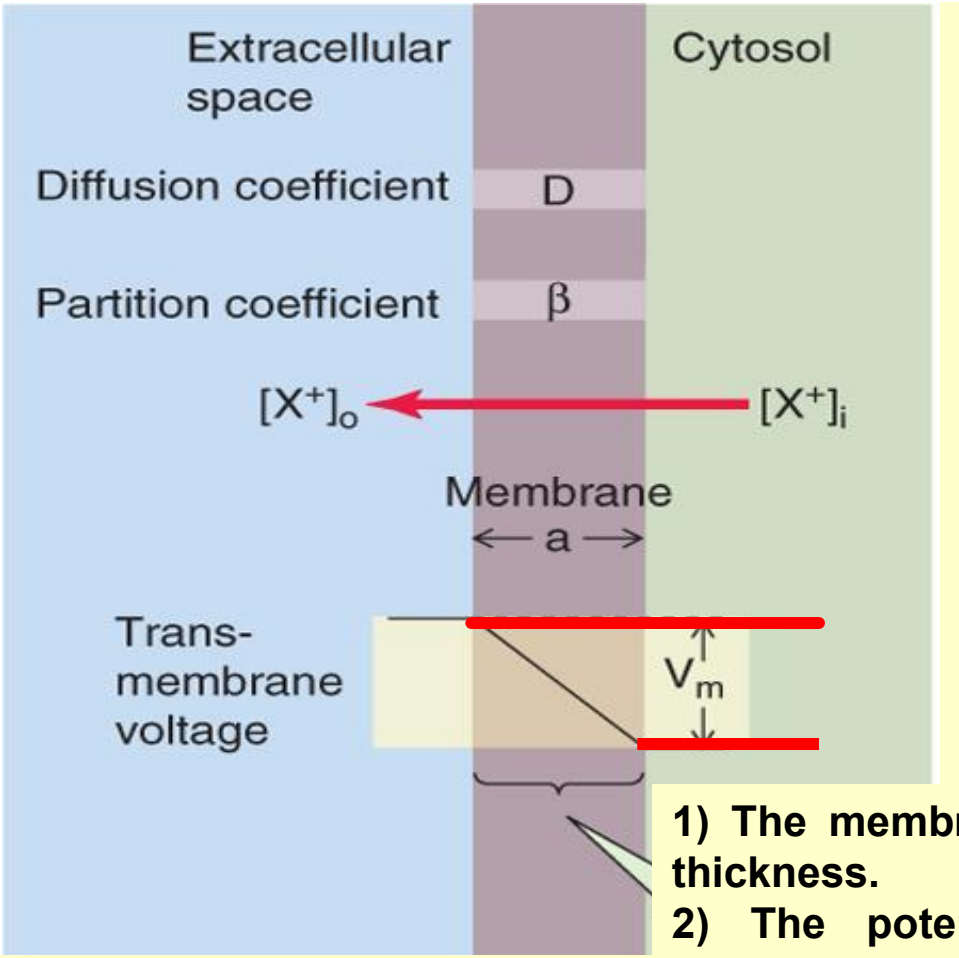
In a resting nerve cell relatively few Na+ channels are open, so the membrane conductance of Na+ is quite low. Thus, despite the large chemical and electrical forces driving Na+ into the cell, the influx of Na+ is small. In contrast, many K+ channels are open in the membrane of a resting cell so that the membrane conductance of K+ is relatively large.
Because of the high relative conductance of K+ to Na+ in the cell at rest, the small net outward force acting on K+ is enough to produce a K+ efflux equal to the Na+ influx.

Dissipation of ionic gradients is prevented by Na-K-pump. The pump requires energy that comes from ATP hydrolysis. The movement of ions through the pump is 10.000 times slower than the flow across ion channels. The pump is ***electrogenic*** because extrudes 3 Na and brings in 2 K. There is a net flux of ions outward

During periods of intense neuronal activity the increased influx of Na leads to increase in Na-K pump activity that generates a prolonged outward current, leading to a prolonged hyperpolarizing after-potential that can last for several minutes. The Na-K pump is inhibited by ouabain or digitalis plant alkaloids.

The Na-K pump is a P-type ATPase like Ca-pump.





The contemporary action of multiple ions on the membrane resting potential is a special case of the theory of electrodiffusion.

To facilitate the application of the theory of electrodiffusion to the specific case of the membrane, some simplification is in order:

1) The membrane is a homogenous piece of constant thickness.
2) The potential difference across the membrane changes linearly with distance. (the electric field of the membrane is constant - principle of the constant field)
3) The movement of an ion across the membrane is independent from the movement of other ions. (Principle of independence).
4) The permeability coefficient of the membrane to an ion X is constant along the entire membrane.

The Goldman-Hodgkin-Katz equation (GHK equation) allow us to calculate the Vm of a cell (neuron). The Vm depends on Ex of each ions that can cross the mb of a cell and on the Px (cm/s) of the mb for that ion. It lies at a level intermediate to E_{Na}, E_K and E_{Cl}

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

This equation applies only when Vm is not changing. When permeability to one ion is exceptionally high, the Goldman equation reduces to the Nernst equation for that ion.
In the squid giant axon at rest Hodgkin and Katz calculated that:

$$P_K : P_{Na} : P_{Cl} = 1.0 : 0.04 : 0.45$$

At the peak of the action potential instead:

$$P_K : P_{Na} : P_{Cl} = 1.0 : 20 : 0.45$$

$$I_{total} = I_K + I_{Na} + I_{Cl} \qquad I_K + I_{Na} + I_{Cl} = 0$$

To better understand how rapidly the Vm changes in response to a change in permeability or the magnitude of I_{Na}, I_K, I_{Cl} we can use the *equivalent circuit* model
The mb is a lipid insulator with electrical capacitance (**1 μF per cm^2 for a neuron**)
The number of ions that must move across the cell mb to create the Vm is a tiny fraction of the total number of ions in the cell.

Let's assume a glial cell with mb permeable to K

Vm = -80mV (-0.08V) cell diamater = 20μm

$$C = Q/V$$

Cell surface area = $4\pi r^2 = 1.26 \times 10^{-5}$ cm^2

$C = 1 \times 10^{-6}$ F/cm^2 x 1.26×10^{-5} cm^2
$= 1.26 \times 10^{-11}$ F

Ergo the charge separation is

$$Q = C \times Vm = 1.26 \times 10^{-11} \times 0.08 = 1.01 \times 10^{-12} \text{ C}$$

Because 1mol of K contains 96480 C to eastablish the Vm

$$1.01 \times 10^{-12} / 96480 = 1.05 \times 10^{-17} \text{ mole of K}$$

With a cell volume of $4\pi r^3/3$ and an intracellular [K] = 120 mmol/L, intracellular K is
$4.19 \times 10^{-12} \times 0.12 = 5.03 \times 10^{-13}$ moles

$$\text{Therefore } 1.05 \times 10^{-17} / 5.03 \times 10^{-13} = 0.002\%$$

The mb is a leaky capacitor because of ion channels. In an equivalent circuit the contribution of K ions is described by this

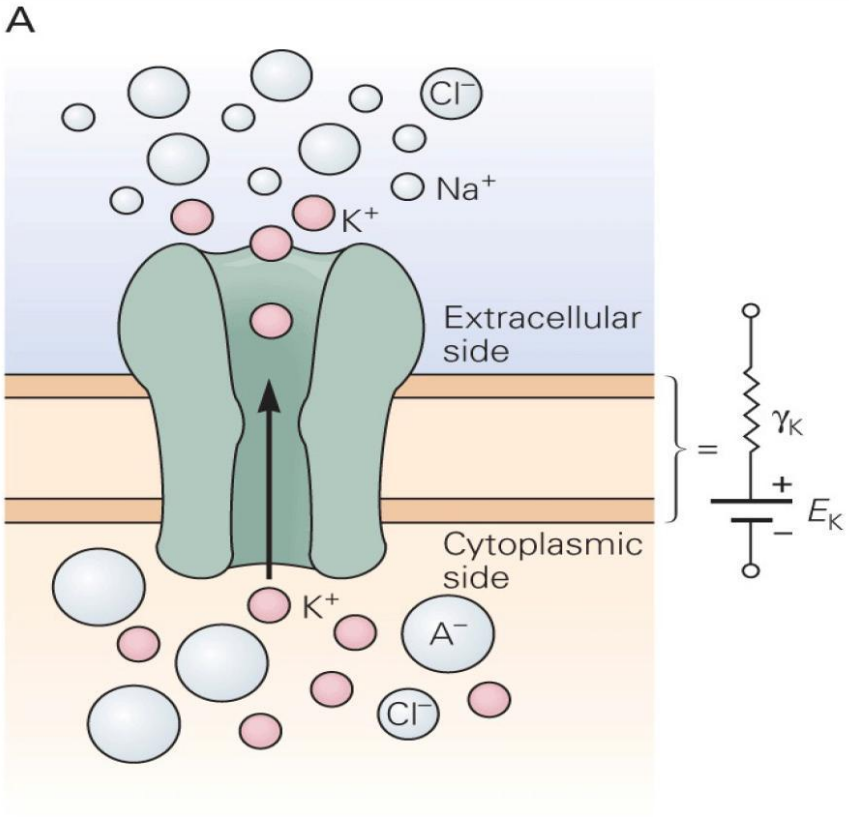


Figure 6-7 Chemical and electrical forces contribute to current through an ion channel.
A. A concentration gradient for K+ gives rise to an electromotive force, which has a value equal to *E*K, the Nernst potential for K+. This can be represented by a battery. In this circuit the battery *E*K
is in series with the conductor γK, representing the conductance of the K+ channel.
B. The current-voltage relation for a K+ channel in the presence of both electrical and chemical
driving forces. The potential at which the current is zero is equal to the K+ Nernst potential.

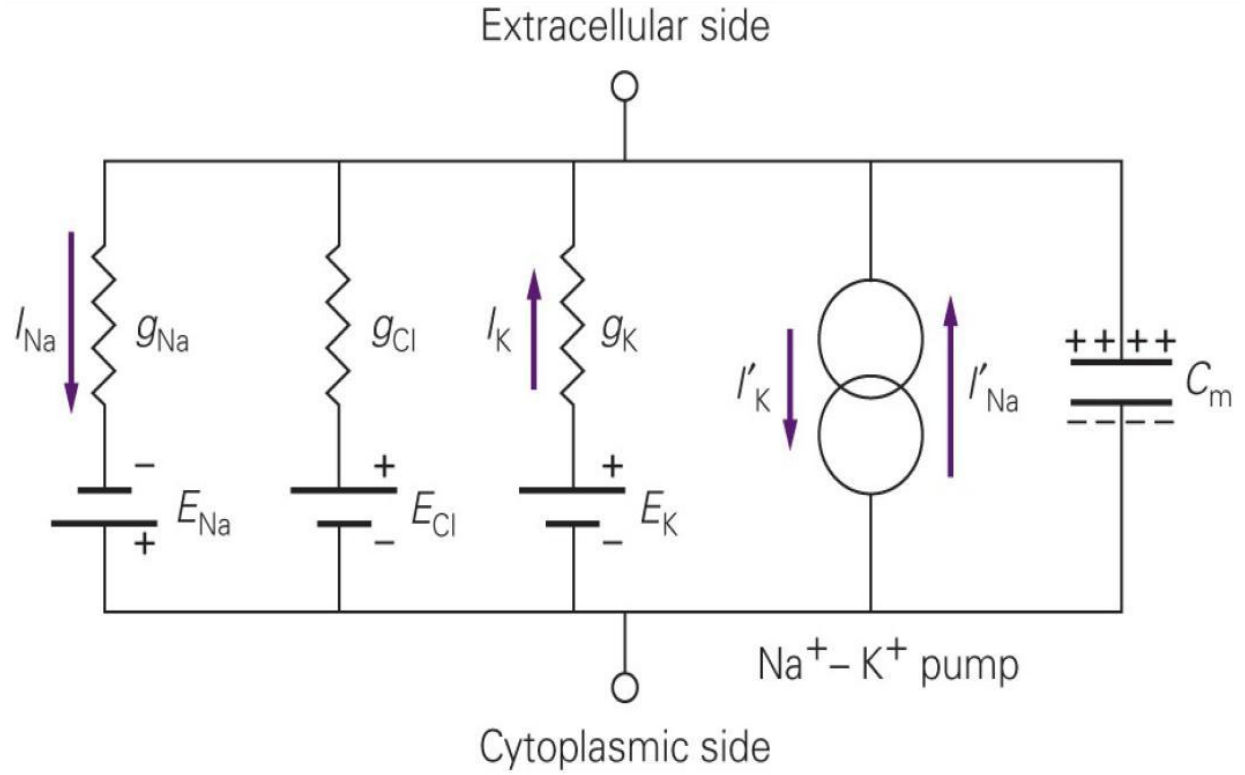
As for convention, the outward movement of positive charge across the mb corresponds to a positive current

$$i_K = (\gamma_K \times V_m) - (\gamma_K \times E_K) = \gamma_K \times (V_m - E_K)$$

This is a modified version of Ohm's equation
Vm – Ek is called the elettrochemical driving force

$$g_K = N_K \times \gamma_K$$

Equivalent circuit of passive and active current in a neuron



The membrane as a capacitor

The model is built on two elements: the first element is the membrane that works as a dielectric between two flat surfaces (the 2 faces of the membrane) with charges on it. This can be seen as a capacitor. Capacitor are characterized by having a capacity (C) = Q (charge) / V (potential difference). C is measured in Farad = Coulomb / Volt

The second element is the resistance, within the ion channels, and the electromotive forces generated by each ion.
Ohm law (I = V/R) can be used to calculate resistance, but commonly the inverse or R is used. 1/R = G (Conductance). Ohm law becomes therefore I = VG (G is measured in Siemens)

The capacitance C of a capacitor increases with the area of the plates and decreases with the separation between the plates according to the relation:

$$C = \frac{Q}{V} = \varepsilon \frac{A}{d}$$

where A is the membrane area, d is the separation between the plates or the membrane thickness and ε is the dielectric constant of the medium interposed between the plates. In the case of the cell membrane, it is more convenient to define the capacitance as independent of the amount of area involved. For this it is used the specific capacitance (Cm) which is defined as the capacitance per unit area or C / A. Replacing this definition in the above equation we find:

$$Cm = \varepsilon / d$$

As the thickness of the membrane is only 2,5 nm, the Cm of the membrane is very high and equivalent to about 1 μF / cm^2.

Ohm's law, using the conductance, becomes

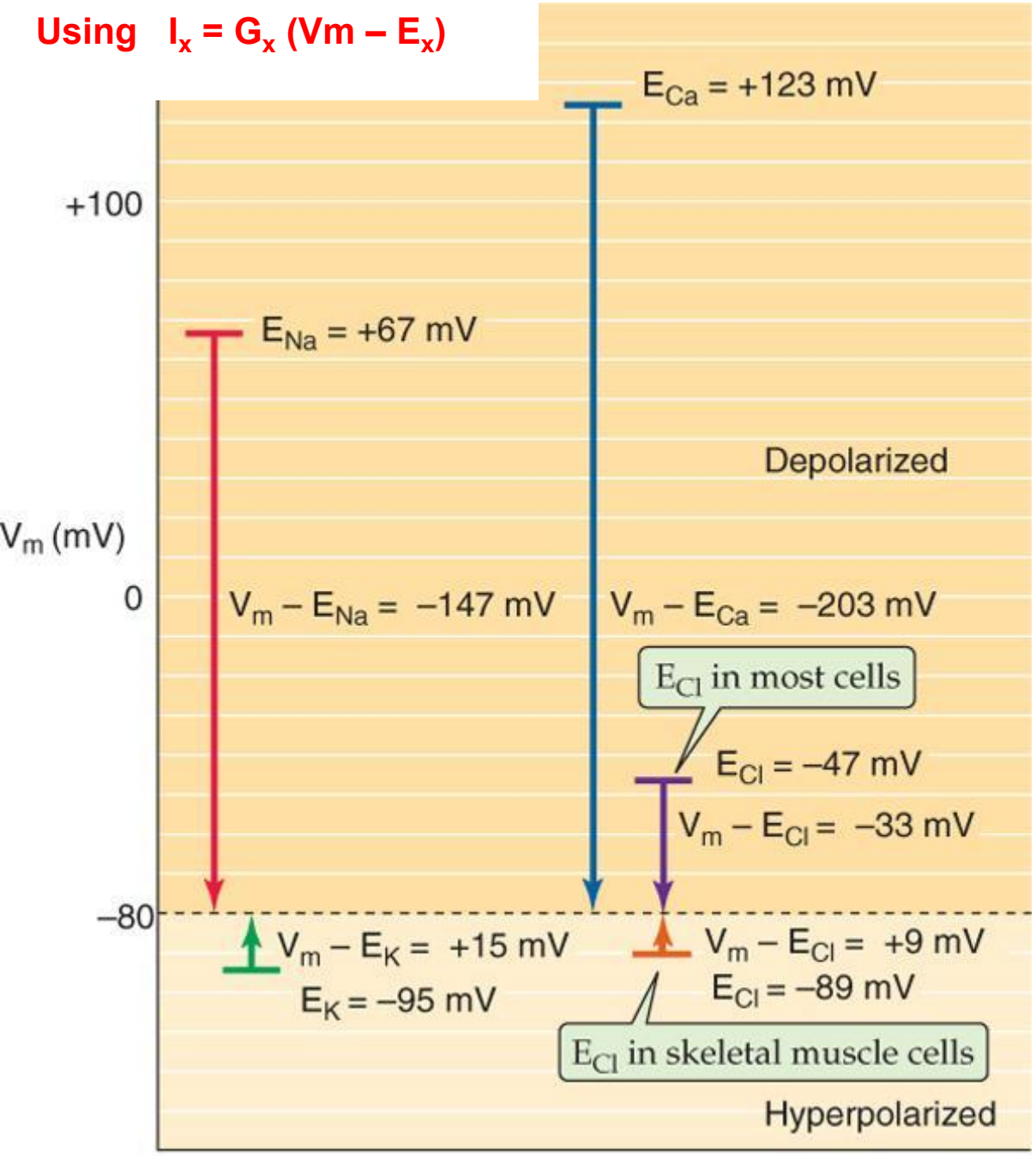
$$I_X = G_X (V_m - E_X)$$

($Vm-E_x$) is the electromotive force that pushes an ion X throught the mb with conductance G_x. If $E_x > Vm$, then I_x becomes negative and a current will enter the cell (inward current). If $Vm > E_x$, a current will flow out of the cell (outward current)

$$I_{total} = I_K + I_{Na} + I_{Cl} \qquad I_K + I_{Na} + I_{Cl} = 0$$

$$V_m = \frac{G_K}{G_m} E_K + \frac{G_{Na}}{G_m} E_{Na} + \frac{G_{Ca}}{G_m} E_{Ca} + \frac{G_{Cl}}{G_m} E_{Cl} \ldots$$

Using $I_x = G_x (Vm - E_x)$



Electrochemical driving forces for different ions.

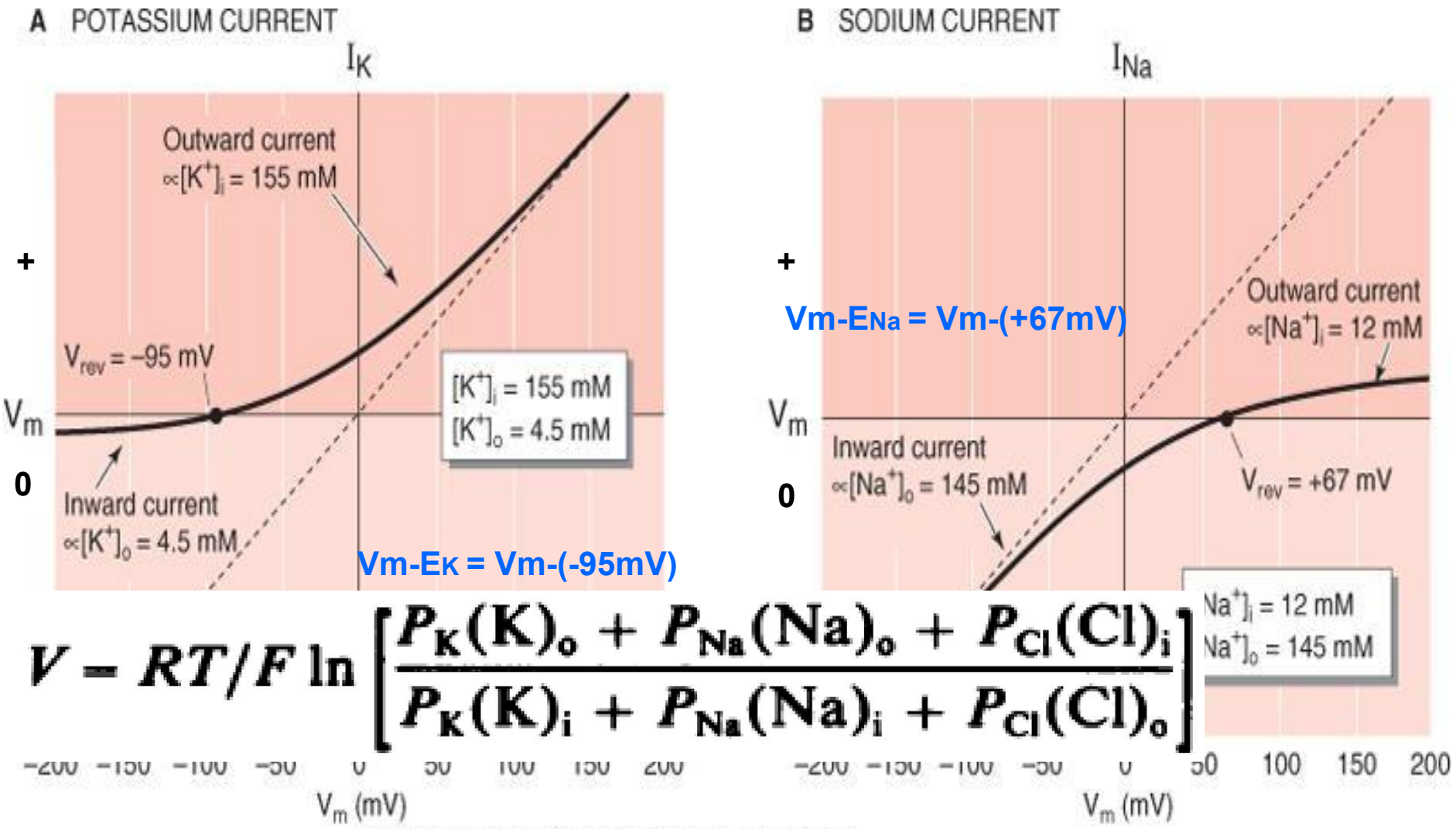
For each ion the equilibrium Nernst potential (e.g. ENa = +67mV) is represented as an horizontal bar and the net electrochemical driving force (e.g. Vm – ENa = -147mV) as an arrow. Values are those typical of a muscle cell.

When Vm becomes less negative (more positive) we have a DEPOLARIZATION.
When Vm becomes more negative (less positive) we have a HYPERPOLARIZATION

An influx of positive ions or an outflux of negative ions induces a depolarization.
The outflux of positive ions and the influx of negative induces a hyperpolarization.

Conventionally, inward currents induce depolarization (+ in), while outward current (+ out) are hyperpolarizing.

CARE with Cl^-

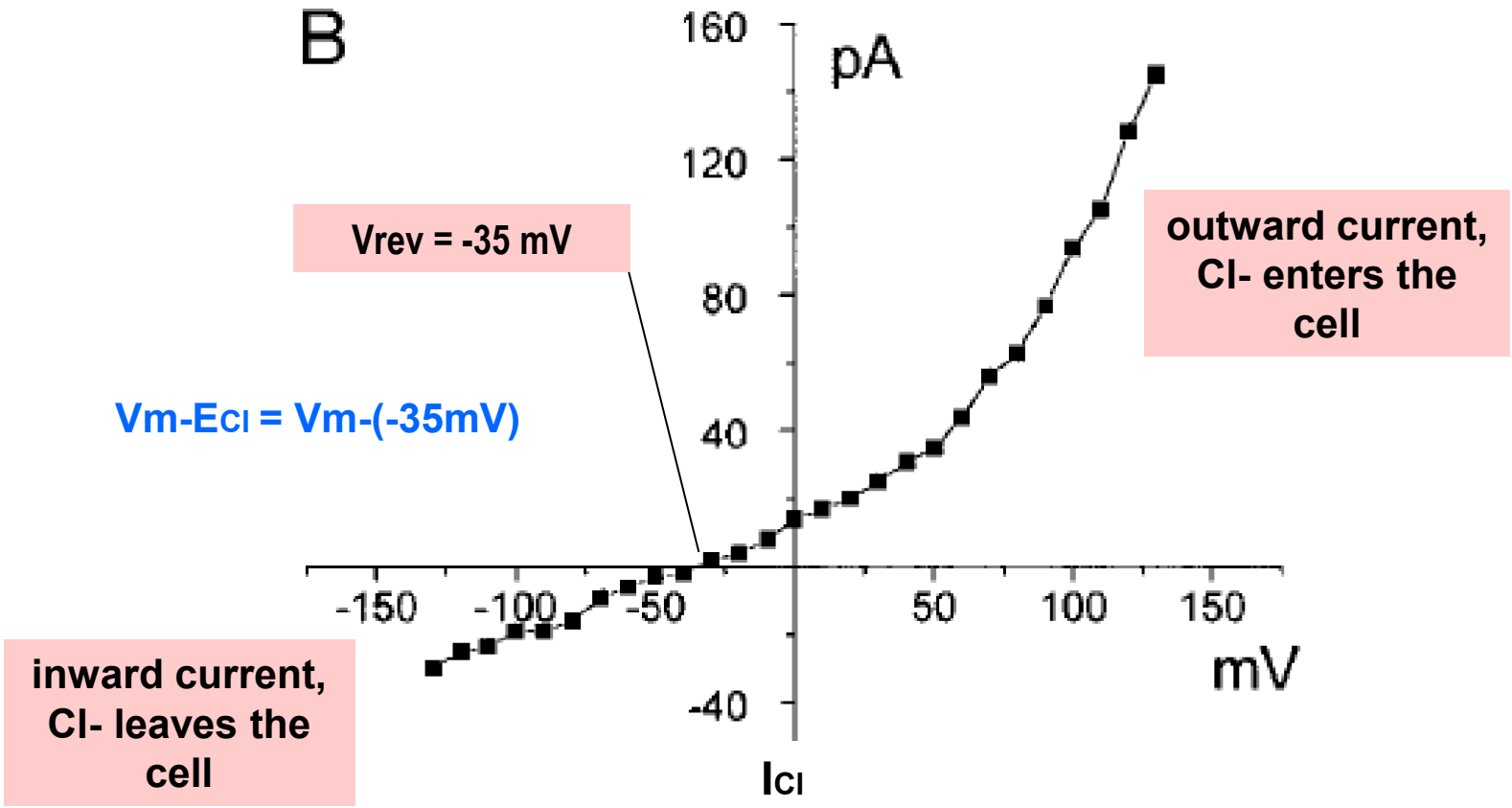


K^+ current and Na^+ current are indicated by the solid black lines and are calculated using the GHK equation using the actual concentrations. Dashed black lines indicates the direct proportionality between current and voltage (according to the Ohm Equation) assuming equal concentration inside and outside the cell. Note that Vrev is the Nernst Potential.

Conventionally, an inward current (IC) is indicated by downward deflection, while an outward current (OC) is indicated by an upward deflection.

IC depolarize the cell; OC hyperpolarize the cell

K+ enters the cell for IC current (Vm < -95mV) while Na+ leaves the cell for OC (Vm> +67mV).



Cl^- current as a function of Vm

When Vm < Vrev (-35mV in this case), Cl^- leave the cell, trying to bring Vm to Vrev. When Vm > Vrev, Cl^- enter the cell for the same reason.

Conventionally, current below Vrev are inward (Cl^- moves in the opposite direction; negative ions leaving the cell = positive ions entering the cell). Current above Vrev are outward: Cl^- enter the cell (Negative ions coming in = Positive ion going out).

TABLE 2.1 Extracellular and Intracellular Ion Concentrations

Ion	Concentration (mM)	
	Intracellular	Extracellular
Squid neuron		
Potassium (K^+)	400	20
Sodium (Na^+)	50	440
Chloride (Cl^-)	40–150	560
Calcium (Ca^{2+})	0.0001	10
Mammalian neuron		
Potassium (K^+)	140	5
Sodium (Na^+)	5–15	145
Chloride (Cl^-)	4–30	110
Calcium (Ca^{2+})	0.0001	1–2

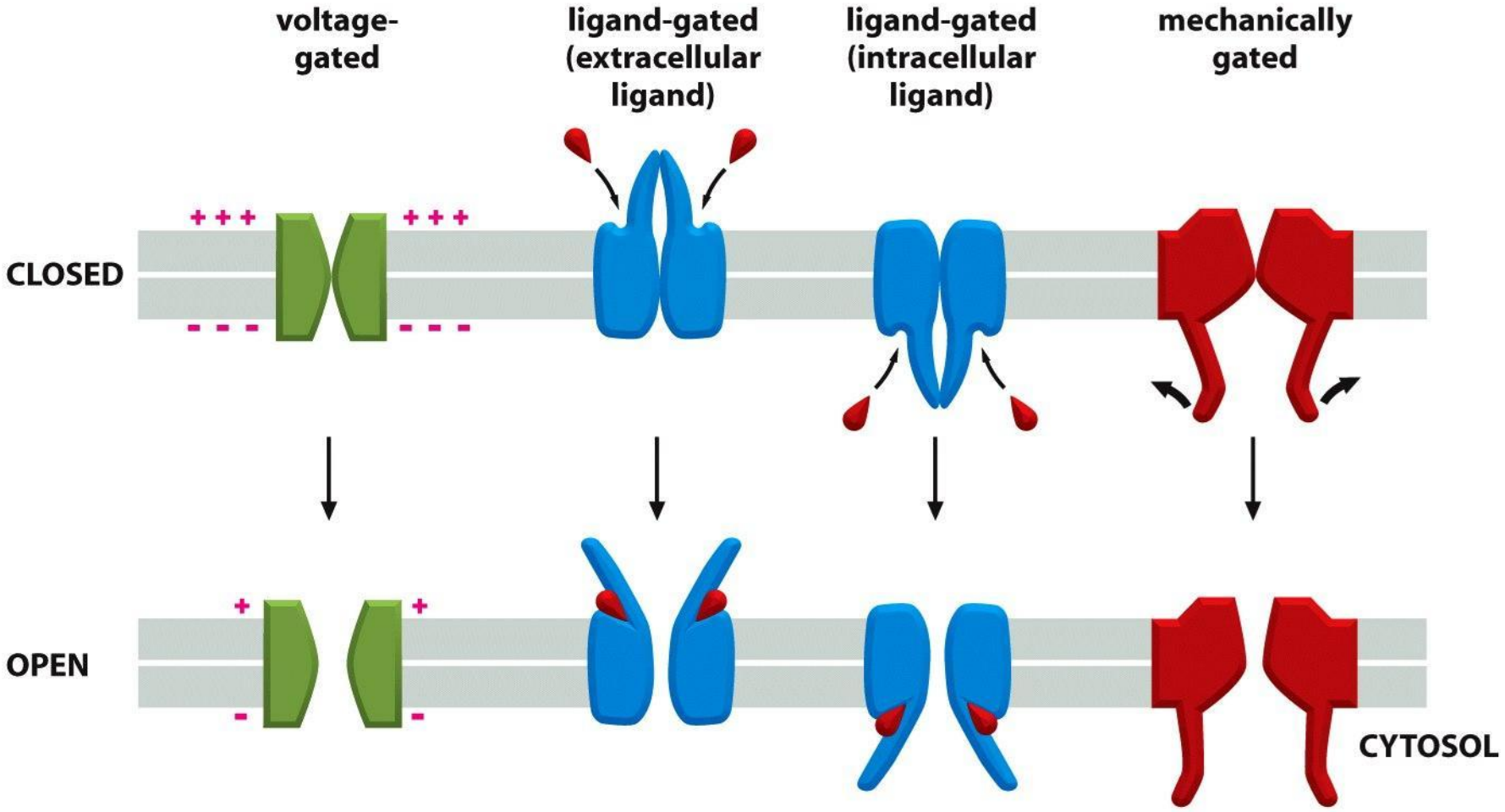


Figure 11-21 Molecular Biology of the Cell 5/e (© Garland Science 2008)

Action potentials

The capacity of nervous cells to carry messages at long distances depend on their ability to generate action potentials, transient and regenerative electrical signals whose amplitude does not tend to decrease along the axon length. In other types of cells, their main function is to activate intracellular processes. In muscle cells, for example, an action potential is the first step in the chain of events leading to contraction.

