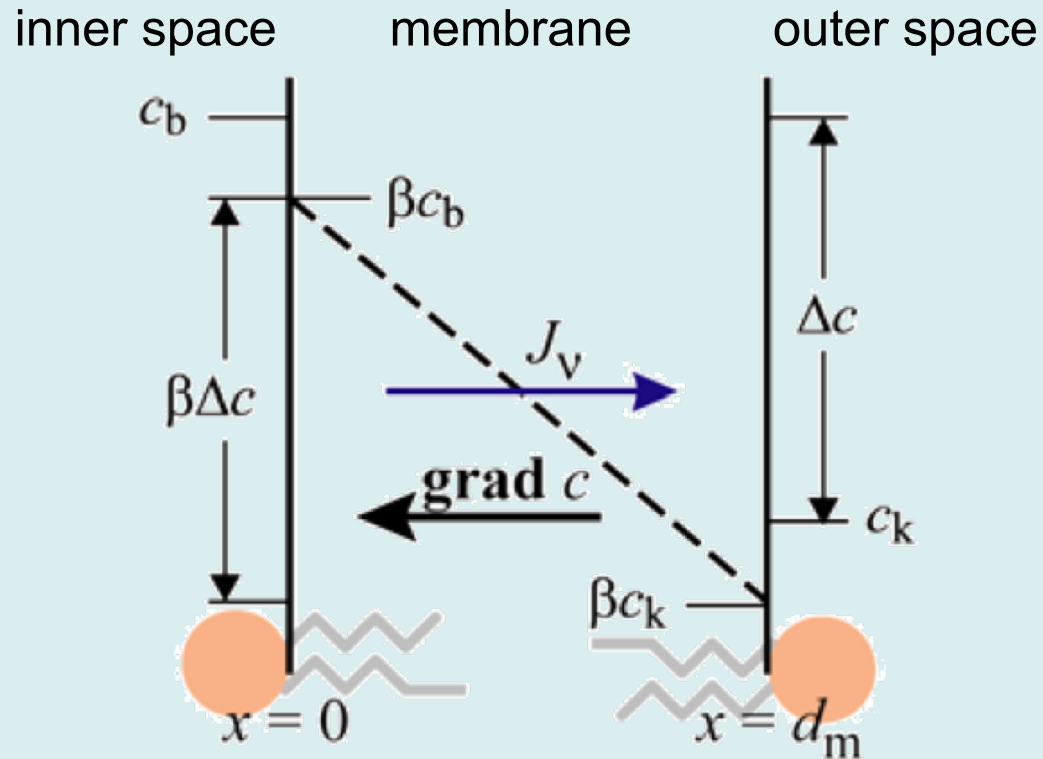


Transport processes-3

MEMBRANE POTENTIAL

17-03-2022
Károly Liliom

Diffusion across membranes



β – partition coefficient

$$\beta = c_m(0)/c_b = c_m(d_m)/c_k$$

Fick I. law:

$$J = -D \Delta c / \Delta x$$

$$= -D_m (c_k^m - c_b^m) / d_m$$

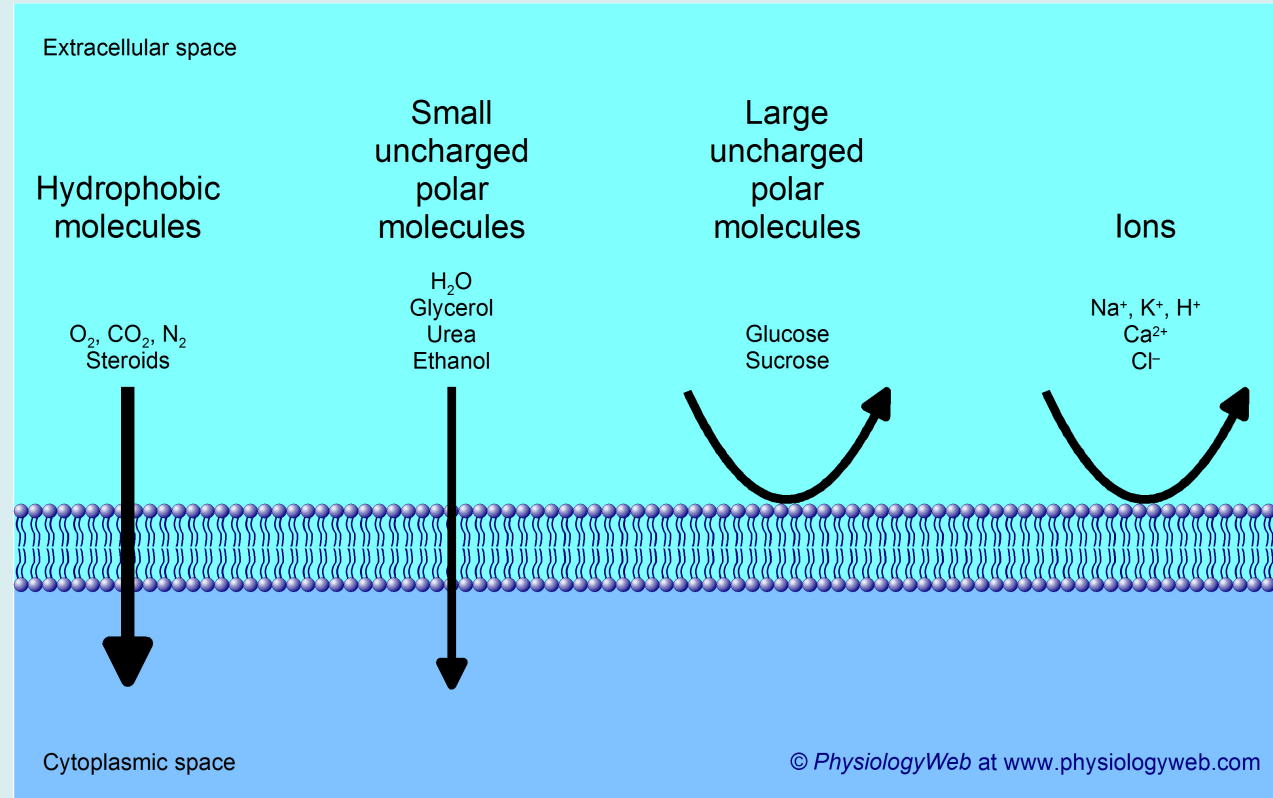
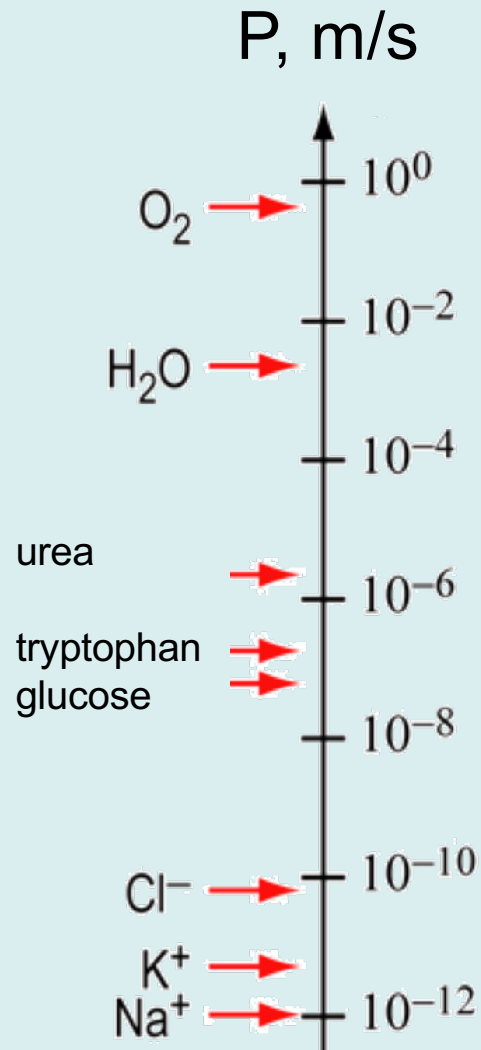
$$= -P_m \Delta c_m$$

$$= -P_m \beta \Delta c = -P \Delta c$$

P: permeability coefficient

$$[P] = \text{m/s}$$

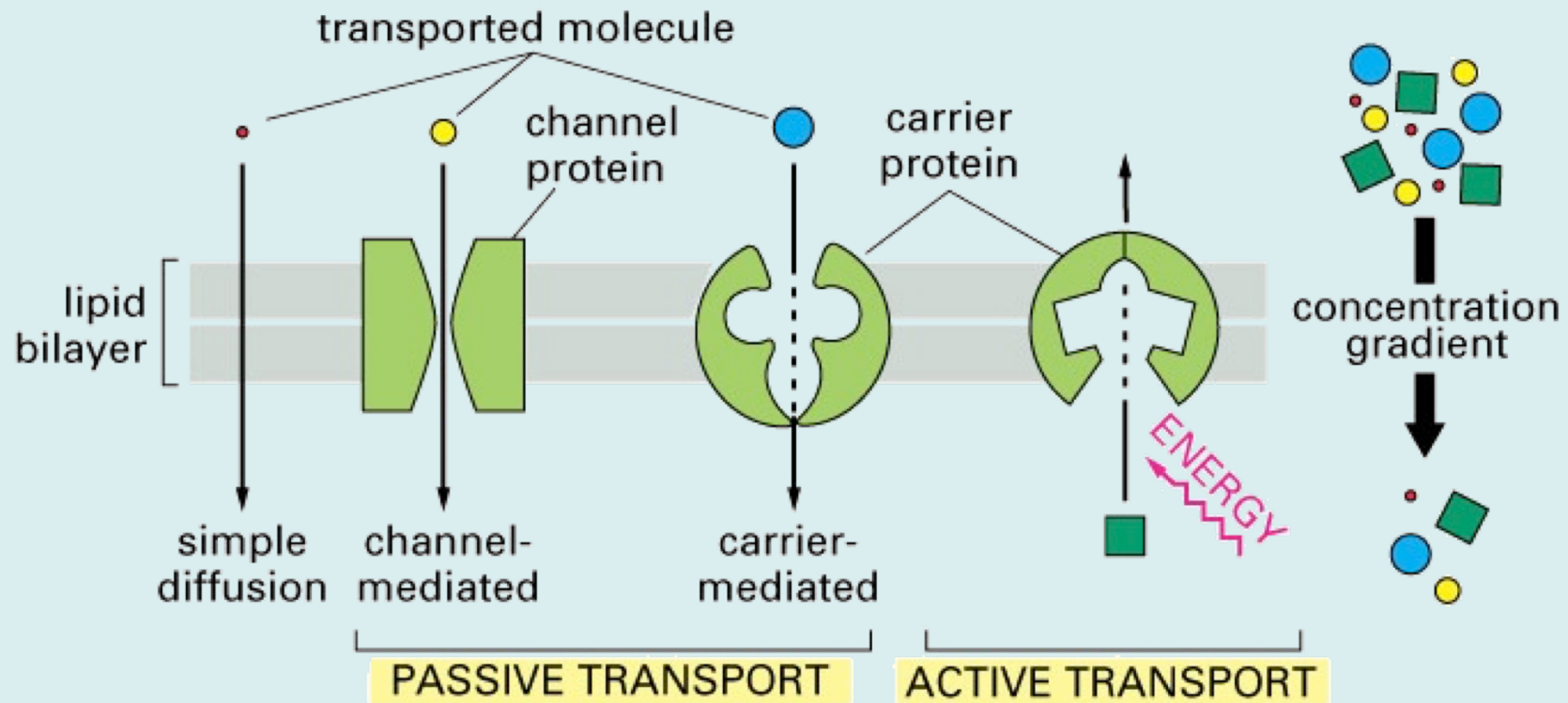
Diffusion across membranes



Na⁺ ions: $P = 10^{-12} \text{ m/s} = 10^{-3} \text{ nm/s}$, so it takes ~2h to get across a 5 nm membrane!

The phospholipid bilayer is practically impermeable for small ions and larger charged molecules!

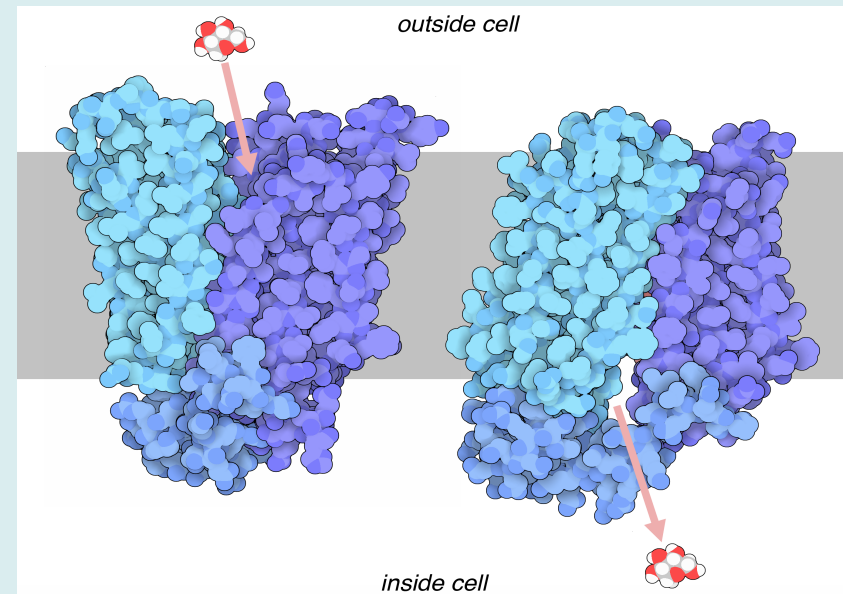
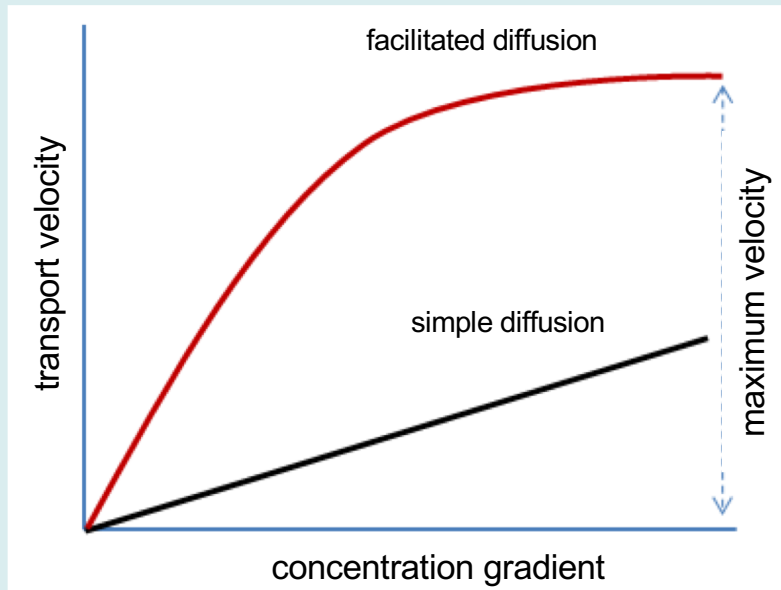
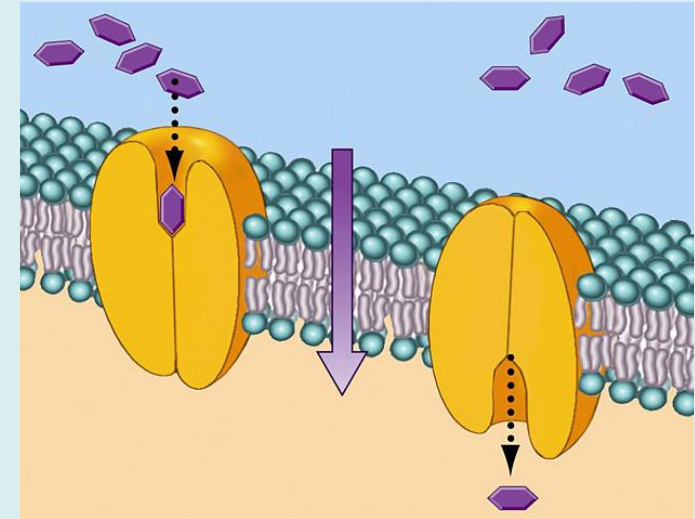
Transport across biological membranes



