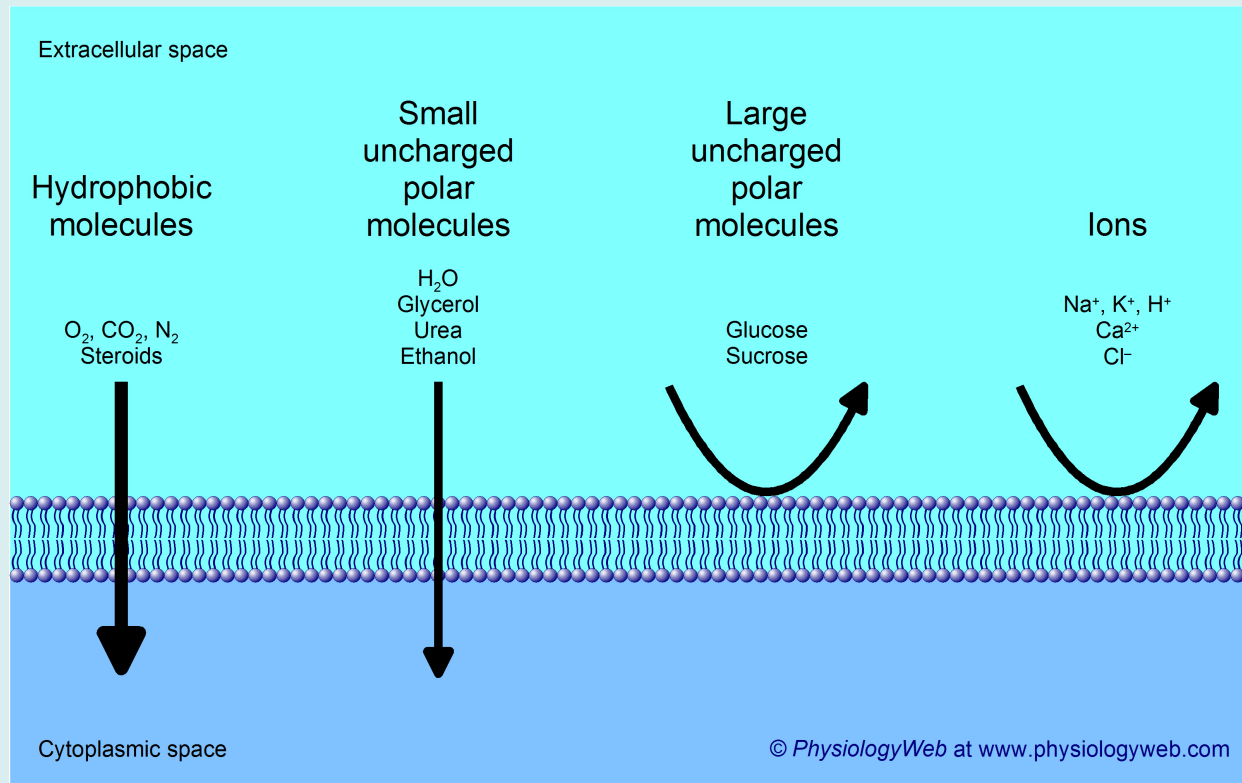
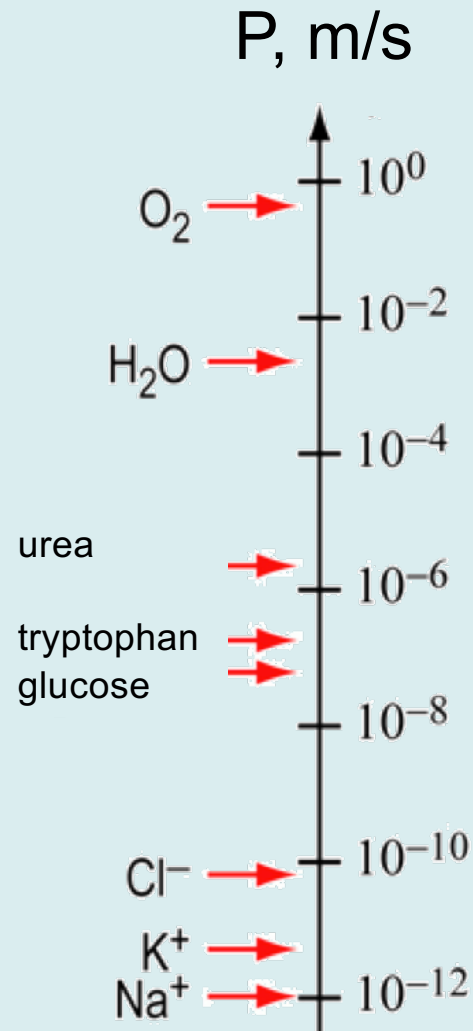


Biophysics2-11

Transport processes-3  
**MEMBRANE POTENTIAL**

26-04-2024  
Károly Liliom

# Diffusion across membranes

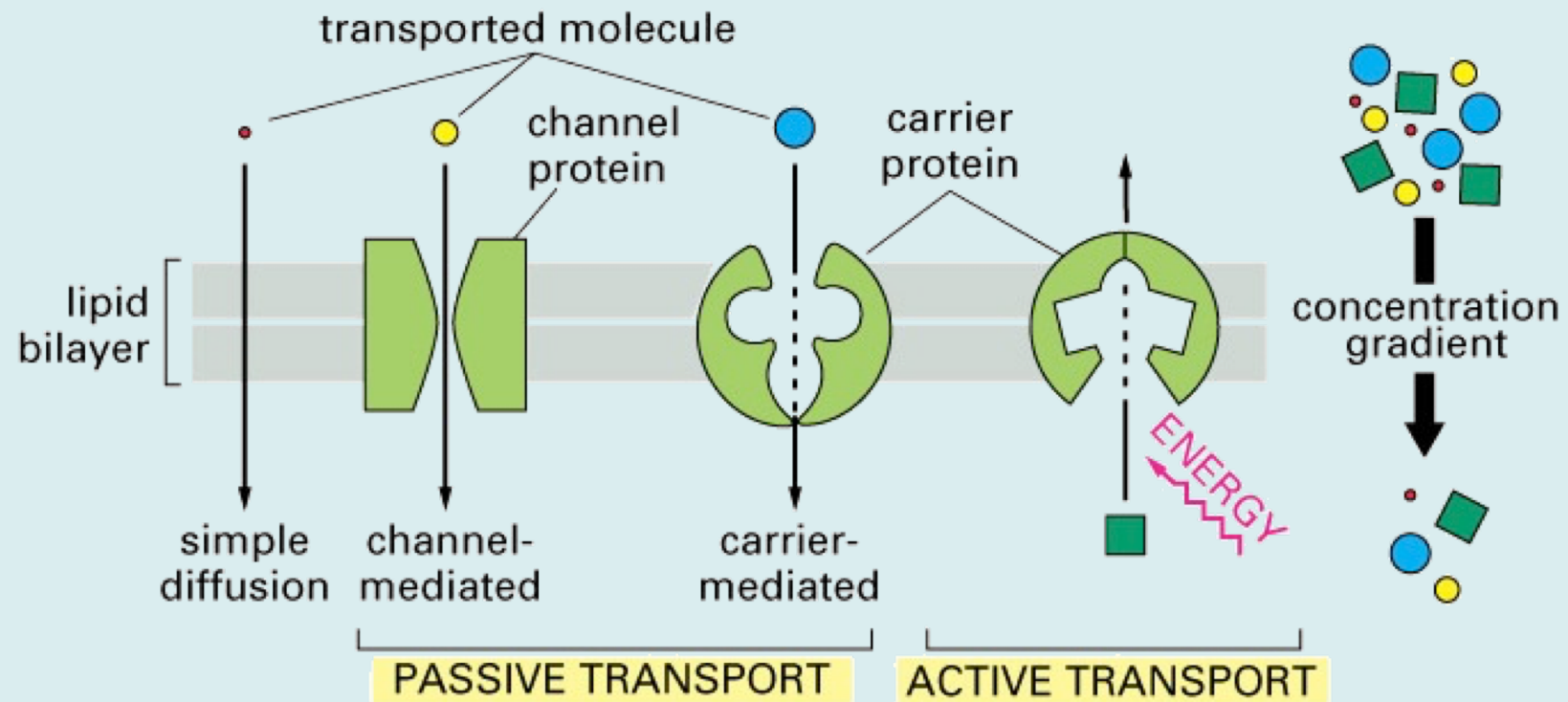


$\text{Na}^+$  ions:  $P = 10^{-12} \text{ m/s} = 10^{-3} \text{ nm/s}$ , so it takes  $\sim 2\text{h}$  to get across a  $5 \text{ nm}$  membrane!

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



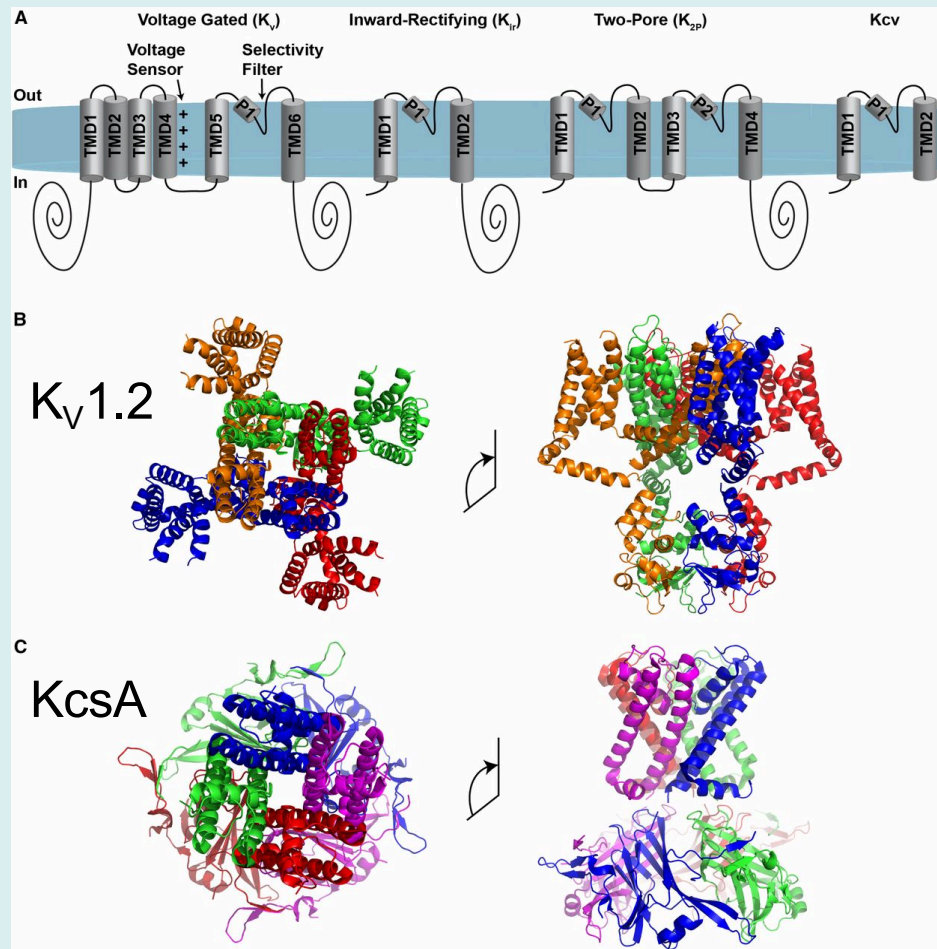
# Transport across biological membranes



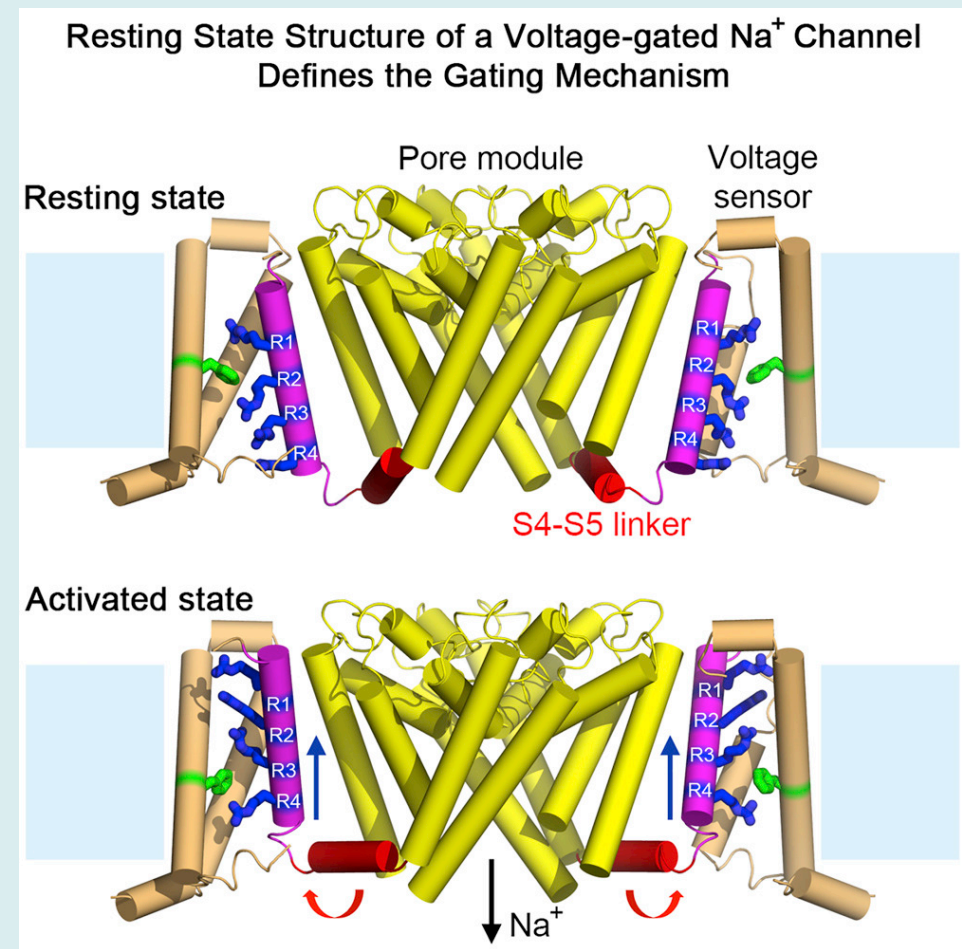
- free diffusion is effective only for small non-polar molecules
- the transport mechanism can be channel-mediated or carrier-mediated
- based on its energy requirement, the transport can be passive or active