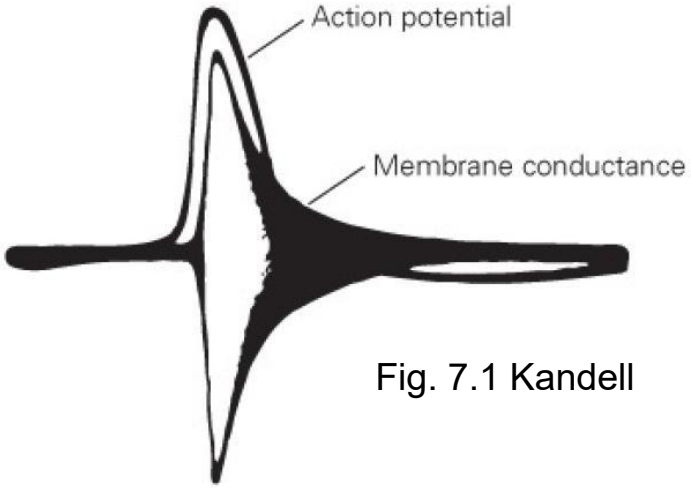
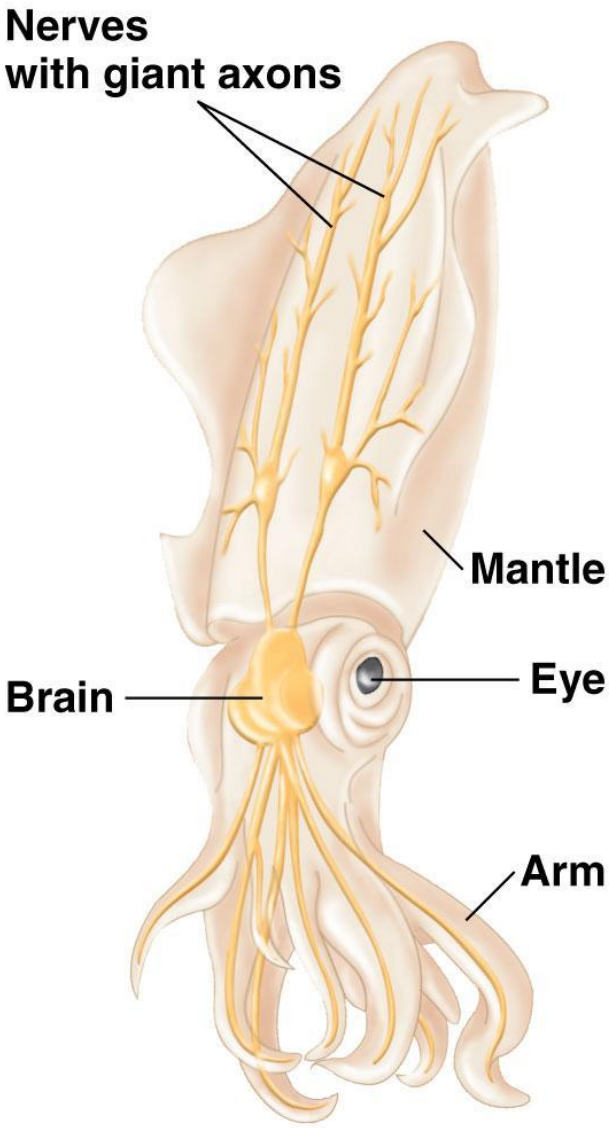


Fig. 7.1 Kandell

In 1938, Cole and Curtis were the first to describe that the action potential was associated with an increase in mb conductance. 10 years later, Hodgkin and Huxley drew the hypothesis that the action potential initiates as a consequence of a depolarization that induces a change in mb conductance. It becomes permeable to Na rather than K.

They were able to describe the ion currents associated with the action potentials by using the voltage clamp technique on the squid giant axon.



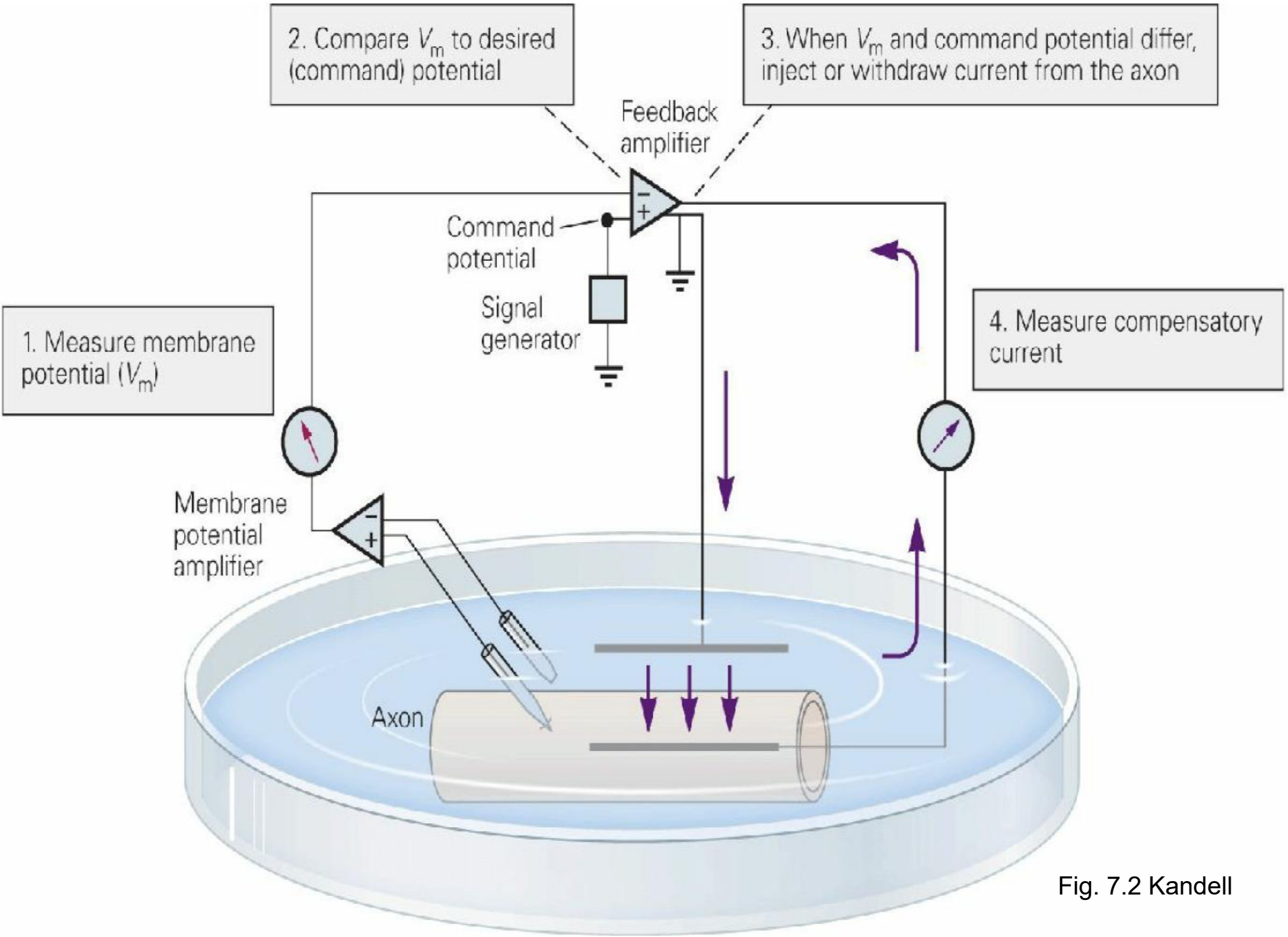
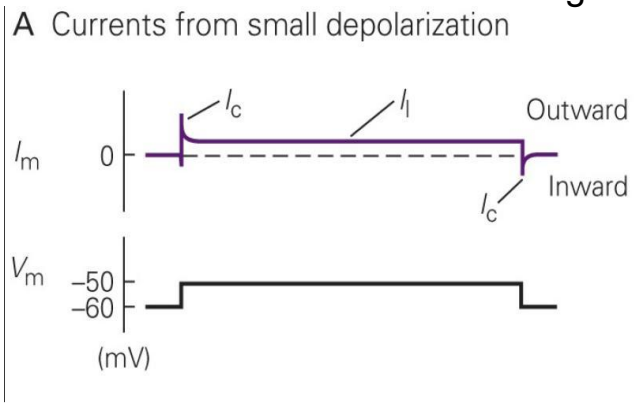


Fig. 7.2 Kandell

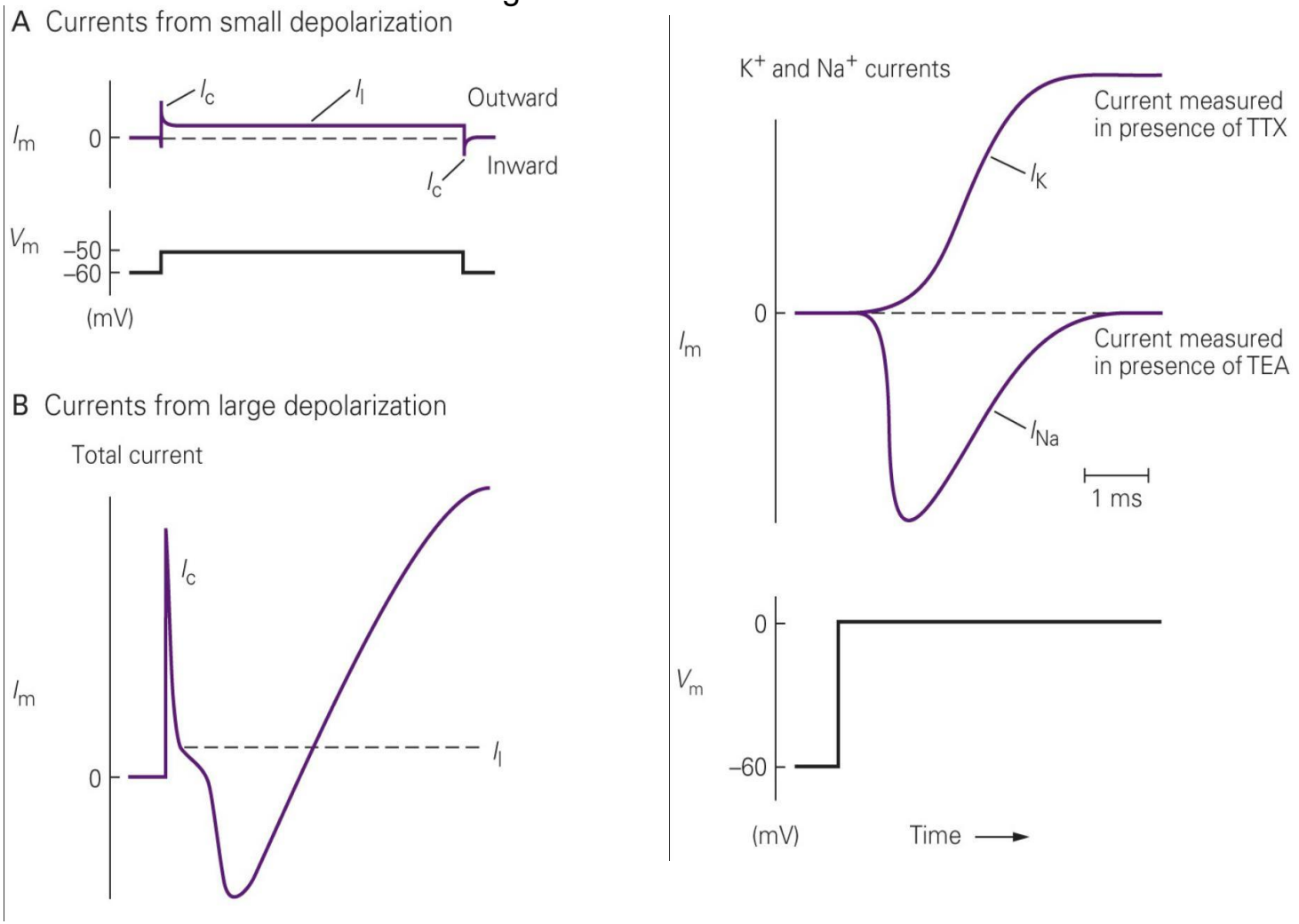
To study the ion currents that subtend the generation of an action potential we only need to analyze the resistive currents and not the capacitive currents. Capacitive currents (Ic) only flow when Vm is changing and during the voltage clamp experiment Ic only flows at the beginning and at the very end of the step change in Vm. Ii = leakage current

Fig. 7.3 Kandell



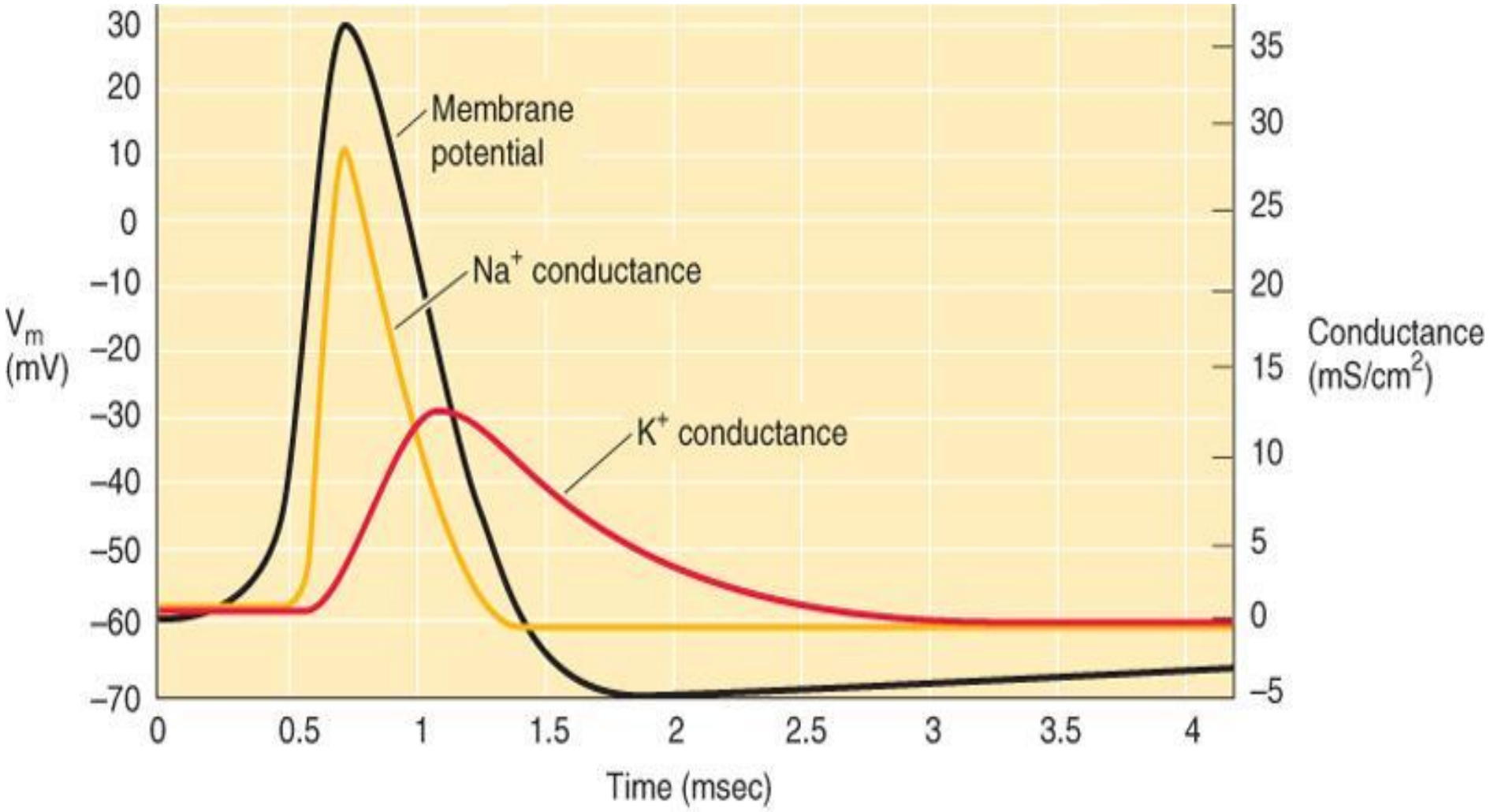
To study the ion currents that underlie the generation of an action potential we only need to analyze the resistive currents and not the capacitive currents. Capacitive currents (Ic) only flow when Vm is changing and during the voltage clamp experiment Ic only flows at the beginning and at the very end of the step change in Vm. Ii = leakage current

Fig. 7.3 Kandell

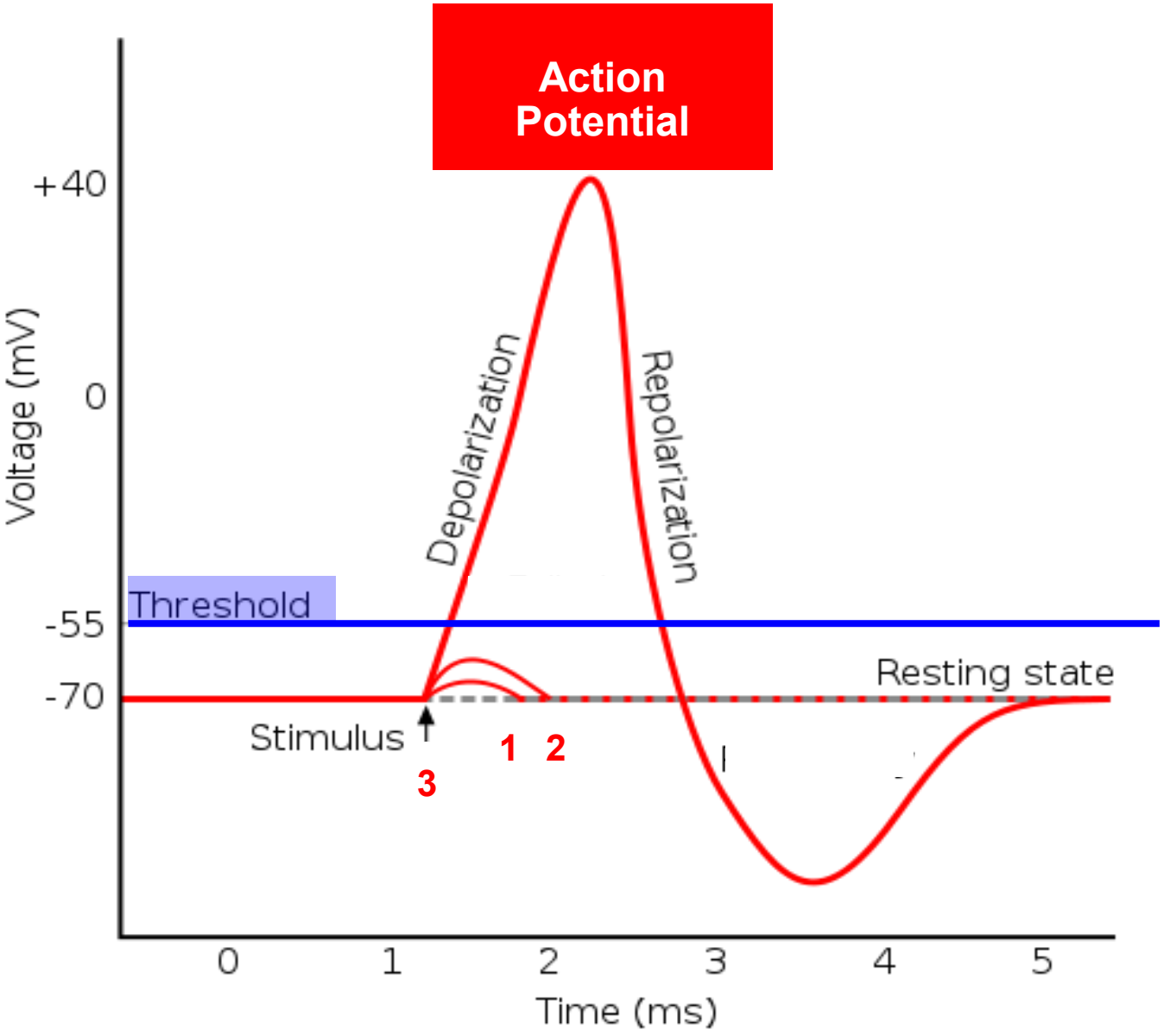


$$I_{Na} = g_{Na} \times (V_m - E_{Na})$$

$$I_K = g_K \times (V_m - E_K).$$



Boron & Boulpaep: Medical Physiology, 2nd Edition.

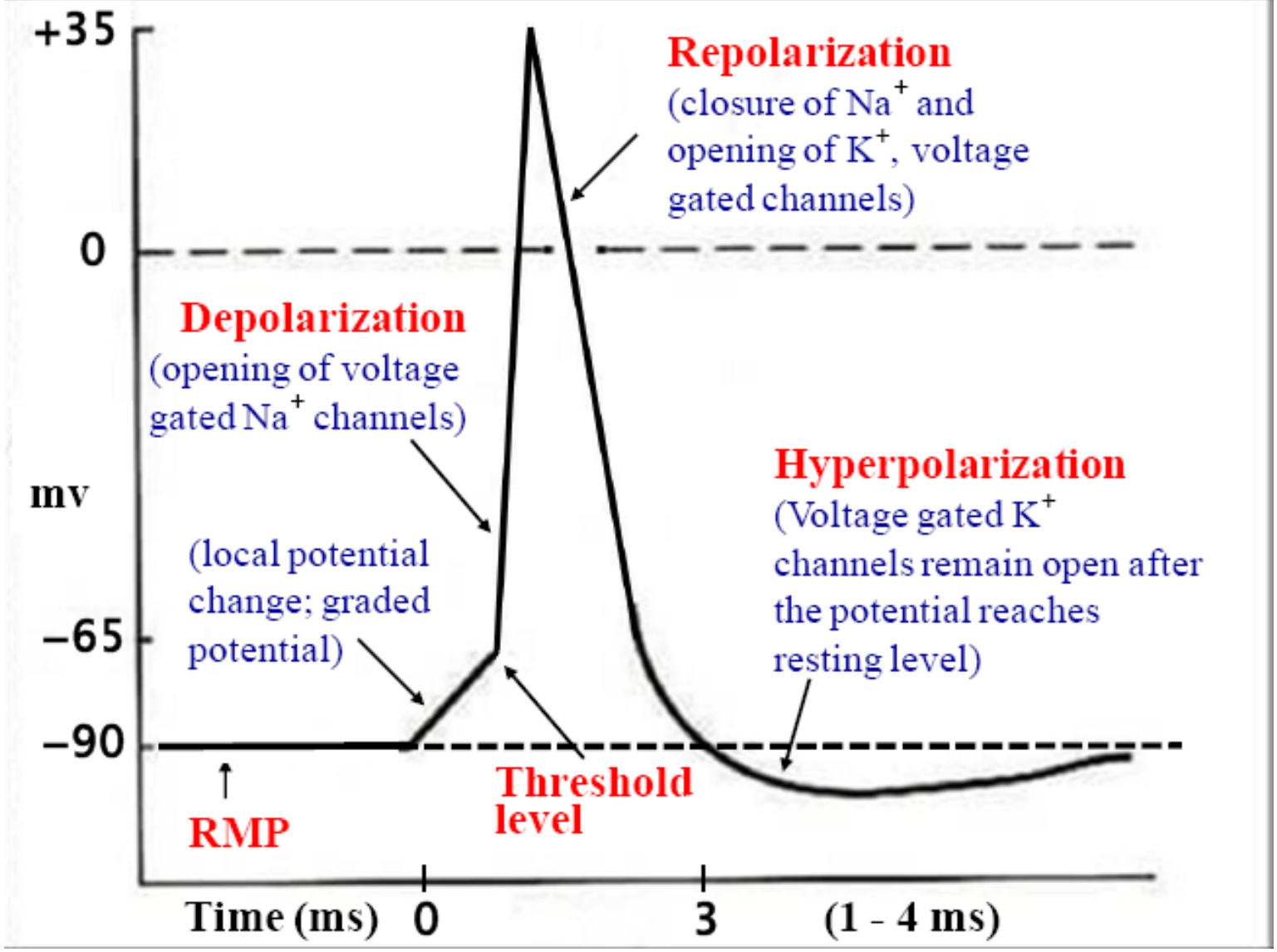


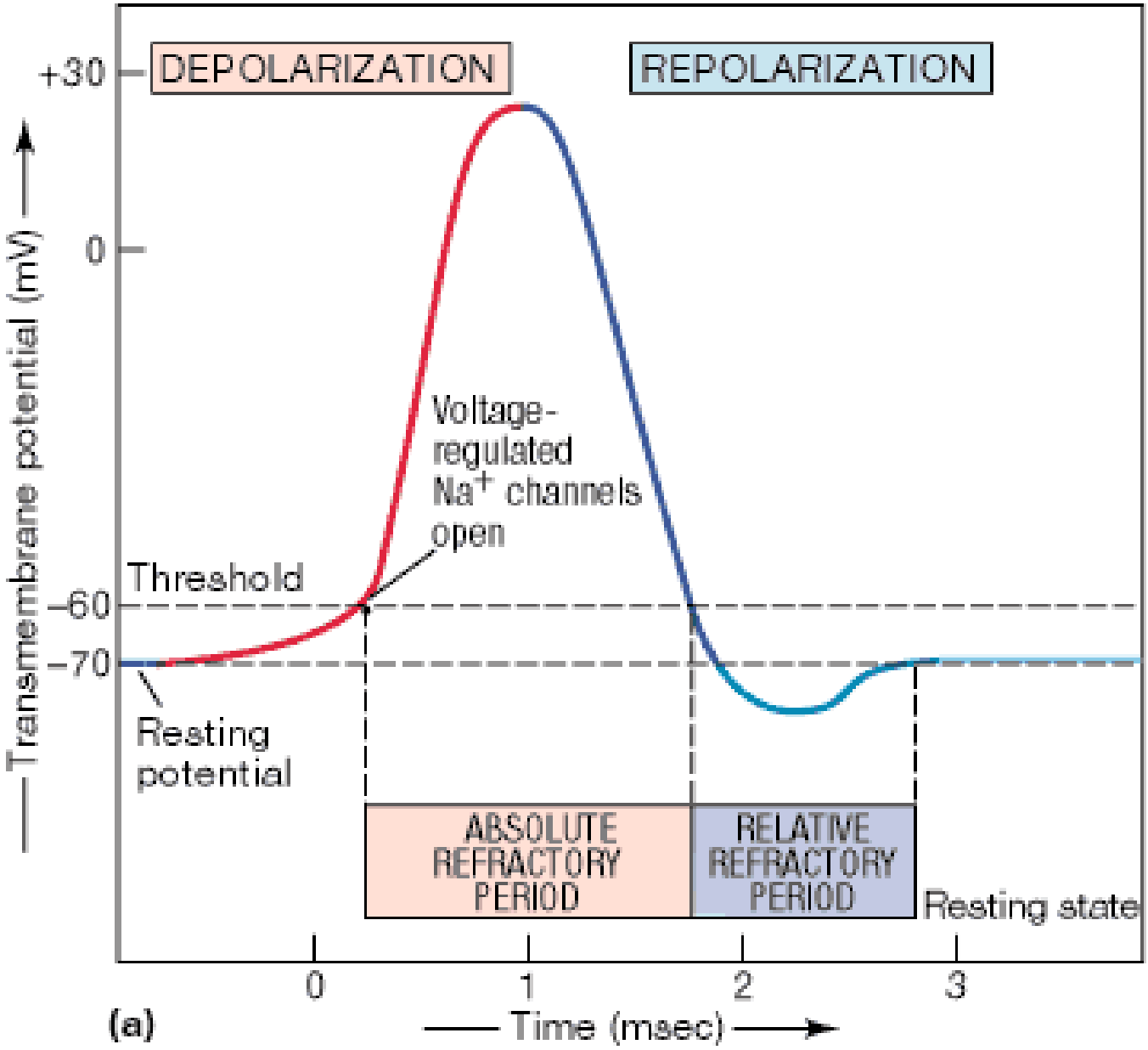
Characteristics of the action potential are its threshold and all or none behavior.

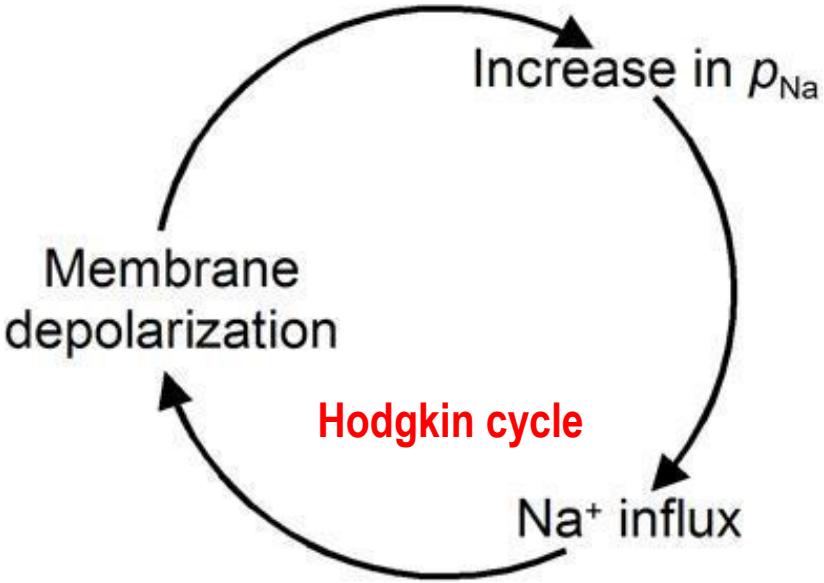
A small subthreshold depolarization increases INa but it also increases IK and Ii.