- free diffusion is effective only for small non-polar molecules
- the transport mechanism can be channel-mediated or carrier-mediated
- based on its energy requirement, the transport can be passive or active

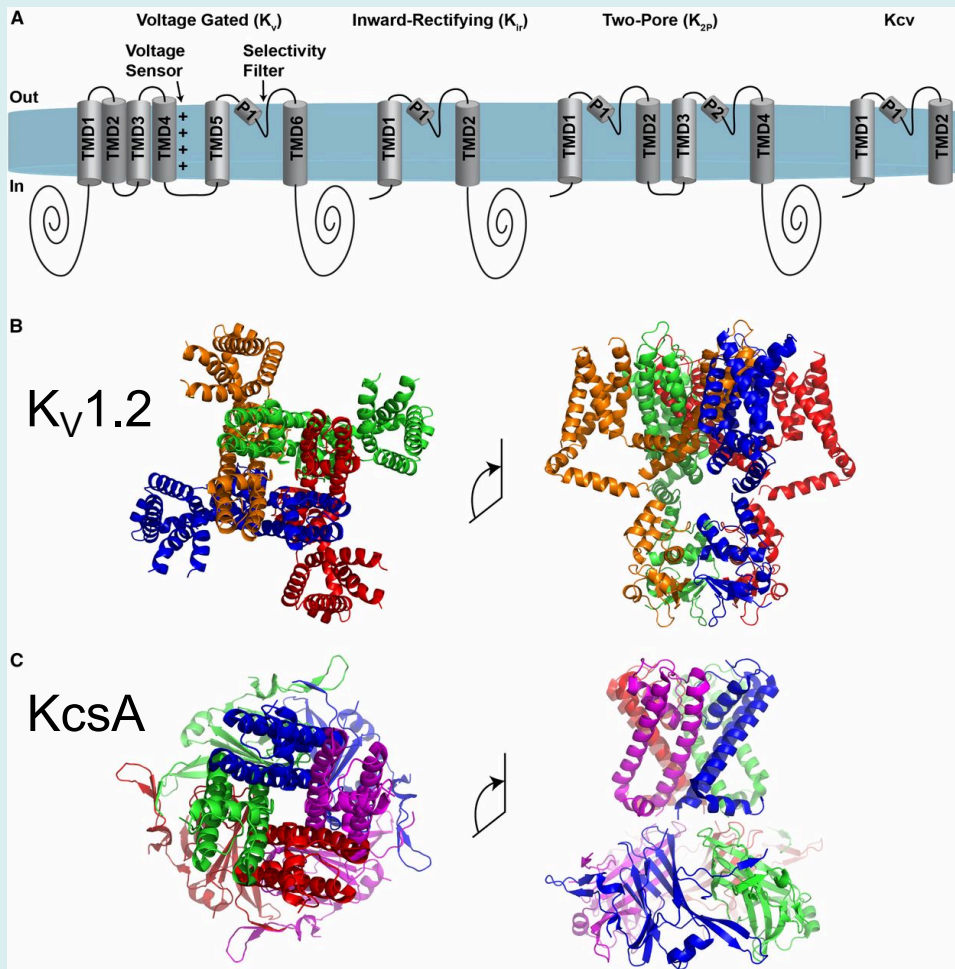
Facilitated diffusion

- utilizing a carrier protein, which binding site has access both on the extracellular and on the intracellular sides
- at a given concentration gradient the transport velocity is higher in the case of facilitated diffusion
- it follows Michalis-Menten kinetics, saturatable and can be selectively inhibited (example: “GLUT” glucose transporters)

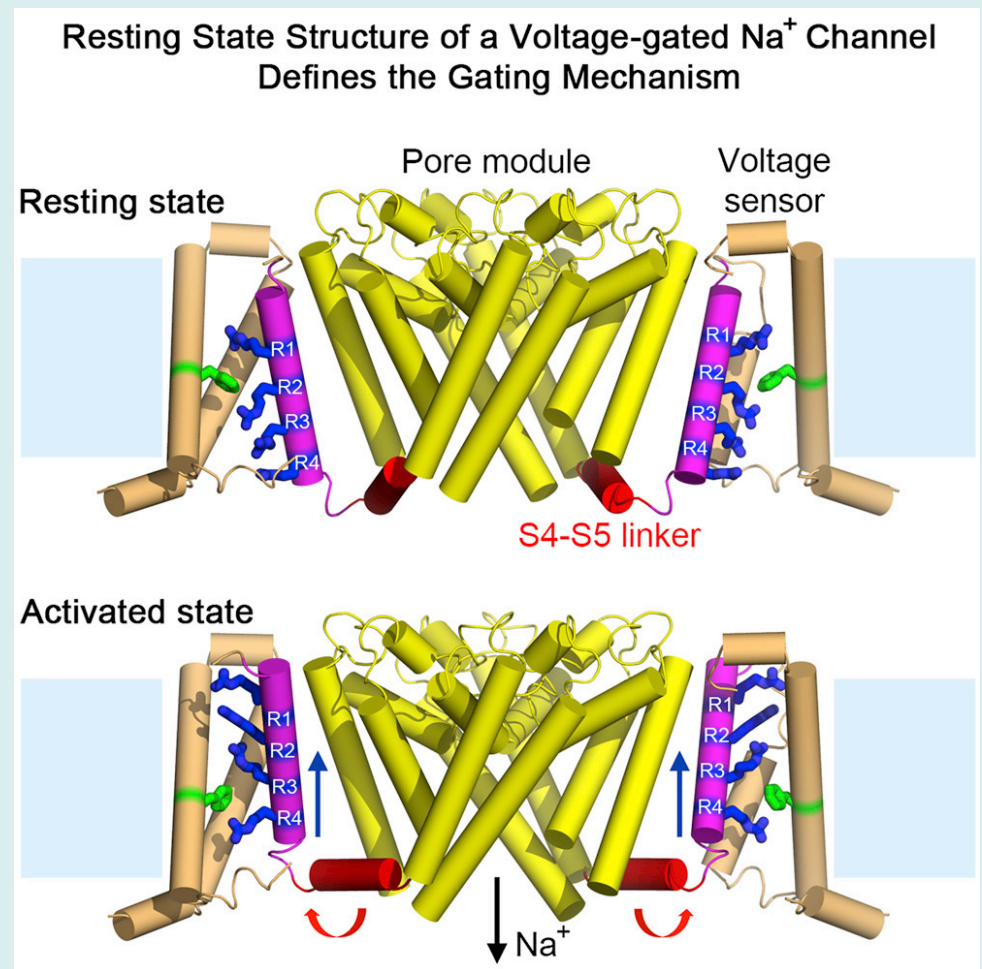


Ion-channels

multisubunit transmembrane proteins, selective for ions, their open/closed states are governed either by regulatory molecules (neurotransmitters, hormones) or by change in membrane potential

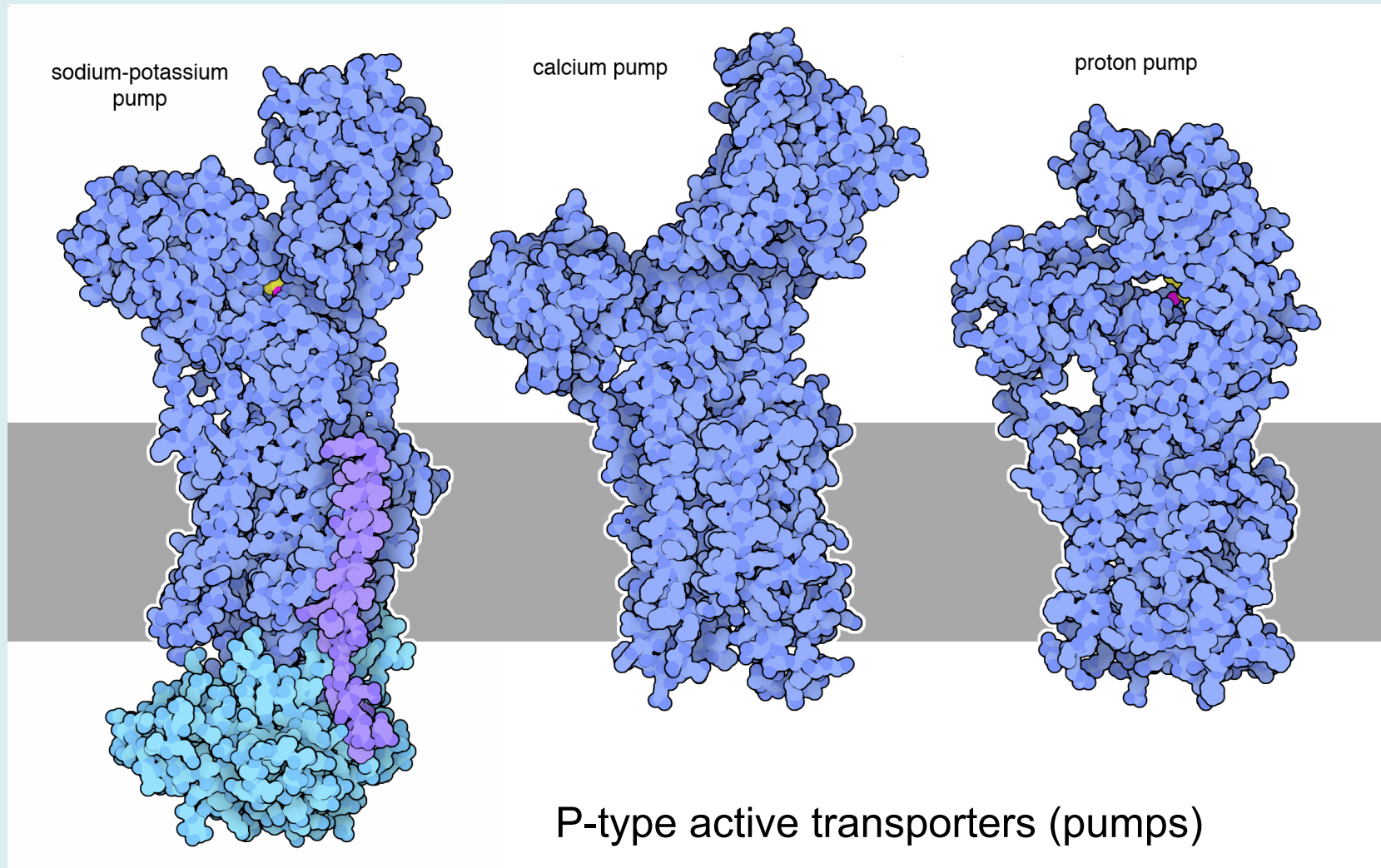


K^+ channels

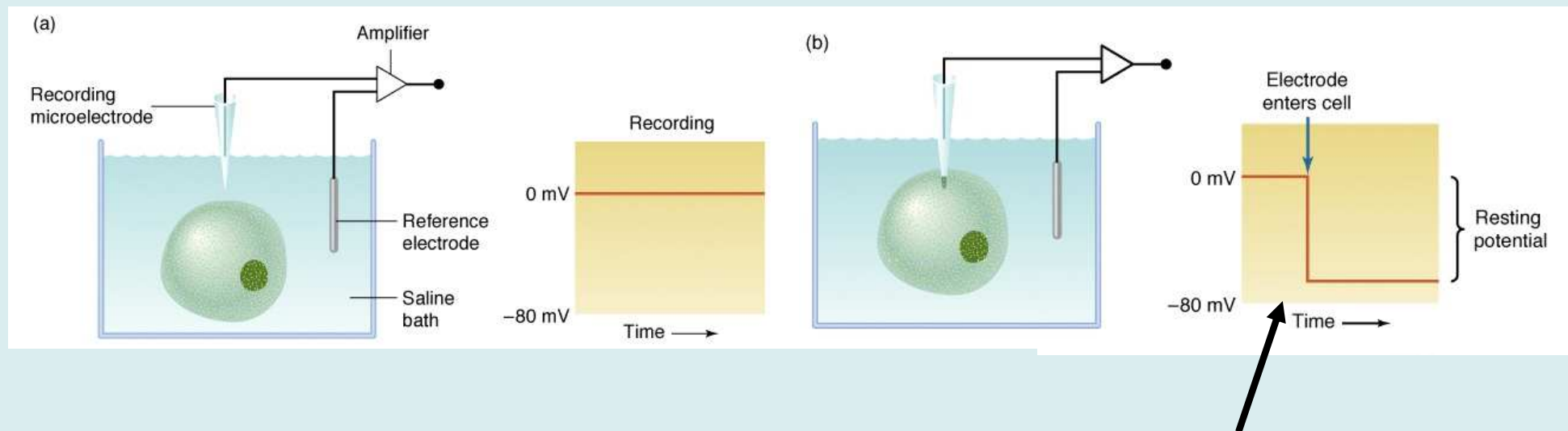


voltage-gated Na^+ channel

Active transporters



Fact1: An electric potential difference can be measured between the outer and inner surface of the cell membrane



membrane potential $\sim -60 - -90$ mV

In resting (not activated) cells the inner surface of plasma membrane is always on negative potential relative to the outer surface.