# 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

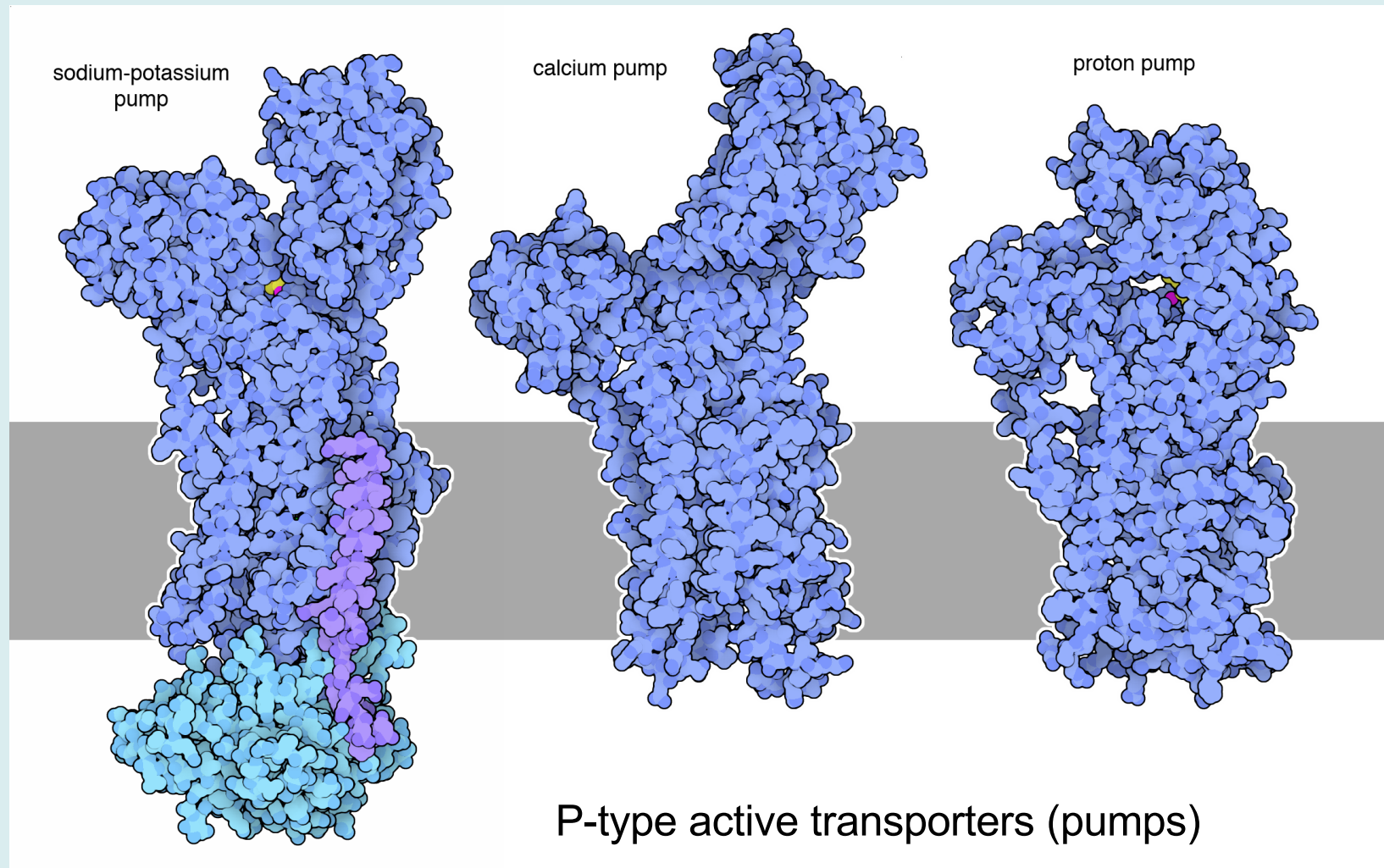


$K^+$  channels

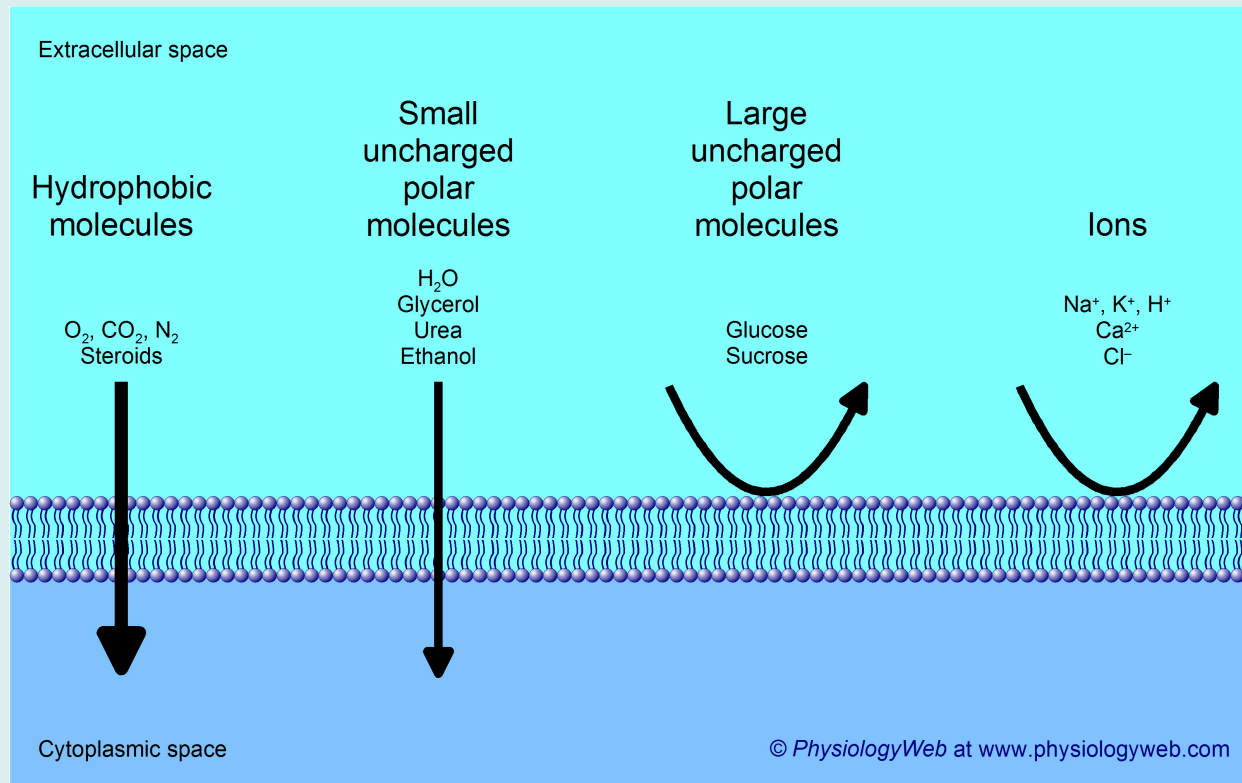
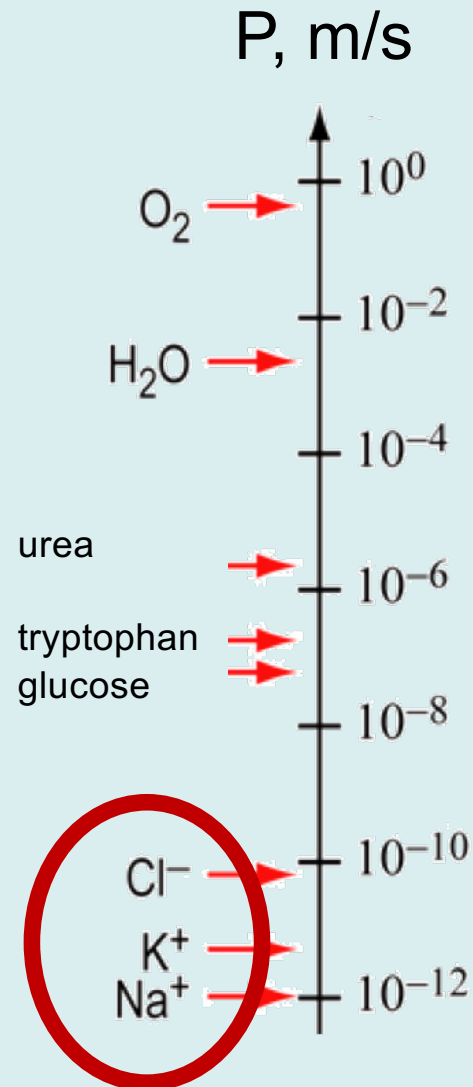


voltage-gated  $Na^+$  channel

# Active transporters



# Diffusion across membranes



Fick 1<sup>st</sup> law:  $J = -D\Delta c/\Delta x = -P\Delta c$

P: permeability coefficient

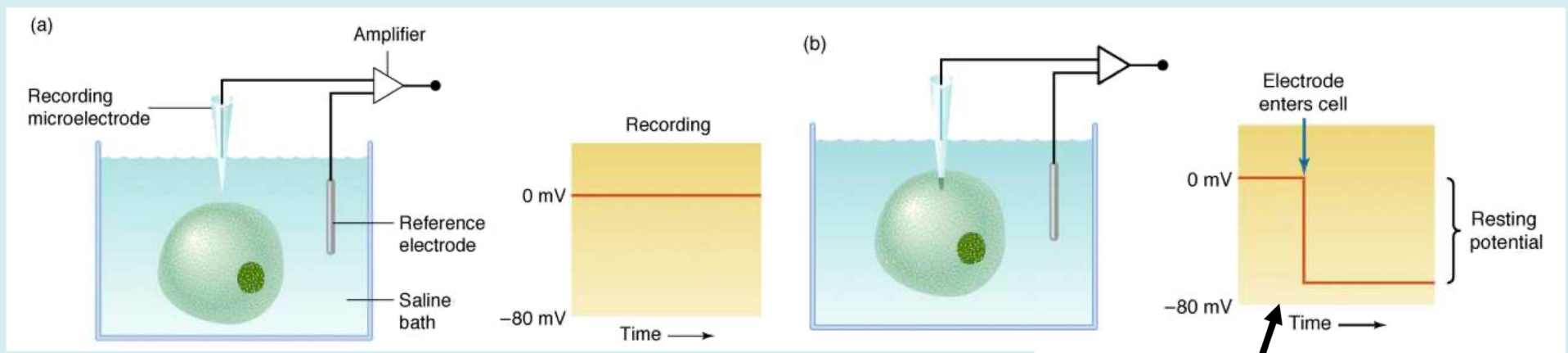
[P] = m/s

Fact1: The ionic composition is characteristically different in the interior and in the exterior of cells

Ion	Intracellular concentration (mM)	Extracellular concentration (mM)
$\text{Na}^+$	15	142
$\text{K}^+$	150	4
$\text{Cl}^-$	5	120
$\text{Ca}^{2+}$	$10^{-4}$	1
$\text{Mg}^{2+}$	1	0.5
$\text{HCO}_3^-$	8	27
Nonpenetrating anions	155	0



Fact2: 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.

# 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


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

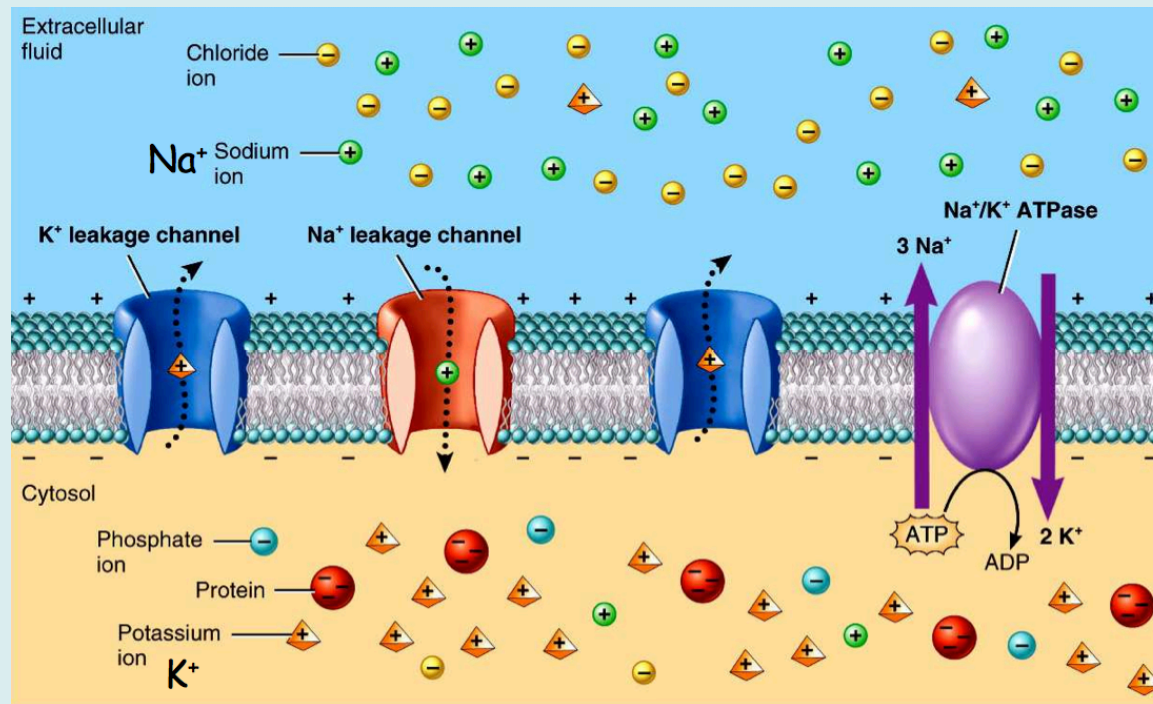
We conclude that the membrane potential cannot be described properly with the Donnan equilibrium model.