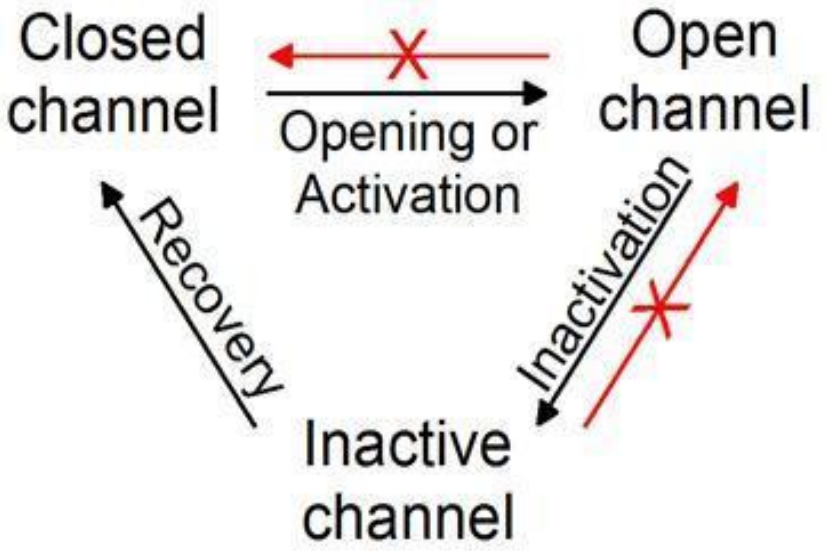
Because of the high voltage sensitivity and the rapid kinetics the increase in INa exceeds IK and Ii. The point when Vm is regenerative (threshold) is when INa+IK+Ii form outward becomes inward

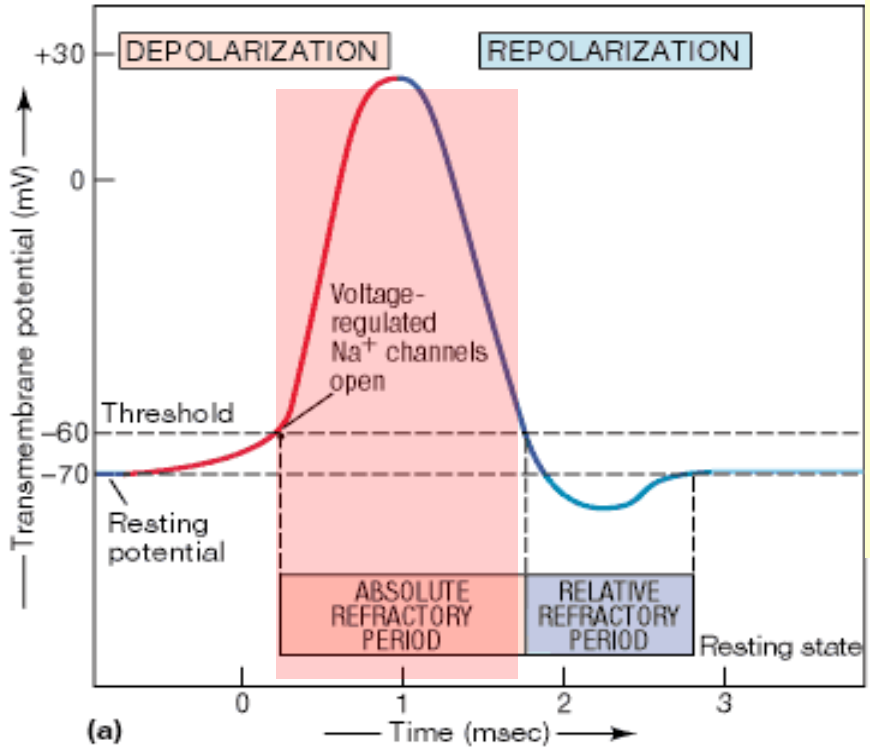
Action potential




DEPOLARIZATION
REPOLARIZATION
+30
0
−60
−70
Transmembrane potential (mV)
Voltage-regulated Na+ channels open
Threshold
Resting potential
ABSOLUTE REFRACTORY PERIOD
RELATIVE REFRACTORY PERIOD
Resting state
0
1
2
3
Time (msec)
(a)

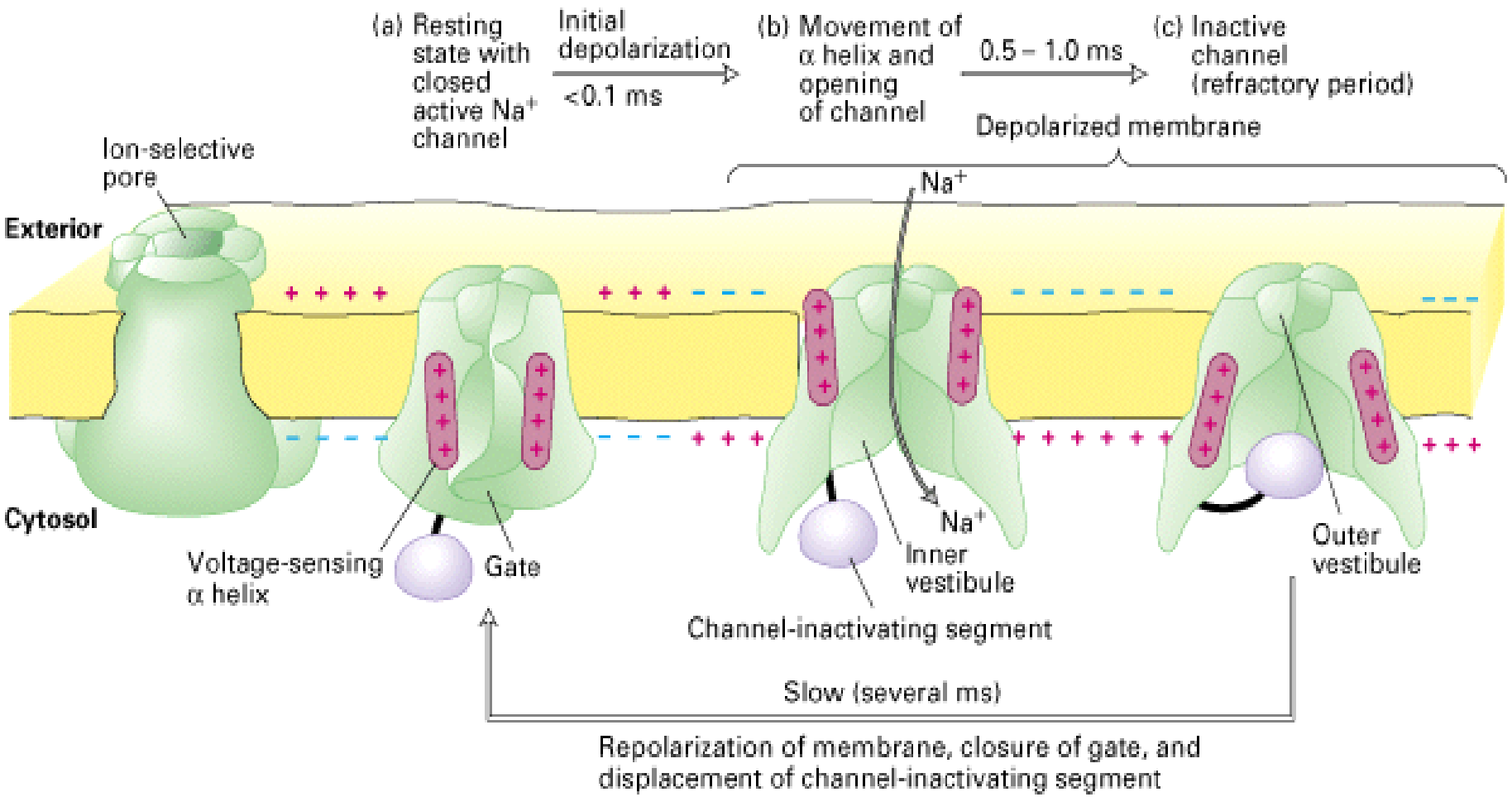






The Hodgkin cycle (depolarization - opening of the Na^+ voltage-gated channels - more depolarization - more channels open - and so on) explain the explosive increase of Vm during the depolarization phase, once the threshold is reached.

However, once opened, Na^+ voltage-gated channels go through a longer cycle (channel open - inactive - close) that explain the duration of the absolute refractory period.


(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
Outer vestibule
Channel-inactivating segment
Slow (several ms)
Repolarization of membrane, closure of gate, and displacement of channel-inactivating segment

Passive electrical properties of the neuron affect electrical signaling

Once an electrical signal is initiated then it is integrated and propagated along the neuron. During signaling the Vm changes continuosly. Important for the electric signaling and conductance are passive electrical properties of the neuron: Cm, Gr (1/Rr) but also r_i, that is the intracellular axial resistance. For a long thin axon it can be substantial.

The cell mb, given its anatomical characteristics, is a mix between a capacitor and a resistor

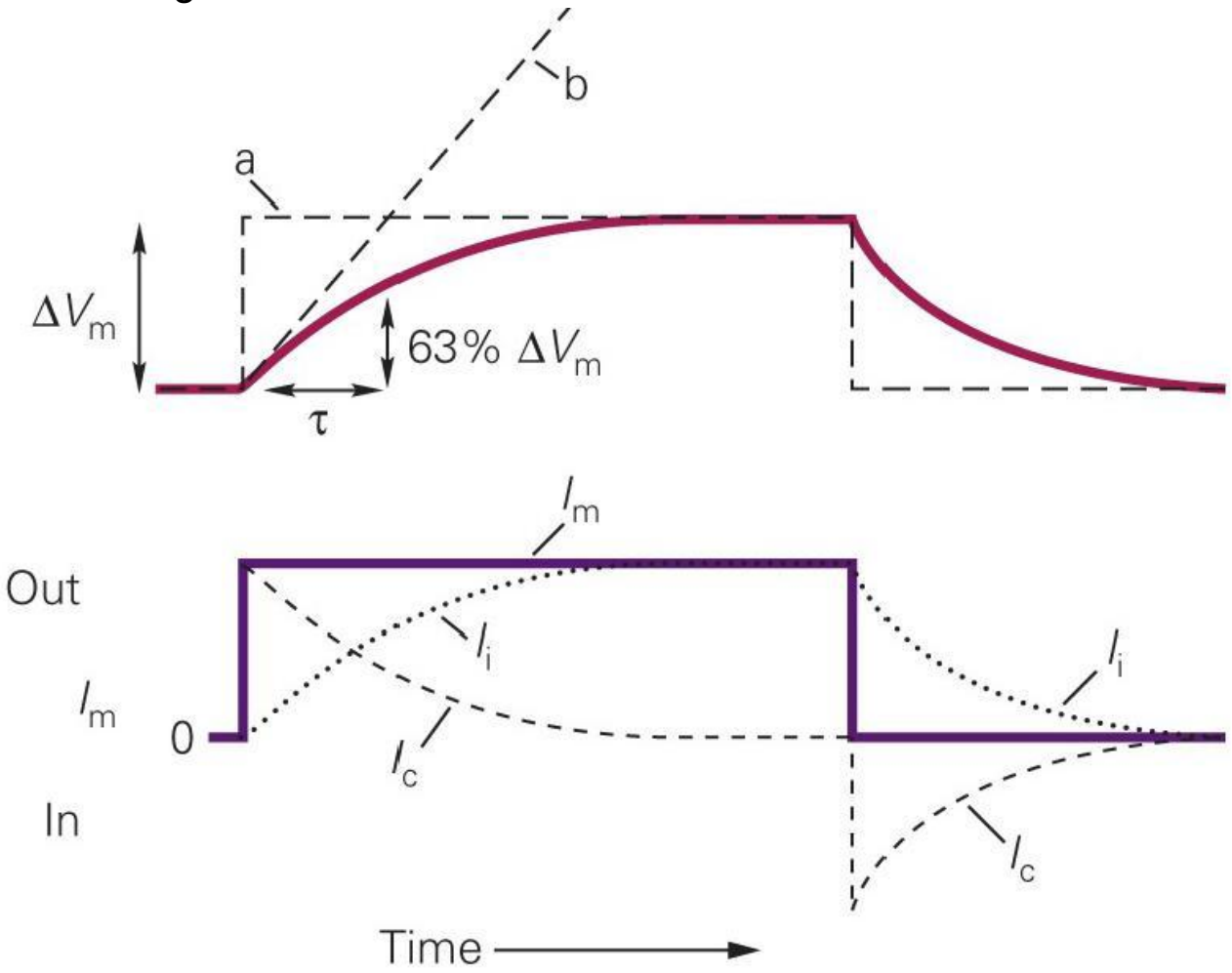
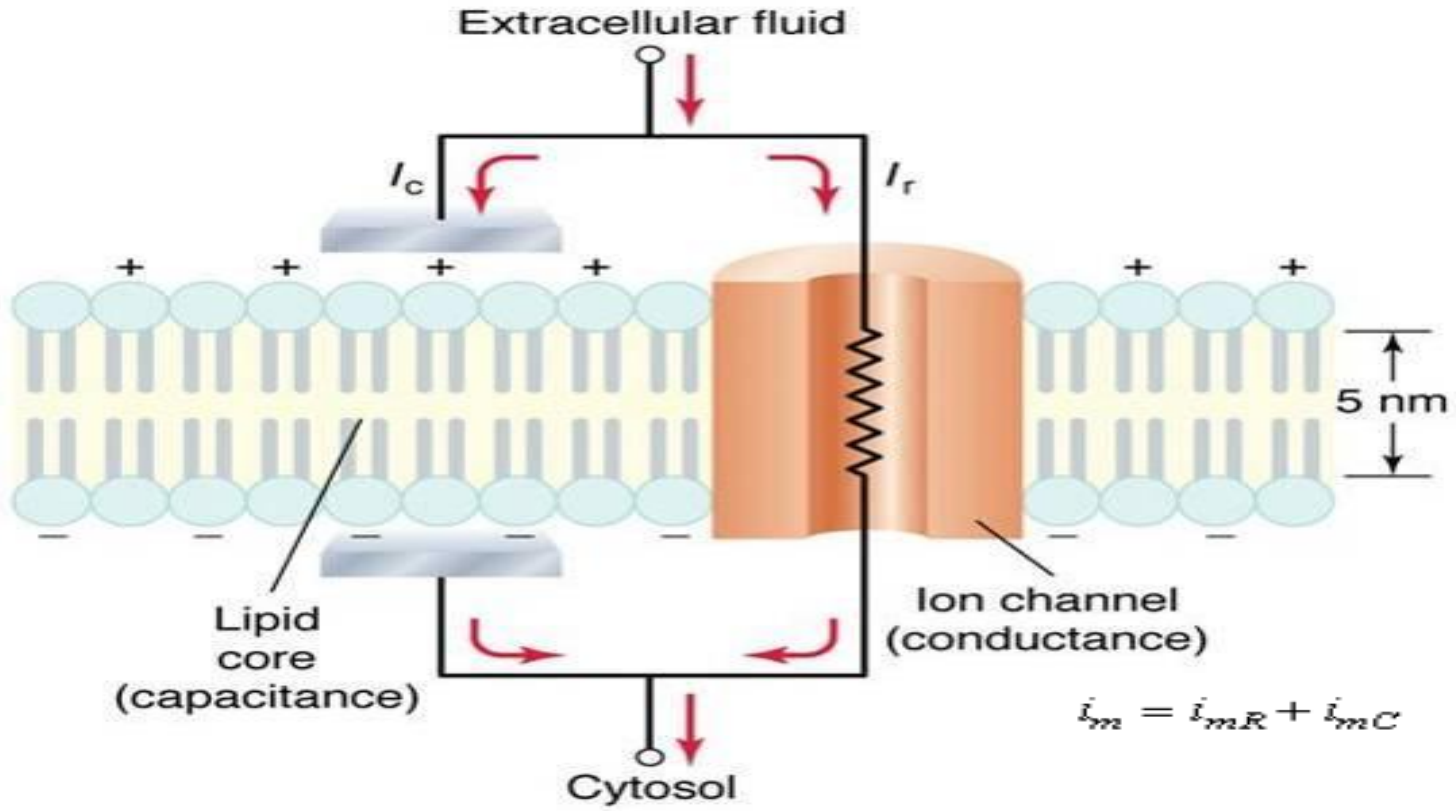


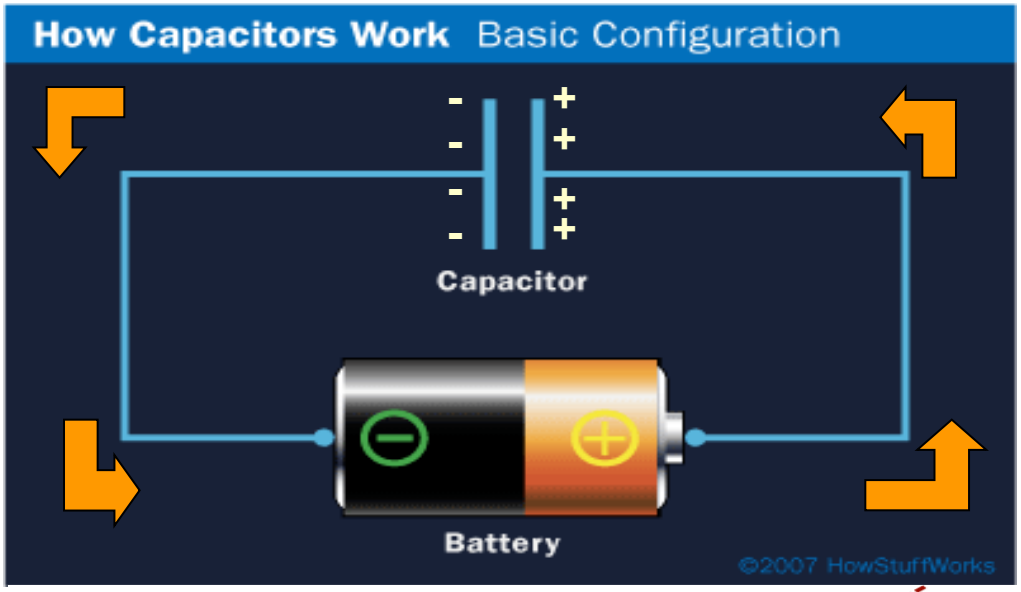
Fig. 6.15 Kandell

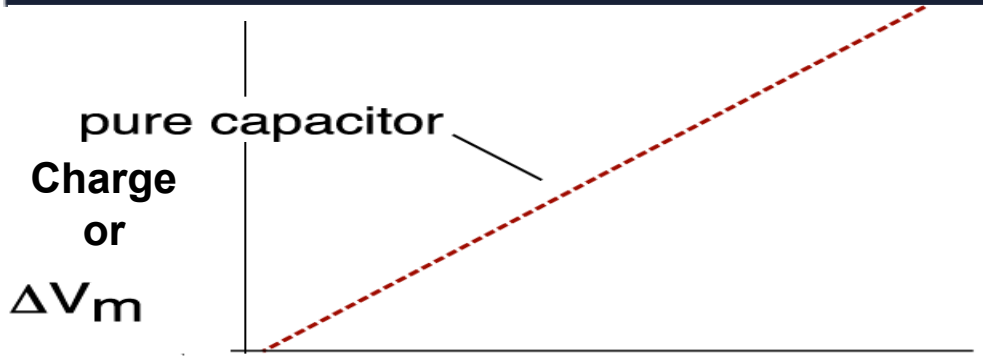


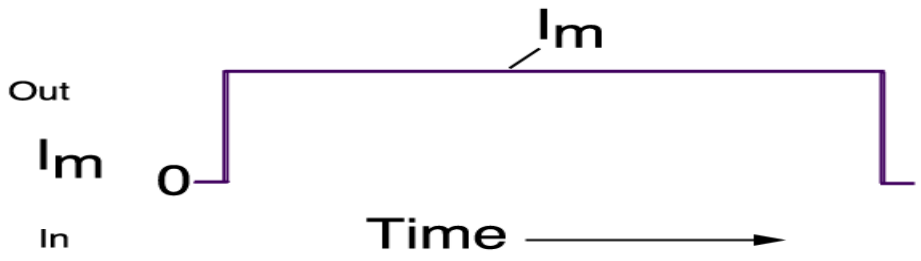
The figure shows a brief recap of the membrane as a capacitor. Ion channels are the resistance, the double lipid layer is the dielectric and the IF and EF the faces of the capacitor.

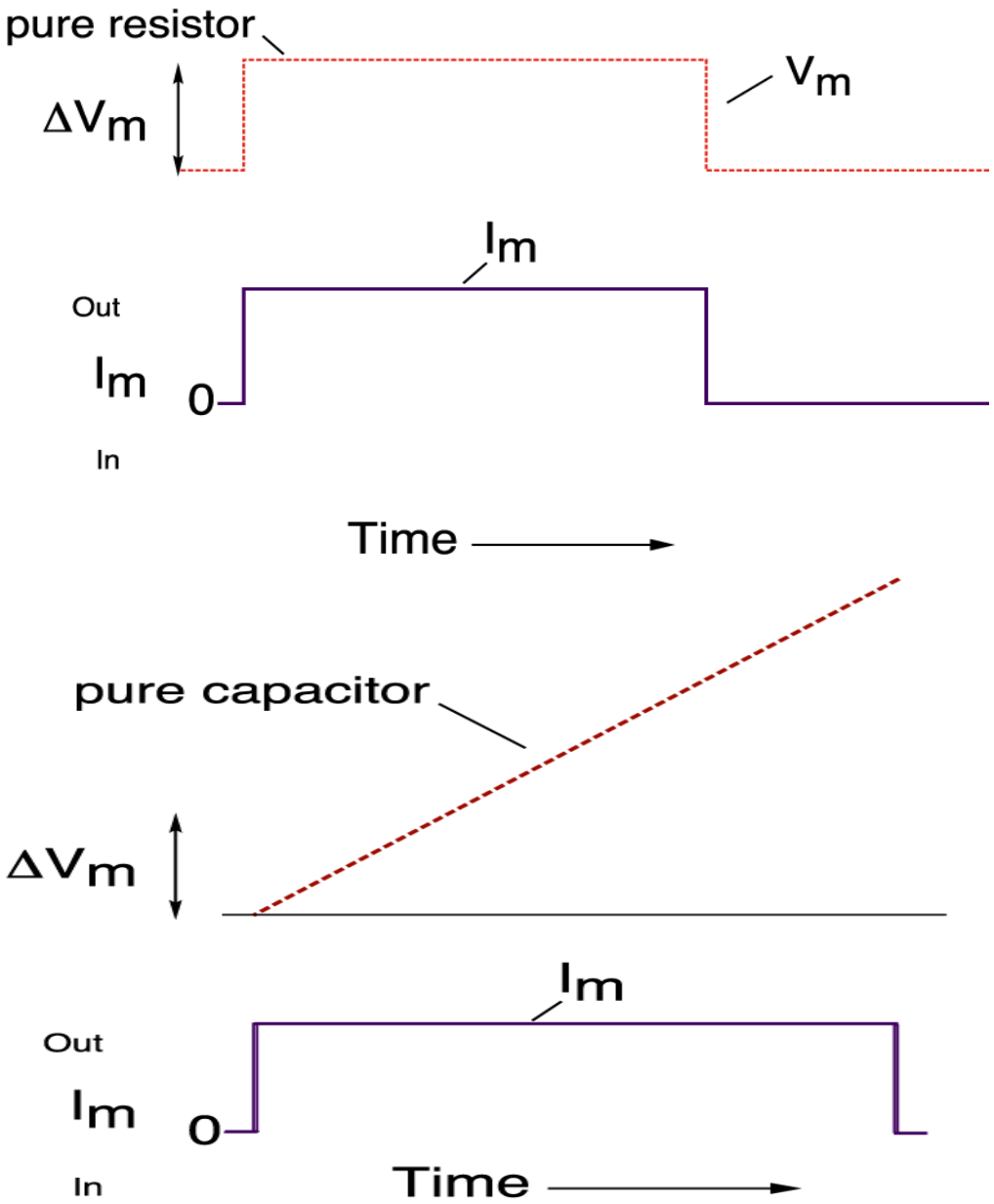
Current runs from the outside (the + in a battery) to the inside (the - in a battery) inward current. Part of the current (the potential energy Vm) is therefore used to charge the faces of the capacitor (a deposit for charges), while part is used to go through the resistance. Therefore, the membrane current (i_m) has two components:

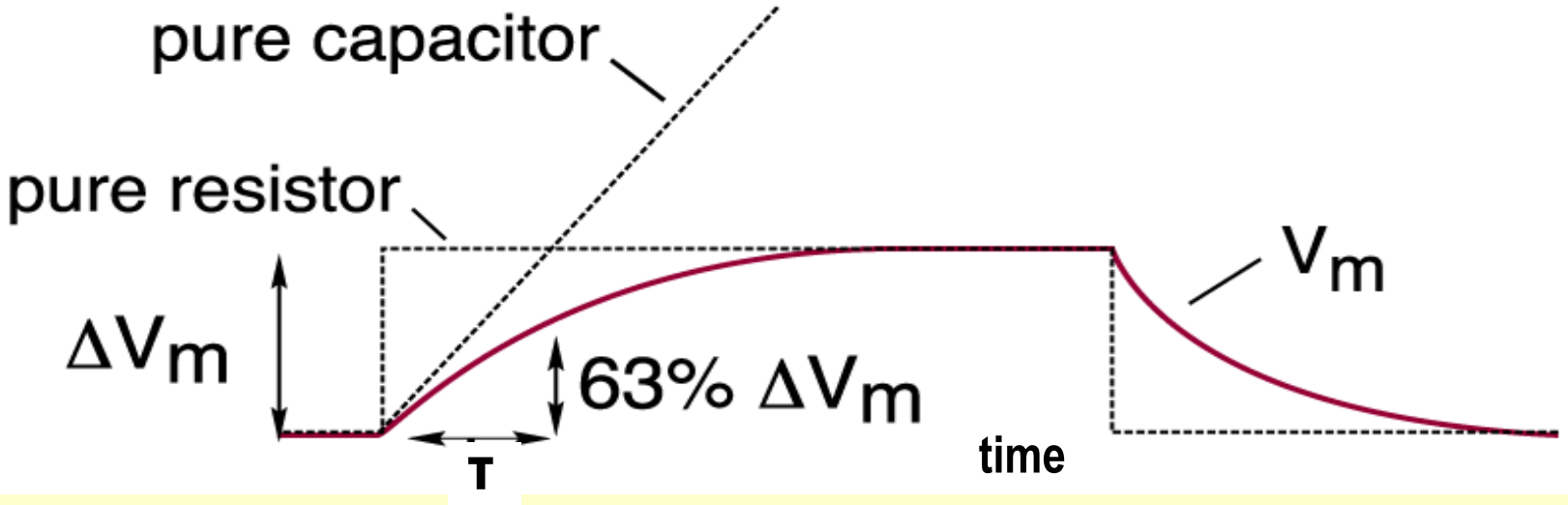
i) resistive(i_{mR}) and ii) capacitive (i_{mC})


How Capacitors Work Basic Configuration
Capacitor
Battery
©2007 HowStuffWorks


pure capacitor
Charge
or
ΔVm


Im
Out
Im
0
In
Time


pure resistor
ΔV_m
V_m
I_m
Out
I_m
0
In
Time
pure capacitor
ΔV_m
I_m
Out
I_m
0
In
Time

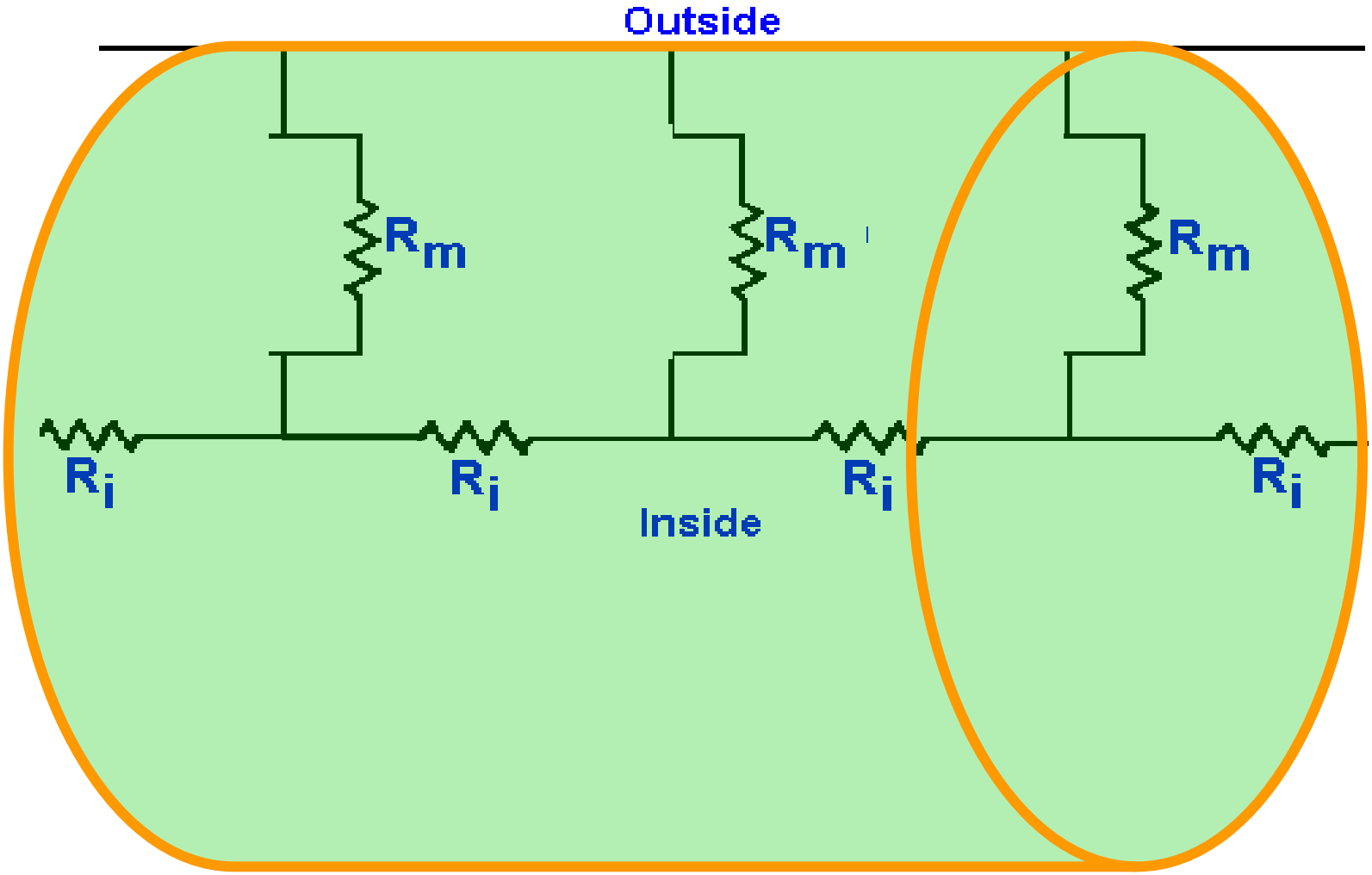


The membrane equivalent circuits has both a resistive and a capacitive component, ΔVm will be affected by both the dynamics. For this reason, ΔVm has an exponential dynamic

$$\Delta V_m(t) = I_m R_m (1 - e^{-t/\tau})$$

Vm at the time t (Vm(t)) depends from the maximum value that Vm reaches at the steady state ($V_{max}=I_m R_m$) and from the time constant τ. τ is the time interval needed for Vm to reach 63% of Vmax (is 37% less than Vmax). The time constant is proportional to the capacitance Cm and to the resistance Rm of the membrane.