Fact2: The ionic composition is characteristically different in the interior and in the exterior of cells

Ion	Intracellular concentration (mM)	Extracellular concentration (mM)
Na^+	15	142
K^+	150	4
Cl^-	5	120
Ca^{2+}	10^{-4}	1
Mg^{2+}	1	0.5
HCO_3^-	8	27
Nonpenetrating anions	155	0

Diffusion of ions across membranes

$$\text{Fick I. } J_m = -D \frac{\Delta c}{\Delta x}$$

for neutral
particles

Diffusion of ions depends both on the chemical and the electric potential – electrochemical potential:

$$\mu_e = \mu + zF\varphi$$

consequence:
k-th ion's flux:

$$J_k = -D_k \left(\frac{\Delta c_k}{\Delta x} + c_k \frac{z_k F}{RT} \frac{\Delta \varphi}{\Delta x} \right)$$

Electrochemical equilibrium

$$\mu_e = \mu + zF\varphi$$



$$\mu_{e,i}^{II} - \mu_{e,i}^I = 0$$



$$\mu_0 + RT \ln c_i^I + zF\varphi_i^I = \mu_0 + RT \ln c_i^{II} + zF\varphi_i^{II}$$



equilibrium potential $\longrightarrow \varphi_i^I - \varphi_i^{II} = \frac{RT}{zF} \ln \frac{c_i^I}{c_i^{II}}$ Nernst equation

Donnan model of membrane potential

- there is an electrochemical equilibrium in resting cells
- the cell membrane is permeable only for K^+ ions


$$\varphi_e - \varphi_i = -\frac{RT}{F} \ln \frac{[K^+]_i}{[K^+]_e}$$

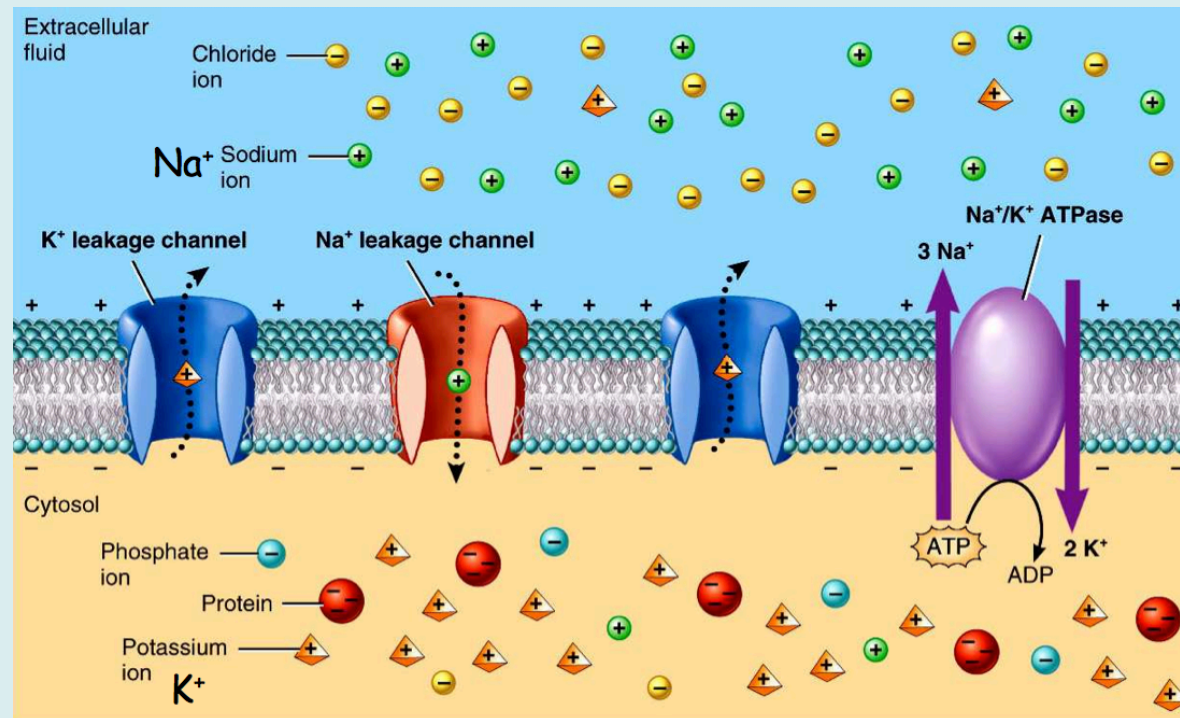
The membrane potential cannot be described properly with Donnan equilibrium model.

Tissue	Resting potential (mV)	
	calculated	measured
Giant axon of squid	<i>91</i>	62
Frog muscle	<i>103</i>	92
Rat muscle	<i>92,9</i>	92

Transport model membrane potential

the membrane is permeable, but to a different extent, to the various ions (e.g. K^+ , Na^+ , Cl^-)

flux of ions $\neq 0$, but the net flux = 0



Transport model membrane potential

$$\Sigma J = J_{K^+} + J_{Na^+} + J_{Cl^-} = 0$$

$$J_k = -D_k \left(\frac{\Delta c_k}{\Delta x} + c_k \frac{z_k F}{RT} \frac{\Delta \varphi}{\Delta x} \right)$$

$$\varphi_e - \varphi_i = -\frac{RT}{F} \ln \frac{\Sigma p_k^+ c_{ke}^+ + \Sigma p_k^- c_{ki}^-}{\Sigma p_k^+ c_{ki}^+ + \Sigma p_k^- c_{ke}^-}$$

Goldman – Hodgkin – Katz equation

$$P_K : P_{Na} : P_{Cl} = 1 : 0,05 : 0,45$$

Transport model membrane potential

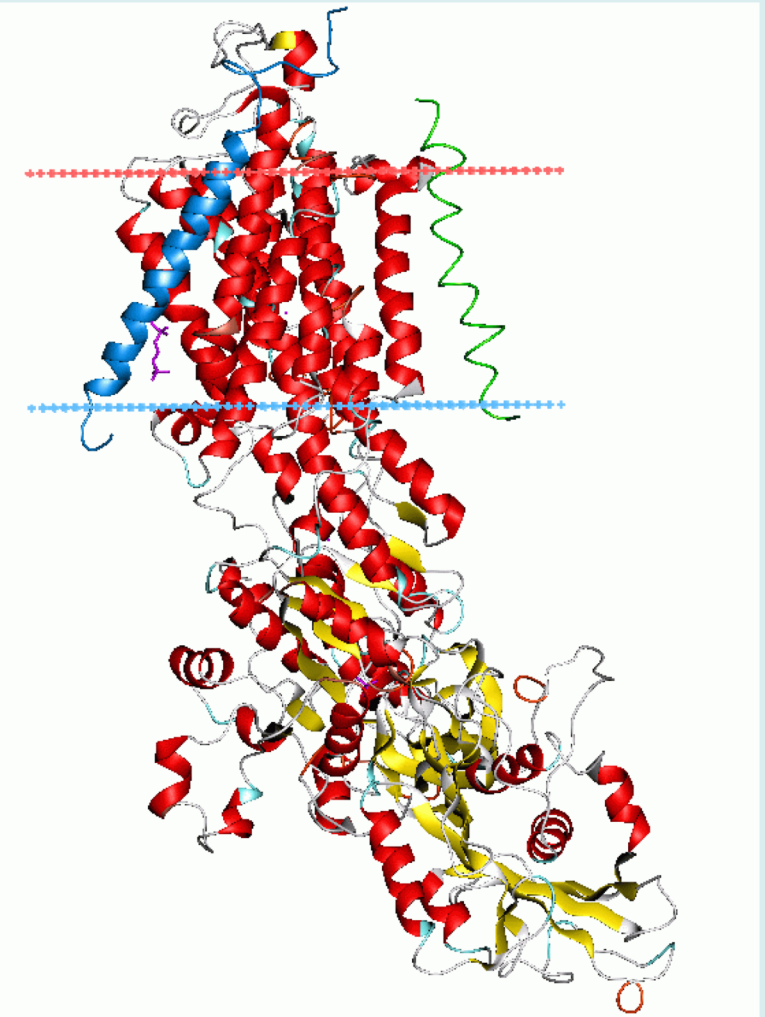
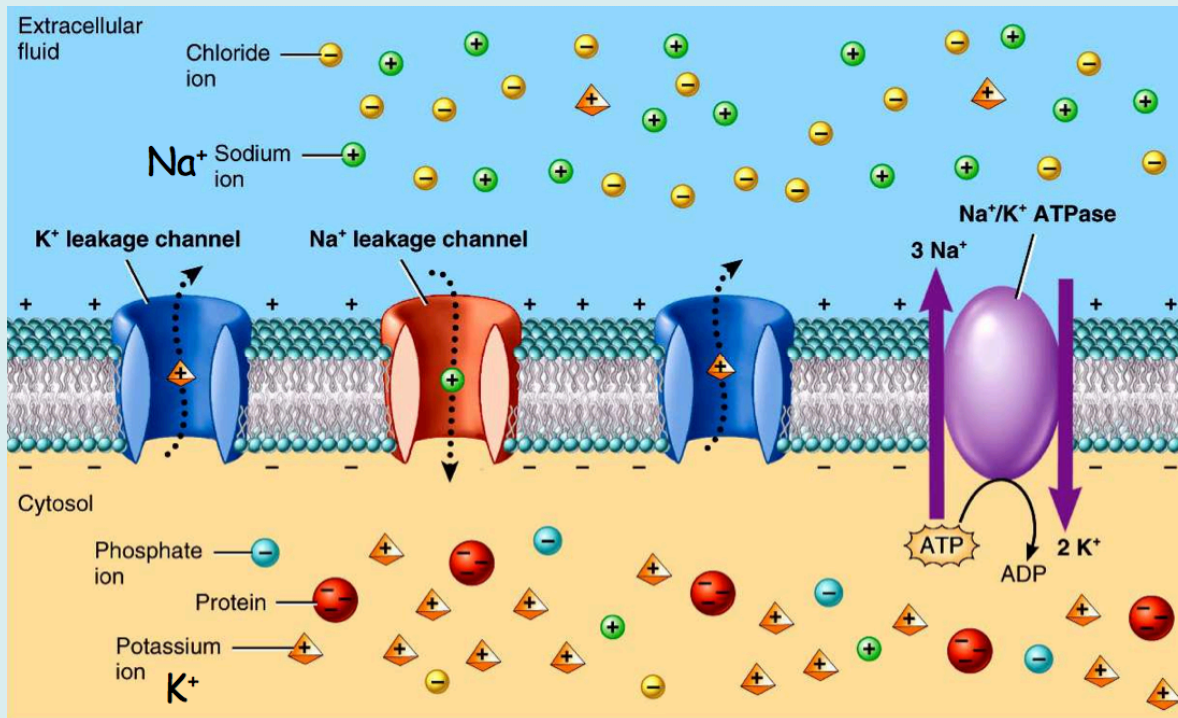
potential (mV)	Squid axon	Rat muscle
U_{measured}	-62	-92
U_{GHK}	-61,3	-89,2

$$\varphi_e - \varphi_i = -\frac{RT}{F} \ln \frac{\sum p_k^+ c_{ke}^+ + \sum p_k^- c_{ki}^-}{\sum p_k^+ c_{ki}^+ + \sum p_k^- c_{ke}^-}$$

$$P_K : P_{Na} : P_{Cl} = 1 : 0,05 : 0,45$$

good agreement with experimental results

The membrane potential is maintained by the Na^+/K^+ ATPase (pump)

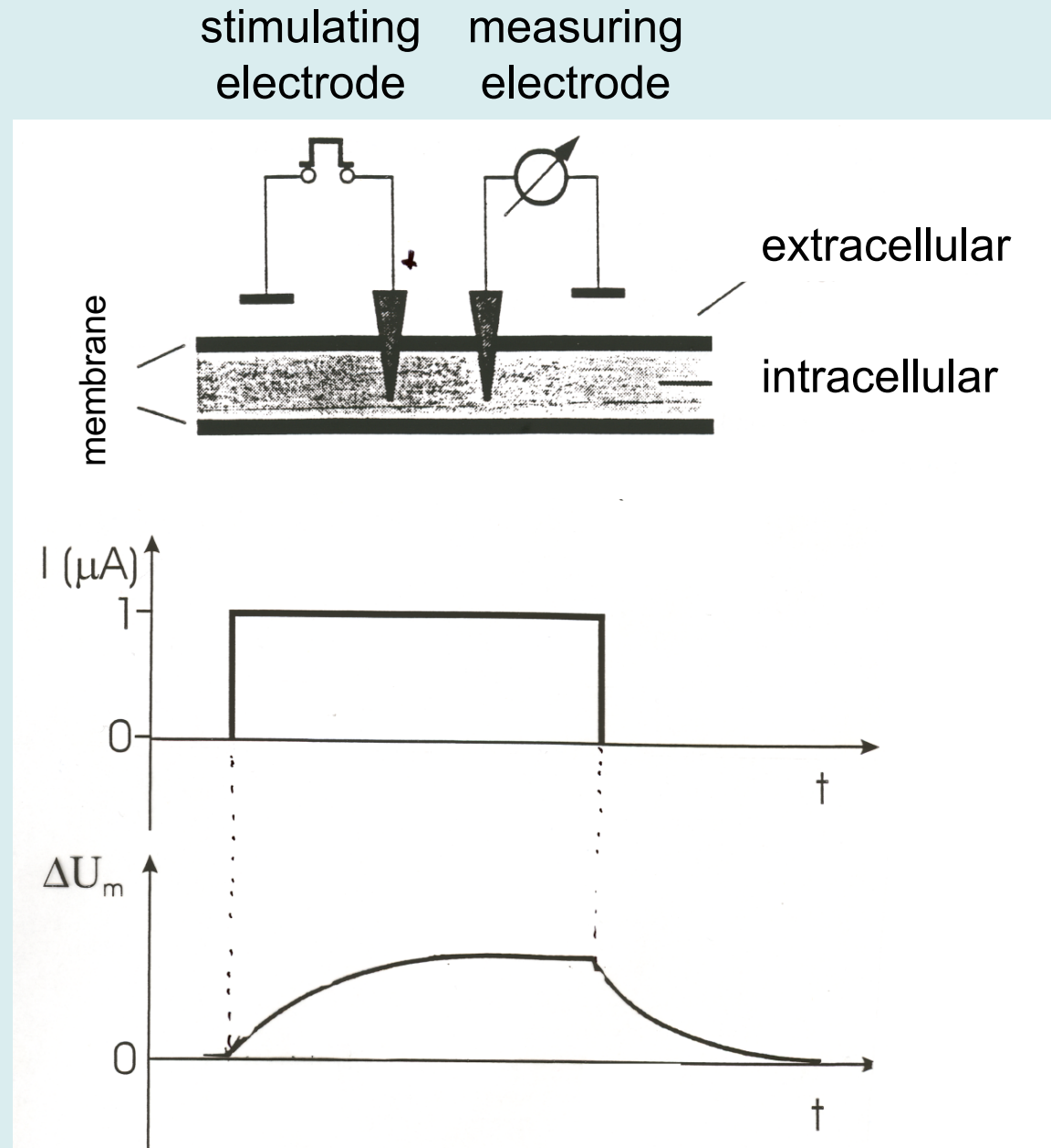


In rest, $\sim 1/4^{\text{th}}$ of all the energy in a cell is consumed by the Na^+/K^+ pump!