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 of 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 of 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

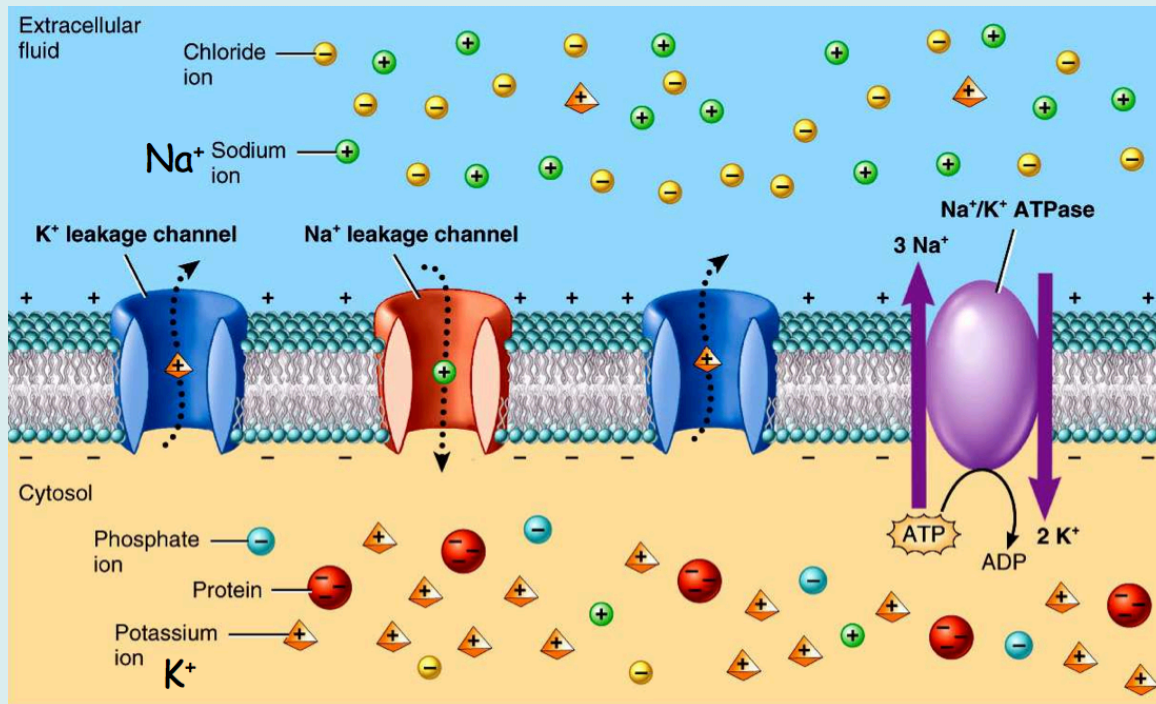
potential (mV)	Squid axon	Rat muscle
$U_{\text{measured}}$	<b>-62</b>	<b>-92</b>
$U_{\text{GHK}}$	-61,3	-89,2

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

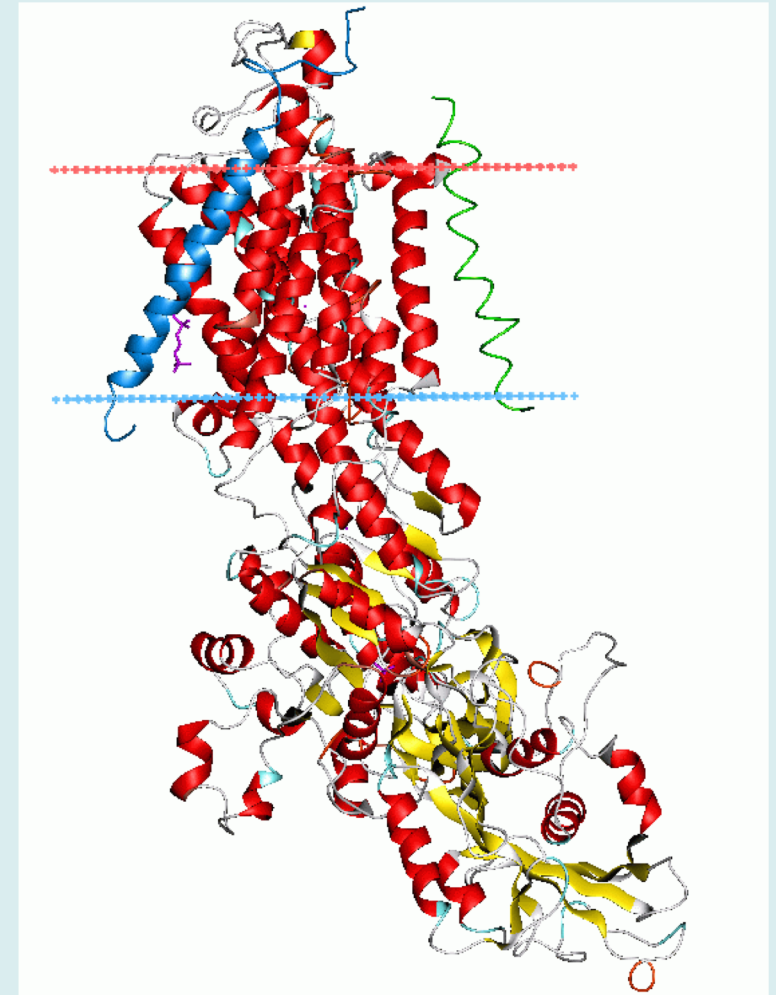
$$\mathbf{P_K : P_{Na} : P_{Cl} = 1 : 0,05 : 0,45}$$

good agreement with experimental results

# The membrane potential is maintained by the $\text{Na}^+/\text{K}^+$ ATPase (pump)



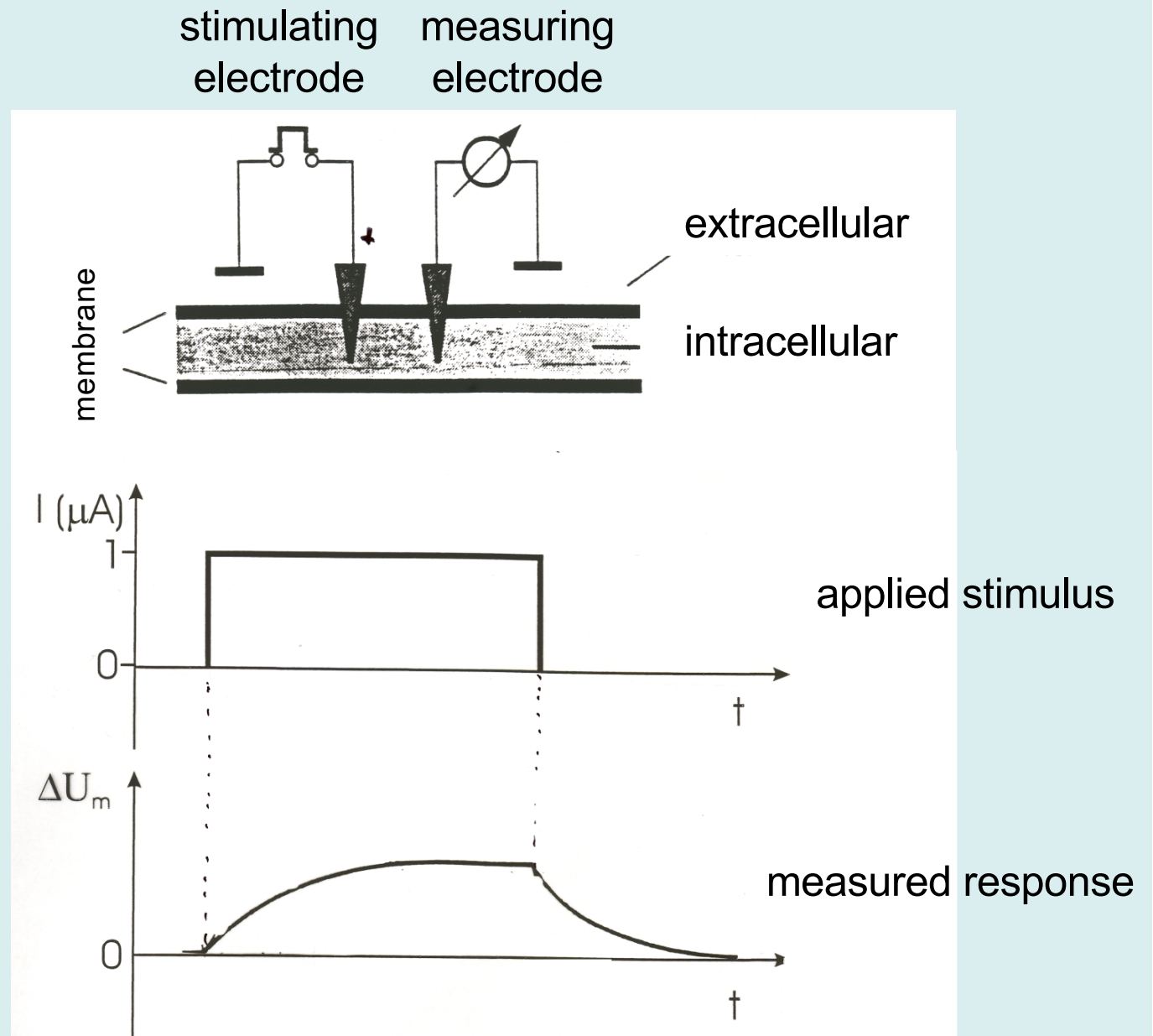
At rest,  $\sim 1/4^{\text{th}}$  of all the energy in a cell is consumed by the  $\text{Na}^+/\text{K}^+$  pump!



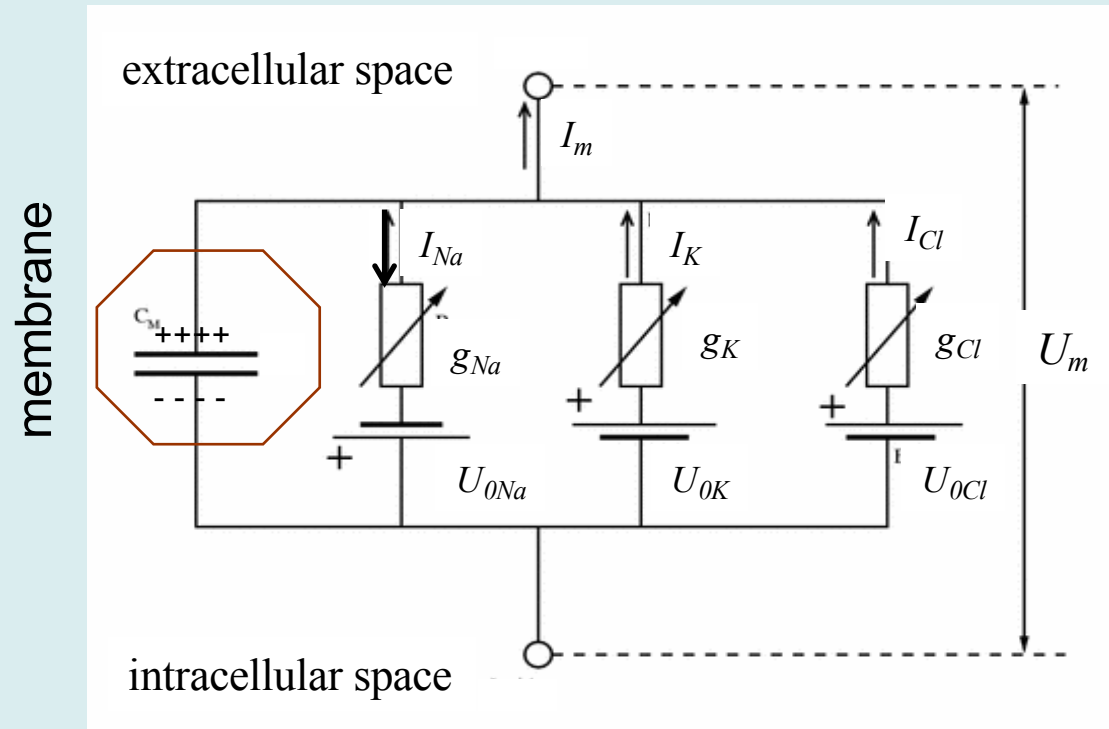
# Passive electric properties of membranes