τ = Rm x Cm

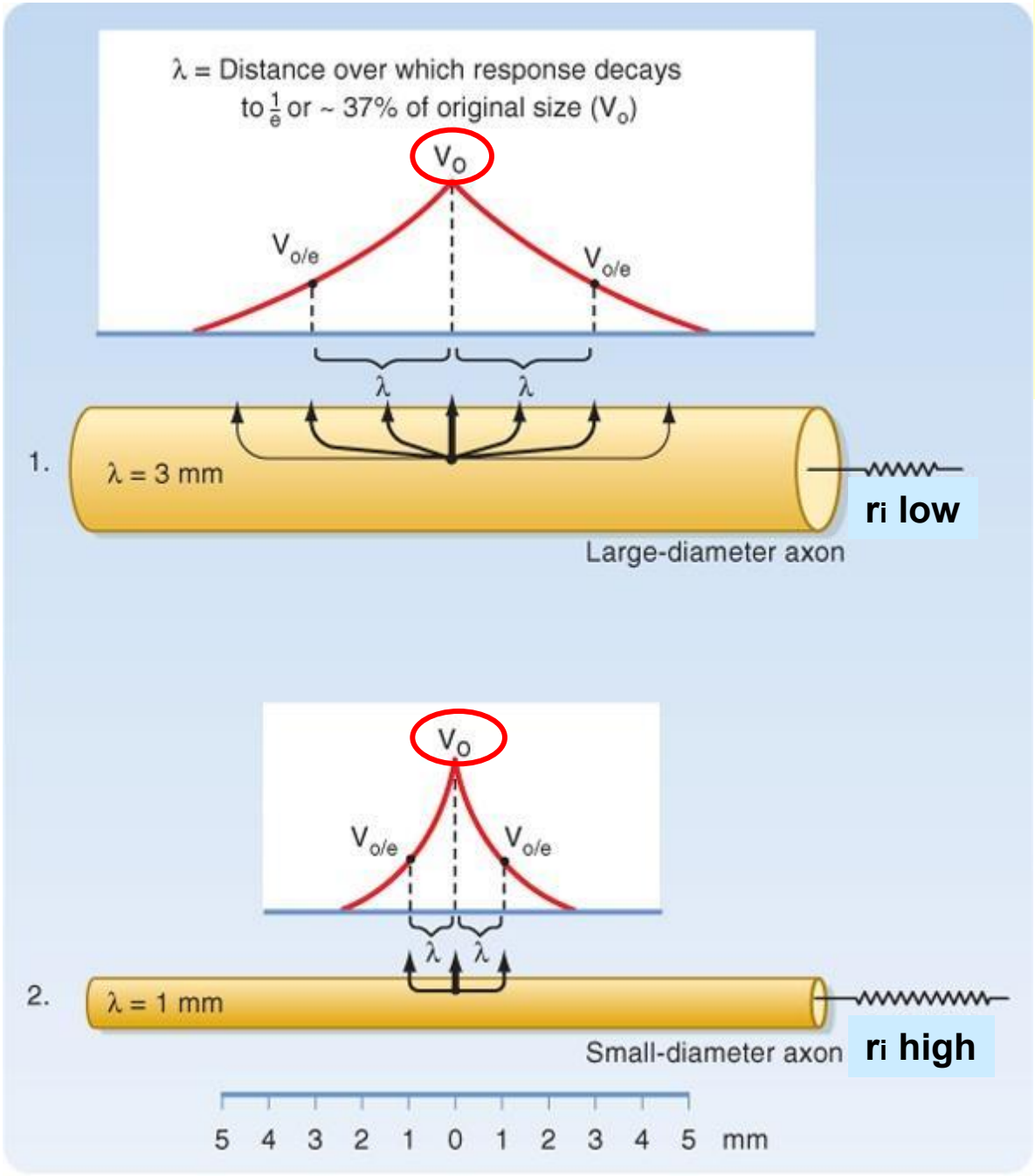


The conduction of the Action Potential faces two different kind of resistance: i) r_i, the internal resistance along the axon; ii) r_m, the resistance across the membrane.

How does the Vm varies along an axon (if we analyse a subthreshold voltage signal)?

Because of r_i it decreases in amplitude from the point it has initiated. If we inject a constant current for t >> τ the membrane capacitance is fully charged, so membrane potential reaches a steady value. The variation of the Vm with distance thus depends solely on the relative values of the membrane resistance in a unit length of dendrite, r_m (units of Ω • cm), and the axial resistance per unit length of dendrite, r_i (units of Ω/cm).

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



The value of the potential at a distance x (V_x) from the point of origin V_0 is =

$$V_x = V_0 [e^{(-x / \lambda)}]$$

where λ, the length constant, is

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

r_m = membrane resistance (per unit length)
r_i = axial (internal) resistance (per unit length)

In practical terms, λ is the distance between the point of origin of the potential (V_0) and the point where V_0 becomes 1/e = 1 / 2,718 = 37% of the original potential.

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

r_m = membrane resistance (per unit length)
r_i = axial (internal) resistance (per unit length)

$$r_m = \frac{R_m}{2\pi a}$$

$$r_i = \frac{R_i}{\pi a^2}$$

R_m = membrane resistivity ($\Omega \cdot cm^2$)
R_i = intracellular resistivity ($\Omega \cdot cm$)
a = axon radius

$$\lambda = \sqrt{\frac{R_m \cdot a}{2R_i}}$$

The general form expresses λ in terms of membrane and axial resistances, while the geometric form relates λ to axon radius and tissue properties.

The efficiency of electrotonic conduction, that depends on time and length constant, **influences temporal and spatial summation**. It also influences action potentials conduction.

It can be very useful to consider the length constant in the conductance of an action potential in a myelinated axon.
In mammals, the length constant for axons range between 0.5 mm for unmyelinated axons to 1-3 mm for the myelinated ones.

Using the previous formula, we can calculate at what distance X the original action potential (amplitude = V_0) produces still a depolarization of 15mV (necessary to reach the threshold)(V_x)

For a large mylenited axon (λ = 3,0 mm):

$$V_x = V_0 [e^{(-X / \lambda)}]; \quad \text{replacing: } 15\ mV = 100\ mV [e^{(-X / \lambda)}]$$

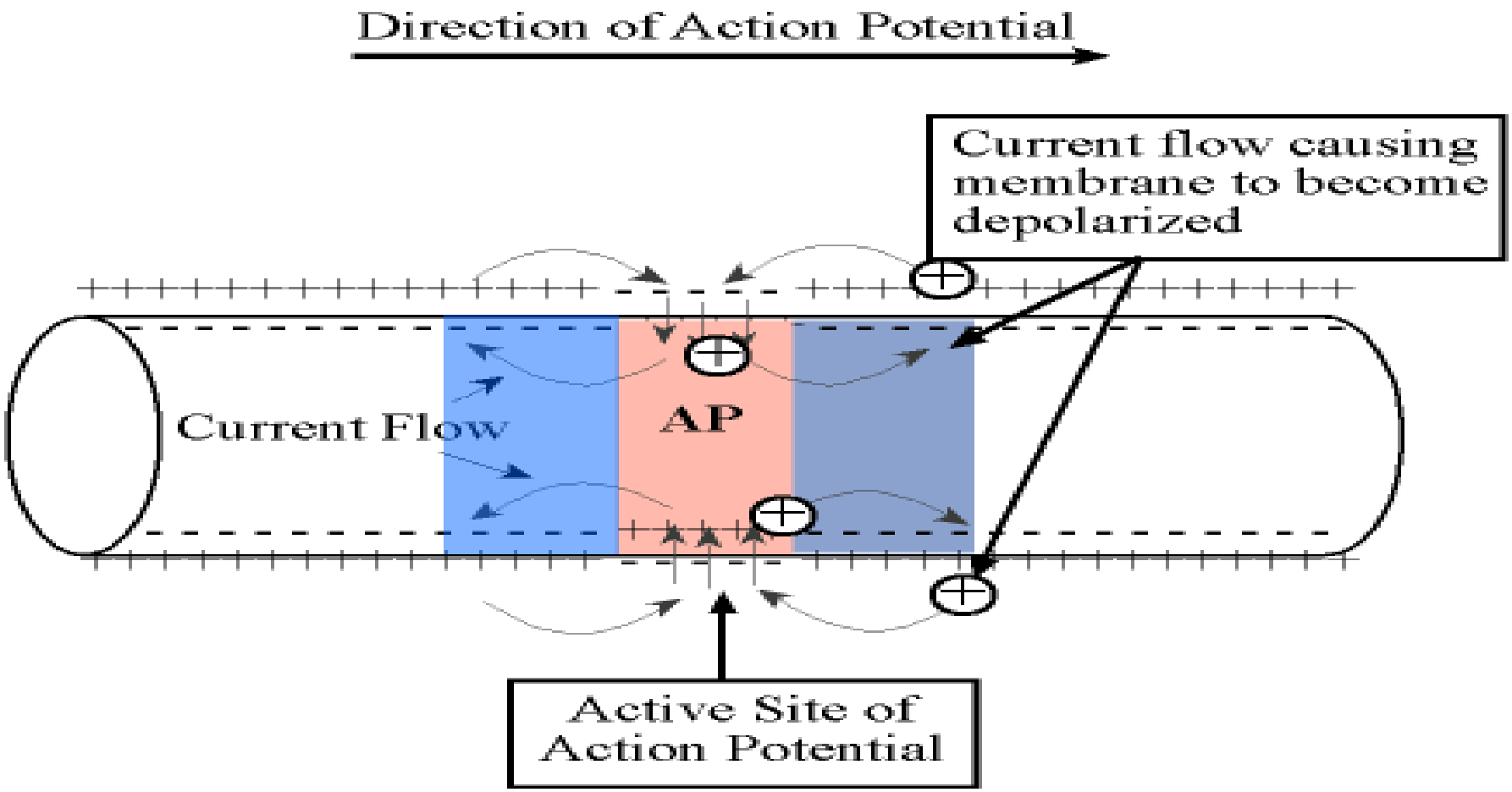
$$15 / 100 = e^{(-X / \lambda)} \rightarrow -X / \lambda = \ln 0{,}15$$

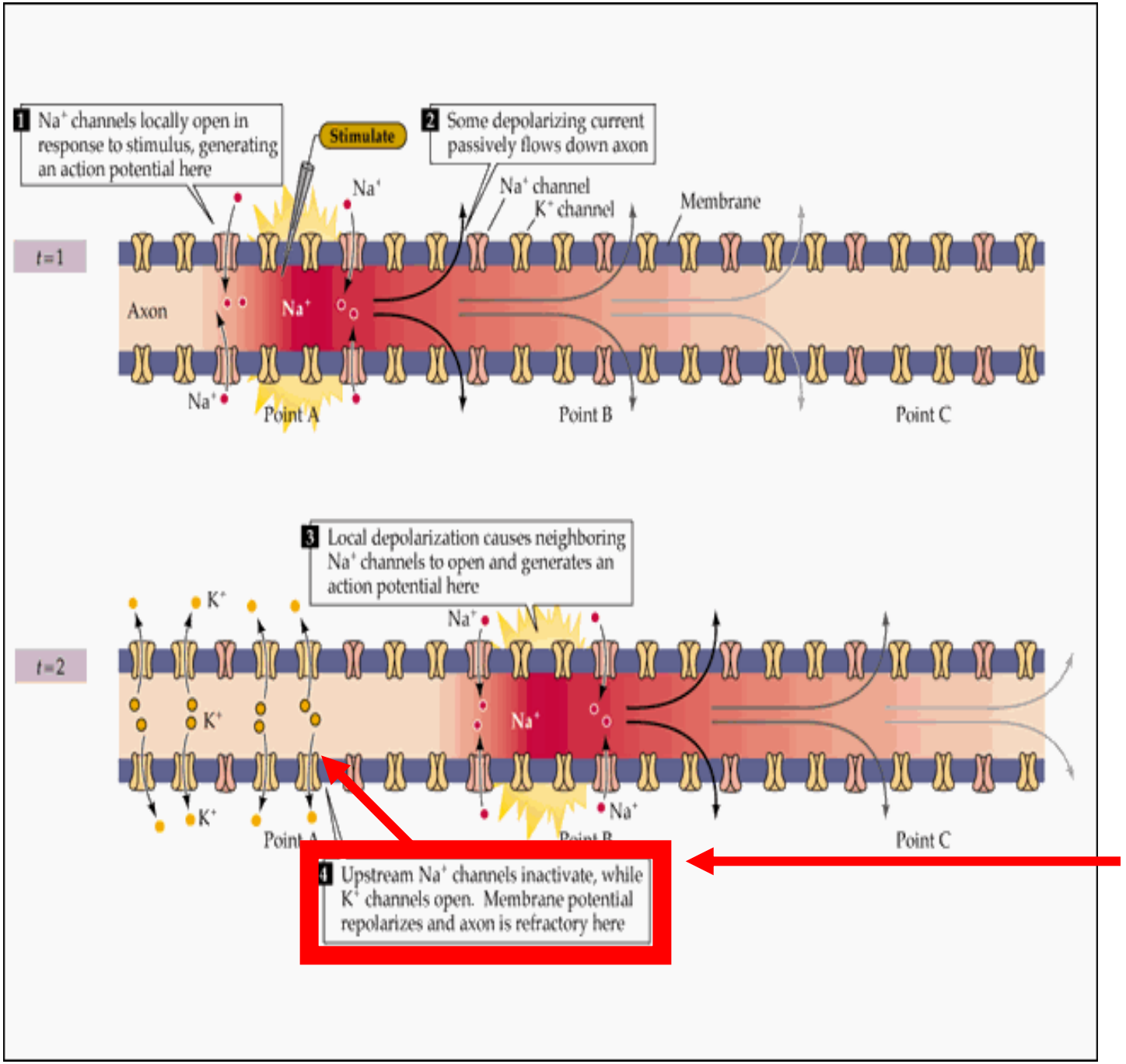
$$-X / 3{,}0 = -1{,}90; \text{ ergo: } X = 5{,}7\ mm$$

Considering that the average internodal distance between two nodes of Ranvier is about 2 mm, the previous calculation tells us that V_0 was large enough to depolarize almost 3 nodes of ranvier from the origin of the action potential.

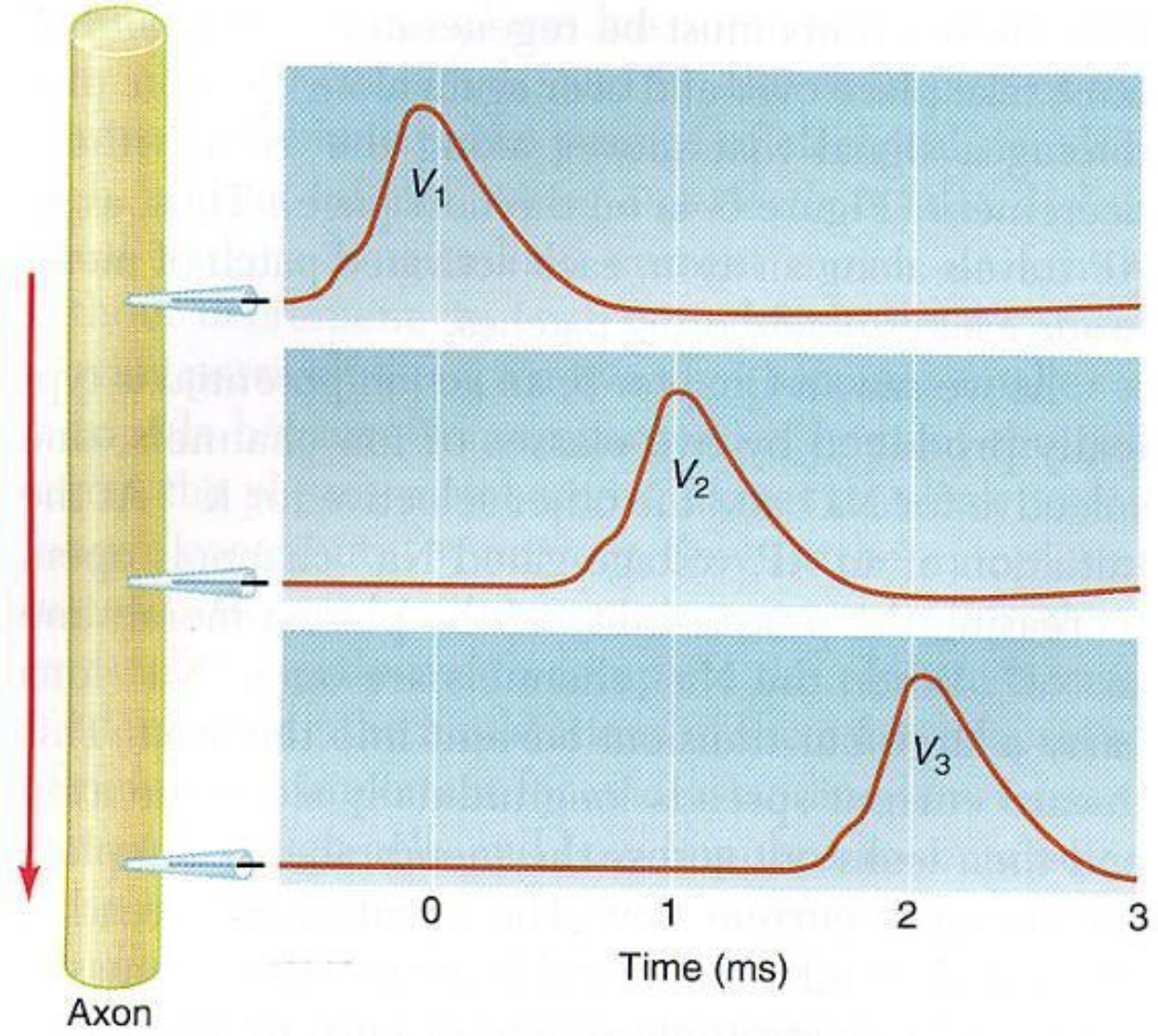
This works as a safety measure to ensure the propagation of the action potential

The local depolarization spreads passively to adjacent areas




1 Na+ channels locally open in response to stimulus, generating an action potential here
Stimulate
2 Some depolarizing current passively flows down axon
Na+
Na+ channel
K+ channel
Membrane
t = 1
Axon
Na+
Na+
Point A
Point B
Point C
3 Local depolarization causes neighboring Na+ channels to open and generates an action potential here
t = 2
K+
K+
K+
Na+
Na+
Point A
Point C
4 Upstream Na+ channels inactivate, while K+ channels open. Membrane potential repolarizes and axon is refractory here

The action potential is transmitted in a non-decremental way, because is regenerated in every spot in a non-myelinated axon, and in the Ranvier Node in a myelinated axon.



Passive Spread and Axon Diameter

- **Current Flow Between Adjacent Segments**

An action potential in one membrane segment generates a **local depolarizing current** that spreads to adjacent regions.
This current gradually brings the next segment to threshold.

- **Role of Axial Resistance (r_i)**

From Ohm's law (I = V/R):
↑ r_i → ↓ current flow along the axon
↓ current → slower depolarization of adjacent segments
High internal resistance slows conduction

- **Role of Membrane Capacitance (C_m)**

The membrane behaves as a **capacitor**
More capacitance → more charge required to change Vm
Higher C_m slows voltage changes

- **Time and Passive Spread**

The speed of passive voltage spread depends on:

$$\text{Speed} \propto \frac{1}{r_i \cdot C_m}$$

Lower r_i and lower C_m → f

- **Effect of Axon Radius (r)**

$r_i \propto 1/r^2$ → larger axon → much lower internal resistance

$C_m \propto r$ → larger surface → higher capacitance

- Length Constant (λ)

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

Larger radius → ↓ r_i → ↑ λ

Voltage spreads farther along the axon

<u>Larger axons conduct faster because they have lower axial resistance and a larger length constant.</u>

Myelination and Conduction Velocity

- **Second Strategy to Increase Conduction Speed**

A second major mechanism to increase conduction velocity is the **formation of a myelin sheath** around the axon.

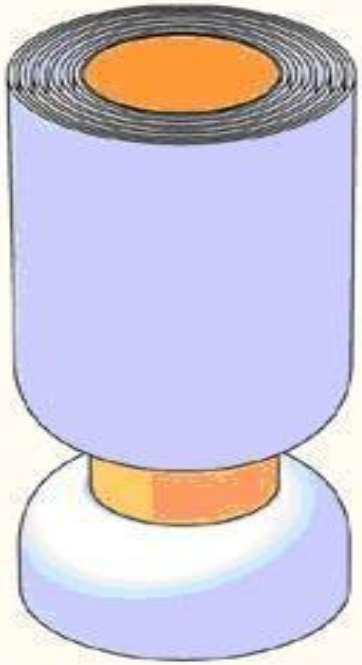
- **Effect on Membrane Properties**

Myelin acts as an electrical insulator:
Capacitance (C_m) decreases (thicker insulation → less charge needed)
Membrane resistance (r_m) increases (less current leakage)
This reduces the time required to change membrane voltage

- **Functional Consequences**

↓ C_m → faster charging of the membrane
↑ r_m → current remains inside the axon and travels farther
Overall: **faster passive spread of depolarization**

Myelination is **more efficient** because it:
decreases C_m
increases r_m

Axons from skin	Aα	Aβ	Aδ	C
Axons from muscles	Group I	II	III	IV
				
Diameter (μm)	13–20	6–12	1–5	0.2–1.5
Speed (m/sec)	80–120	35–75	5–30	0.5–2
Sensory receptors	Proprioceptors of skeletal muscle	Mechanoreceptors of skin	Pain, temperature	Temperature, pain, itch

Axons can be either myelinated or unmyelinated. Myelinated axons are ensheathed along their entire length. The axon caliber (diameter) in mammalian PNS ranges from 0.1 μm to 20 μm, with unmyelinated axons being less than 2 μm and myelinated axons being more than 1–2 μm in diameter. In the human CNS, almost all axons with diameters greater than 0.2 μm are myelinated.

In cross section, the myelinated axon appears as a nearly circular profile surrounded by a spirally wound multilamellar sheath. Amazingly, a large myelinated axon may have up to 250 to 300 turns of myelin wrapping around it.

The ratio between axon diameter and that of the total nerve fiber (axon and myelin) is 0.6–0.7, a ratio that is well maintained regardless of the axon caliber.

Between two adjacent myelin segments, there are approximately 1 μm long gaps called nodes of Ranvier. At the nodes, the axon is exposed to the extracellular space. They prevent the action potentials to die out. The nodal mb is rich in voltage-gated Na channels and thus can generate an intense depolarizing inward Na current.
This organization is favourable also from the metabolic point of view because current only flows at the nodes and Na-K-pumps spend less energy to restore chemical gradient.

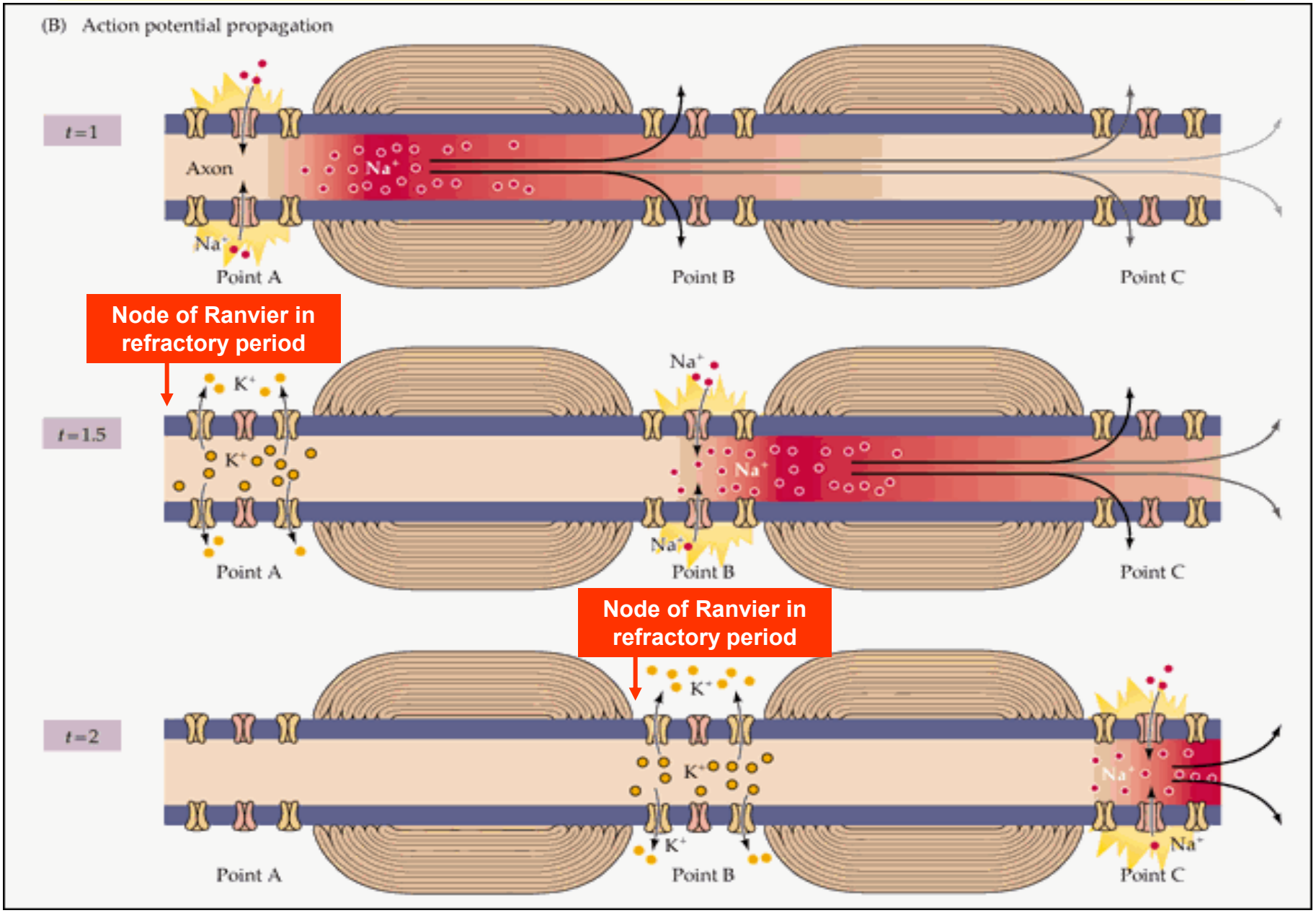
	Myelin		
Substance	Human	Bovine	Rat
Protein	30.0	24.7	29.5
Lipid	70.0	75.3	70.5

Myelin composition in mammals

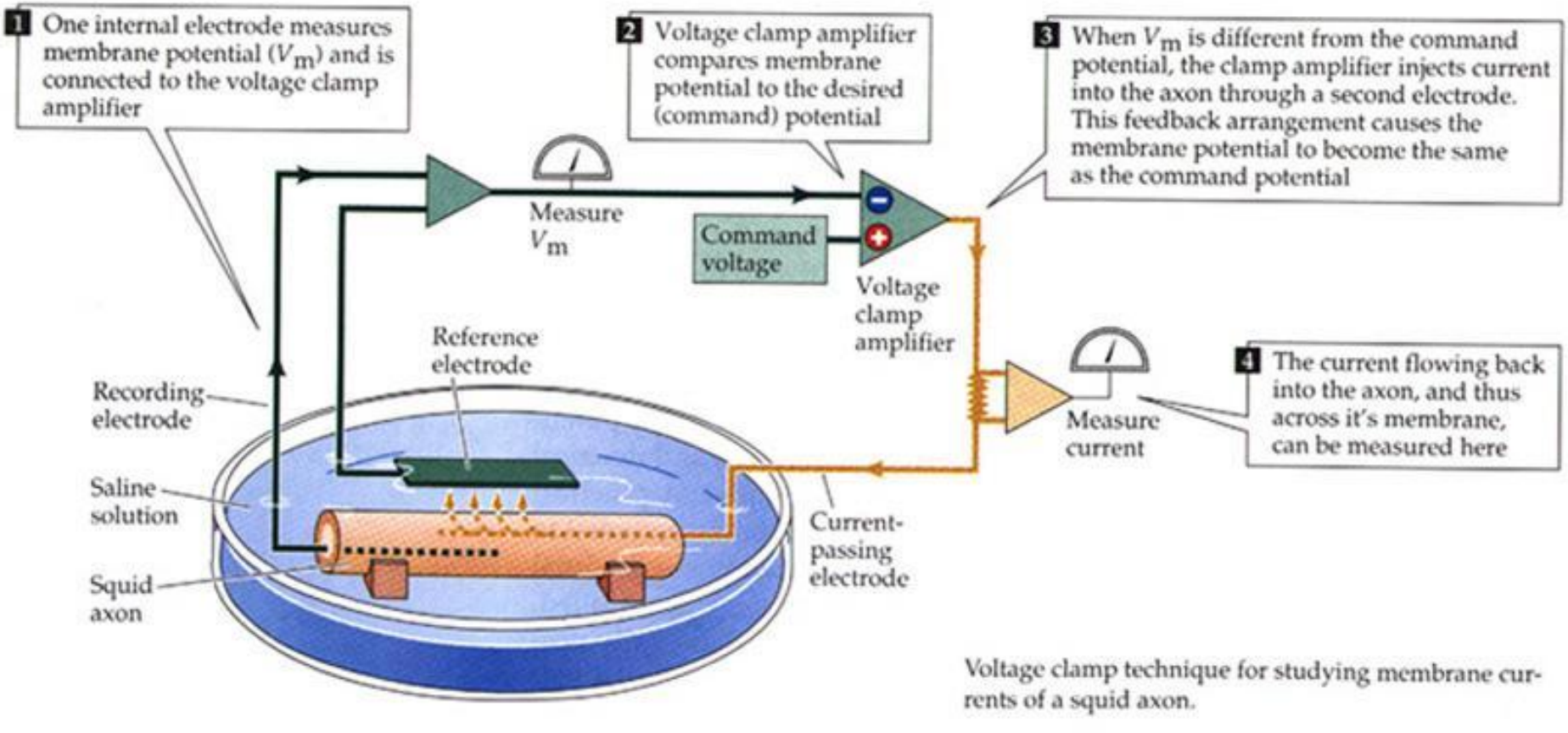
Lipids: cholesterol, phospholipid and galactolipid. The composition of myelin in the CNS is similar to the one in the PNS.

Proteins: two main groups that differ between CNS and PNS. Within the CNS: i) the proteolipid protein (PLP); ii) the myelin basic protein (MBP). Within the PNS: i) the major peripheral nerve protein (P0); ii) a smaller concentration of PLP

Saltatory conduction (slowing down at the Ranvier node)



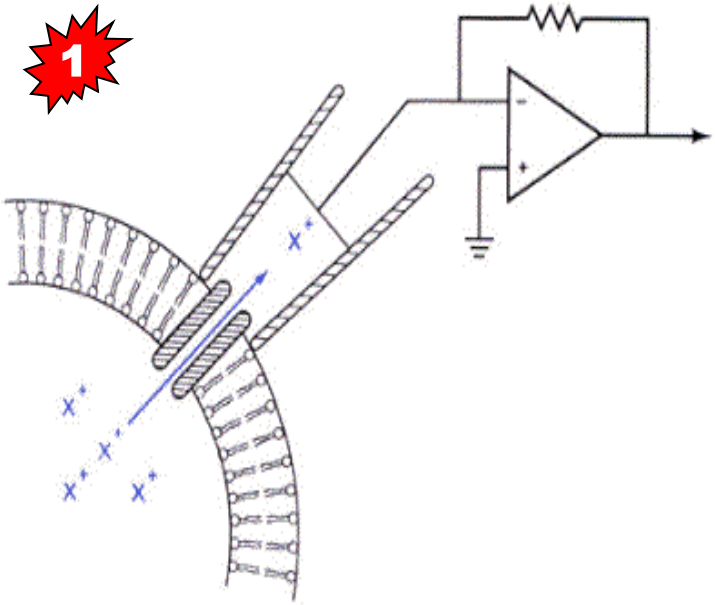
https://www.khanacademy.org/science/biology/human-biology/neuron-nervous-system/v/saltatory-conduction-neurons



Voltage clamp technique for studying membrane currents of a squid axon.

Dale Purves,1997,Neuroscience,Sinauer Associates, Inc., P.53.