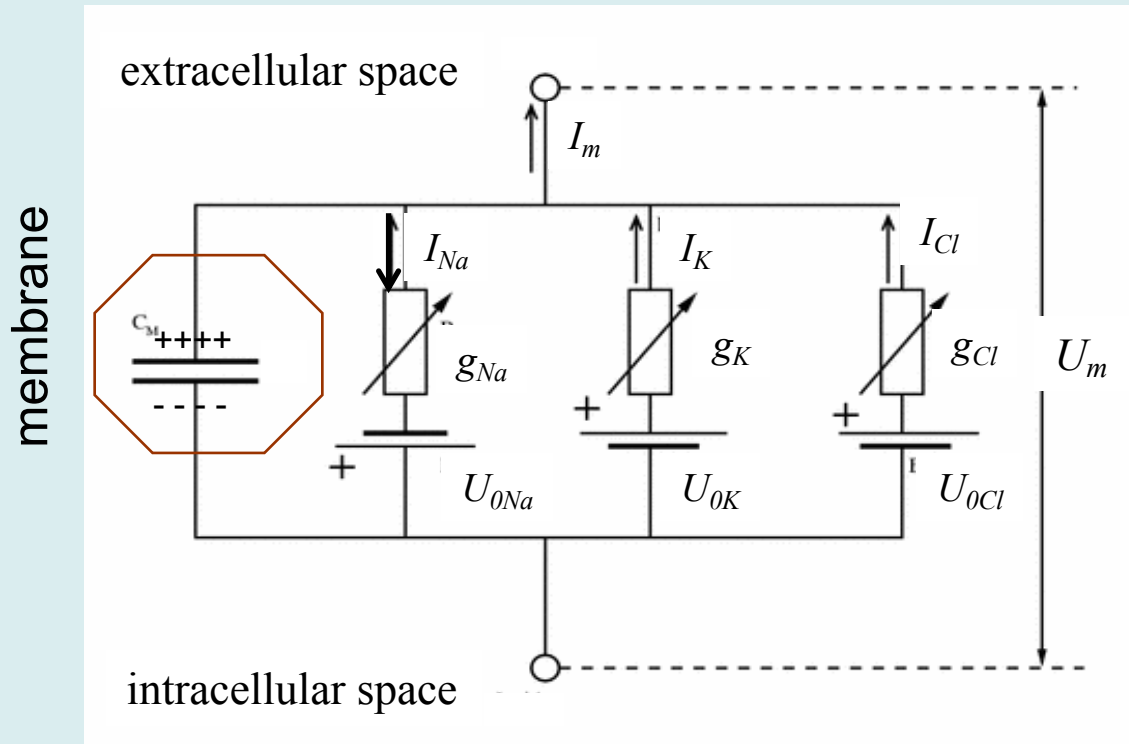
Passive electric properties of membranes

Experiment:

The direction of current is the direction of the flow of positive charges



The electric model of membranes



resistors
(ion conductivity)

capacitor
(capacitance)

membrane current:
$$I_m = I_{ion} + I_c$$

conductive
current

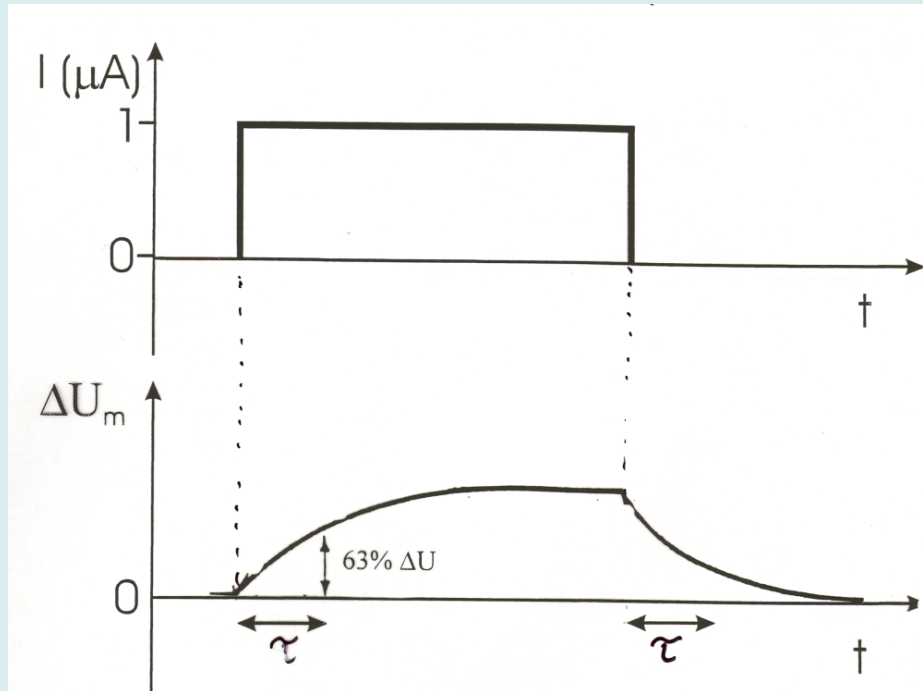
changes along the changes
in conductivity

capacitive current

$$I_c = C_m \frac{\Delta U_m}{\Delta t}$$

Local changes in membrane potential

transient changes of membrane potential limited in space and time



membrane capacitance membrane resistance

$$\tau = C_m R_m$$

$$U_m(t) = U_t \left[1 - e^{-\frac{t}{R_m C_m}} \right]$$

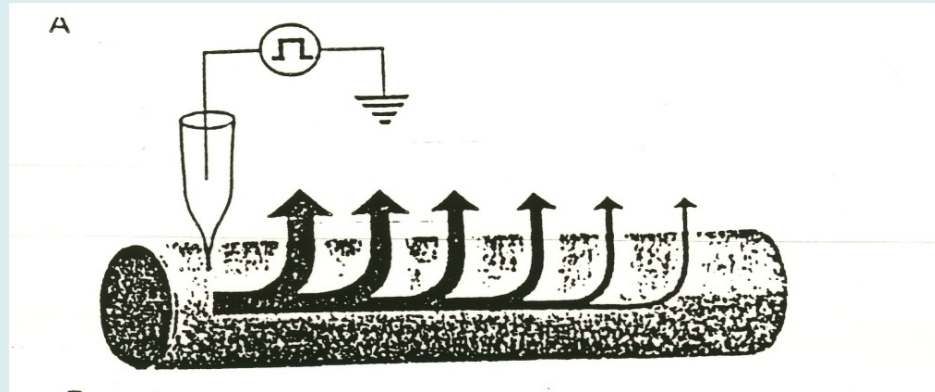
τ = time constant of the membrane:

the time needed for the change in membrane potential

- to reach 63% of its maximum value
- to drop to the e-th of its value at the end of stimulation

Local changes in membrane potential

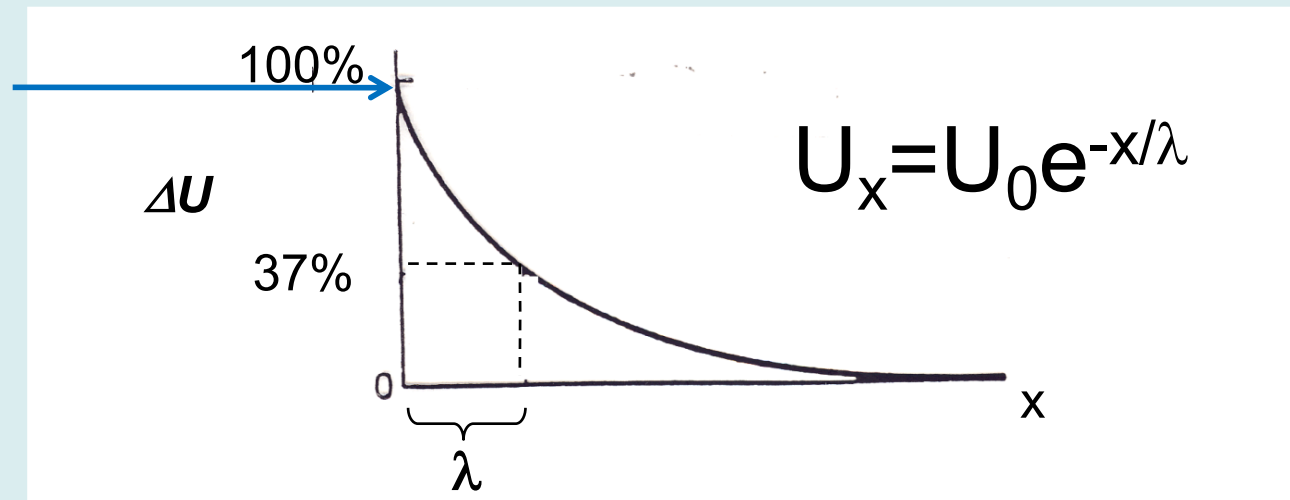
transient changes of membrane potential limited in space and time



$$\lambda \sim \sqrt{\frac{R_m}{R_i}}$$

R_i : resistance of intracellular space

local change
in membrane
potential
(stimulation)



$\lambda = \text{space constant of the membrane:}$

the distance where the amplitude of stimulus
is the e-th of its initial value

Local changes in membrane potential

transient changes of membrane potential limited in space and time

Induced by:

- current pulses experimentally
- adequate stimulus at receptor cells
- neurotransmitters at postsynaptic membranes:
 - excitatory potential - depolarization
 - inhibitory potential - hyperpolarization

Properties:

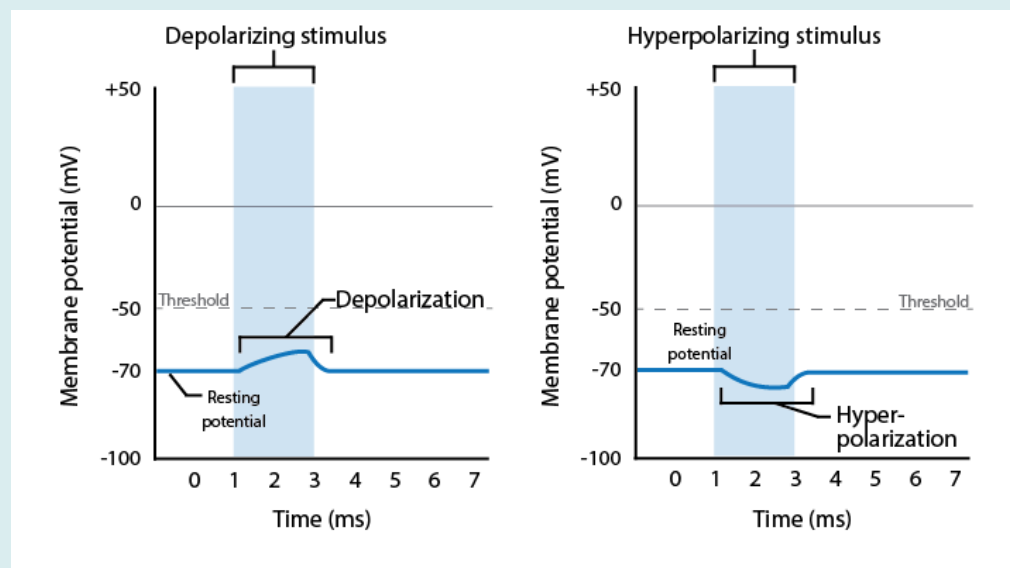
obligate, graded

magnitude and direction

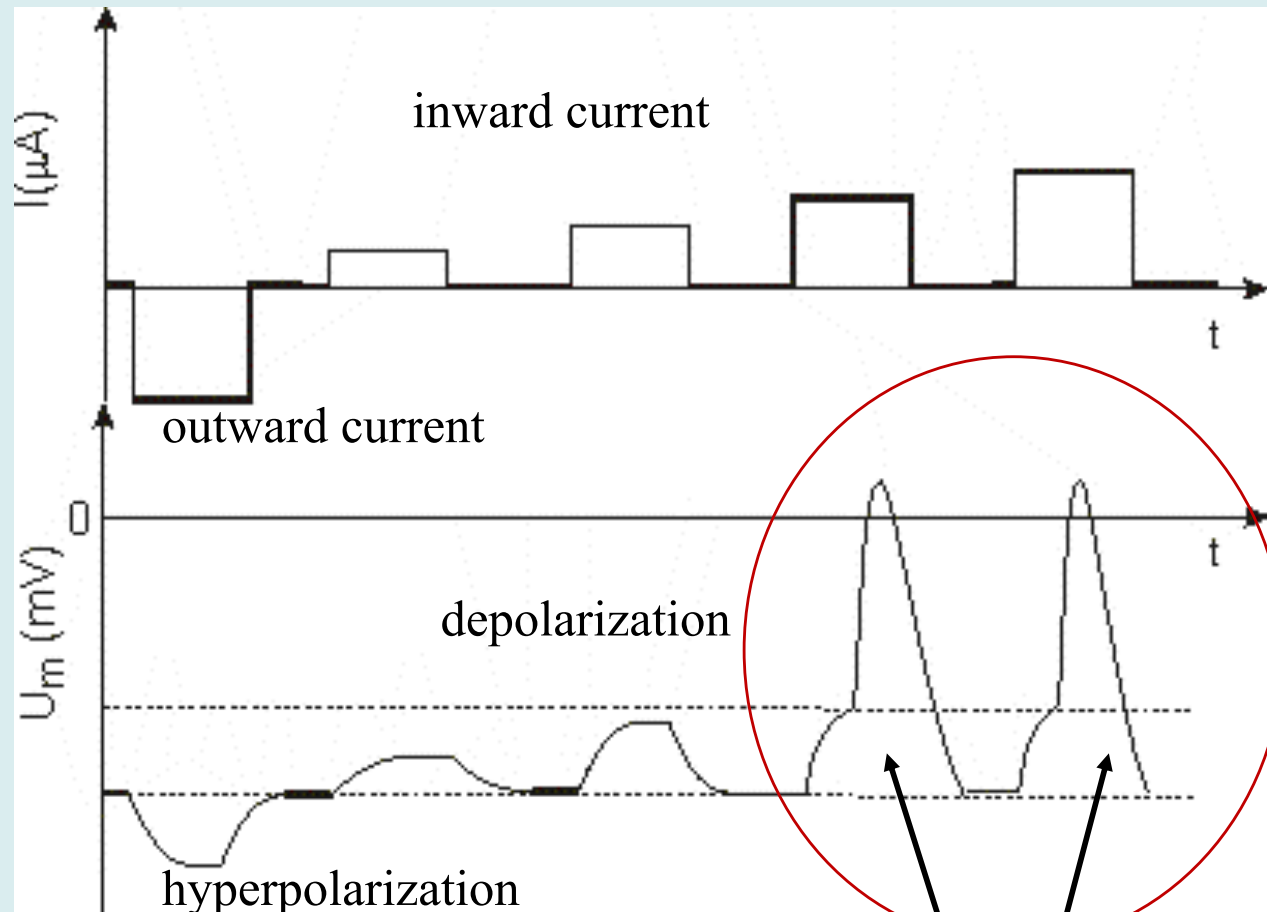
varies with stimuli

localized (limited)