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

capacitive current

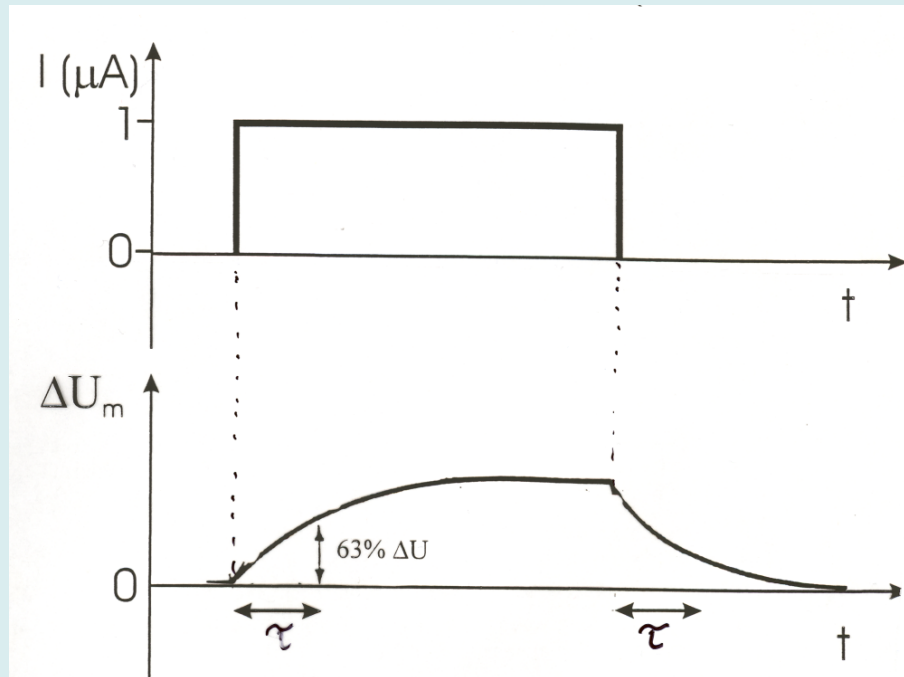
changes in conductivity

$I = g U$

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

# Local changes in membrane potential

transient changes of membrane potential limited in space and time



membrane capacitance      membrane resistance

$$\tau = C_m R_m$$

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

**$\tau$  = time constant of the membrane:**

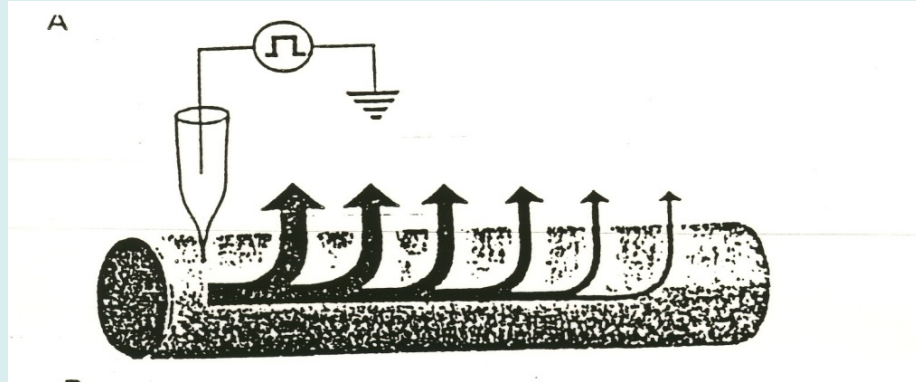
the time needed for the change in membrane potential

- 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

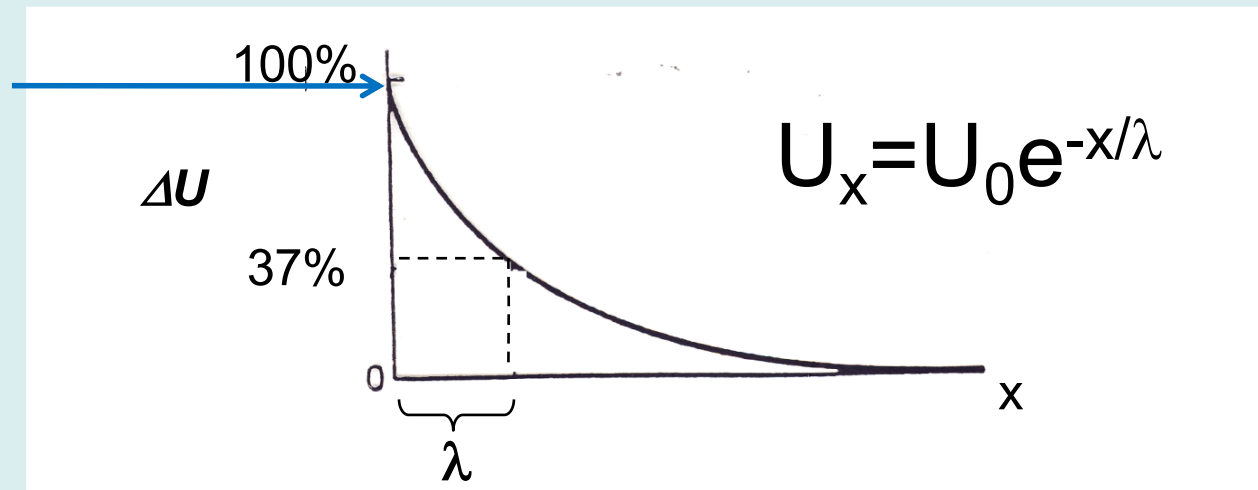
transient changes of membrane potential limited in space and time



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

$R_i$ : resistance of intracellular space

local changes in  
membrane  
potential  
(after  
stimulation)



$\lambda$  = space constant of the membrane:

the distance where the amplitude of stimulus

is the  $e^{\text{th}}$  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:*

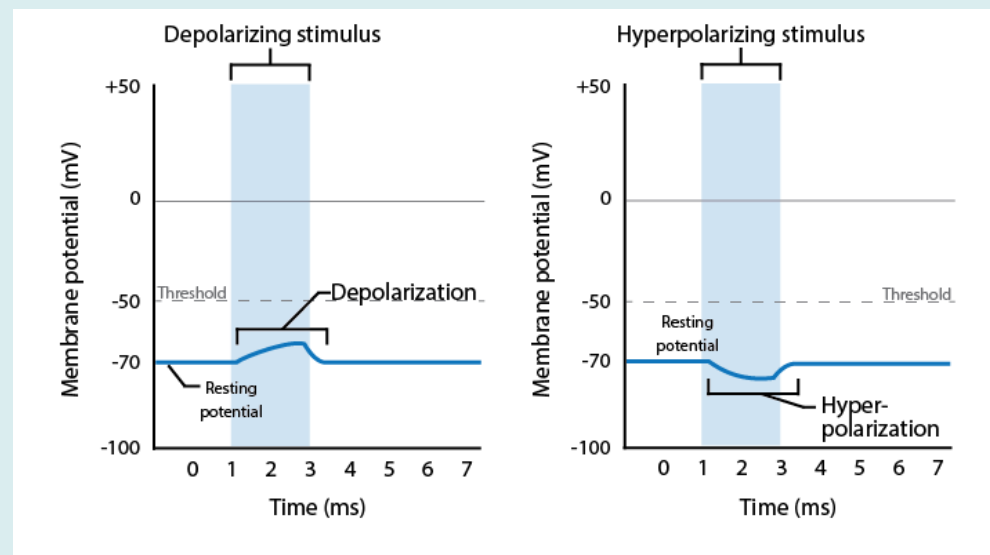
*obligate, graded*

*magnitude and direction*

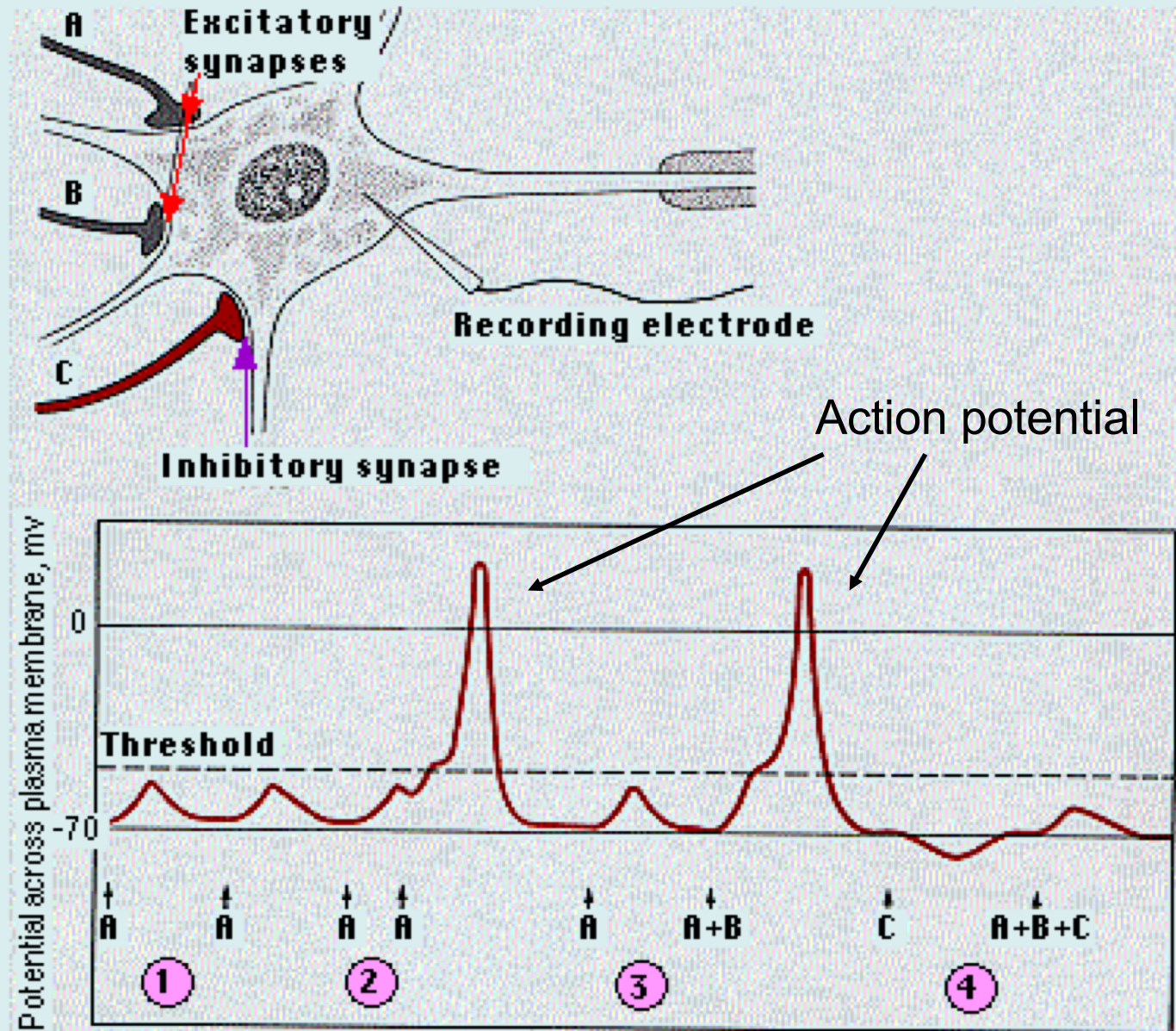
*varies with stimuli*

*localized (limited)*

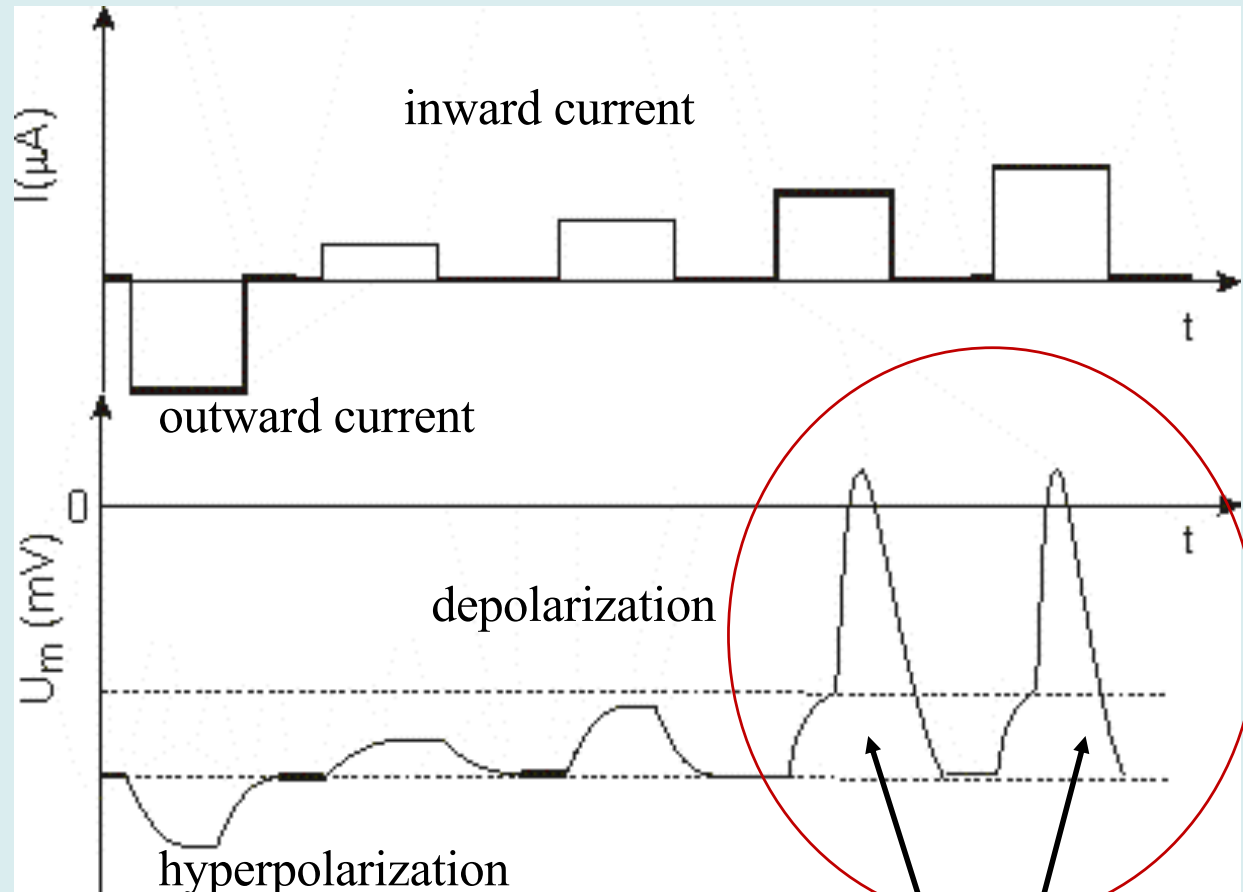
SUMMATION in space and time = summation of local potential changes