1



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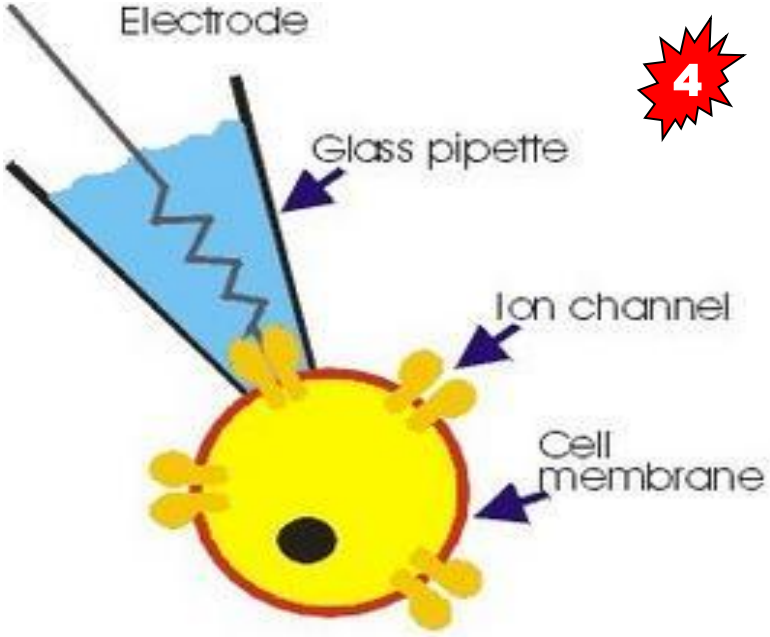
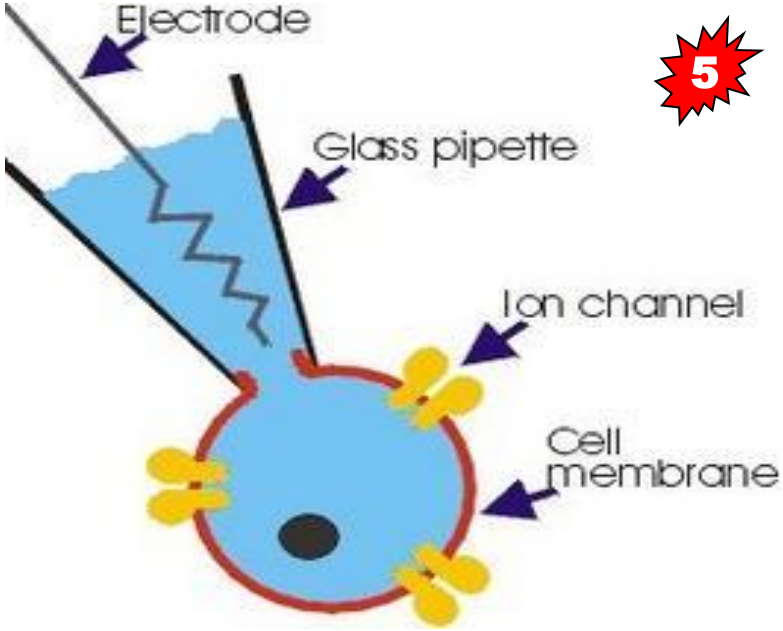

Electrode
Glass pipette
Ion channel
Cell membrane

4


Electrode
Glass pipette
Ion channel
Cell membrane

5

Voltage-gated ion channels

Calcium-Activated Potassium Channels
CatSper and Two-Pore Channels
Cyclic Nucleotide-Regulated Channels
Inwardly Rectifying Potassium Channels
Transient Receptor Potential Channels
Two-P Potassium Channels
Voltage-Gated Calcium Channels
Voltage-Gated Potassium Channels
Voltage-Gated Sodium Channels

Most neurons contain voltage-gated Ca channels that open in response to depolarization and help depolarizing the cell (there is a strong electrochemical gradient for Ca, Eca=123mV)

Some neurons have voltage gated Cl channels that contribute to mb repolarization

Many neurons have cation channels that are activated in response to hyperpolarization. These hyperpolarization-activated cation (or HCN) channels are permeable to both K+, and Na+, and have a reversal potential around –40 to –30 mV. As a result, they give rise to an inward depolarizing current, referred to as Ih, when the membrane repolarizes to negative resting potentials or becomes hyperpolarized during synaptic inhibition

There are different kind of voltage-activated K channels:(1) The slowly activating K+ channel described by Hodgkin and Huxley is called the delayed rectifier. (2) The calcium-activated K+ channel is activated by an increase in intracellular Ca2+ when nearby voltage – gated Ca2+ channels open in response to depolarization. One subclass of calcium-activated K+ channels is voltage-dependent. The binding of Ca2+ to a site on the cytoplasmic surface of the channel shifts its voltage-gating to allow the channel to open at more negative potentials. (3) The *A-type K+ channel* is activated rapidly by depolarization, it also inactivates rapidly if the depolarization is prolonged. (4) The M-type K+ channel requires only small depolarizations from the resting potential to open; however, it activates very slowly, requiring tens of milliseconds to open. One distinctive feature of the M-type channel is that it is closed by a neurotransmitter, acetylcholine.

There are also at least five major types of voltage-gated Ca2+ channels and eight types of voltage-gated Na+ channels are expressed in the nervous system.

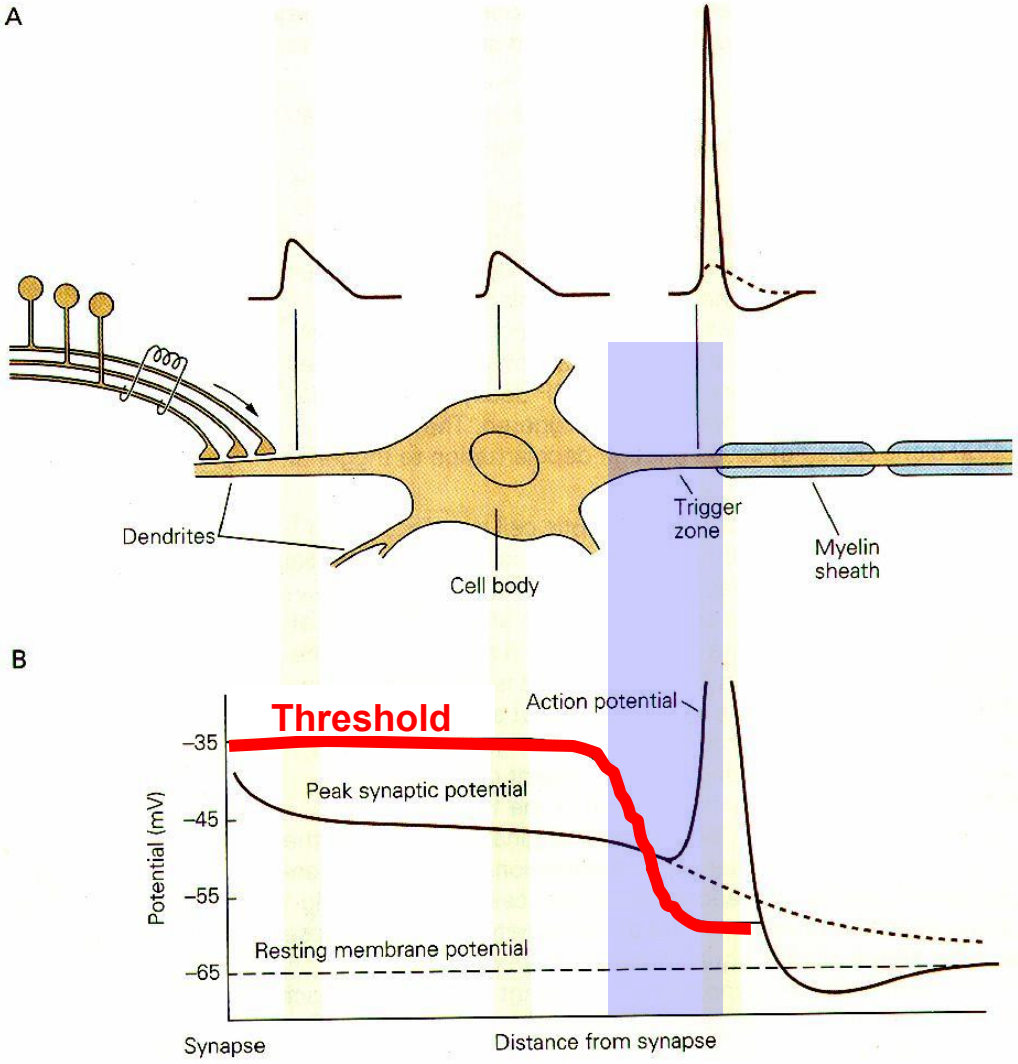
In a typical neuron the opening and closing of certain voltage-gated ion channels can be modulated by various cytoplasmic factors.

Calcium concentration is one important cytoplasmic factor that modulates ion channel activity. This is because concentration of free Ca++ in the cytoplasm is very low (10^{-7}M) and when voltage activated Ca channels open up its concentration may change many fold.

Calcium activated voltage sensitive K channels may open.

Changes in the intracellular concentration of Ca2+ can also influence a variety of cellular metabolic processes, including neurotransmitter release and gene expression.

The activity of voltage-gated channels can also be regulated by the action of neurotransmitters through the recruitment of second-messenger pathways. These pathways typically affect the kinetics or voltage sensitivity of channel gating



The action potential typically is generated at the axon hillock.

This region has the lowest threshold because of the number of Voltage-gated Na channels. It also has other voltage gated channels that are very sensible to relatively small deviations from the Vr (including M-type and A-type K channels or low voltage activated Ca channels).

Conduction of action potential is function of voltage gated Na channels and K channels (as in squid axon).

Moreover, both central and peripheral myelinated axons have fairly high densities of K+ channels under the myelin sheath near the two ends of each internodal segment. The normal function of these K+ channels is to suppress any action potential that may be generated by axon membrane under the myelin sheath. In demyelinating diseases these channels become exposed and thus inhibit the ability of the bare axon to conduct action potentials

Voltage-gated channels are transmembrane proteins controlling the ion traffic across the membrane.

We can divide the class of the voltage-gated channels into two large classes:

1) cation channels;

2) anion channels.

CATION CHANNELS

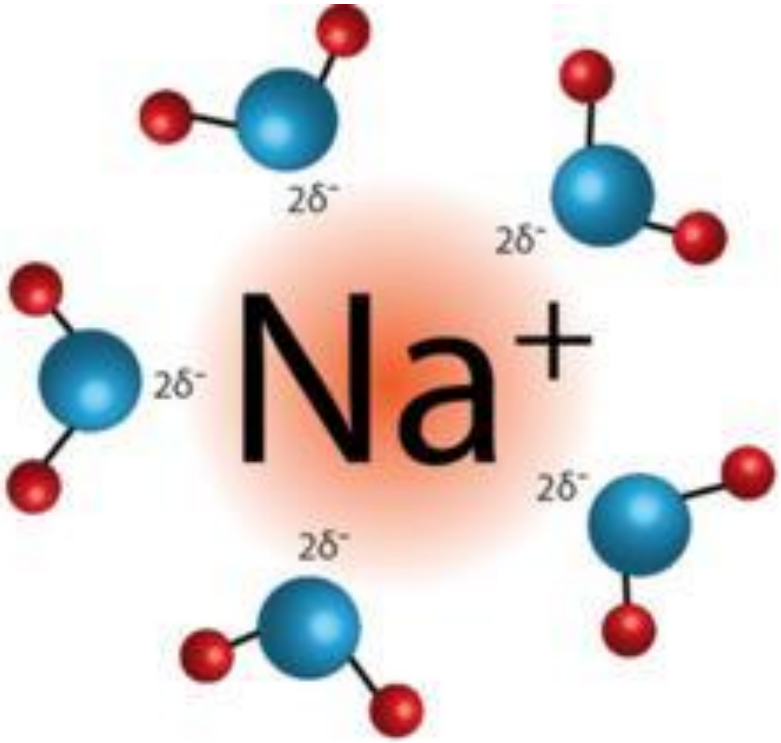
The main function of cation channels is generation and propagation of the cell bioelectricity. The main cation channels are:

A) Na^+ voltage-gated channels. Mostly involved in the process of membrane depolarization.

B) Ca^{2+} voltage-gated channels. Mostly involved in mediating specific cell responses.

C) K^+ voltage-gated channels. Mostly involved in the fine tuning of membrane potentials.

Slightly positive hydrogen are attracted to chlorine anions



Slightly negative oxygen are attracted to sodium cations

Because of their electric charge, ions interact with the polar molecules of the solvent (solvation). When the solvent is water, the process is called hydration.

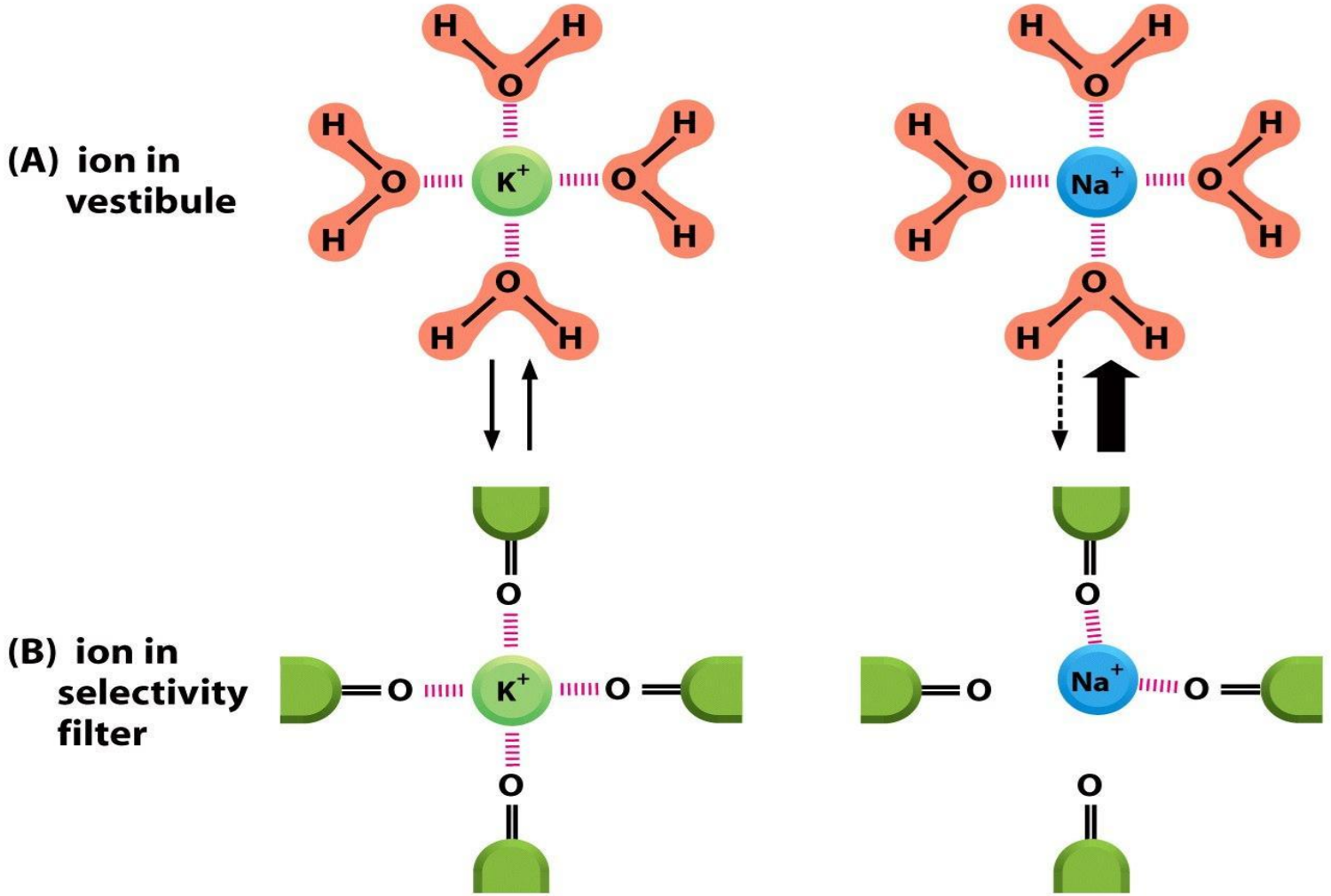
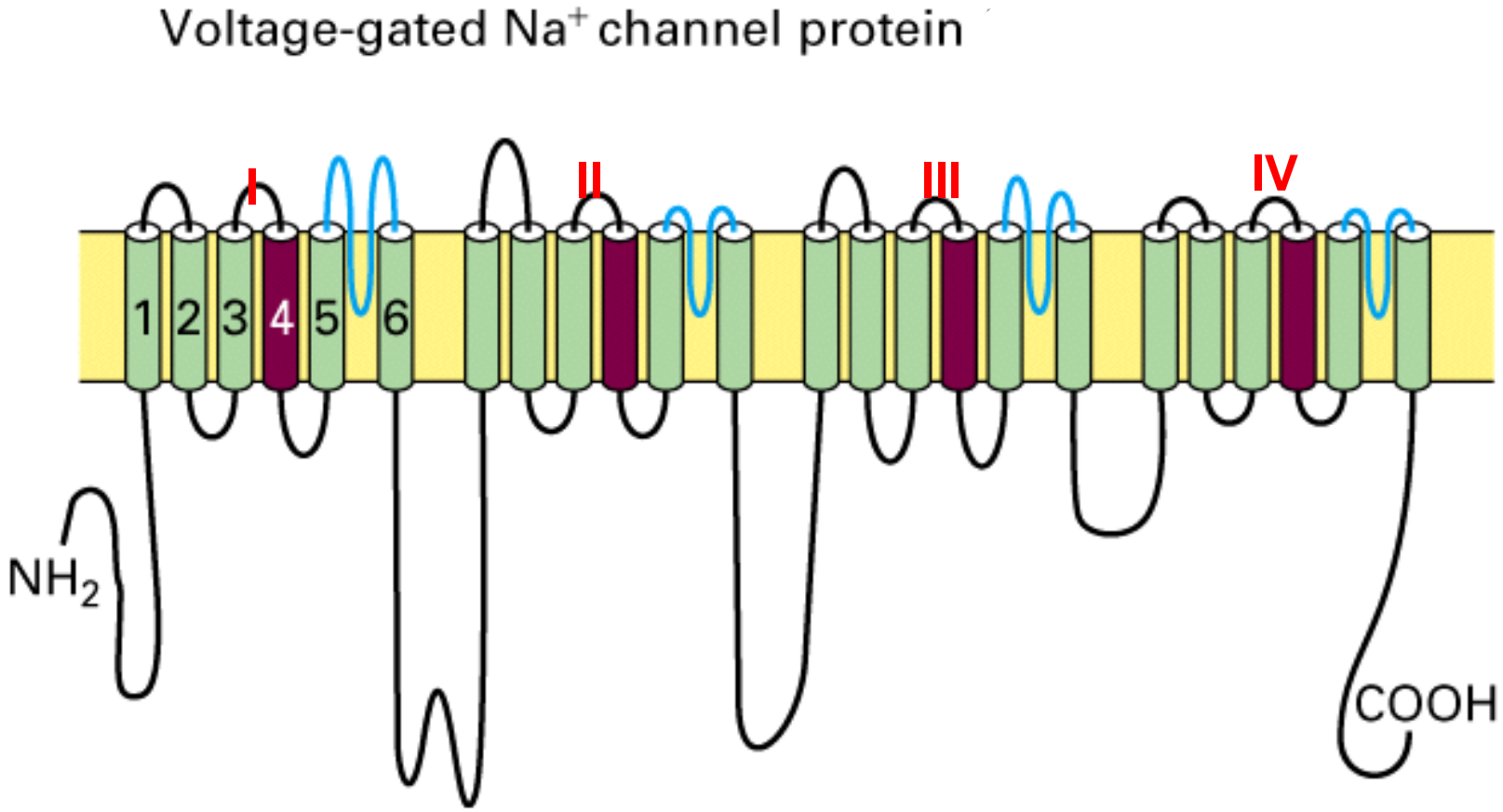
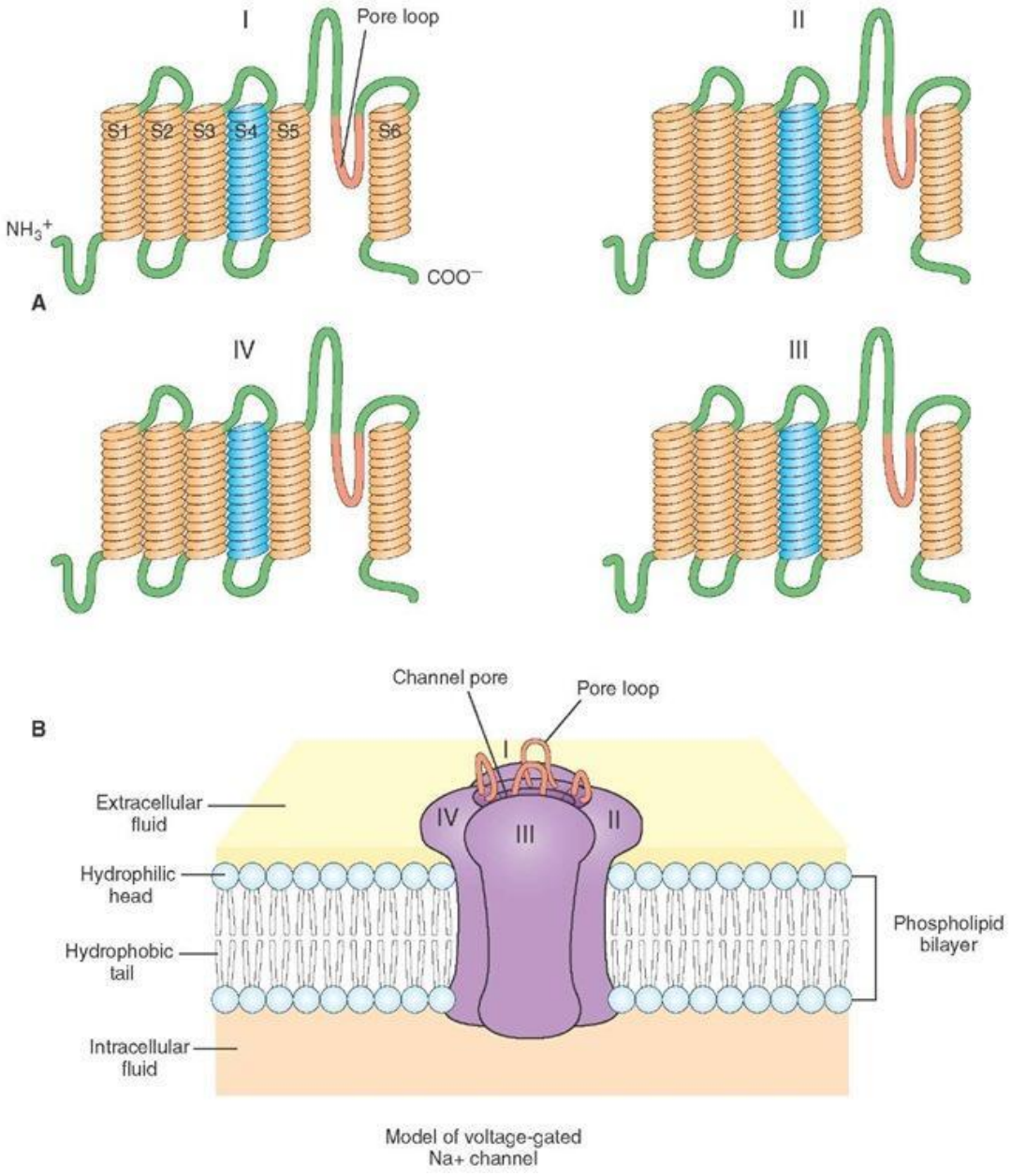


Figure 11-24 Molecular Biology of the Cell 5/e (© Garland Science 2008)

Ions lose their hydration while entering a channel. Cation channels use the C=O bond to filter for cations (Especially the interaction between the O_2 and the ion). Na does not enter K channels because Na has a smaller radium and its interaction with water is stronger. Furthermore, its small diameter precludes the interaction with O2 in the selectivity filter. Na channels are larger than K and allow the passage of one Na still hydrated with two molecules of water. This is energetically favourable



Voltage-gated sodium channels (Nav) are formed from a single polypeptide (α-subunit) that consists of 4 domains (I–IV, each with 6 transmembrane segments). Of each domain: the 4th segment (S4) contains positively charged lysine and arginines, that are primarily responsible for voltage sensing, whilst S5 and S6 segments form the loop of the channel pore region. Voltage-gated sodium channels associate single transmembrane proteins (called β-subunits, not shown in the Figure) that have an immunoglobulin-like extracellular domain and regulate Nav channels.



Model of voltage-gated Na+ channel

The four domains pair their voltage-sensitive segments (S4) and segments that build the wall of the pore (S5, S6).

Voltage-dependent Na channels

Table 1 Voltage-gated sodium channel nomenclature, chromosomal location and tissue distribution

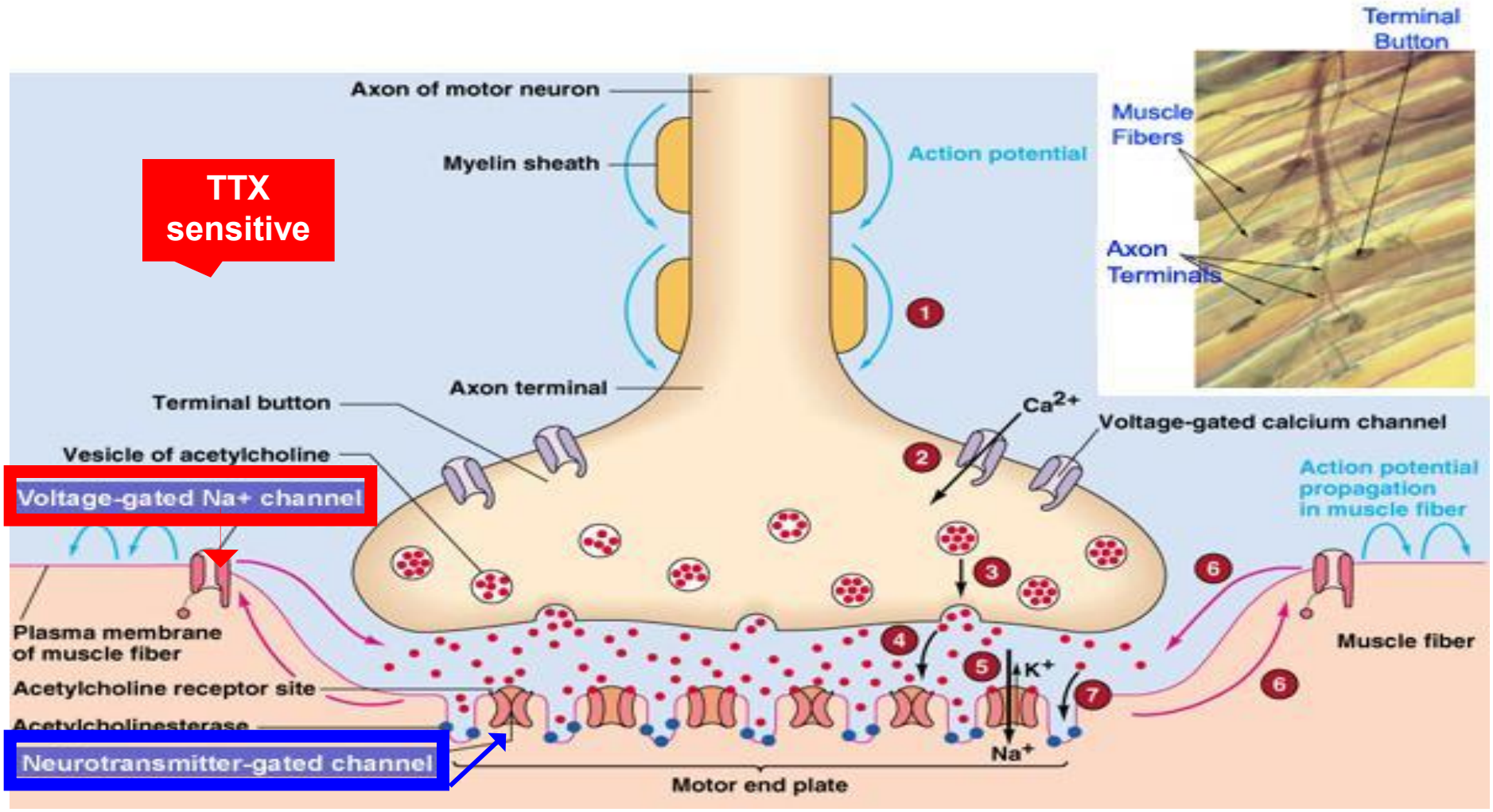
Channel nomenclature	*Gene*	*Chromosomal location (human)*	*Tetrodotoxin sensitivity*	*Major tissue expression*	*Effect of mutation*
Nav1.1	*SCN1A*	2q24	✓	CNS, PNS	Epilepsy
Nav1.2	*SCN2A*	2q23–24	✓	CNS, PNS	Epilepsy
Nav1.3	*SCN3A*	2q24	✓	CNS, PNS	None reported
Nav1.4	*SCN4A*	17q23–25	✓	Skeletal muscle	Myotonia, periodic paralysis
Nav1.5	*SCN5A*	3p21	X	Heart	Long QT, Brugada syndrome, progressive familial heart block
Nav1.6	*SCN8A*	12q13	✓	CNS, PNS	Cerebellar atrophy
Nav1.7	*SCN9A*	2q24	✓	PNS (SNS and PAs)	Increased and decreased pain sensitivity
Nav1.8	*SCN10A*	3p21–24	X	PNS (PAs)	None reported
Nav1.9	*SCN11A*	3p21–24	X	PNS (PAs)	None reported
Nax	*SCN6/7A*	2q21–23	Non-functional	Glia	–

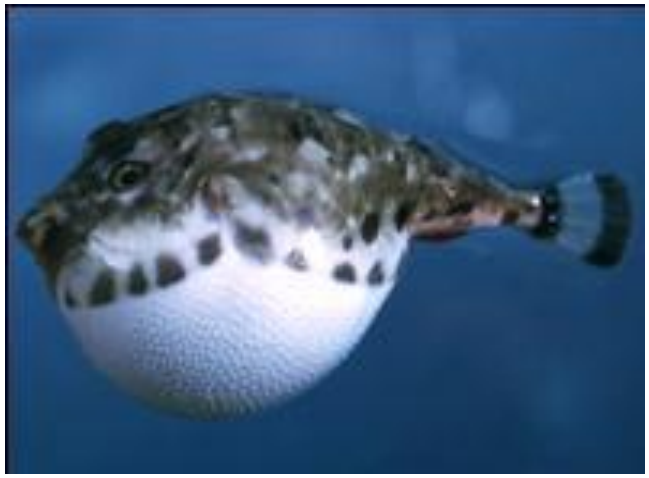
CNS, central nervous system; PAs, primary afferent neurones; PNS, peripheral nervous system; SNS, sensory nervous system.

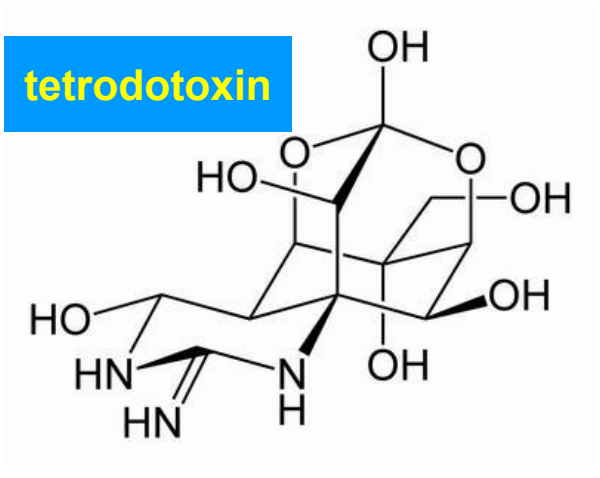
TTX-resistant

There are 2 distinct types of voltage-gated sodium channels present in humans: 1) the tetrodotoxin-sensitive voltage-gated sodium channel (TTX-S Na+ channel); 2) the tetrodotoxin-resistant voltage-gated sodium channel (TTX-R Na+ channel).
TTX binds to TTX-S Na+ channels with a nanomolar binding affinity, while the TTX-R Na+ channels bind TTX with low micromolar affinity. Cells containing TTX-R Na+ channels are located primarily in cardiac tissue, while cells containing TTX-S Na+ channels dominate the rest of the body.

The Neuromuscular Junction







The family of puffer fish (Tetraodontidae) has more than 120 species. Puffer fish use their highly elastic stomachs to quickly ingest huge amounts of water to turn themselves into a virtually inedible ball several times their normal size. Some species also have spines on their skin to make them even less palatable. Almost all puffer fishes contain in the skin, liver, intestine and gonads tetrodotoxin (TTX), a substance that makes them foul tasting and is often lethal. To humans, TTX is deadly since it blocks action potentials in nerves by binding to the voltage-gated fast Na+ channels in nerve cell membranes, essentially preventing any affected nerve cells from firing. The binding site of this toxin is located at the pore opening of the voltage-gated Na+ channel.