SUMMATION in space and time = summation of local potential changes



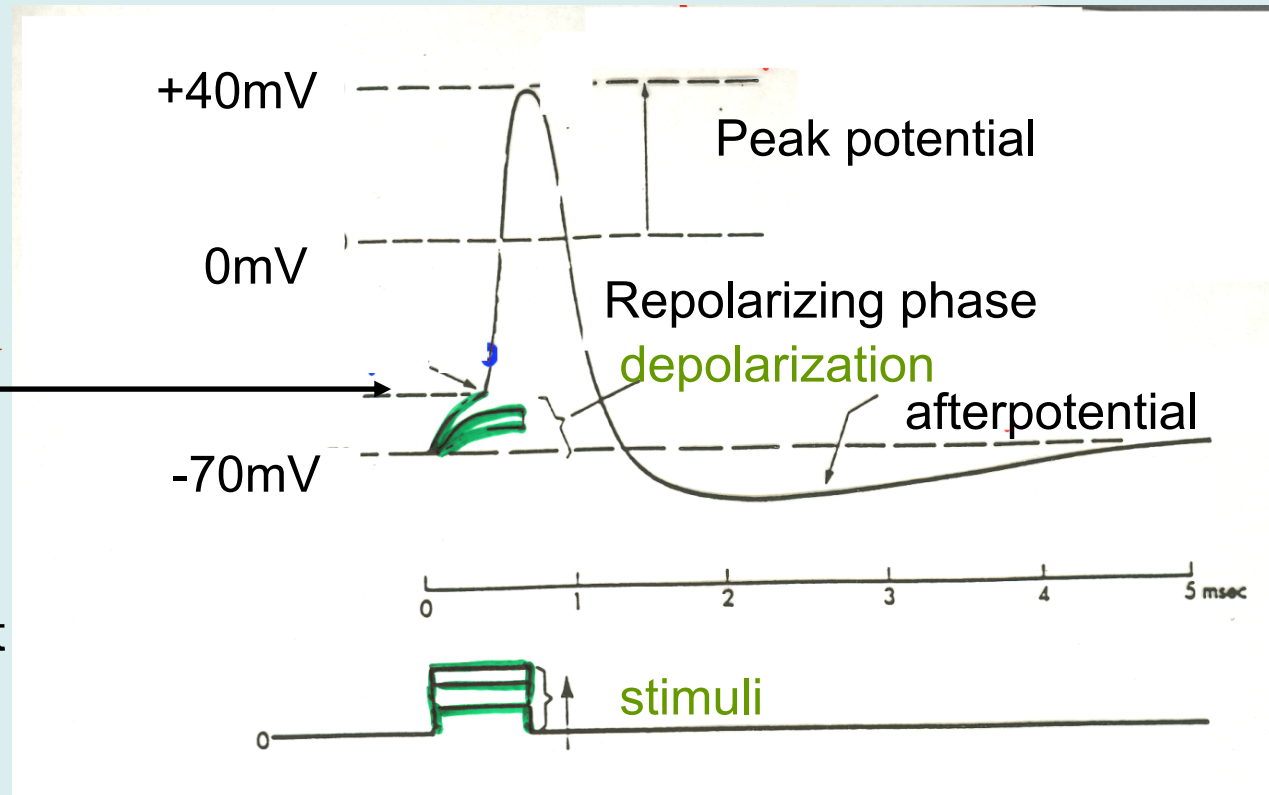
Observation



Action potential

Characteristics of the action potential


Threshold potential
critical membrane potential level at which an action potential can occur

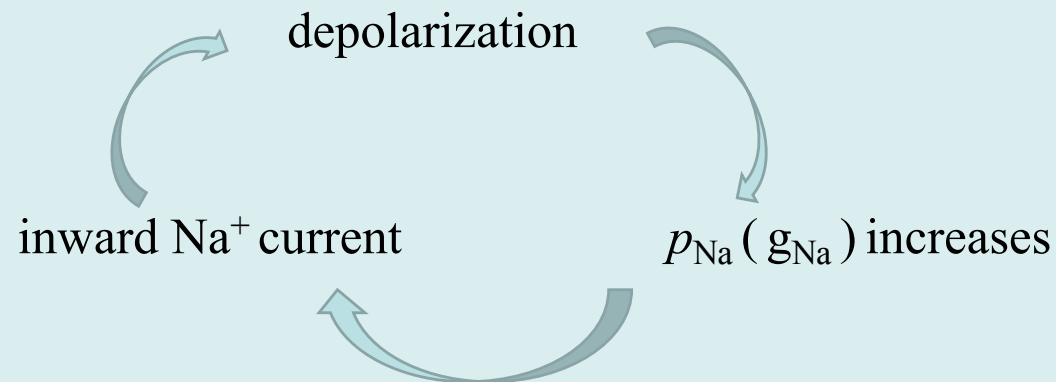


facultative
“All-or-none” amplitude
conducted with constant amplitude

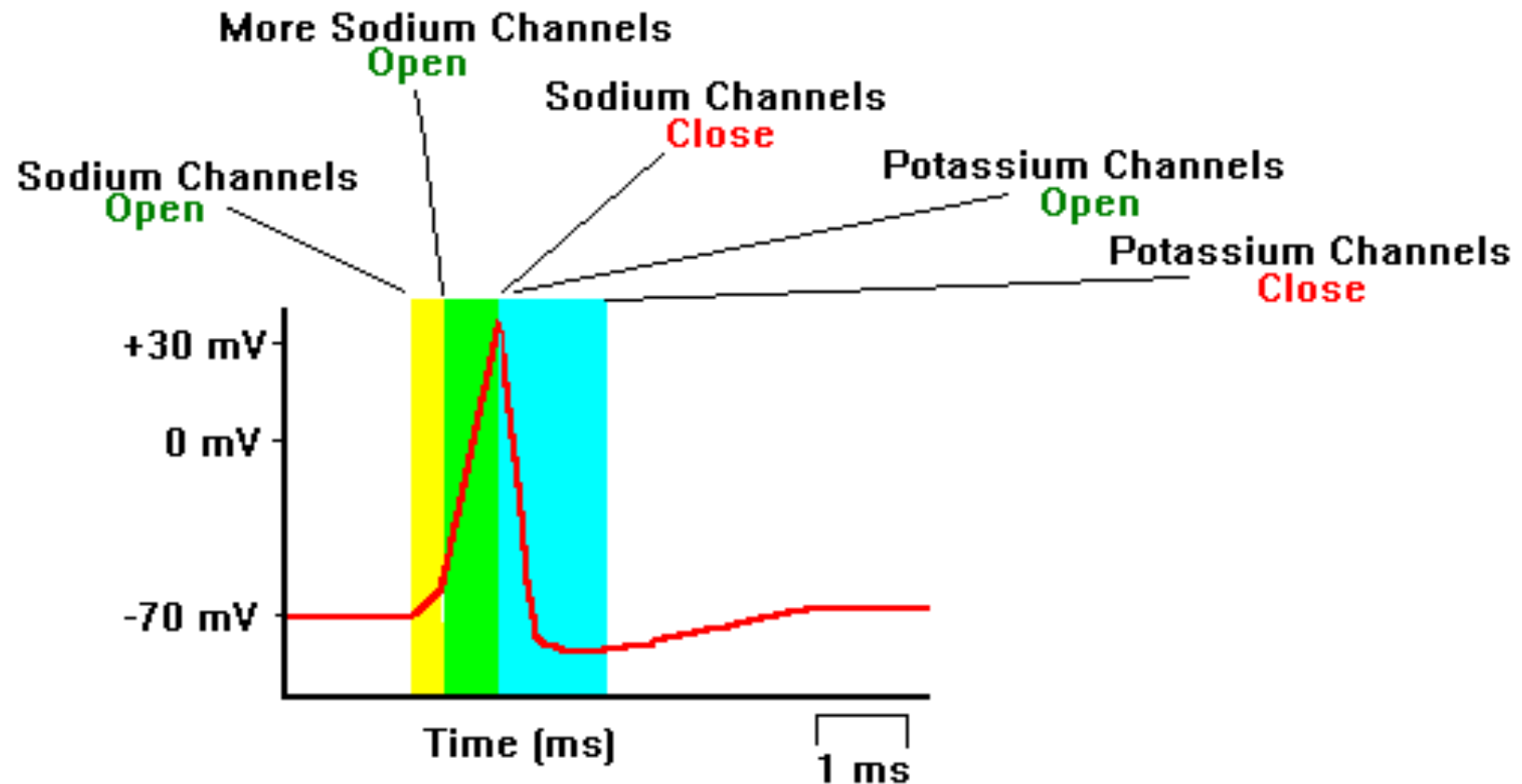
Hodgkin-Katz hypothesis of action potential generation

Voltage-gated, potential sensitive ion channels

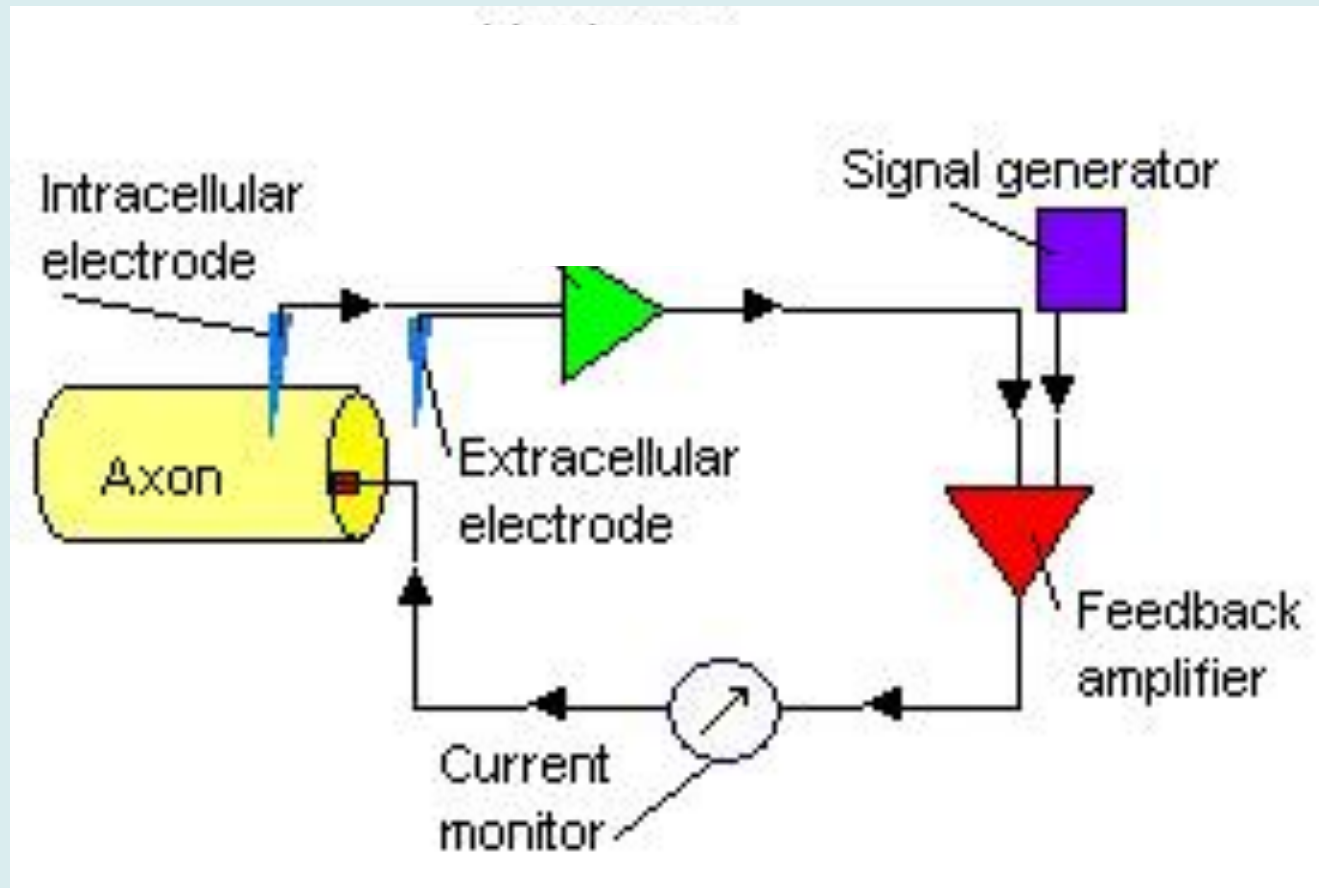

$$\varphi_e - \varphi_i = -\frac{RT}{F} \ln \frac{\sum p_k^+ c_{ke}^+ + \sum p_k^- c_{ki}^-}{\sum p_k^+ c_{ki}^+ + \sum p_k^- c_{ke}^-}$$