# Temporal and spatial summation

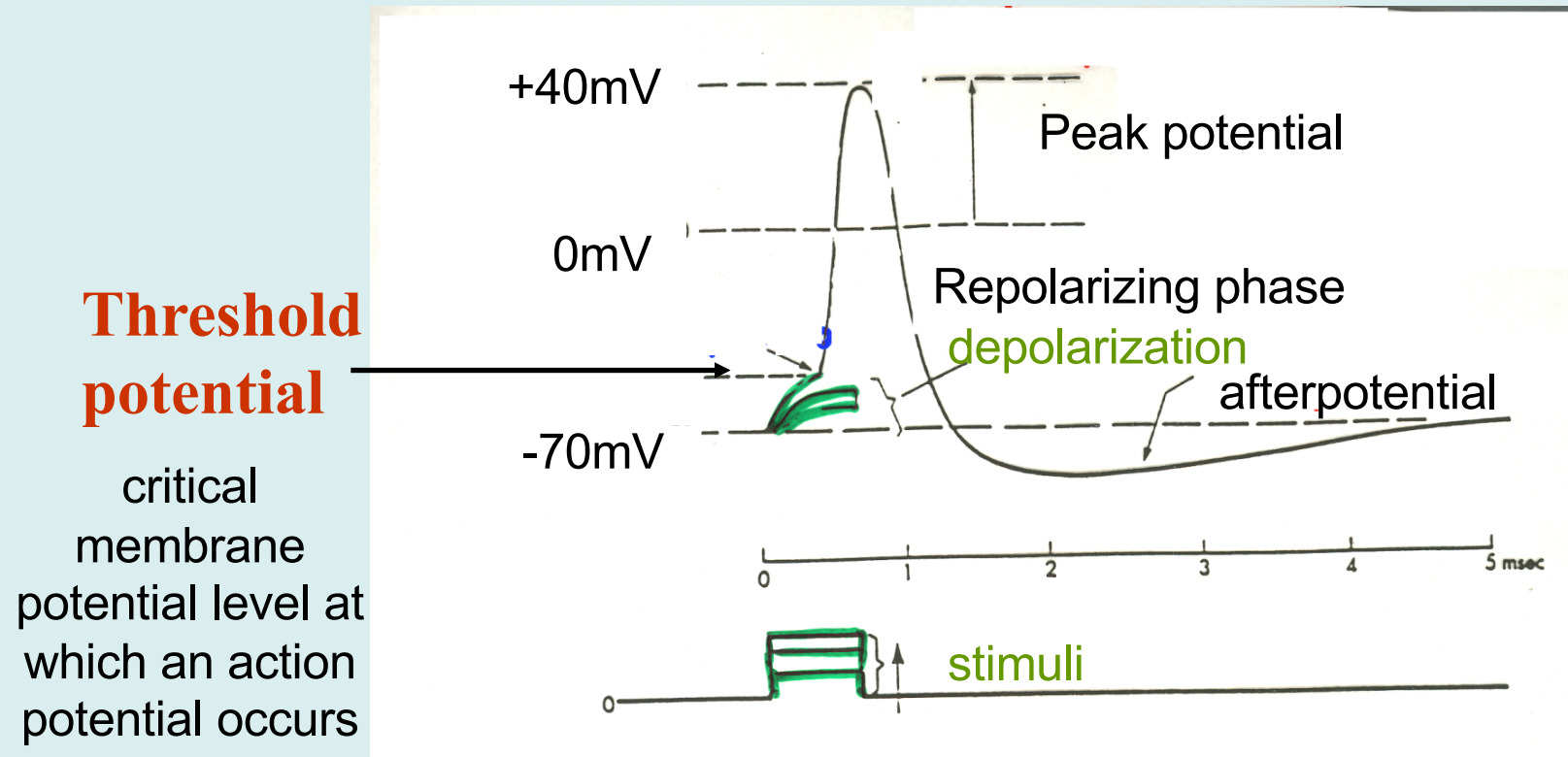


# Observation



Action potential

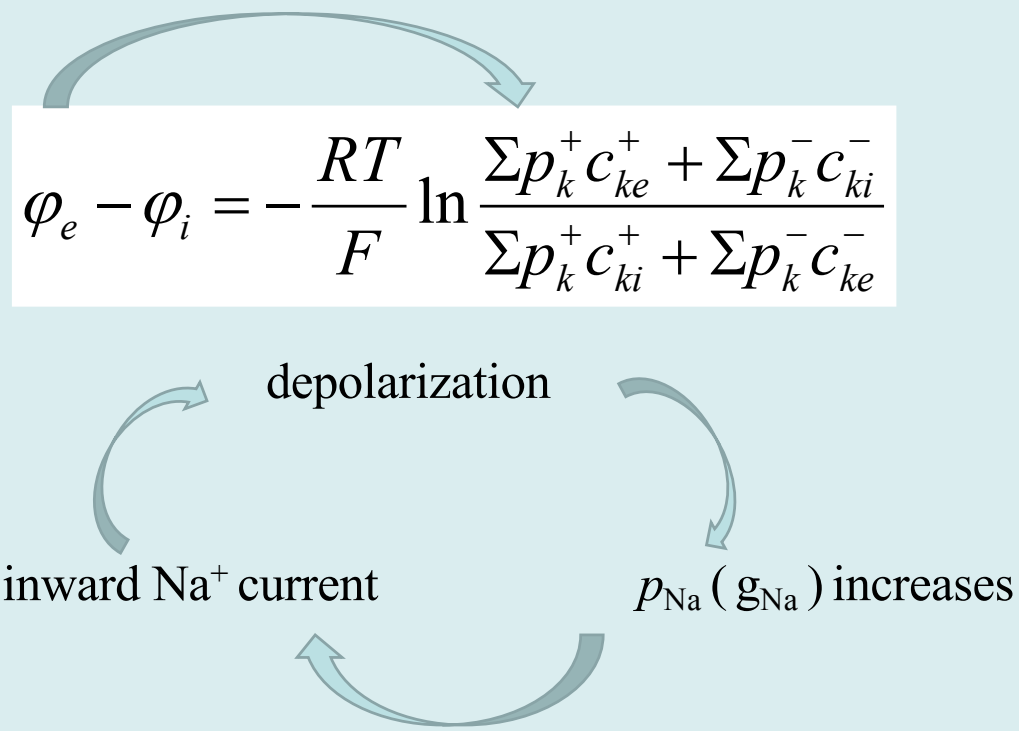
# *Characteristics of the action potential*

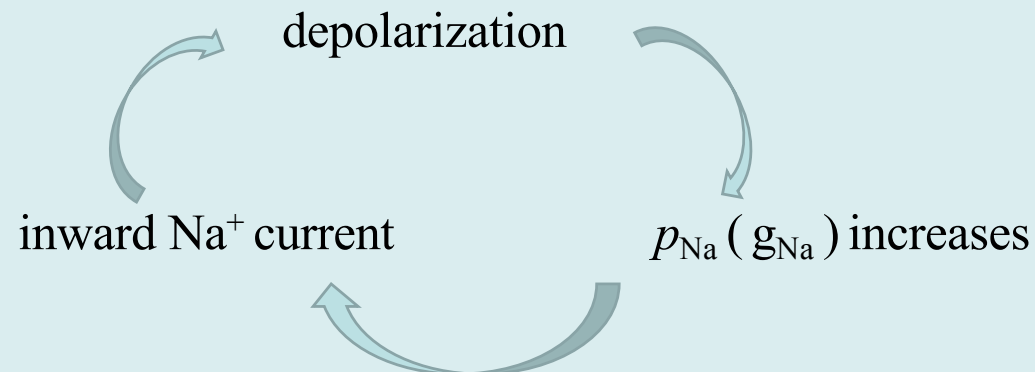


facultative  
“All-or-none” amplitude  
conducted with constant amplitude

# Hodgkin-Katz hypothesis of action potential generation

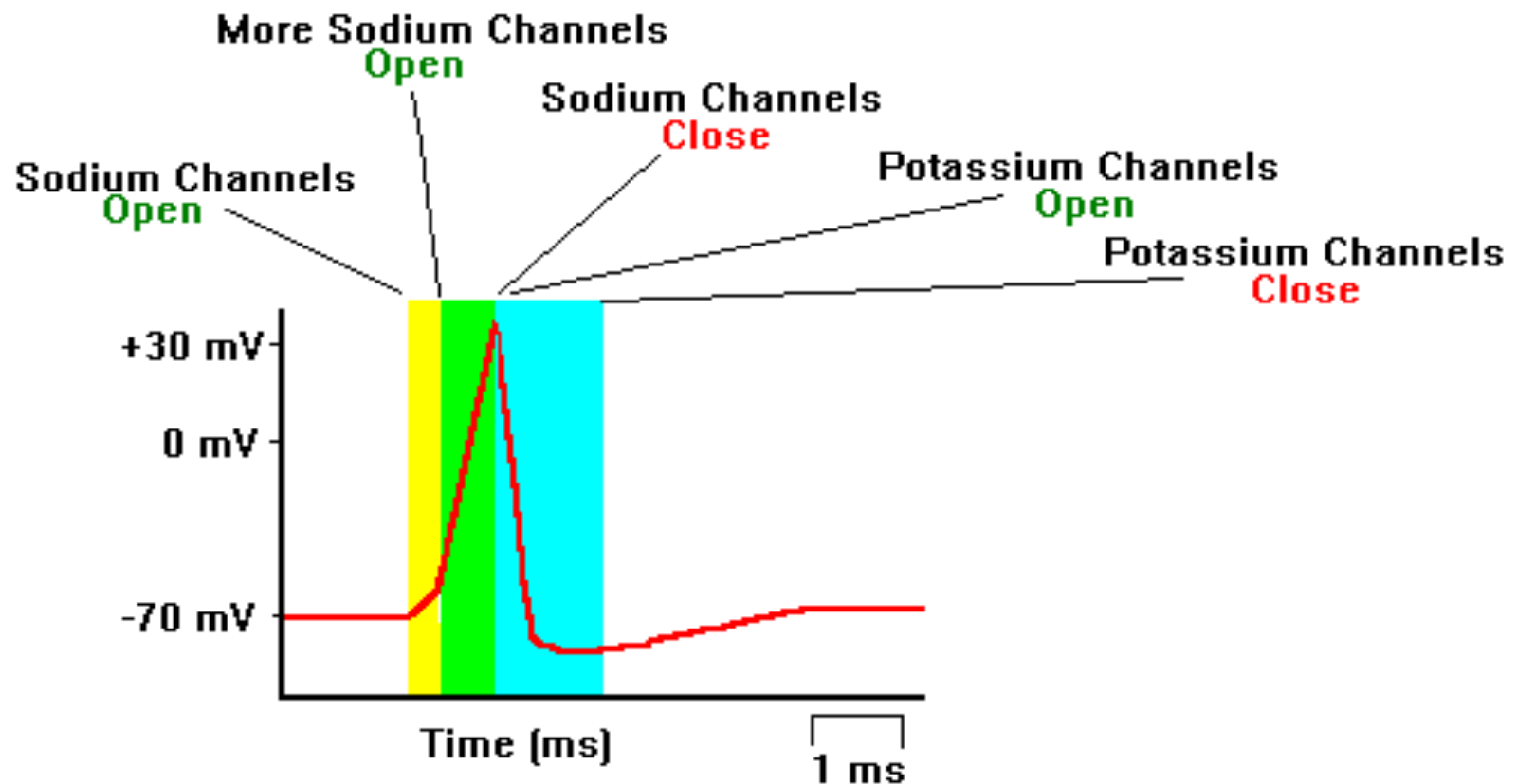
Voltage-gated, potential sensitive ion channels