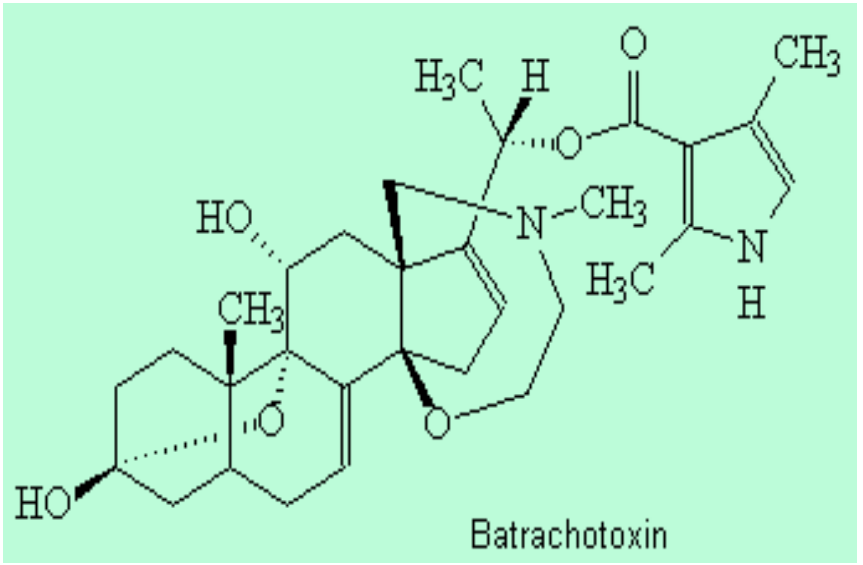
In Japan, the meat of some puffer fish is considered a delicacy, called fugu, which only licensed chefs, trained for almost 3 years, are allowed to prepare. Since TTX is apparently produced by Vibrio bacteria within the digestive system, the chef's main skill is to remove viscera from fish without contaminating the meat.

Captain James Cook and his German naturalists J.R. Forster junior and J.A.G. Forster were the first to record cases of TTX poisoning during the second Cook's voyage (1774): his crew ate some local tropic fish, then fed the remains to the pigs kept on board. The crew experienced numbness and shortness of breath, while all the pigs died.

Table 3. Clinical grading system in tetrodotoxication according to
A. Fukuda and A.Tani, 1941

Degree	Symptoms
First	Oral numbness and paraesthesia, sometimes accompanied by gastrointestinal symptoms (nausea[a)])
Second	Numbness of face and other areas, advanced paraesthesia, motor paralysis of extremities, incoordination, slurred speech, but still normal reflexes
Third	Gross muscular incoordination, aphonia, dysphagia, dyspnoea, cyanosis, drop in blood pressure, fixed/dilated pupils, precordial pain, but victims are still conscious
Fourth	Severe respiratory failure and hypoxia, severe hypotension, bradycardia, cardiac arrhythmia, heart continues to pulsate for a short period

Local anesthetics such as lidocaine and procaine prevent the generation of action potentials by inhibiting voltage-gated Na+ channels of sensory neurons.



The golden poison-dart frog (Phyllobates terribilis), endemic to the Pacific coast of Colombia, is a social animal, often considered innocuous, due to their small size and bright colours. However, wild specimens are lethally toxic and can kill humans who touch them directly. When stressed or scared they release a colourless or milky secretion containing Batrachotoxin (BTX) from skin glands. BTX is an extremely potent cardiotoxic and is the most potent alkaloid neurotoxin known.

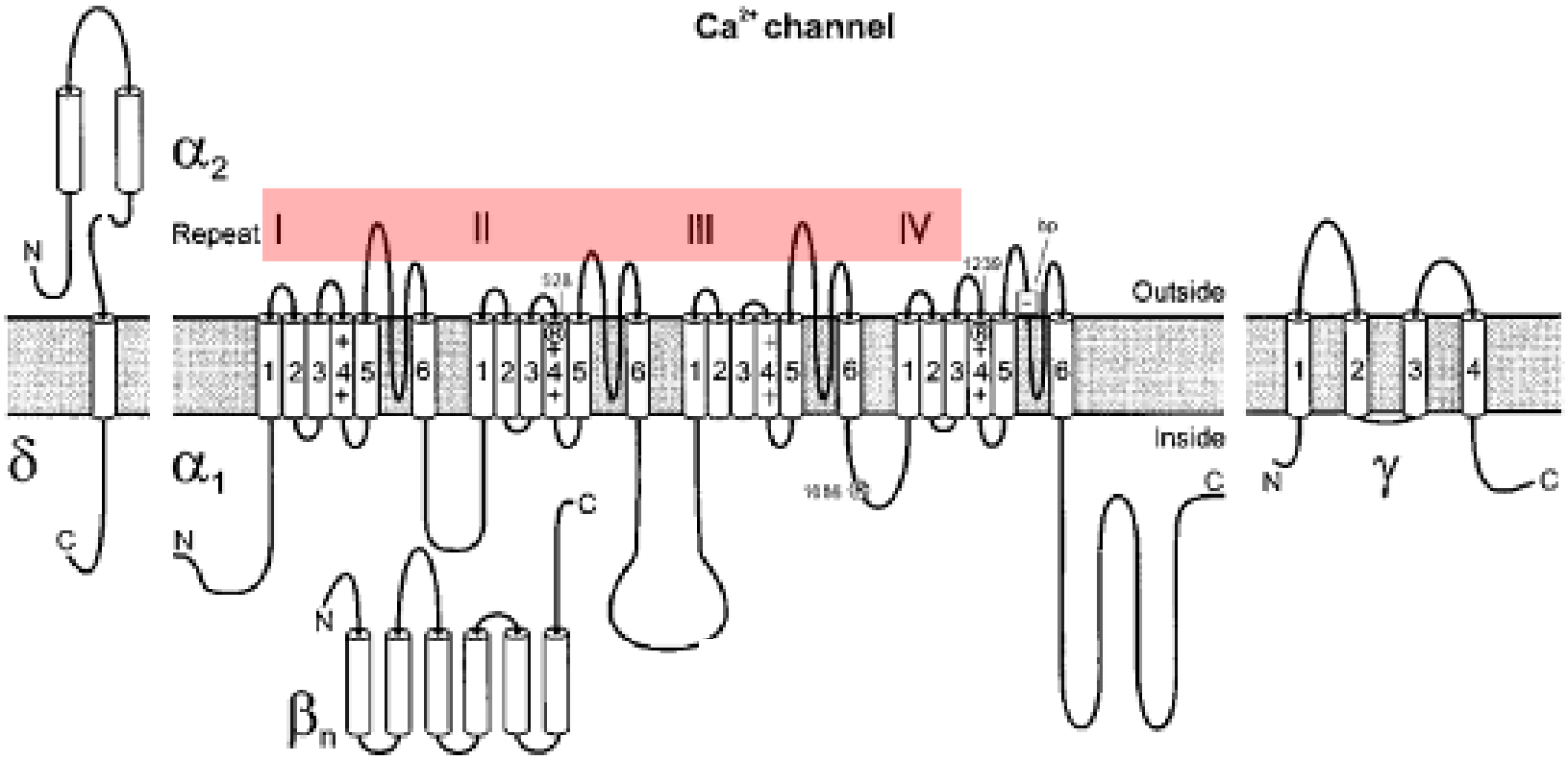
In the peripheral nervous system BTX binds, selectively and almost irreversibly, to the alpha subunit of the voltage-gated Na+ channels, which become persistently active (open) at the resting membrane potential. The influx of sodium permanently depolarizes cell membrane blocking the insurgence of any AP.

Also, BTX interferes with the conduction of action potential in the heart, causing arrhythmias, extrasystoles and ventricular fibrillation.

Golden poison-dart frogs do not produce the toxins themselves: when raised in captivity with no alkaloids in their diets, they do not possess detectable concentrations of BTX. They probably obtain the toxins from their diet, possibly from poisonous beetles (*Choresine beetles*), which contain BTX in high concentrations.

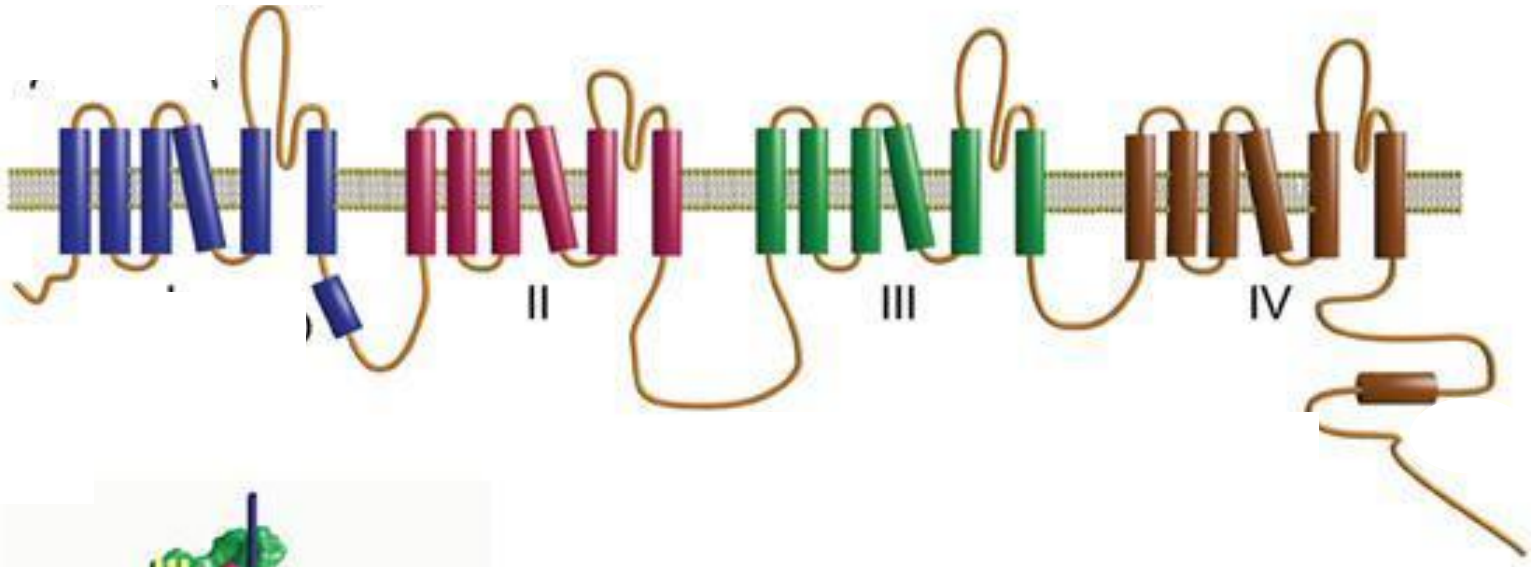
Current evidence indicates that beetles cannot synthesize steroids and probably obtain the BTX backbone from the phytosterols in the plants they eat.

Poison-dart frogs are able to sequester these toxins without being killed by them because they have evolved voltage-gated Na+ channels that are unaffected by BTX.



Voltage-gated calcium channels (Cav) are closely related to Nav channels. As Nav channels, they are formed by a single polypeptide (α-subunit) consisting of 4 domains, each having 6 transmembrane segments. Positively charged arginines or lysines, in the 4th segment of each domain (S4), are primarily responsible for voltage sensing and segments S5 and S6 form the pore loop region.

Voltage-gated calcium channels are associated to auxiliary subunits: an α2-δ-complex, an intracellular β-subunit and, occasionally, to a γ-subunit with 4 transmembrane segments.

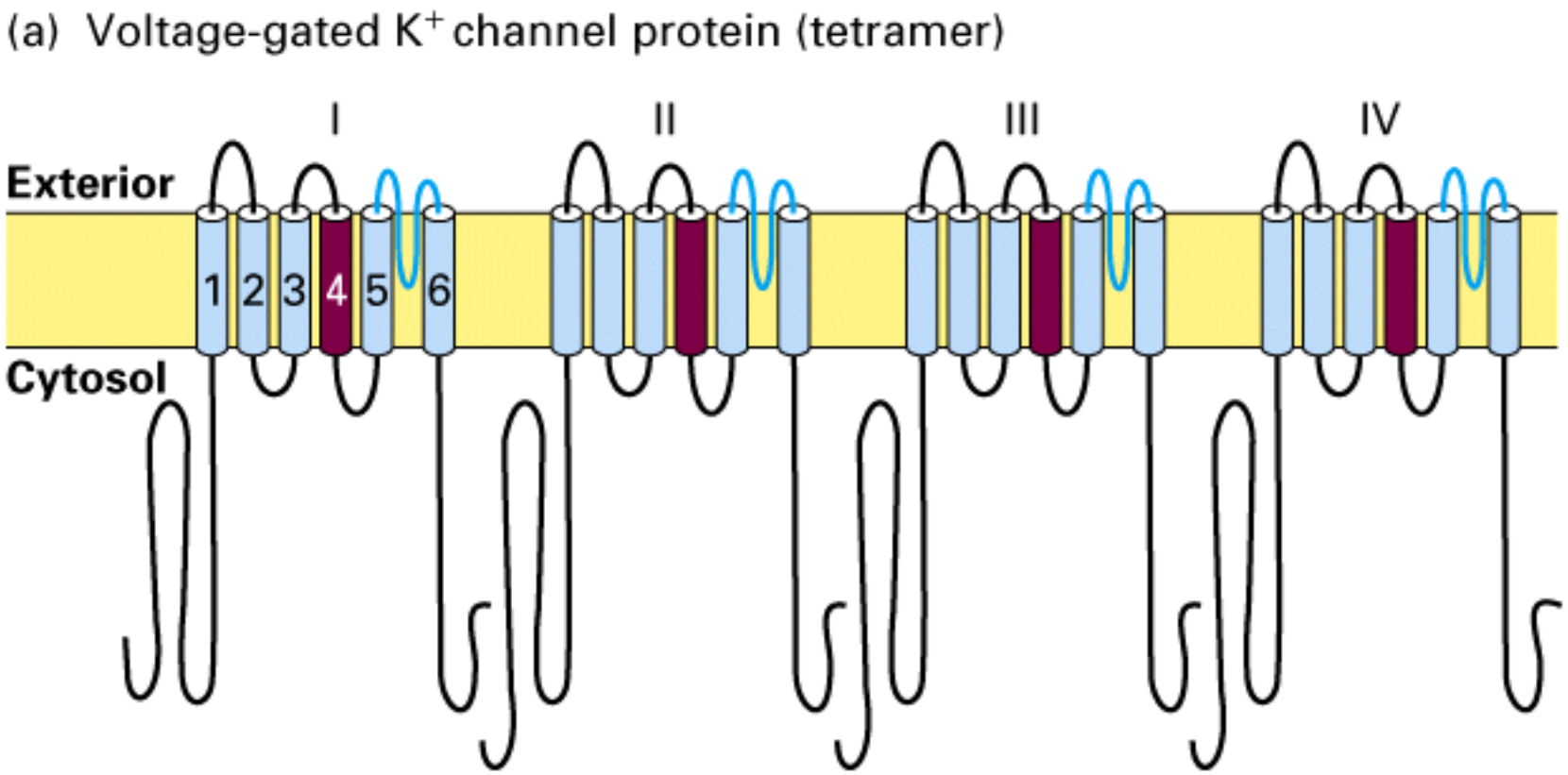


The four subunits of the Ca^{2+} voltage-gated channels also pair functionally-analogous sections.

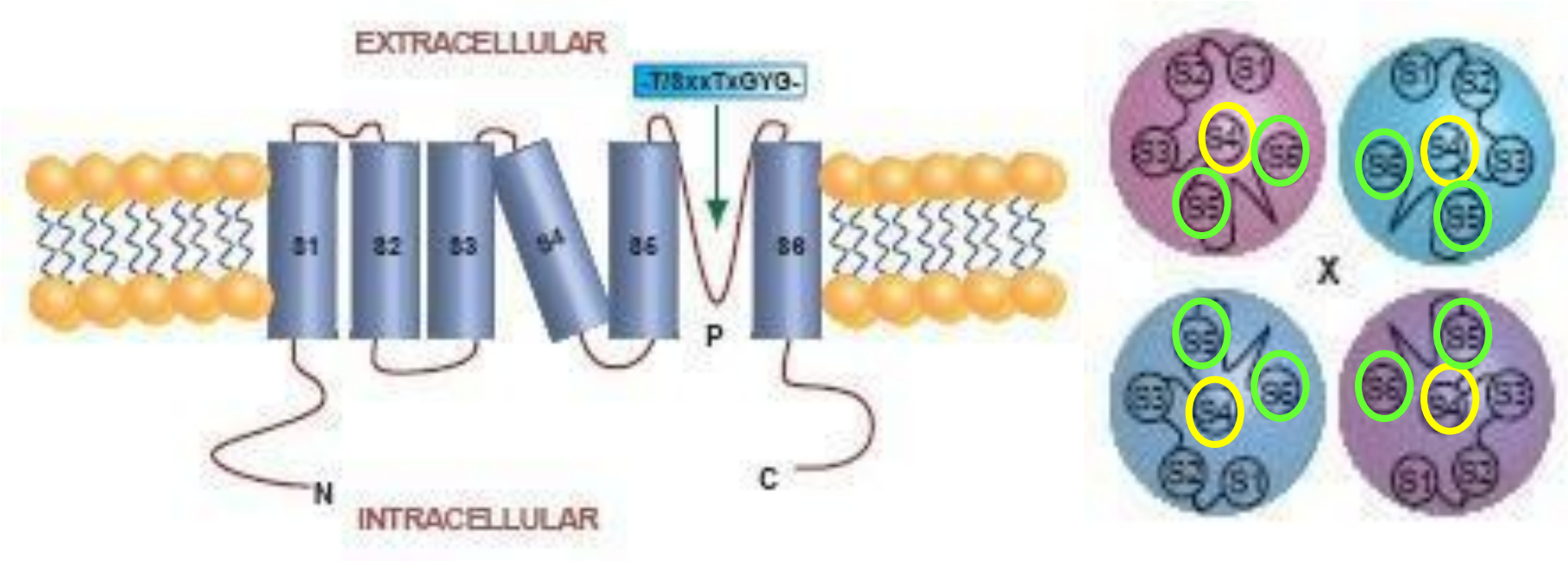
Physiological function and pharmacology of calcium channels

Channel	Current	Localization	Specific Antagonists	Cellular Functions
$Ca_V1.1$	L	Skeletal muscle; transverse tubules	Dihydropyridines; phenylalkylamines; benzothiazepines	Excitation-contraction coupling
$Ca_V1.2$	L	Cardiac myocytes; smooth muscle myocytes; endocrine cells; neuronal cell bodies; proximal dendrites	Dihydropyridines; phenylalkylamines; benzothiazepines	Excitation-contraction coupling; hormone release; regulation of transcription; synaptic integration
$Ca_V1.3$	L	Endocrine cells; neuronal cell bodies and dendrites; cardiac atrial myocytes and pacemaker cells; cochlear hair cells	Dihydropyridines; phenylalkylamines; benzothiazepines	Hormone release; regulation of transcription; synaptic regulation; cardiac pacemaking; hearing; neurotransmitter release from sensory cells
$Ca_V1.4$	L	Retinal rod and bipolar cells; spinal cord; adrenal gland; mast cells	Dihydropyridines; phenylalkylamines; benzothiazepines	Neurotransmitter release from photoreceptors
$Ca_V2.1$	P/Q	Nerve terminals and dendrites; neuroendocrine cells	ω-Agatoxin IVA	Neurotransmitter release; dendritic Ca^{2+} transients; hormone release
$Ca_V2.2$	N	Nerve terminals and dendrites; neuroendocrine cells	ω-Conotoxin-GVIA	Neurotransmitter release; dendritic Ca^{2+} transients; hormone release
$Ca_V2.3$	R	Neuronal cell bodies and dendrites	SNX-482	Repetitive firing; dendritic calcium transients
$Ca_V3.1$	T	Neuronal cell bodies and dendrites; cardiac and smooth muscle myocytes	None	Pacemaking; repetitive firing
$Ca_V3.2$	T	Neuronal cell bodies and dendrites; cardiac and smooth muscle myocytes	None	Pacemaking; repetitive firing

L= Long lasting; P = Purkinje; N = Neither T nor L; R = Resistant to blockers; T = Transient.



K^+ voltage-gated channels are build from 4 monomer, each with 6 trans-membrane sections, with functions similar to the Na^+ and Ca^{2+} voltage-gated channels.



The four monomer of the K+ voltage-gated channels also pair their functionally analogous sections.

K_V channel families Gene names shown are those assigned by the IUPHAR and HGNC in addition to some other commonly used names

IUPHAR	HGNC	Other
$K_v1.1$	*KCNA1*	*Shaker*-related family
$K_v1.2$	*KCNA2*	
$K_v1.3$	*KCNA3*	
$K_v1.4$	*KCNA4*	
$K_v1.5$	*KCNA5*	
$K_v1.6$	*KCNA6*	
$K_v1.7$	*KCNA7*	
$K_v1.8$	*KCNA10*	
$K_v2.1$	*KCNB1*	*Shab*-related family
$K_v2.2$	*KCNB2*	
$K_v3.1$	*KCNC1*	*Shaw*-related family
$K_v3.2$	*KCNC2*	
$K_v3.3$	*KCNC3*	
$K_v3.4$	*KCNC4*	
$K_v4.1$	*KCND1*	*Shal*-related family

1. K+ voltage-gated channels (HGNC, Human Gene Nomenclature Committee)

K_V channel families Gene names shown are those assigned by the IUPHAR and HGNC in addition to some other commonly used names

$K_v4.2$	*KCND2*	
$K_v4.3$	*KCND3*	
$K_v5.1$	*KCNF1*	Modifier
$K_v6.1$	*KCNG1*	Modifiers
$K_v6.2$	*KCNG2*	
$K_v6.3$	*KCNG3*	
$K_v6.4$	*KCNG4*	
$K_v7.1$	*KCNQ1*	*KVLQT*
$K_v7.2$	*KCNQ2*	*KQT2*
$K_v7.3$	*KCNQ3*	
$K_v7.4$	*KCNQ4*	
$K_v7.5$	*KCNQ5*	
$K_v8.1$	*KCNV1*	Modifiers
$K_v8.2$	*KCNV2*	
$K_v9.1$	*KCNS1*	Modifiers
$K_v9.2$	*KCNS2*	
$K_v9.3$	*KCNS3*	
$K_v10.1$	*KCNH1*	*eag1*
$K_v10.2$	*KCNH5*	*eag2*
$K_v11.1$	*KCNH2*	*erg1*

K_V channel families Gene names shown are those assigned by the IUPHAR and HGNC in addition to some other commonly used names

$K_v11.2$	KCNH6	erg2
$K_v11.3$	KCNH7	erg3
$K_v12.1$	KCNH8	elk1, elk3
$K_v12.2$	KCNH3	elk2
$K_v12.3$	KCNH4	elk1

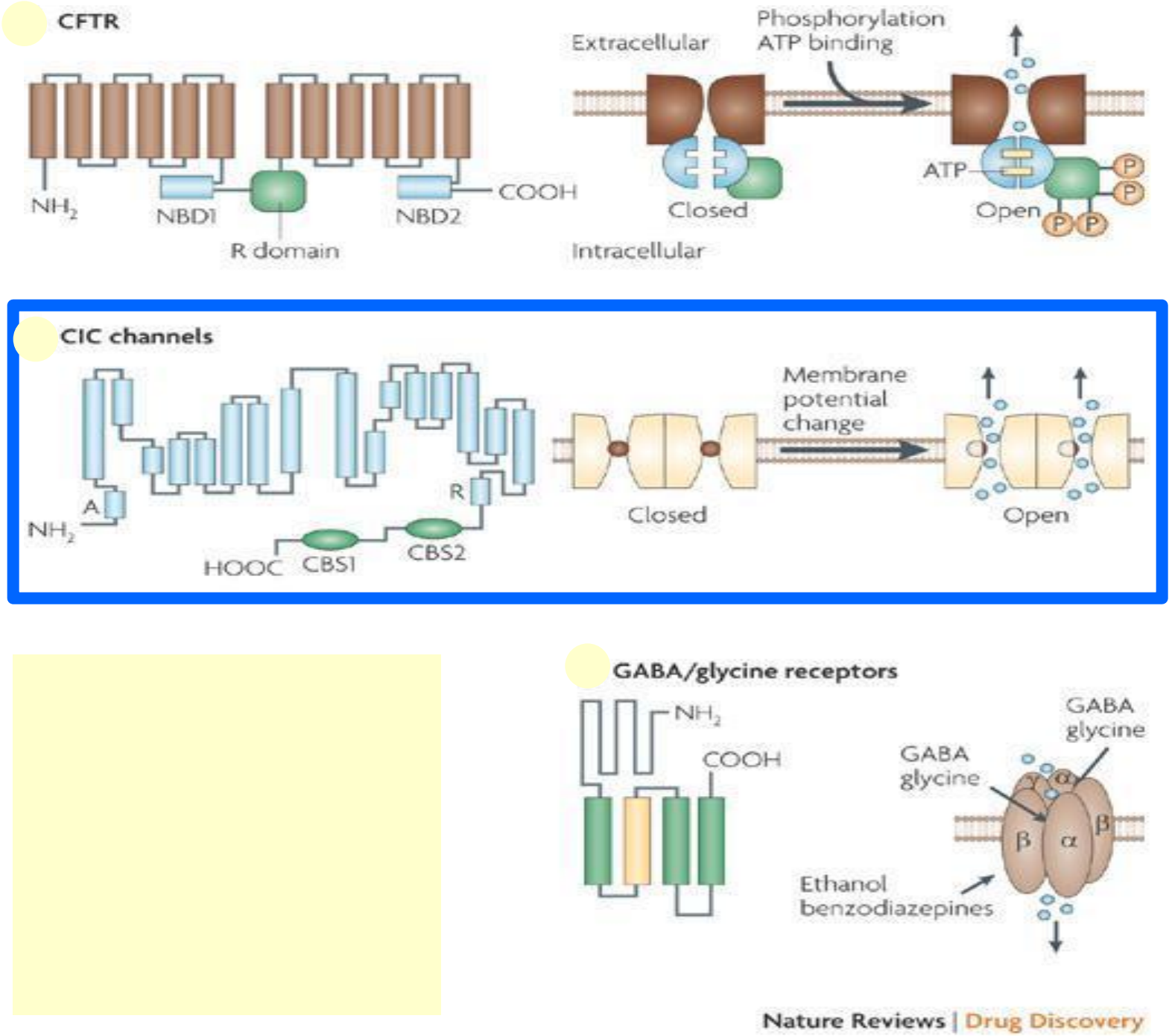
ANION CHANNELS

The main voltage-gated anion channel is the CLC (Cl^- voltage-gated channel). The channel CLC-1 is particularly abundant in the membrane of the myocytes.

ClC channels have a complex structure. They are built by dimer of monomer, each made from 10-12 transmembrane helices. CLC voltage sensibility is not given by a specific segments, but by the movement of cation and anion associated with its complex structure. They are not selective for Cl- and are involved in setting and restoring the resting mb potential of skeletal muscles.

The cystic fibrosis transmembrane conductance regulator (CFTR) is another important anion channel, but it's not voltage-sensitive.