Hodgkin-Katz hypothesis of action potential generation

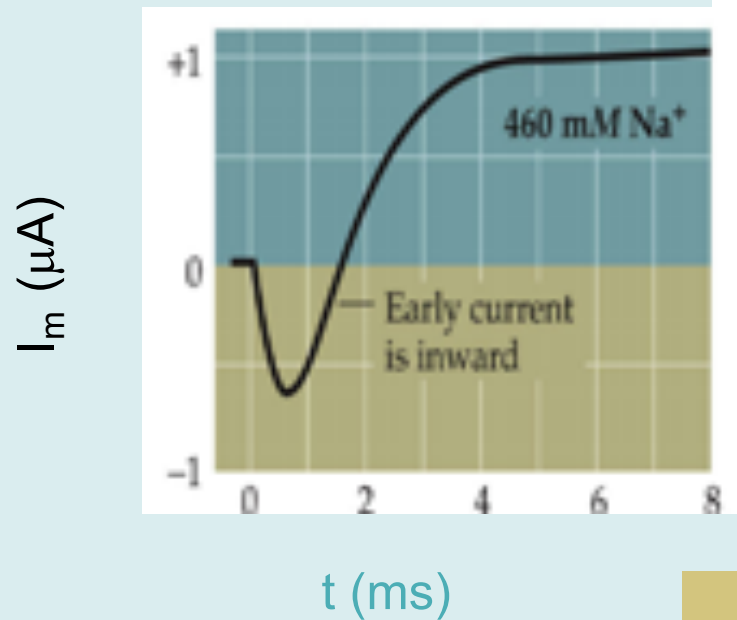


Voltage Clamp

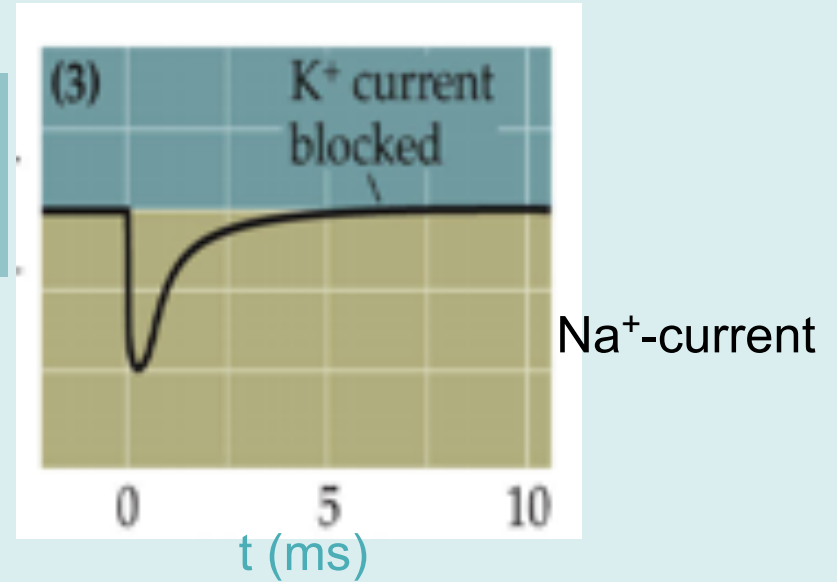


- Membrane potential is kept constant
- ion-current is measured

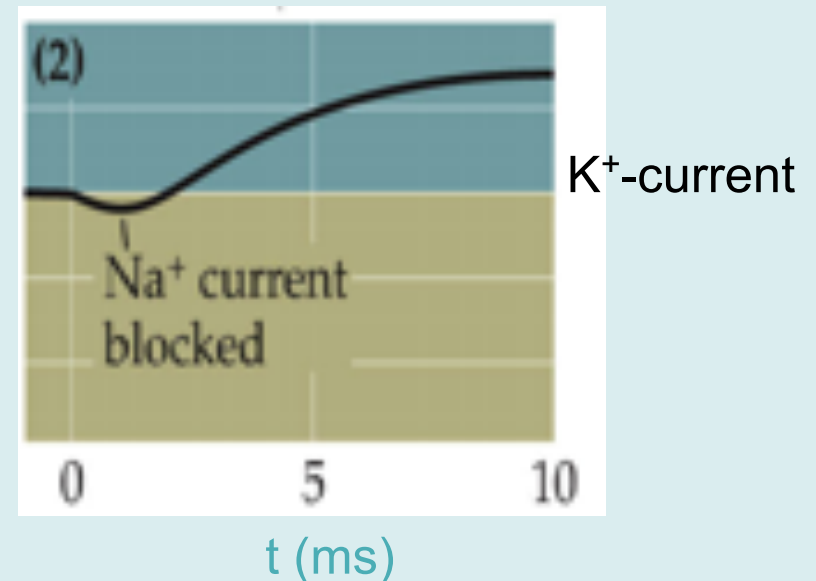
Measurement of separated ionic currents



Inhibited K^+ -channels

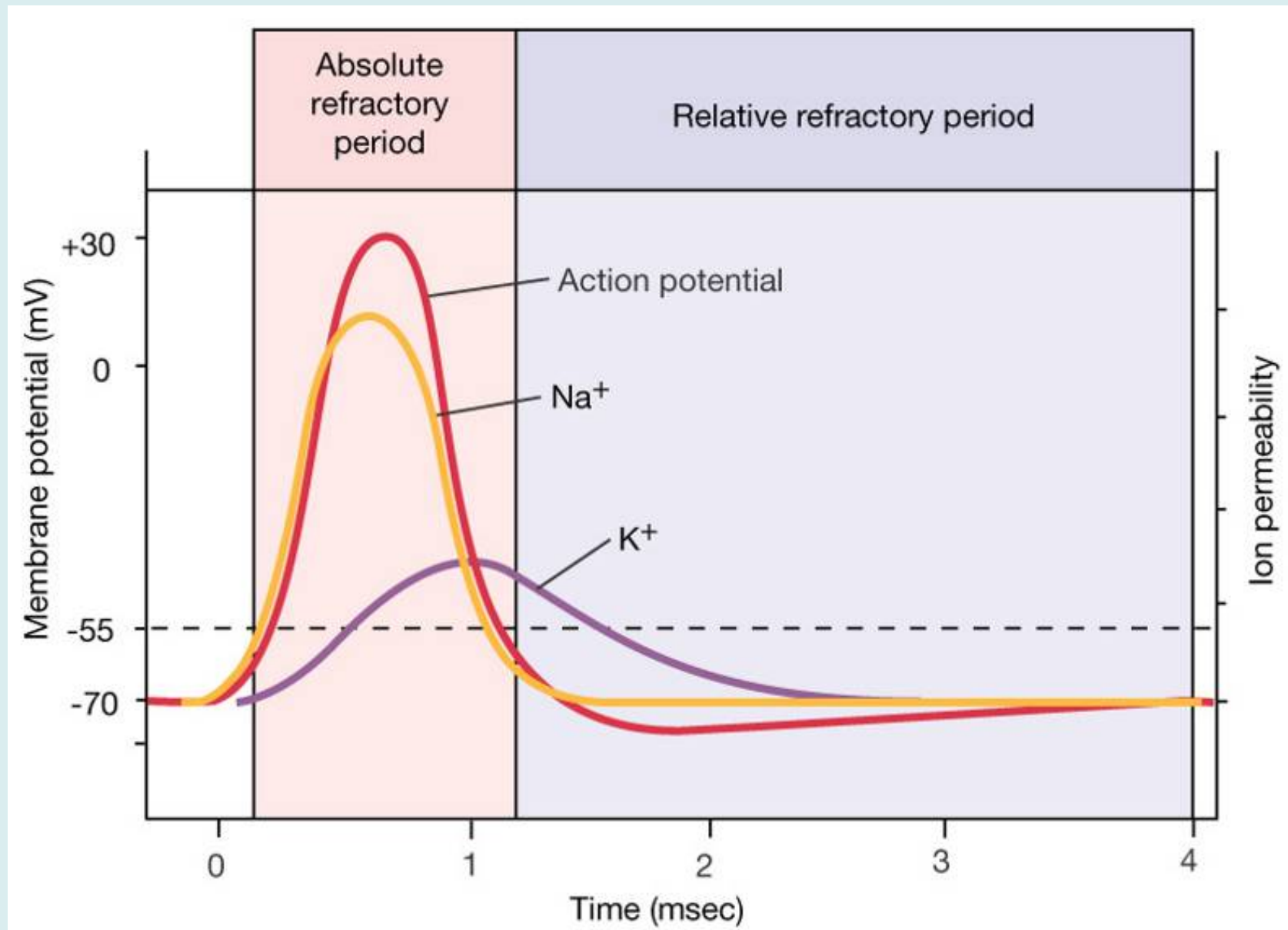


Inhibited Na^+ -channels

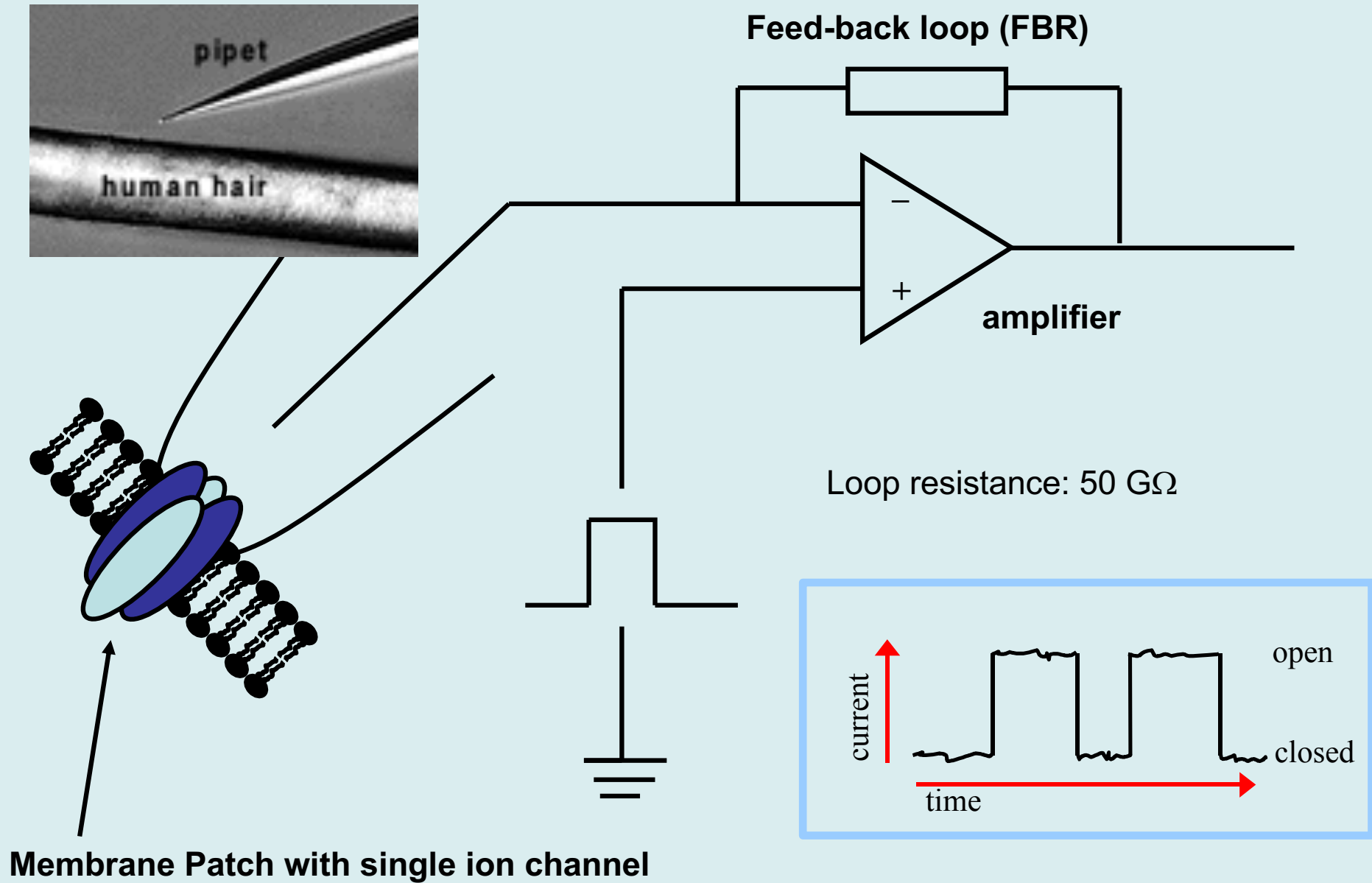


Voltage-Gated Na^+ and K^+ Channels

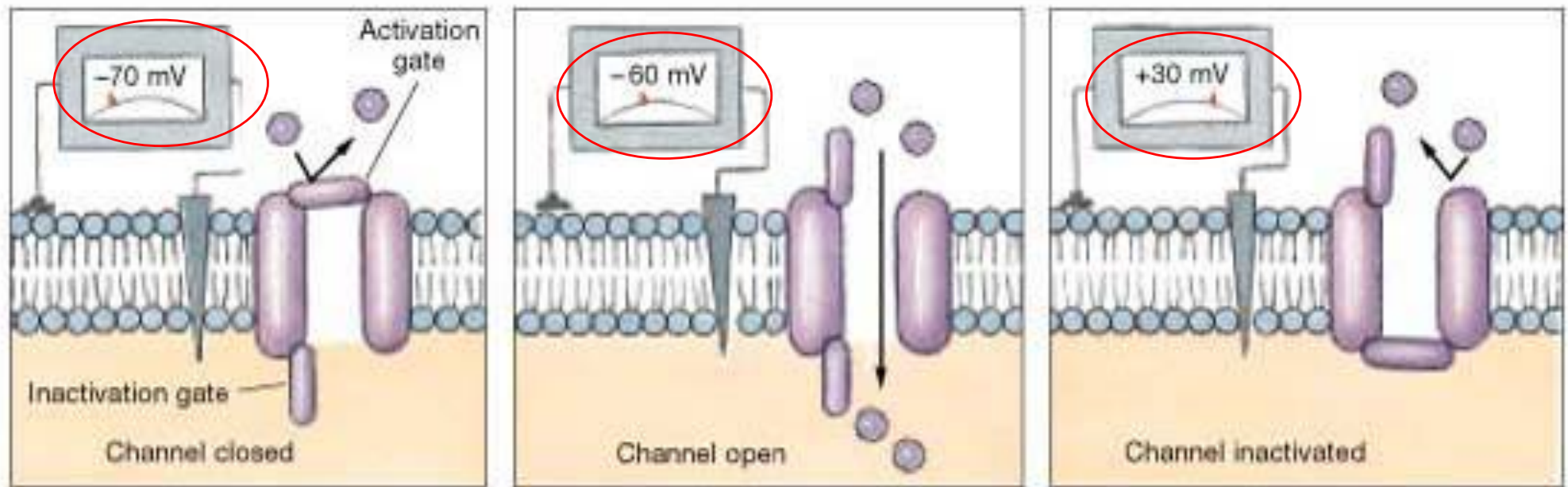
Conductivities during action potential



Patch-Clamp



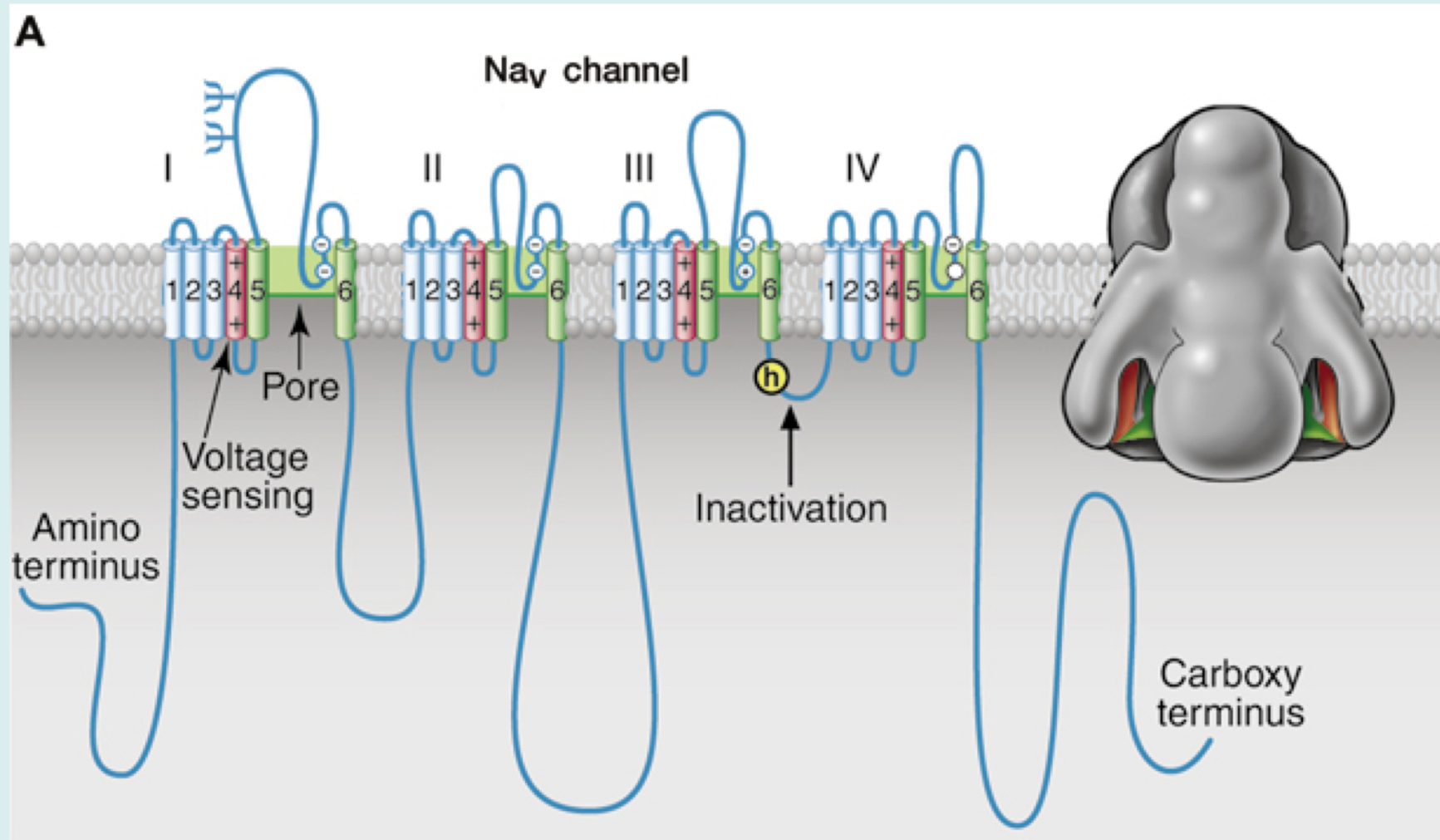
States of voltage-gated sodium channels



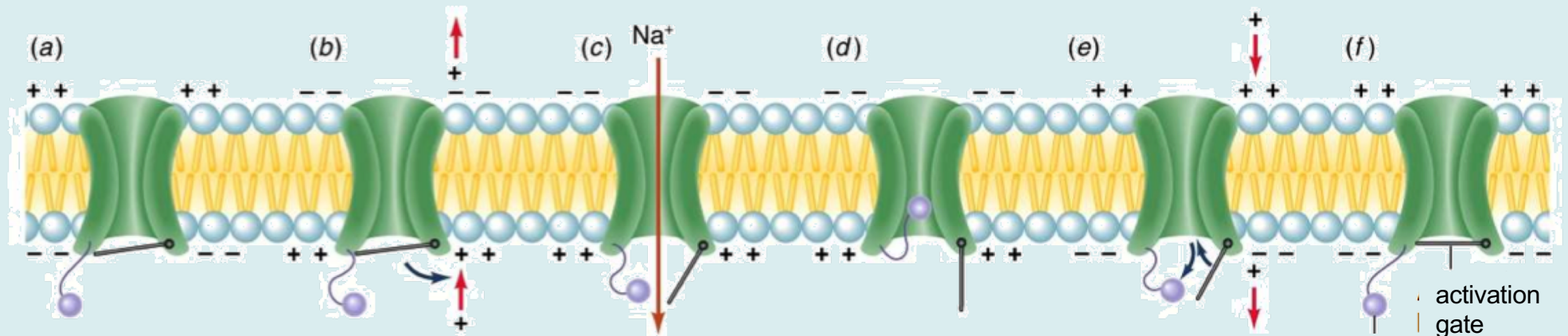
(c)

at depolarization threshold

Structure of the fast Na⁺ channel