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

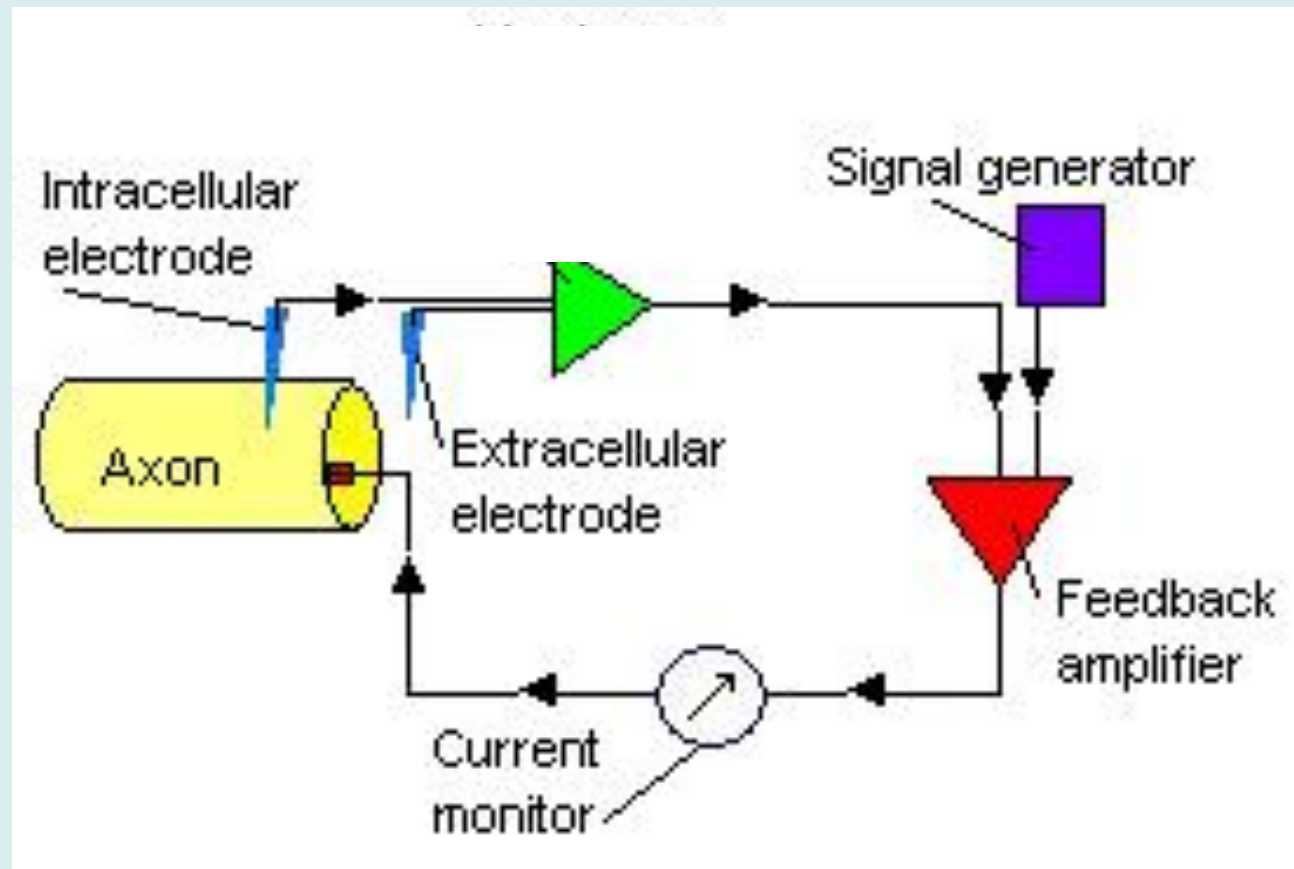




# Hodgkin-Katz hypothesis of action potential generation



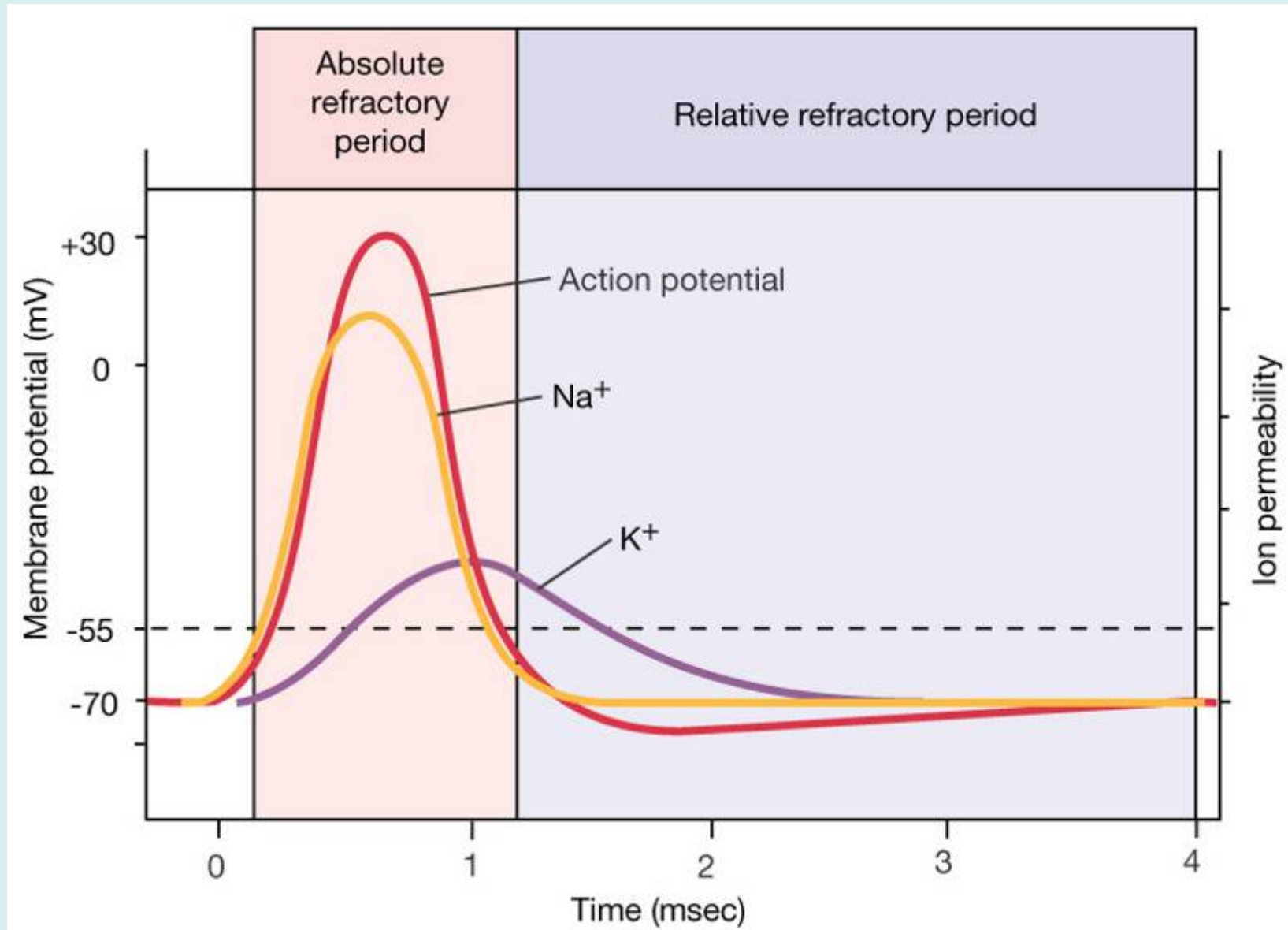
# Voltage Clamp



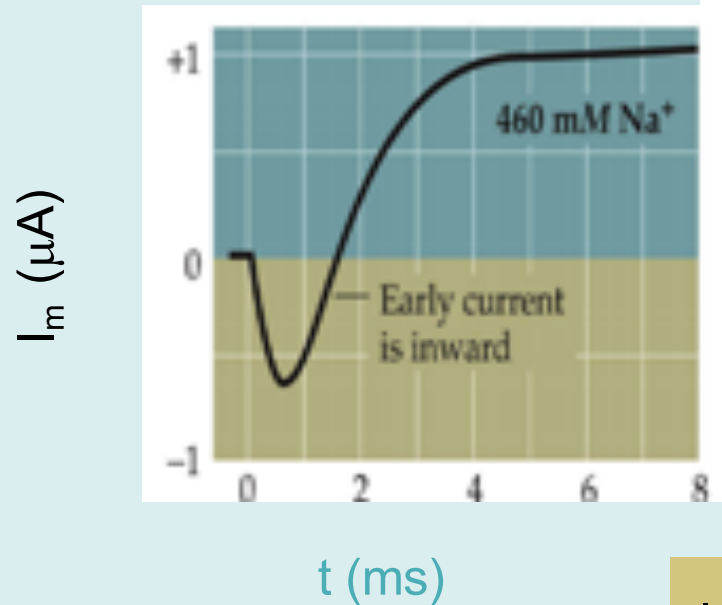
- Membrane potential is kept constant
- ion-current is measured



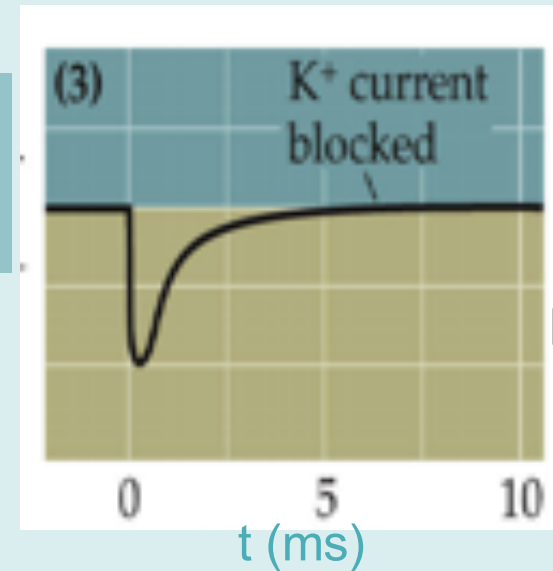
# Conductivities during action potential



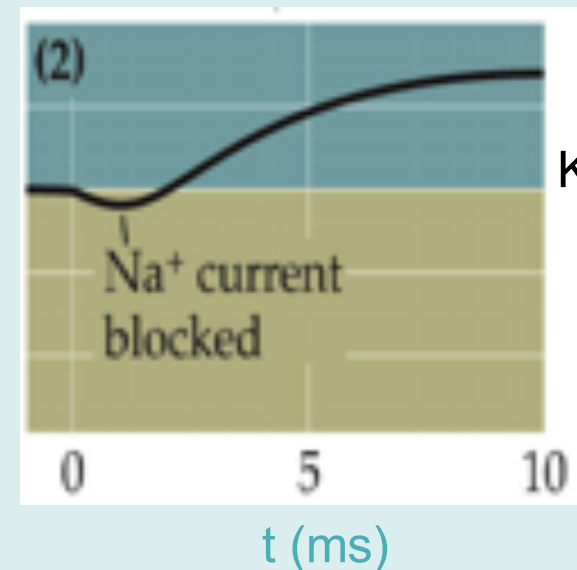
# Measurement of separated ionic currents



Inhibited  $K^+$ -channels



$Na^+$ -current

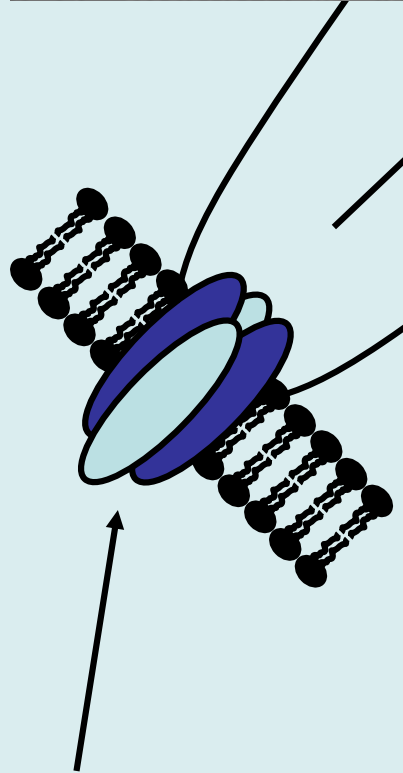
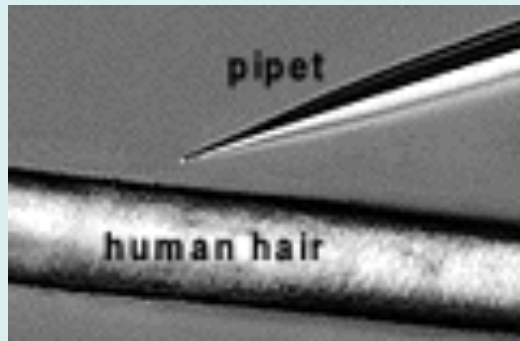


$K^+$ -current

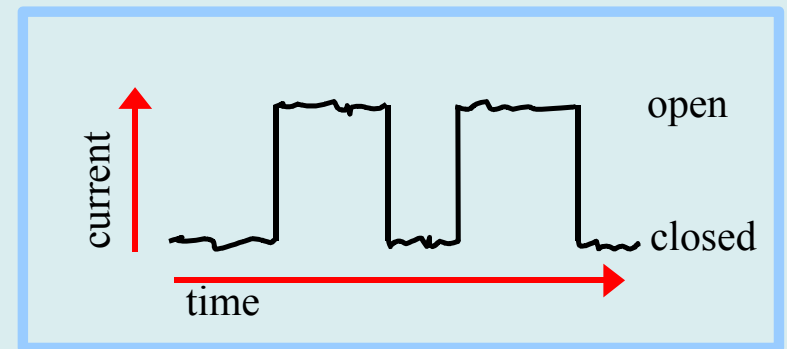
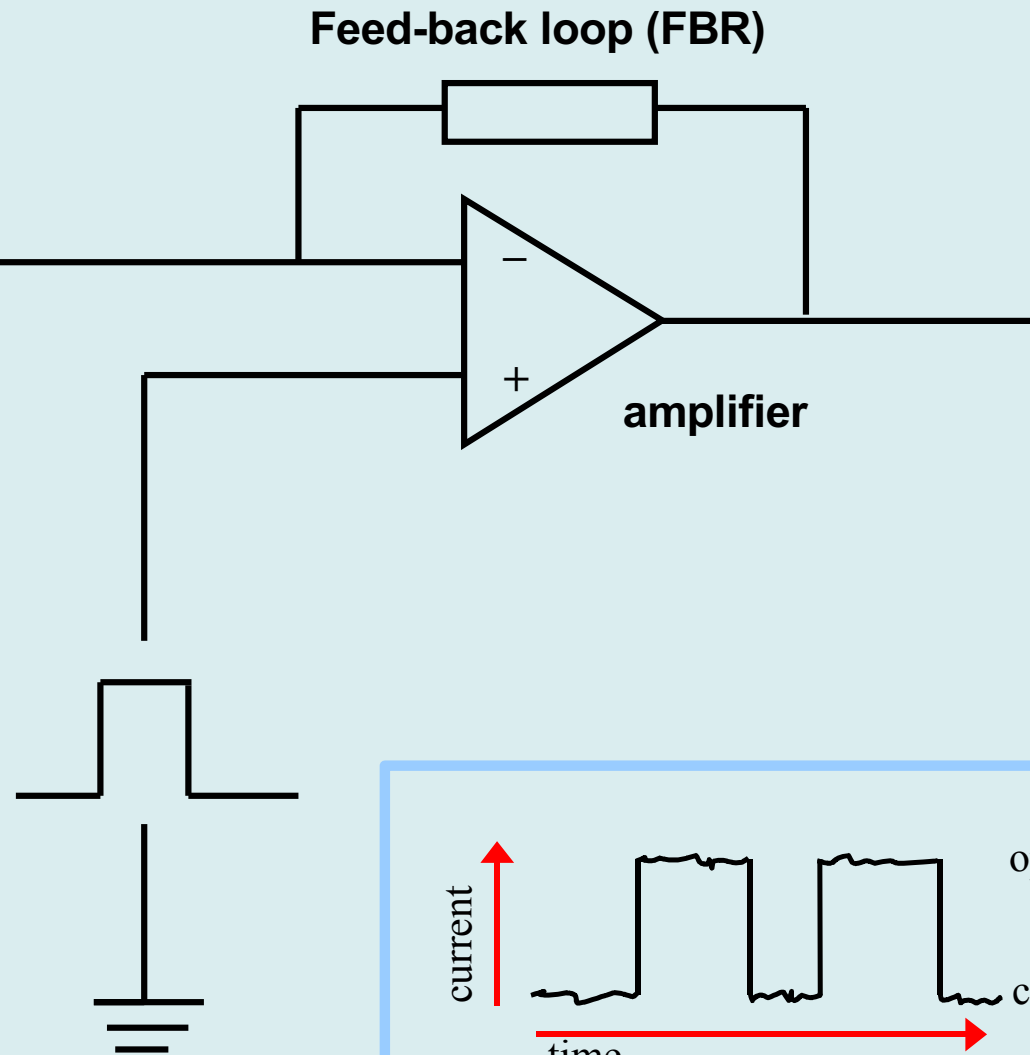
Inhibited  $Na^+$ -channels