GABA-A and Glycine receptors are also Cl^- channels


CFTR
NH2
NBD1
R domain
NBD2
COOH
Extracellular
Phosphorylation
ATP binding
Closed
Intracellular
ATP
Open
P
CIC channels
A
NH2
HOOC
CBS1
CBS2
R
Membrane
potential
change
Closed
Open
GABA/glycine receptors
NH2
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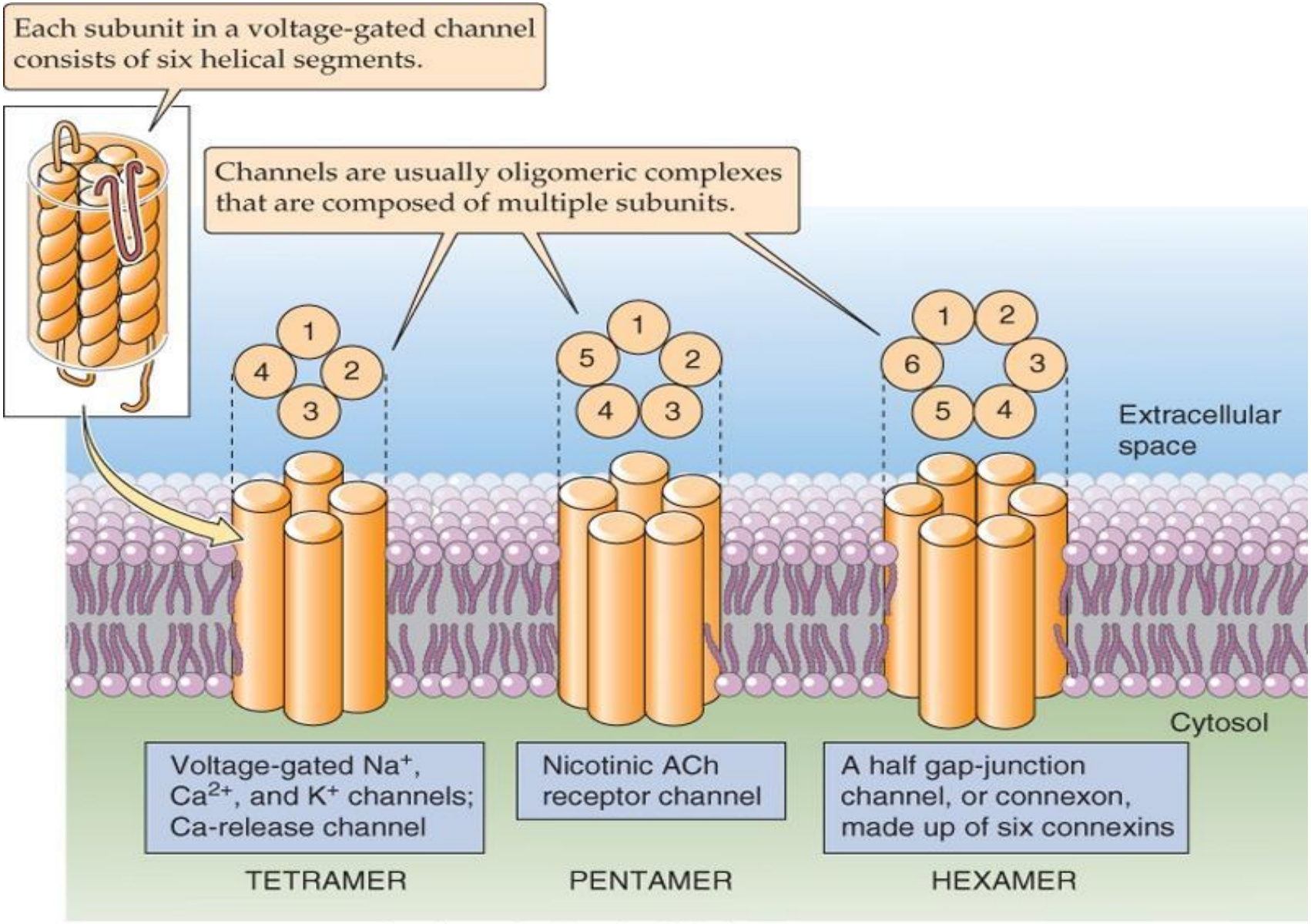
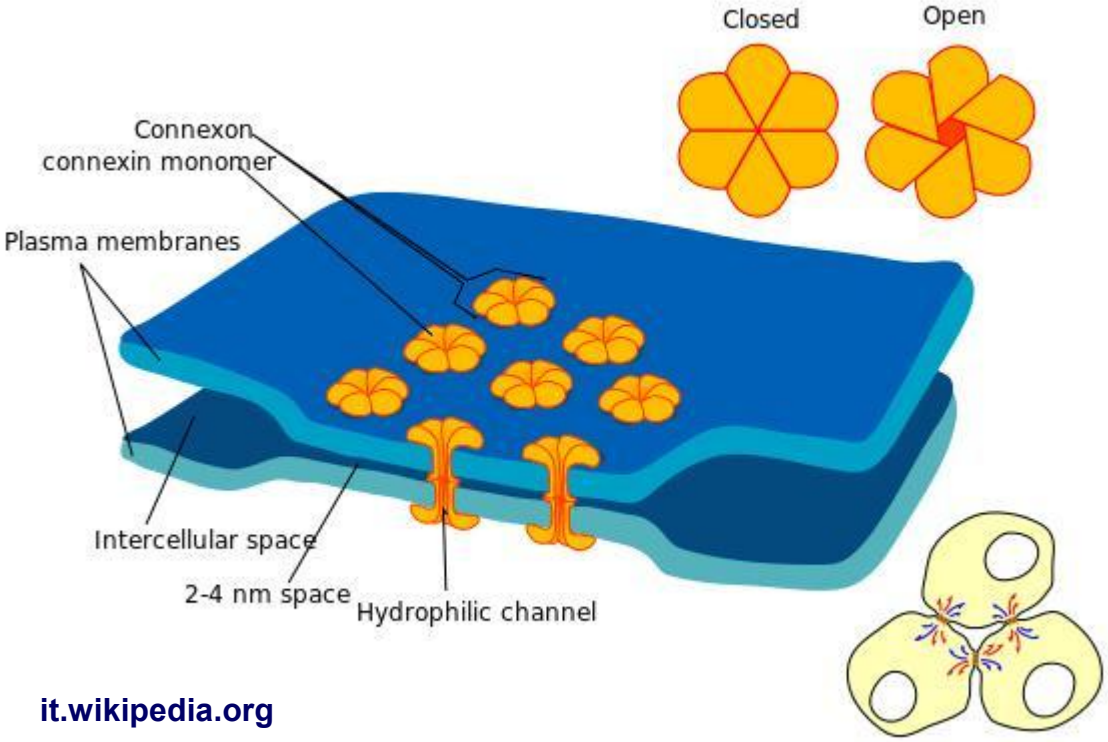
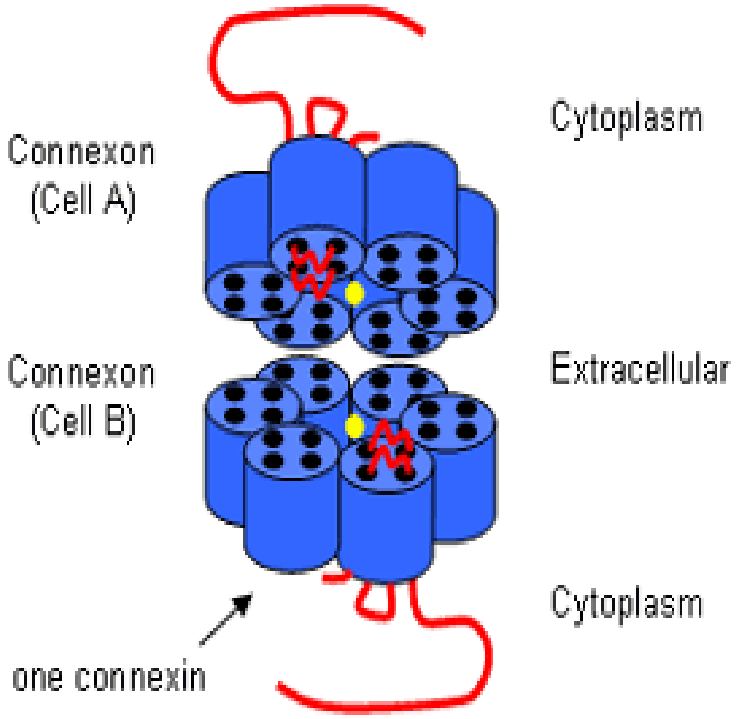
GABA
glycine
GABA
glycine
γ
α
β
α
β
Ethanol
benzodiazepines
Nature Reviews | Drug Discovery





it.wikipedia.org

Gap junctions



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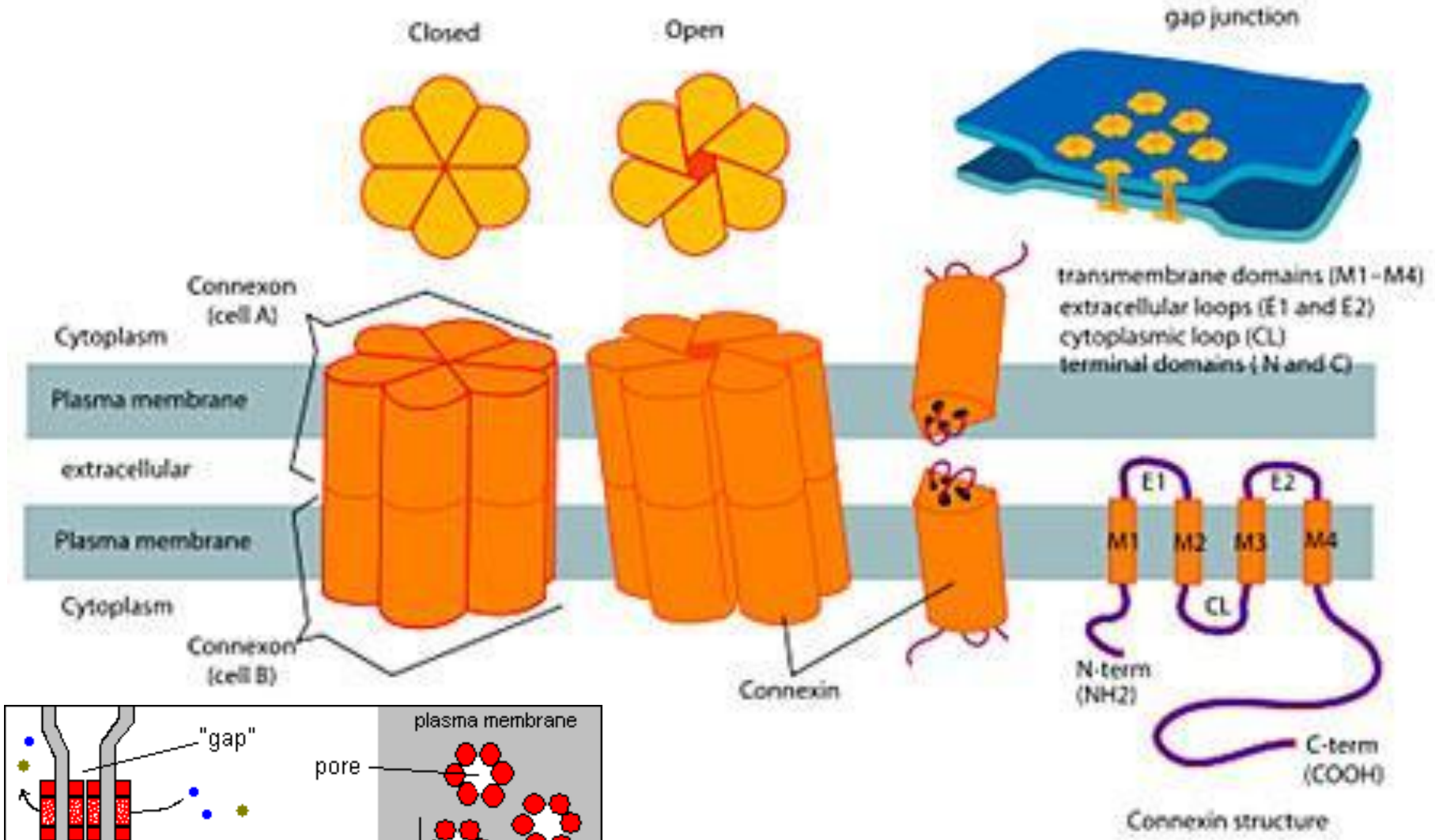
Closed
Open
gap junction
Connexon
(cell A)
Cytoplasm
Plasma membrane
extracellular
Plasma membrane
Cytoplasm
Connexon
(cell B)
Connexin
transmembrane domains (M1–M4)
extracellular loops (E1 and E2)
cytoplasmic loop (CL)
terminal domains (N and C)
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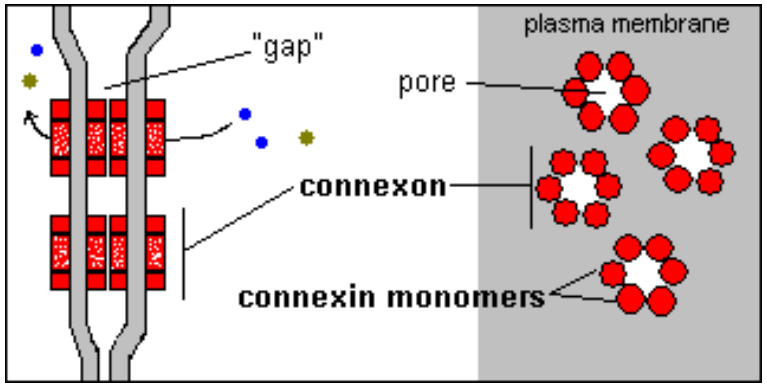
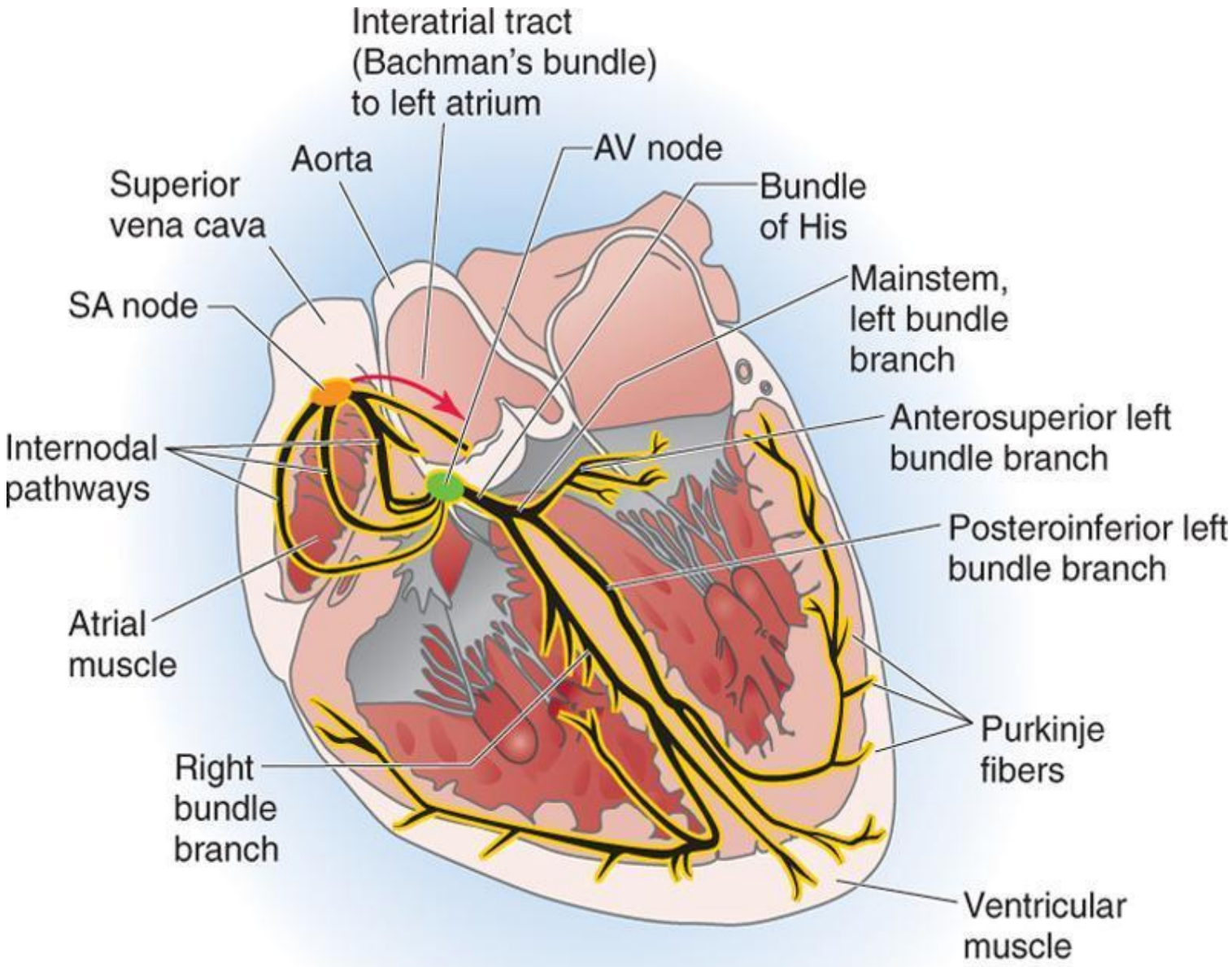
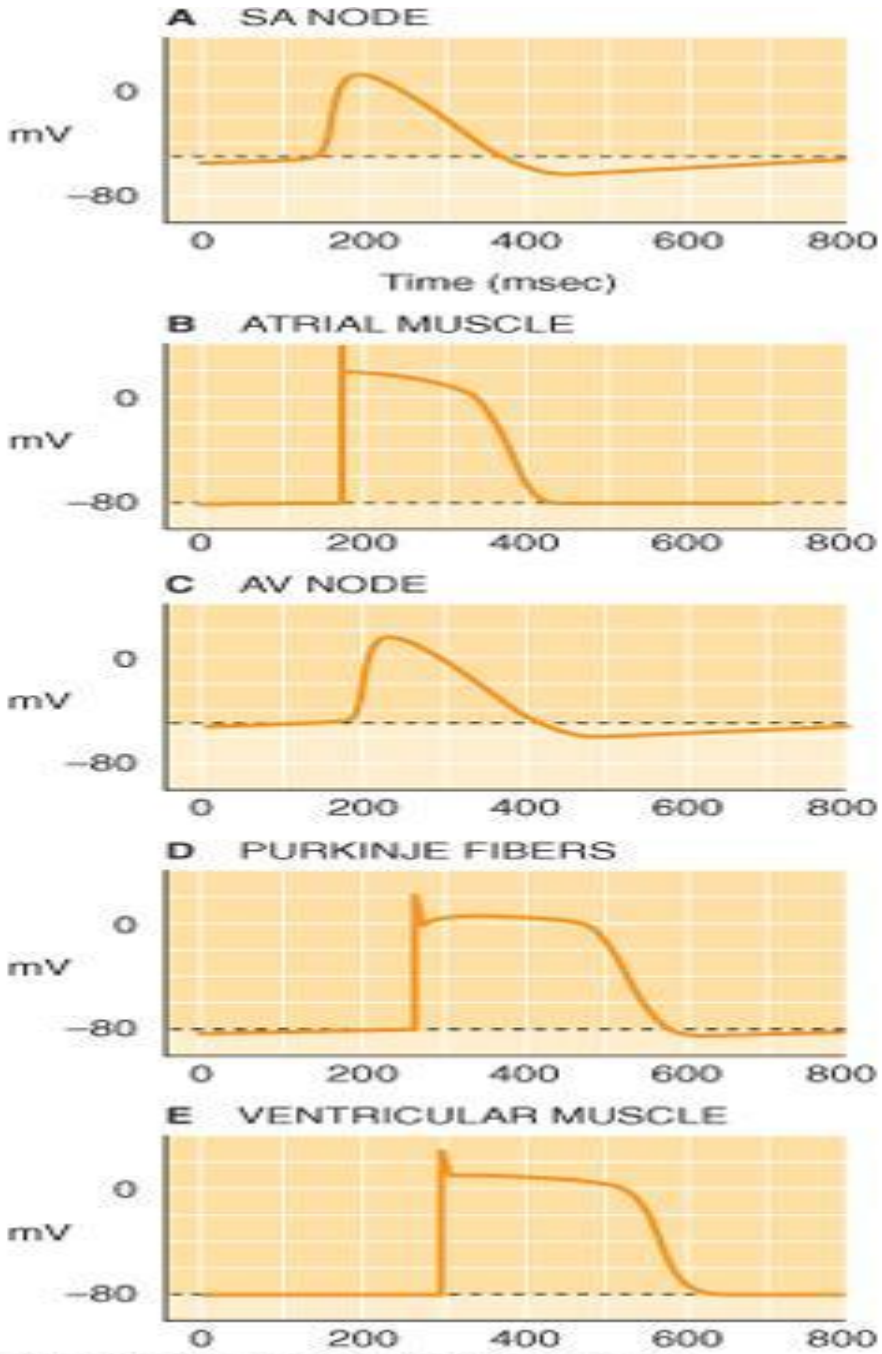
E2
M1
M2
M3
M4
CL
N-term
(NH2)
C-term
(COOH)
Connexin structure


"gap"
plasma membrane
pore
connexon
connexin monomers





The initiation time, shape, and duration of AP are distinctive for different parts of the heart, reflecting their different functions.

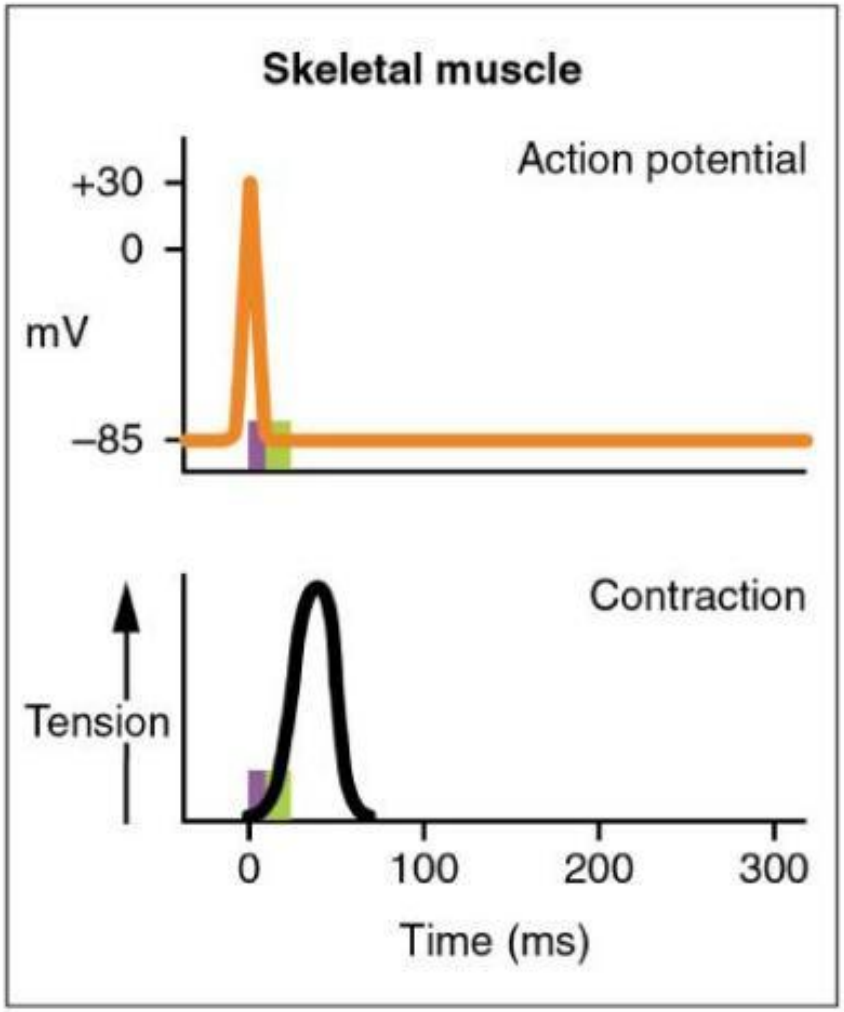
Cardiac AP is shaped by 4 major membrane currents which are voltage-gated:

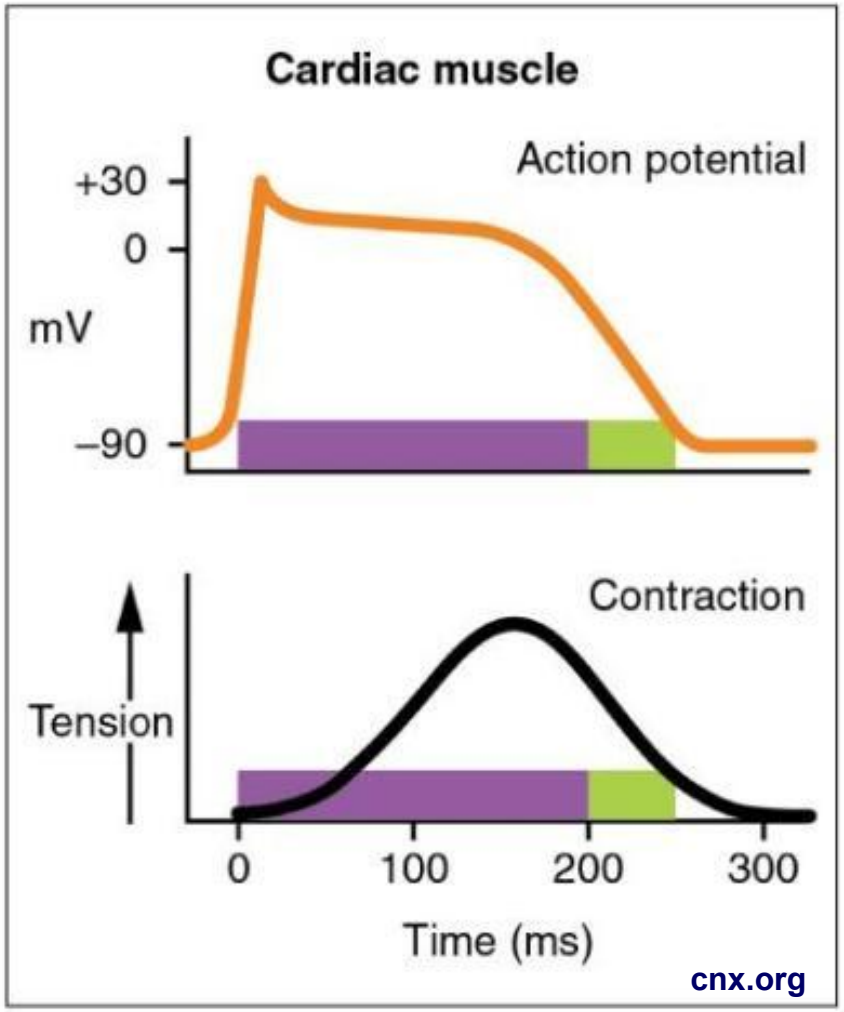
1. The Na+ current (INa) is responsible for the rapid depolarizing phase of the action potential in atrial and ventricular muscle and in Purkinje fibers.

2. The Ca2+ current (ICa) is responsible for the rapid depolarizing phase of the action potential in the SA node and AV node; also, in all cardiomyocytes it is responsible of the plateau phase which triggers contraction.

3. The K+ current (IK) is responsible for the repolarizing phase of the action potential in all cardiomyocytes.

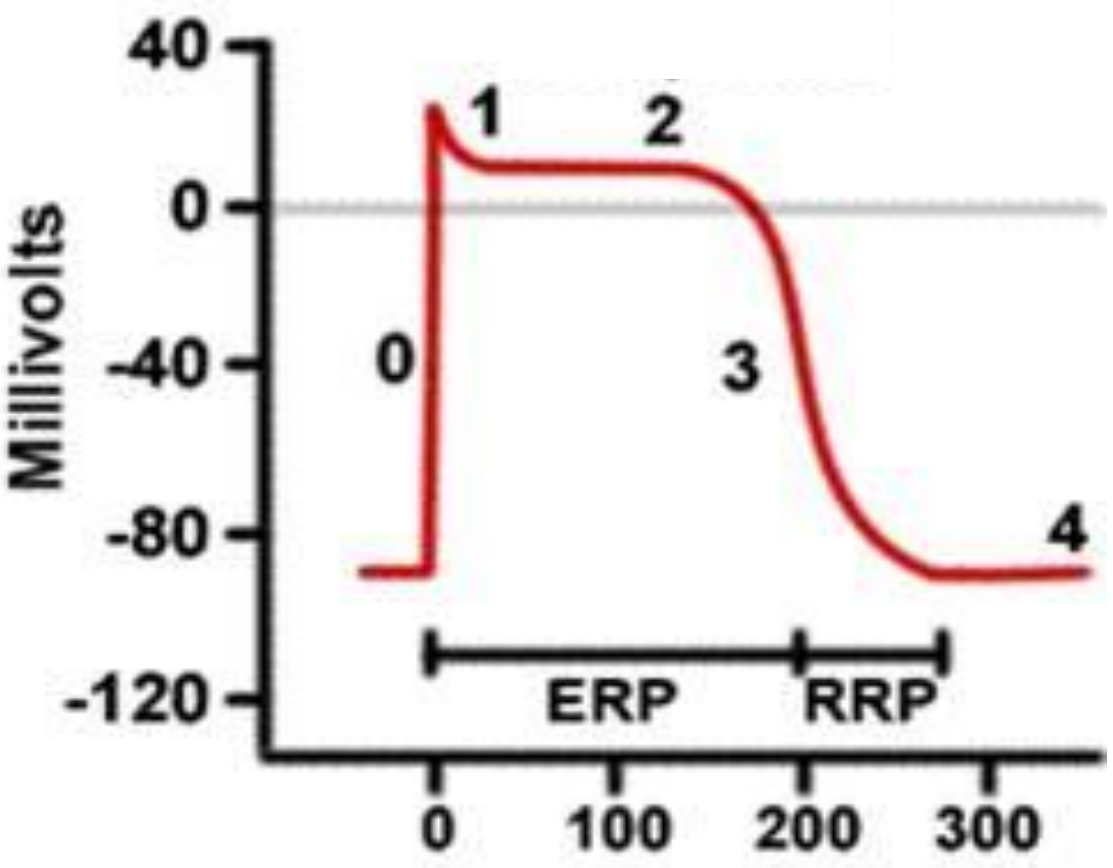
4. The pacemaker current (If) is responsible for the rate of pacemaker activity in SA nodal cells, AV nodal cells and Purkinje fibers.

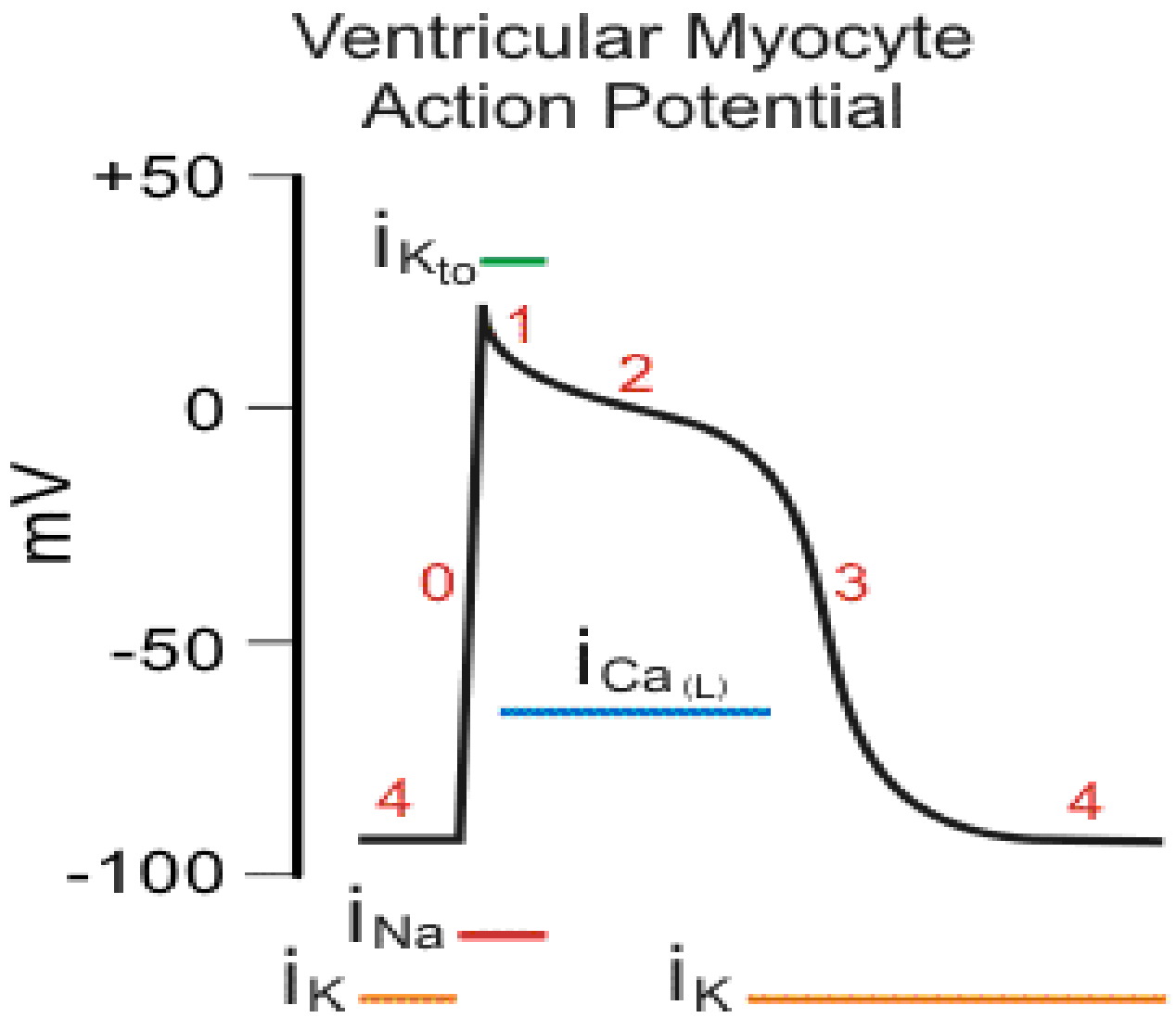

Skeletal muscle
Action potential
+30
0
mV
–85
Contraction
Tension
0
100
200
300
Time (ms)


Cardiac muscle
Action potential
+30
0
mV
–90
Contraction
Tension
0
100
200
300
Time (ms)

cnx.org

Phase 0 = depolarization
Phase 1 = partial repolarization
Phase 2 = plateau
Phase 3 = repolarization
Phase 4 = resting potential
ERP, effective refractory period
RRP, relative refractory period




Ventricular Myocyte
Action Potential
+50
0
-50
-100
mV
$i_{K_{to}}$
1
2
0
3
$i_{Ca\,(L)}$
4
4
i_{Na}
i_K
i_K

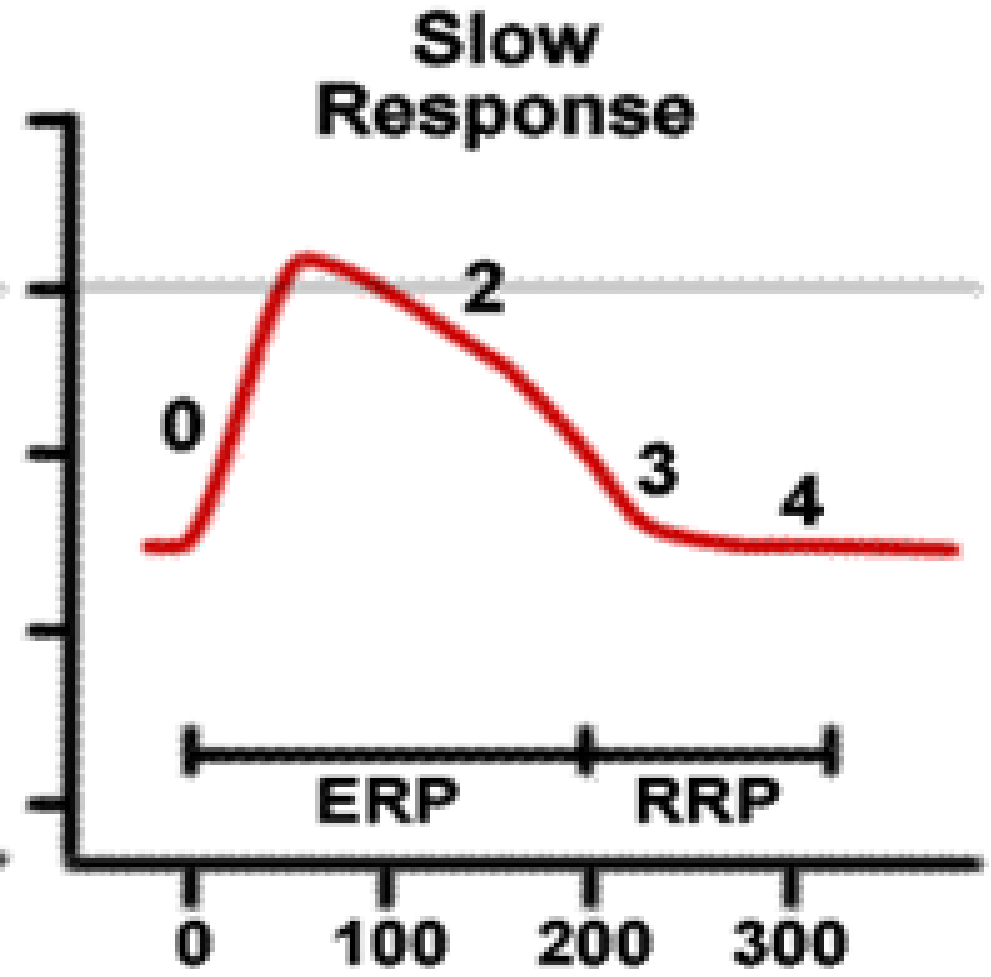
Cardiac contraction has an absolute requirement for Ca2+ influx through L-type Ca2+ channels during AP. This induces an increase in Ca2+ cellular concentration that is not, however, sufficient to initiate contraction.