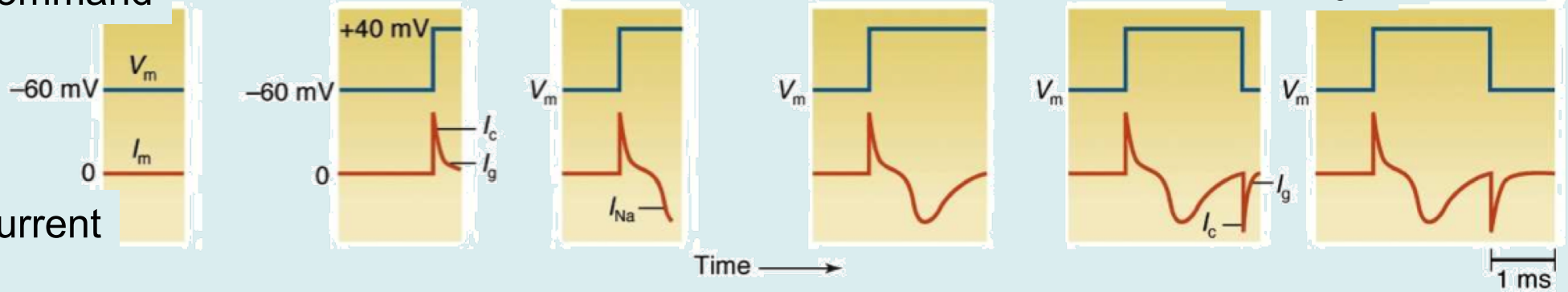


Function of the fast Na^+ channel



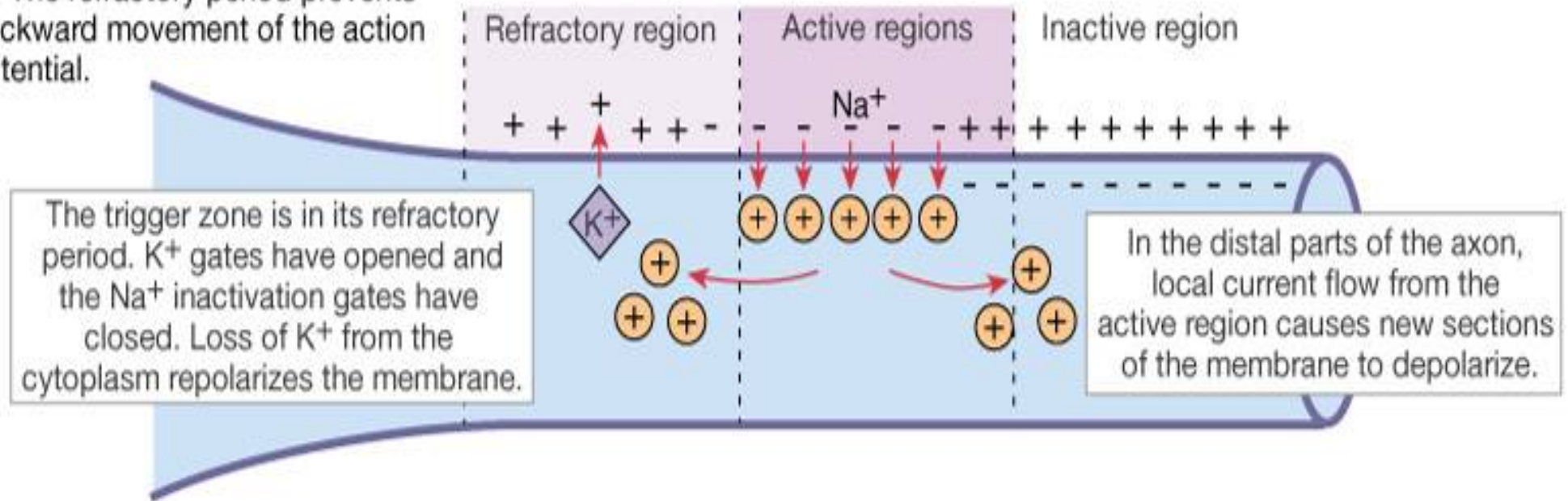
Command

Current



Propagation of action potential

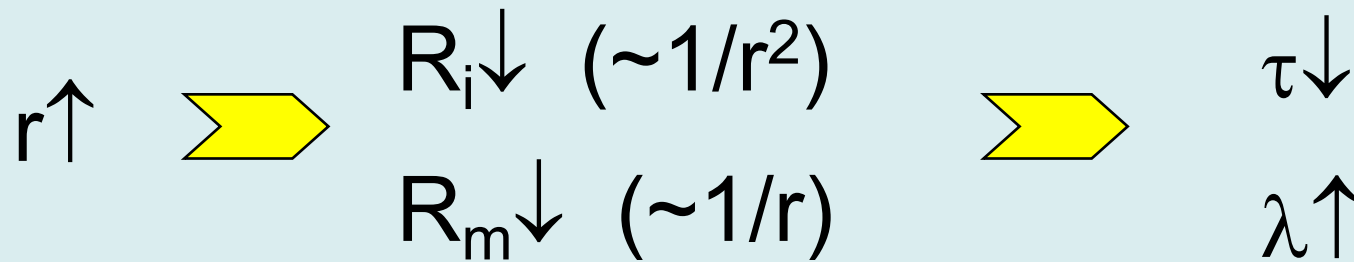
(c) The refractory period prevents backward movement of the action potential.



Speed and distance of propagation?

How are the *time constant* and the *space constant* related to propagation velocity of action potentials

Effect of axon diameter:

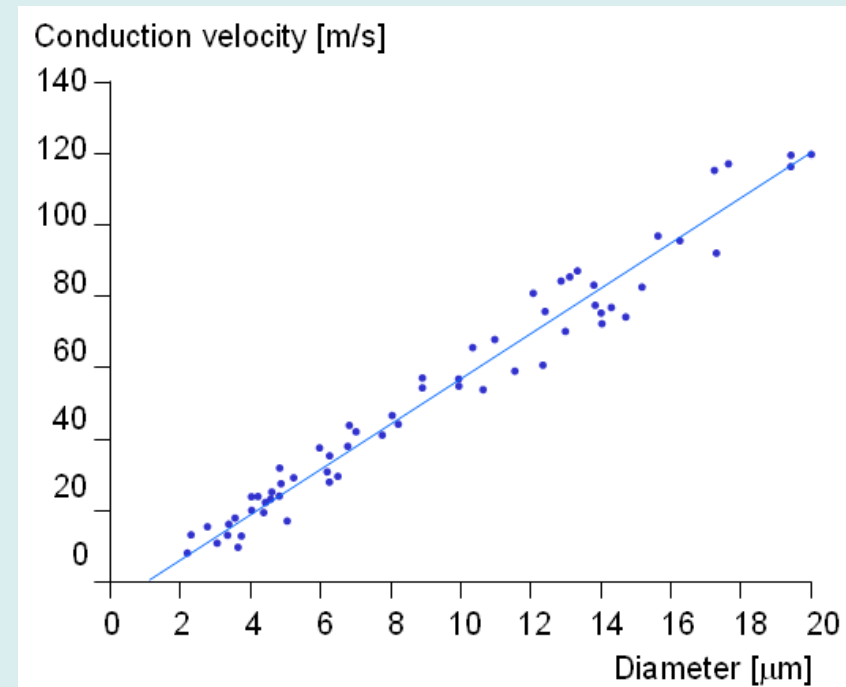


$$\tau = C_m R_m$$

$$\lambda \sim \sqrt{\frac{R_m}{R_i}}$$

Squid giant axon $r = 250 \mu\text{m}$
 $v = 25 \text{m/s}$

human nerve cell $r = 10 \mu\text{m}$
 $v \neq 0.5 \text{m/s} \text{ ?}$



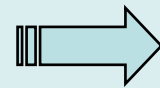
Myelination!