Voltage-Gated  $Na^+$  and  $K^+$  Channels

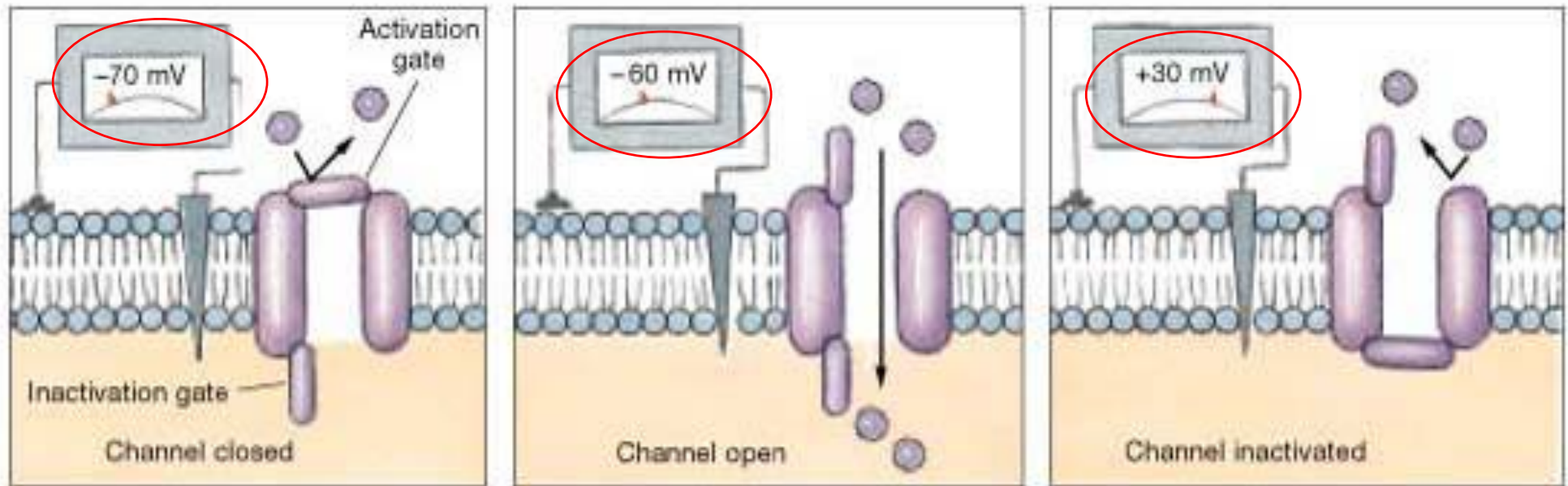
# Patch-Clamp



Membrane Patch with single ion channel



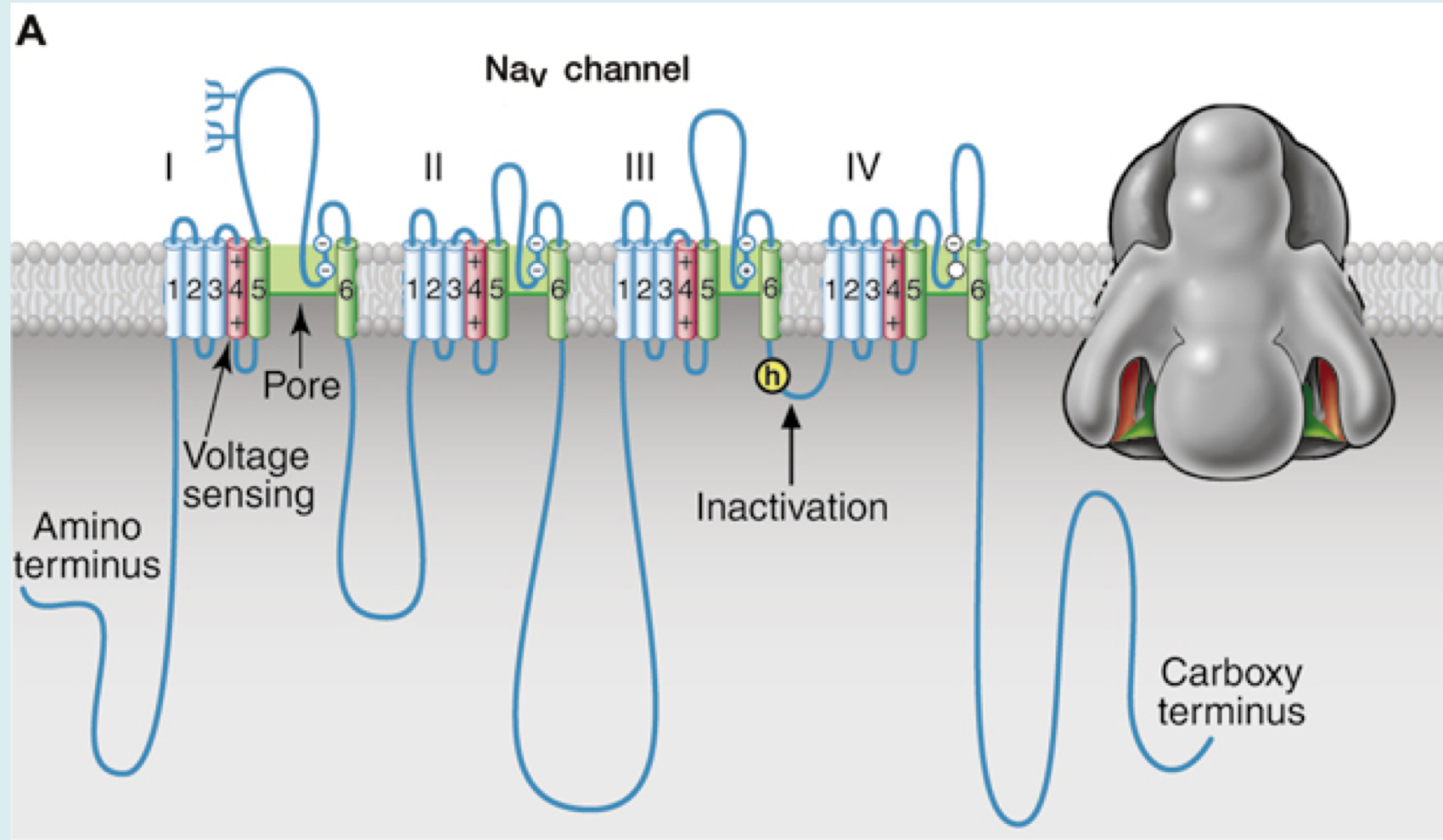
# States of voltage-gated sodium channels



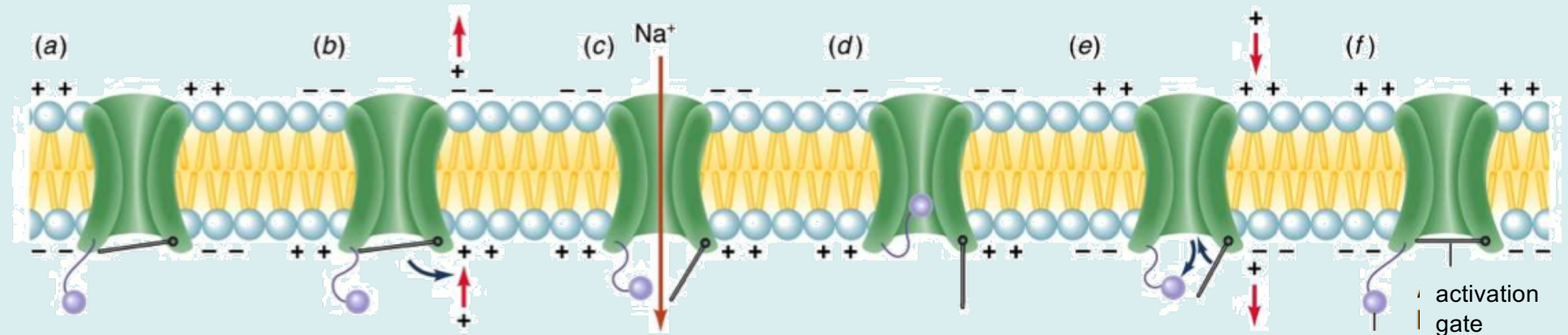
(c)

at depolarization threshold

# Structure of the fast Na<sup>+</sup> channel

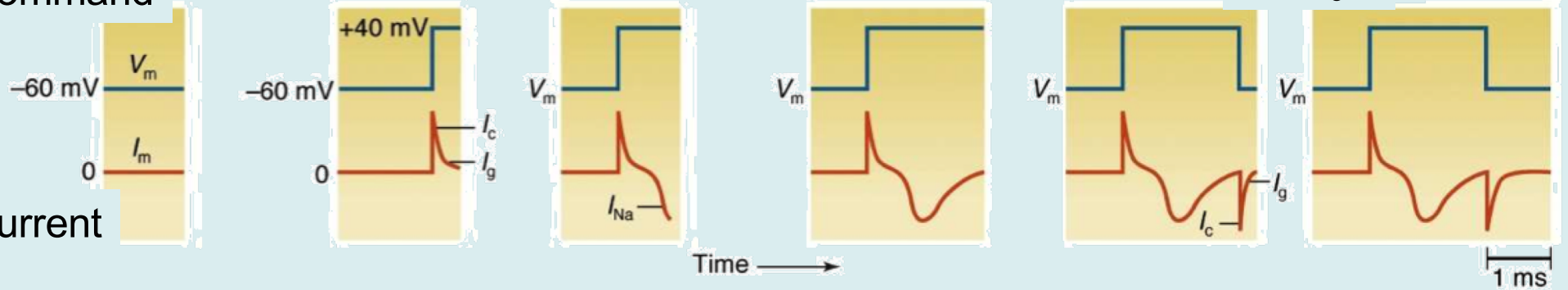


# Function of the fast $\text{Na}^+$ channel



Command

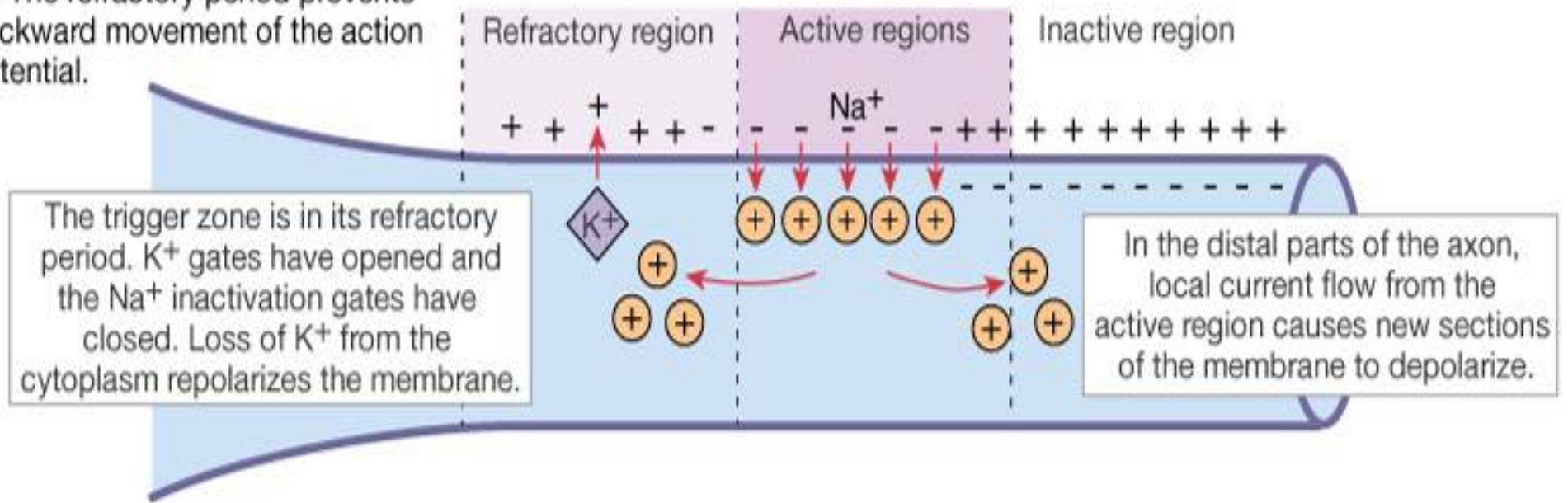
Current





# Propagation of action potential

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

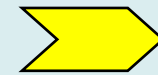


Speed and distance of propagation?