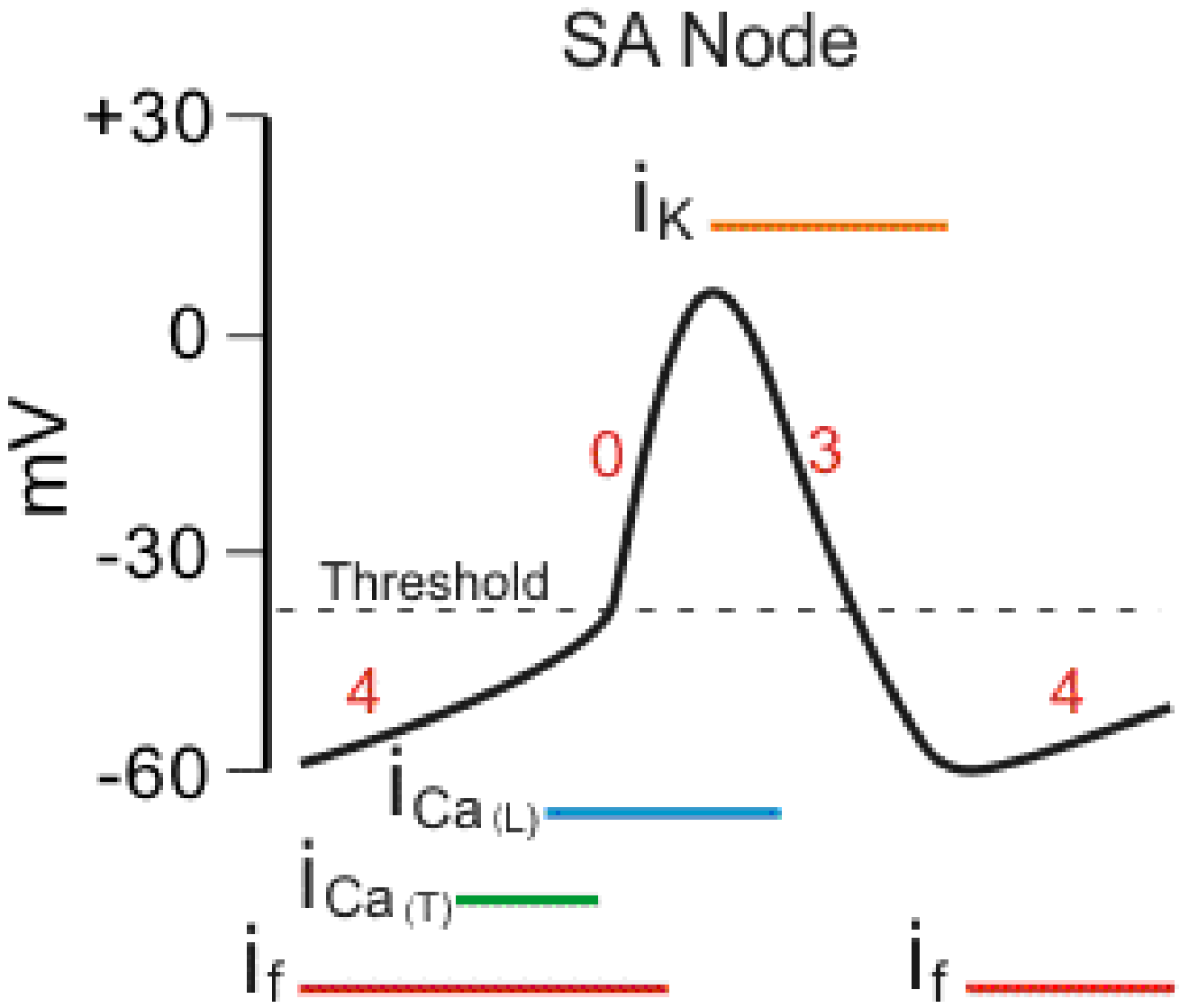
Thus, the Ca2+ influx by the L-type Ca2+ channels is greatly amplified by the mechanism of the Ca2+-induced Ca2+ release (CICR) from the SR through the Ca2+-release channels.

Since these channels remain open for a longer period than do L-type Ca2+ channels, the contribution of CICR to the rise in the cellular concentration of Ca2+ is far greater than that by the L-type Ca2+ channels of the T tubules.
It appears that each L-type Ca2+ channel controls only one SR Ca2+-release channel. This is due to the physical proximity of L-type Ca2+ channels of the T-tubule membrane and the Ca2+-release channel in the SR.

The membrane of cardiomyocytes can extrude Ca2+ by means of the Na+ / Ca2+ exchanger (NCX) and the Ca2+ pump.

Phase 0 = depolarization
Phase 2 = repolarization
Phase 3 = repolarization
Phase 4 = spontaneous depolarization
ERP, effective refractory period
RRP, relative refractory period




SA Node
+30
0
-30
-60
mV
Threshold
0
3
4
4
i_K
$i_{Ca\,(L)}$
$i_{Ca\,(T)}$
i_f
i_f

In cardiac pacemaker cells, AP is due to the opening, at threshold, of L-type Ca^{2+} channels (phase 0). The IK current corresponds to the opening of voltage dependent K^+ channels as in the myocardium.

The most important current of pacemaker cells is the so called pacemaker or "funny" current (If). It received these denominations for its fundamental role in initiating the depolarization of SA cells, AV cells, Purkinje fibers and for the unusual characteristics to be activated during hyperpolarization (end of phase 3).

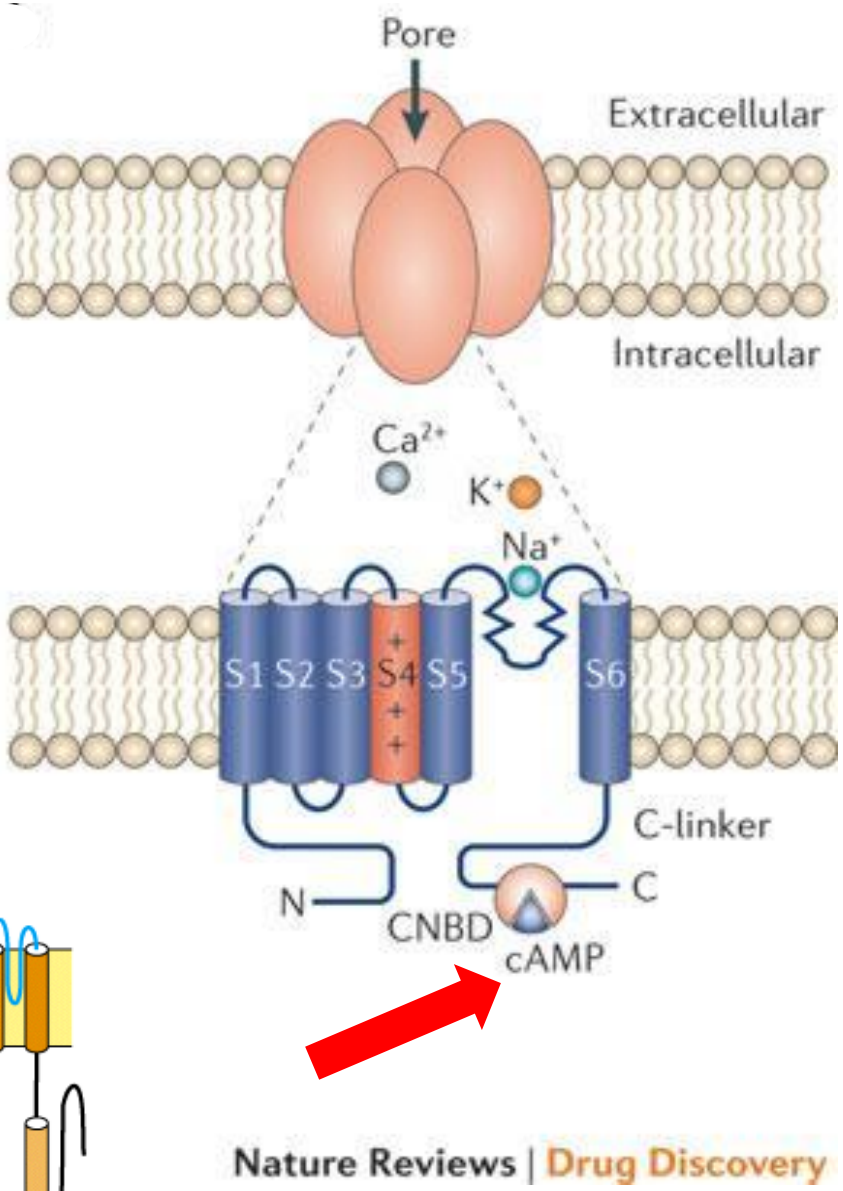
The pacemaker If current is an inward currrent produced by a nonspecific cation channel called HCN (hyperpolarization activated, cyclic nucleotide gated) because they respond to both voltage and chemical messenger (cAMP). Because HCN channels conduct both K+ and Na+, the reversal potential of If is around -20 mV (between the Nernst potentials for K+, about -90 mV, and for Na+, about +50 mV in the heart). Note that If is concomitant with an inward Ca2+ current that depends on the phasic opening of transient Ca2+ voltage-dependent channels (iCaT).

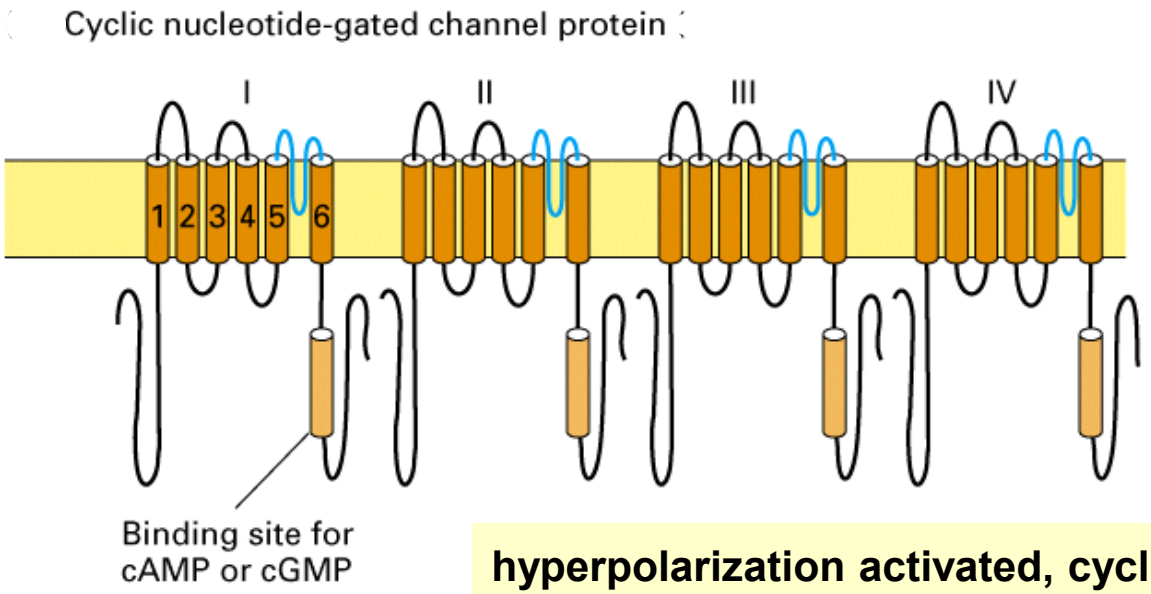
As explained above, HCN channels have the unusual or "funny" property that they do not conduct at positive potentials but are slowly activated by the hyperpolarization characterizing the end of phase 3.

As the other voltage dependent K+ channels, the HCN channels have 4 similar or identical α-subunits, each having 6 transmembrane segments.

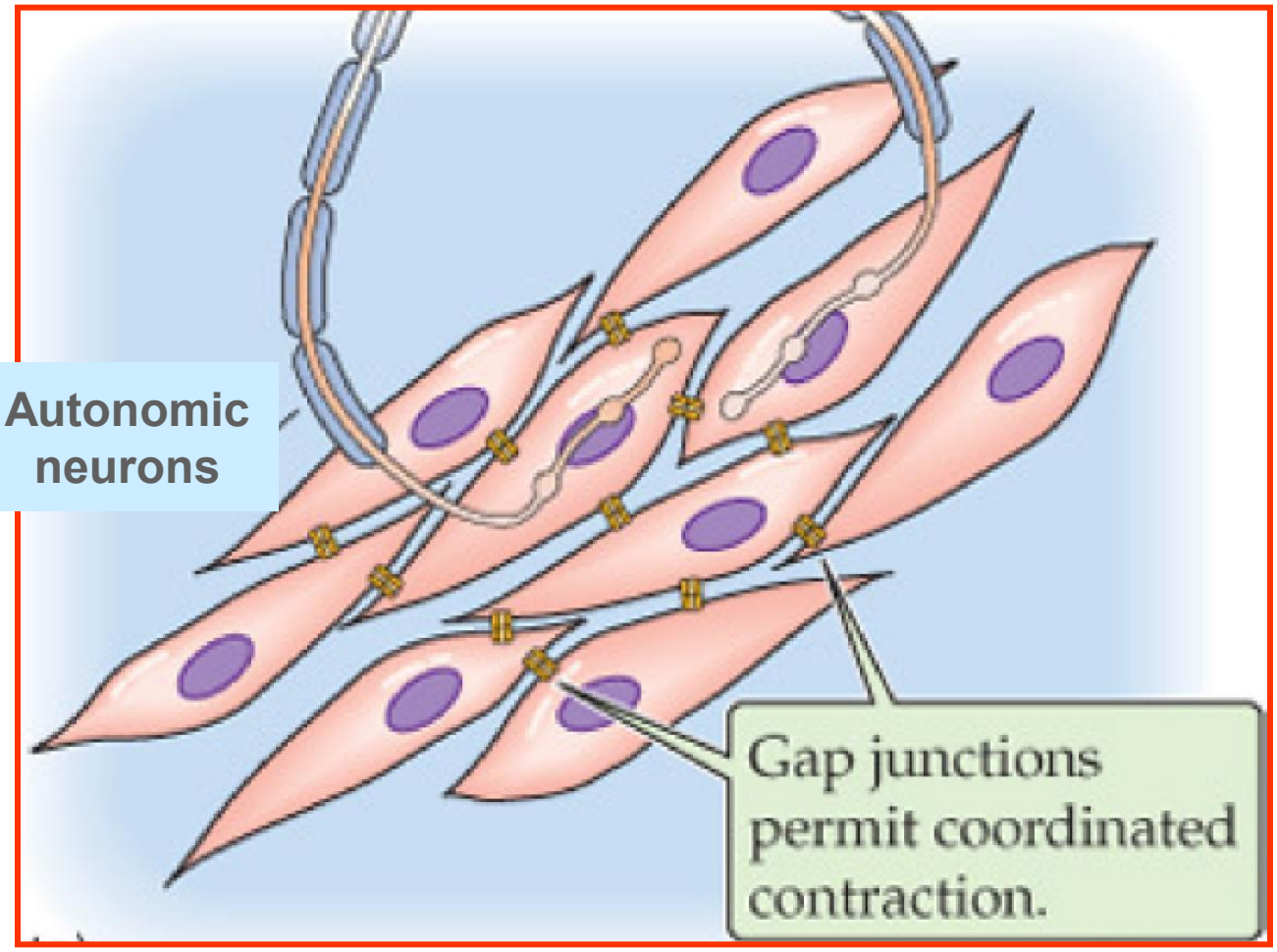
The channel is modulated by cAMP through a direct action on the channel itself, not by phosphorylations, as usually happens with other types of ionic channels.

The cAMP binding to HCN channels induces a conformational change of the protein: this increases the probability that the channel is open during hyperpolarization.



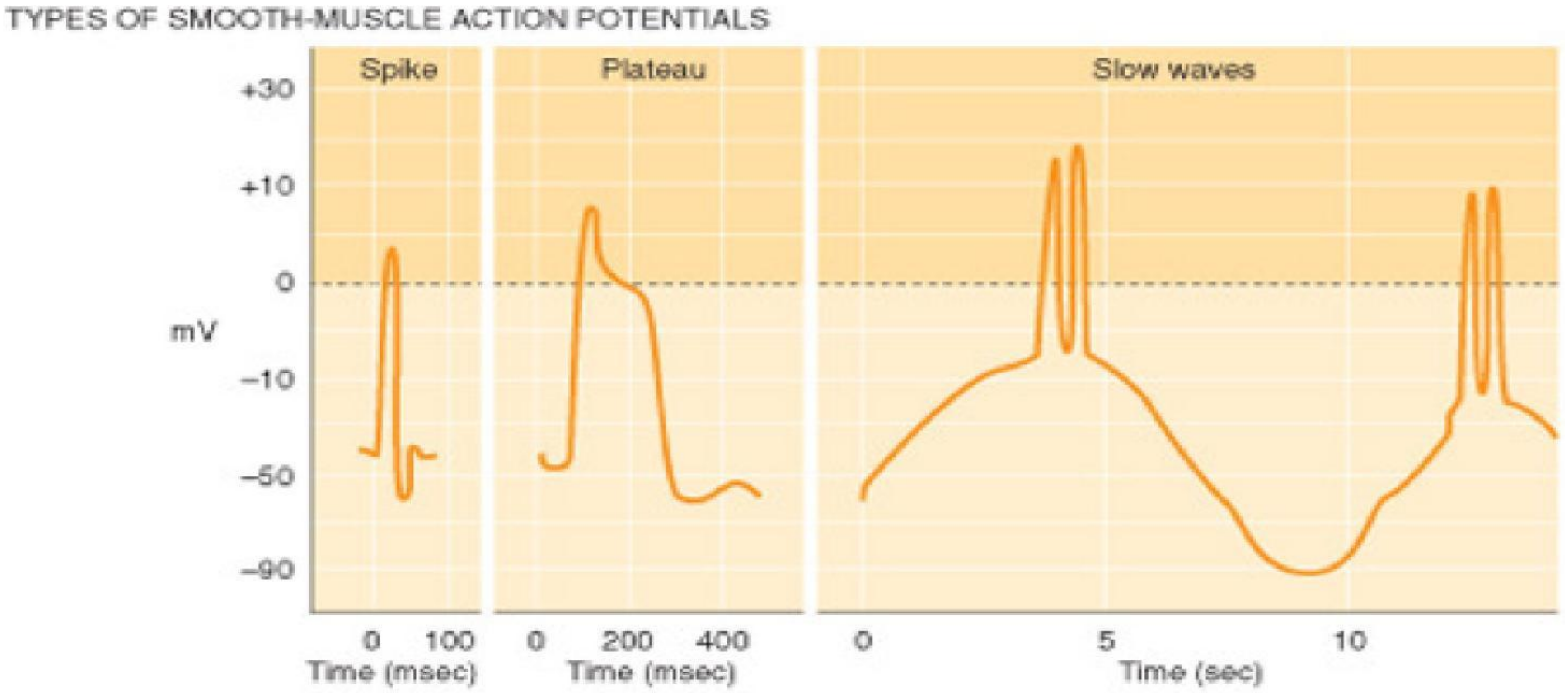


hyperpolarization activated, cyclic nucleotide gated channel



Unitary smooth muscle is the predominant smooth muscle type within the walls of visceral organs such as the gastrointestinal tract, the uterus, and many blood vessels.

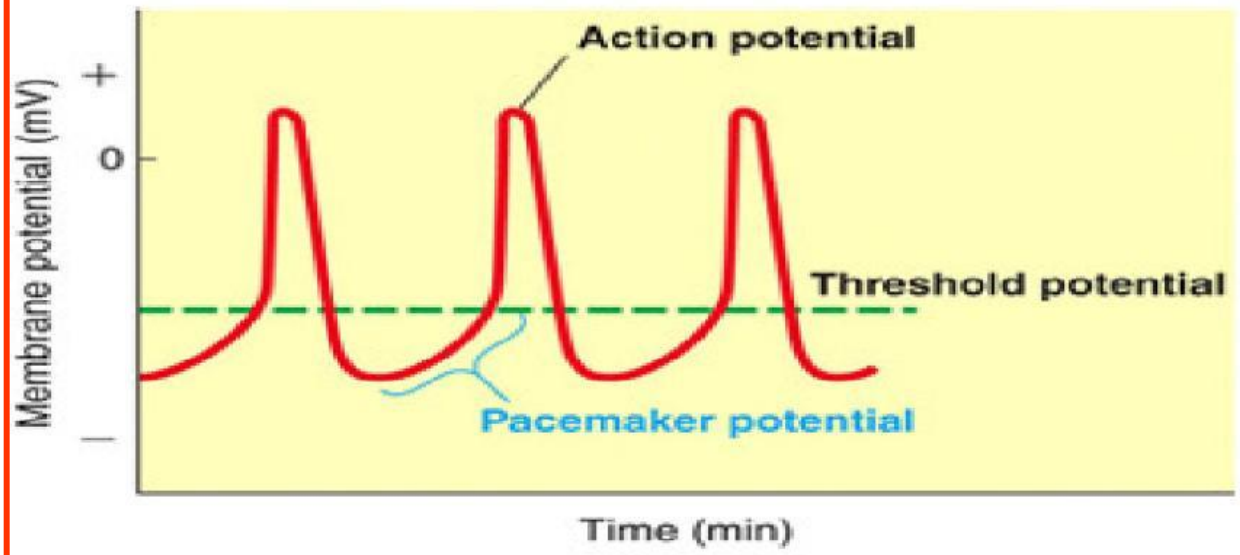
For this reason, unitary smooth muscle is often referred to as visceral smooth muscle.



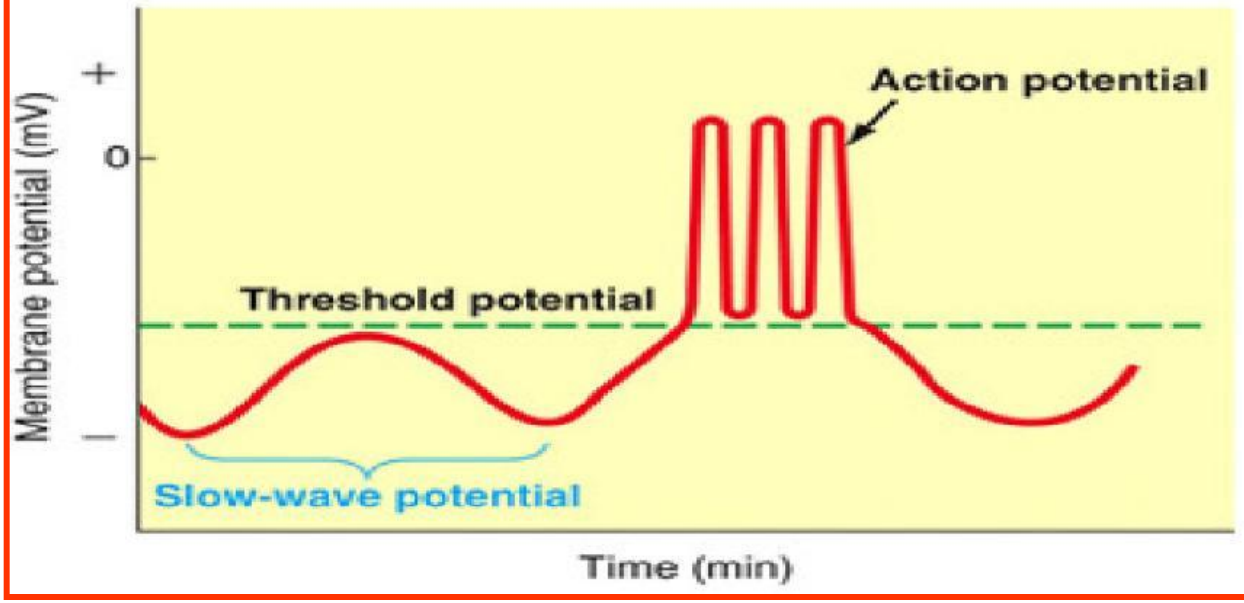
Action potentials (AP) are usually seen in unitary smooth muscle. They have a slower upstroke and longer duration (up to about 100 ms) than in skeletal muscle (about 2 ms). The AP in a smooth muscle cell can be:

i) a simple spike; ii) a spike followed by a plateau; iii) a series of spikes on top of slow waves of Vm.

The depolarizing phase of AP reflects the opening of voltage-gated Ca2+ channels. The inward Ca2+ current further depolarizes the membrane causing more voltage-gated Ca2+ channels to open. Thus, some smooth muscle cells can undergo the same type of regenerative depolarization that is seen in skeletal muscle, but AP in smooth muscle rises with a lower rate because Ca2+ channels open more slowly than Na+ channels.



Pacemaker potential



Slow wave potential

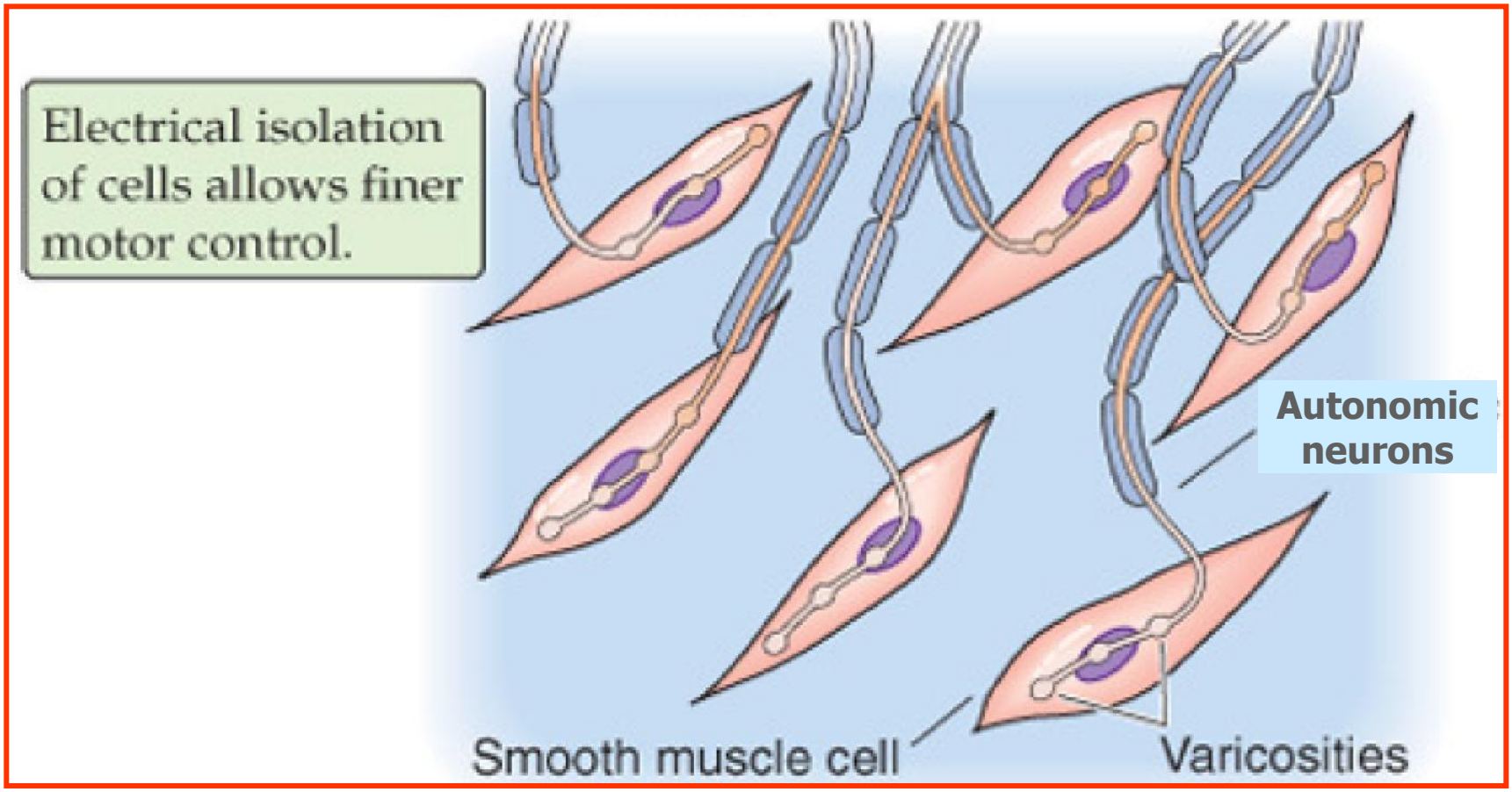
Smooth muscle cells can change Vm in response to neural, hormonal, or mechanical stimulation.

Also, many smooth muscle cells are capable of initiating spontaneous electrical activity, called pacemaker potential.

Currents of pacemaker potential result from spontaneous increases in inward, or depolarizing currents (e.g., voltage-gated Ca2+ currents) or a spontaneous decrease in outward, or hyperpolarizing currents (e.g., voltage-gated K+ currents).

The pacemaker currents cause the cell to depolarize until Vm reaches threshold, triggering an action potential.

In other smooth muscle cells, this spontaneous electrical activity results in regular, repetitive oscillations in Vm. These Vm oscillations occur at a frequency of several oscillations per minute and are referred to as slow waves.



Multiunit smooth muscles are capable of finer control. Multiunit smooth muscle is found in the iris and ciliary body of the eye, the piloerector muscles of the skin, and some blood vessels.

Action potentials usually do not occur in multiunit smooth muscle. For example, in the smooth muscle that regulates the iris, excitatory neurotransmitters cause a local depolarization, the **junctional potential**, which is similar to the end-plate potential in skeletal muscle.

Junctional potentials spread electrotonically throughout the muscle fiber, thereby altering Vm and triggering the entry of Ca^{2+} through voltage-gated L Ca^{2+} channels.

Thus, whereas action potential generation is essential for initiating contraction of skeletal and cardiac muscle, many smooth muscle cells contract despite being unable to generate an action potential.

For example, **changes in Vm** may modulate, by an unknown mechanism, the activity of the enzyme phospholipase C, which cleaves membrane phosphoinositides to release the intracellular second messengers **diacylglycerol** (DAG) and **IP3** (**pharmaco-mechanical coupling**).