R_m – very high

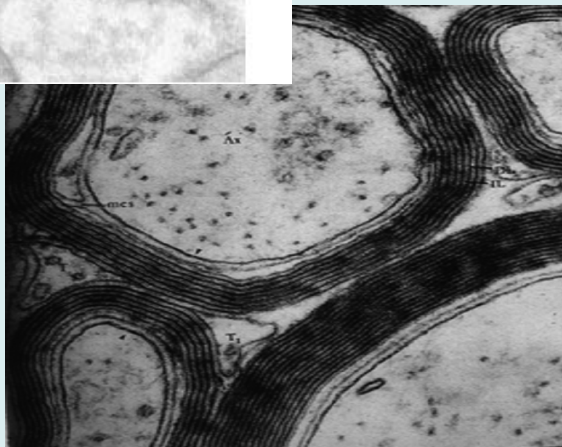
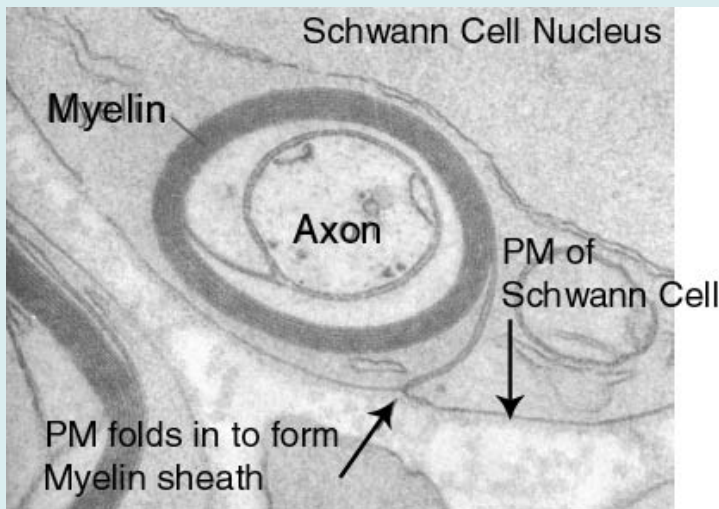


big space constant

C_m – very small



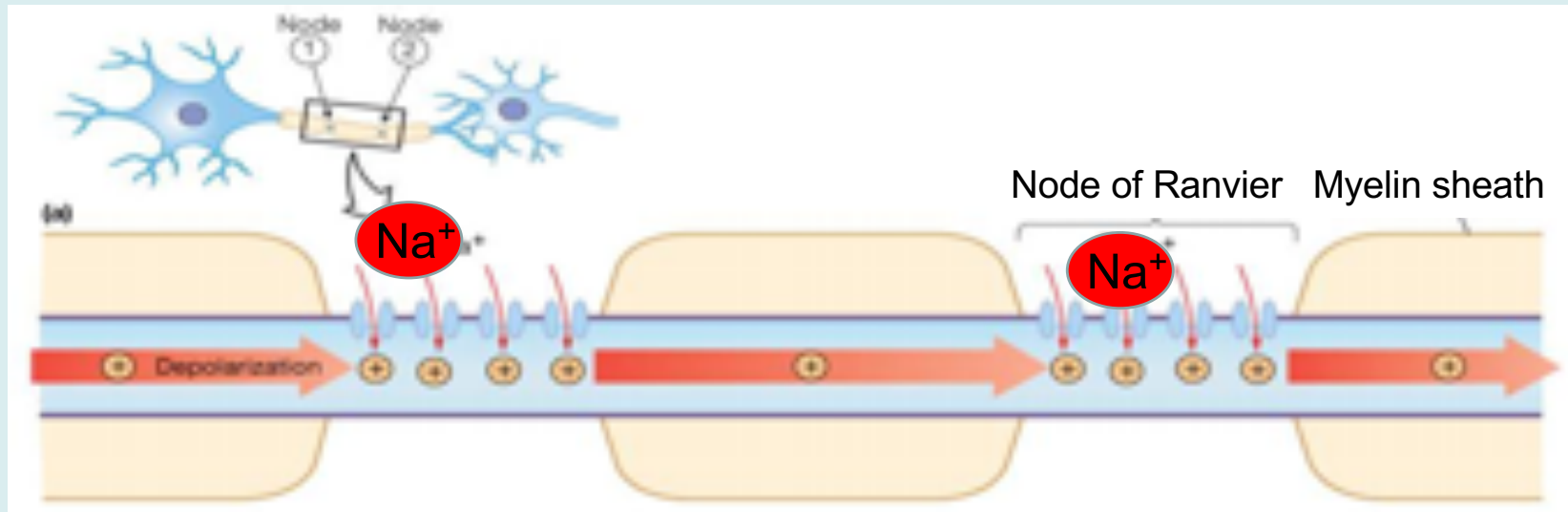
small time constant



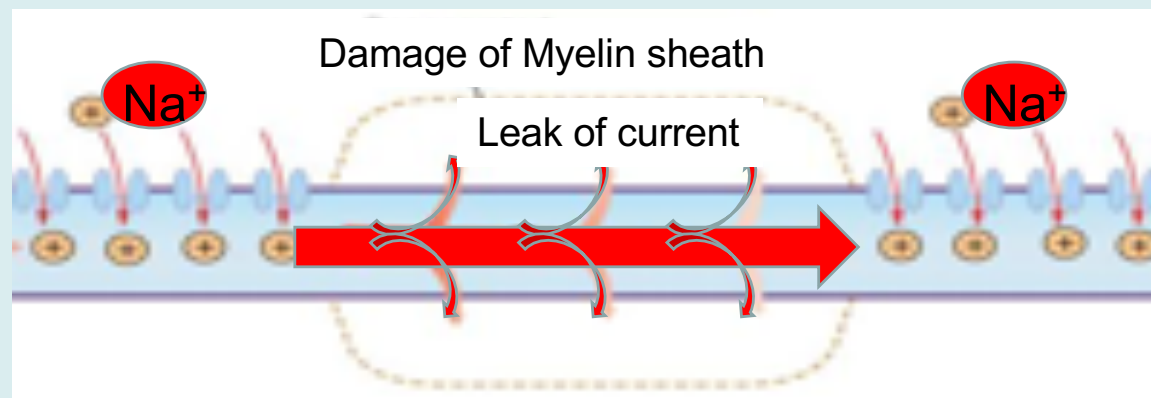
human nerve cell $r = 10 \mu\text{m}$

$v \sim 100 \text{ m/s}$

Saltatory conduction - quick, energy saving



Myelin prevents ions from entering or leaving the axon along myelinated segments.

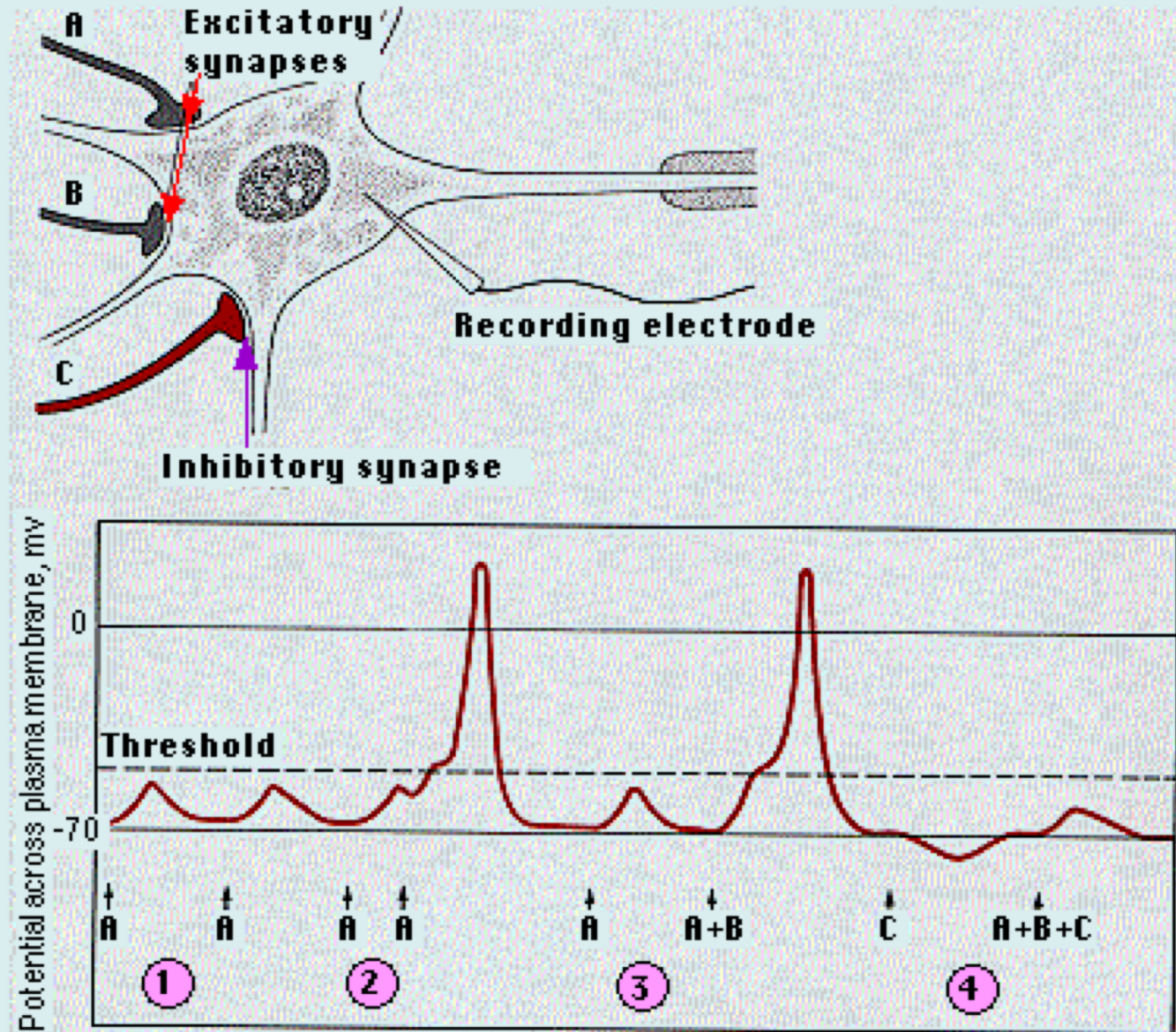


Effect of axon diameter and Myelination

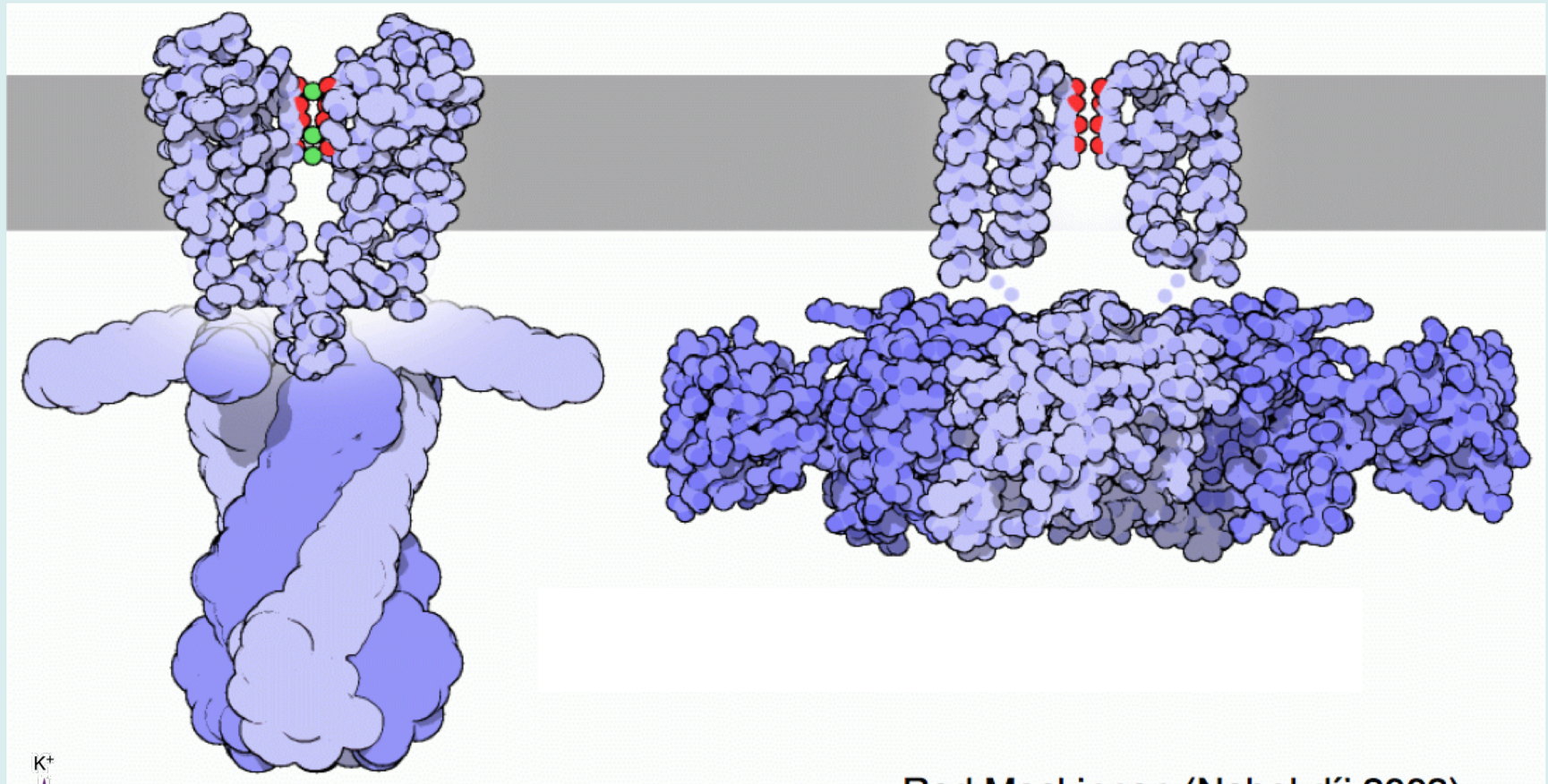
The diameter of frog axons and the presence or absence of myelination control the conduction velocity.

Fiber type	Average axon diameter (μm)	Conduction velocity ($\text{m} \cdot \text{s}^{-1}$)
Myelinated fibers		
A α	18.5	42
A β	14.0	25
A γ	11.0	17
B	Approximately 3.0	4.2
Unmyelinated fibers		
C	2.5	0.4–0.5

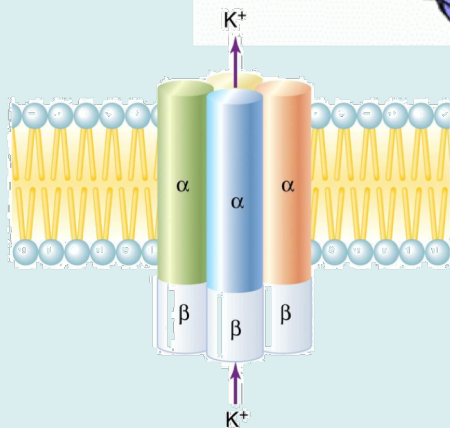
Temporal and spatial summation



Operation of the voltage-gated K⁺ channel



Rod Mackinnon (Nobel-díj 2003)



**$\sim 50 \text{ mV} / 5 \text{ nm} \rightarrow$
 $10.000.000 \text{ V/m}$**



Related chapters:

Damjanovich, Fidy, Szöllősi: Medical Biophysics

III./4.

4.1

4.2

4.3

4.4

Practicals: ECG, sensor