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

## *Effect of axon radius on propagation velocity:*

$$r \uparrow \Rightarrow \begin{matrix} R_i \downarrow (\sim 1/r^2) \\ R_m \downarrow (\sim 1/r) \end{matrix}$$

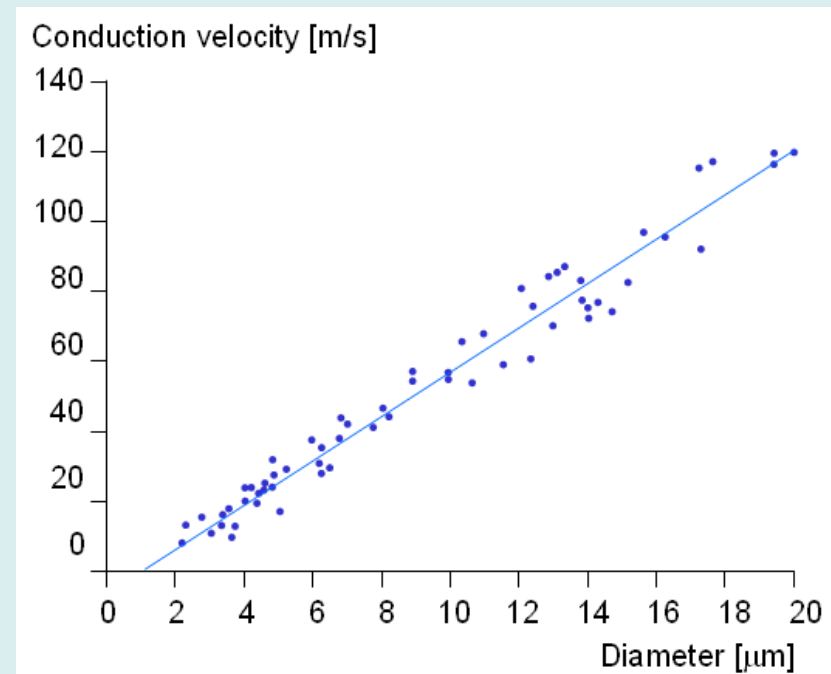


$$\begin{matrix} \tau \downarrow \\ \lambda \uparrow \end{matrix}$$

$$\tau = C_m R_m$$
$$\lambda \sim \sqrt{\frac{R_m}{R_i}}$$

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

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





# Myelination!

$R_m$  – very high

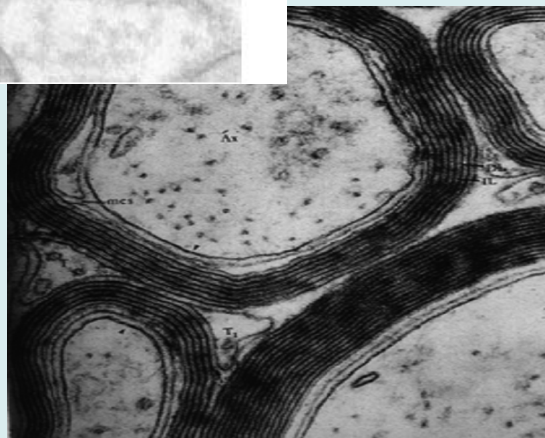
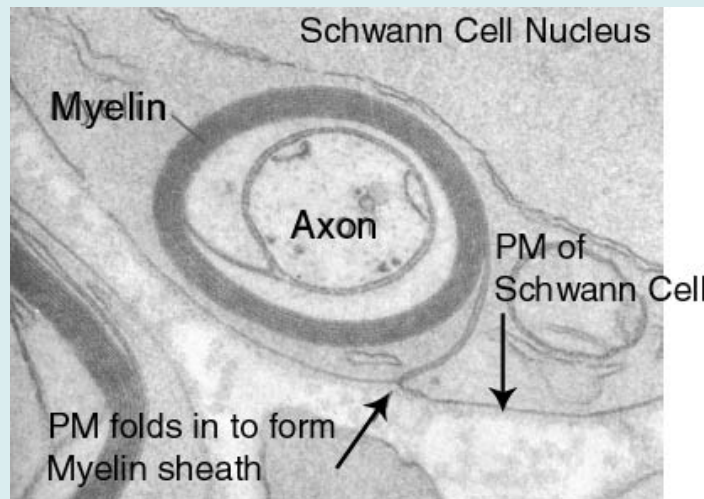


big space constant

$C_m$  – very small



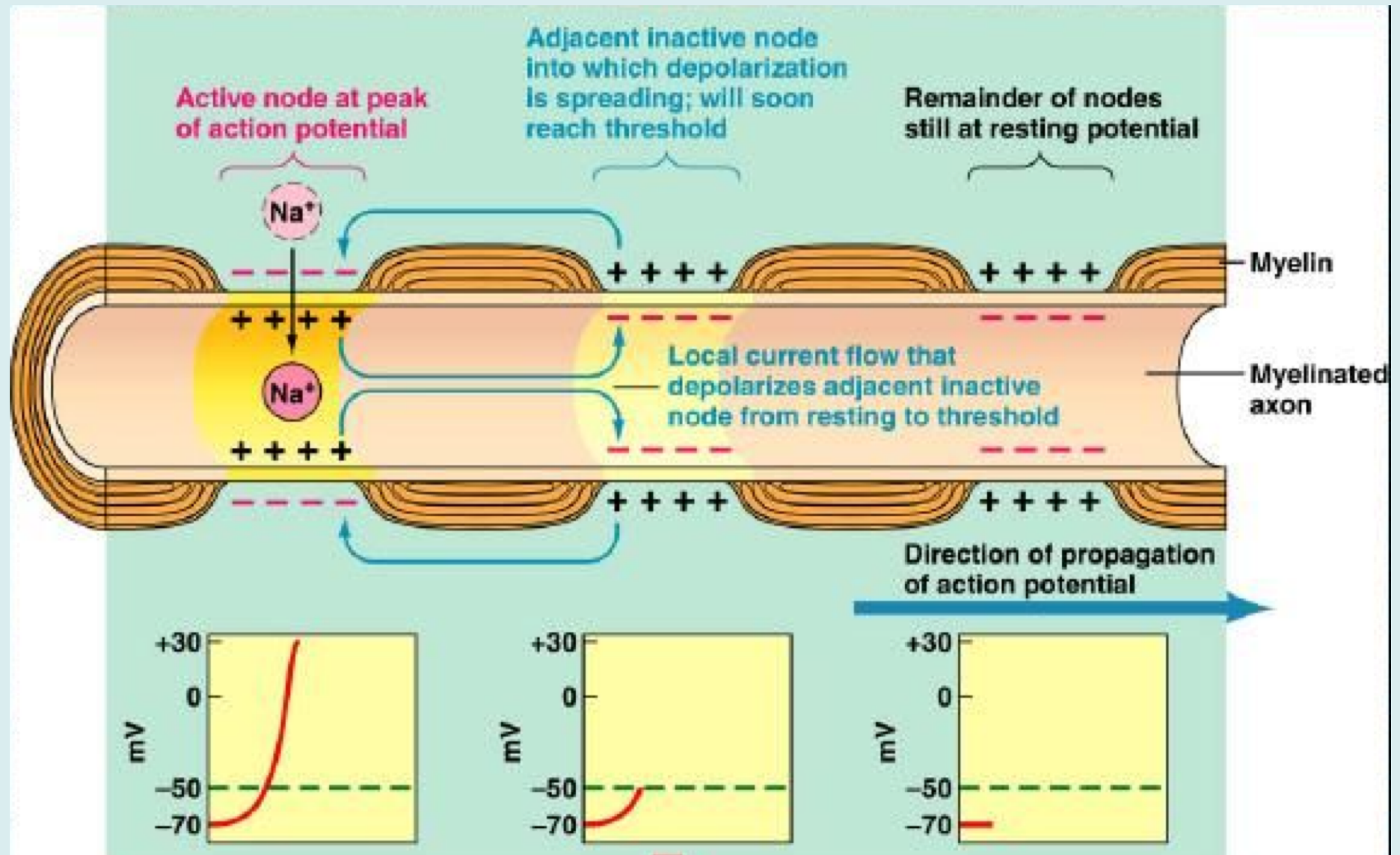
small time constant



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

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

# Saltatory conduction



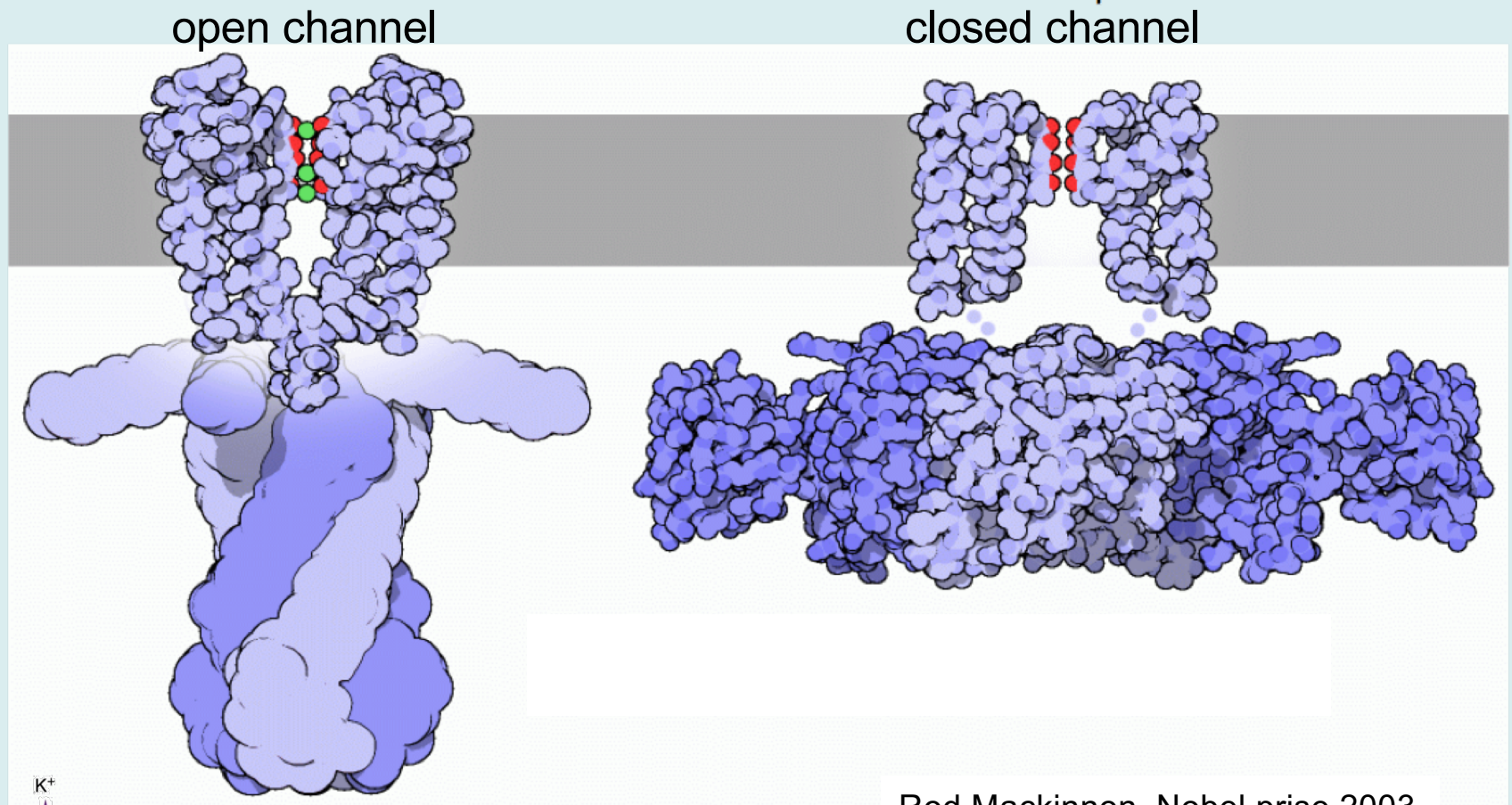
# Effect of axon diameter and Myelination

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

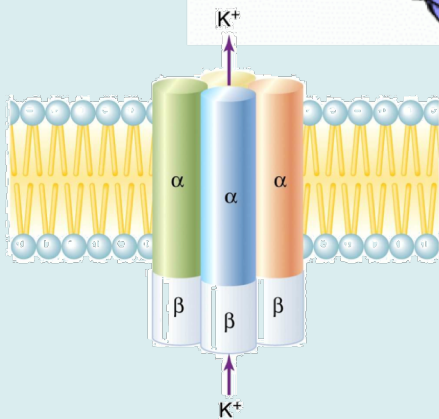
Fiber type	Average axon diameter ( $\mu\text{m}$ )	Conduction velocity ( $\text{m} \cdot \text{s}^{-1}$ )
<b>Myelinated fibers</b>		
A $\alpha$	18.5	42
A $\beta$	14.0	25
A $\gamma$	11.0	17
B	Approximately 3.0	4.2
<b>Unmyelinated fibers</b>		
C	2.5	0.4–0.5



# Operation of the voltage-gated K<sup>+</sup> channel



Rod Mackinnon, Nobel prize 2003



**~50 mV / 5 nm →  
10.000.000 V/m**



Related chapters:

*Damjanovich, Fidy, Szöllősi: Medical Biophysics*

III./4.

4.1

4.2

4.3

4.4

*Practicals: ECG, sensor*