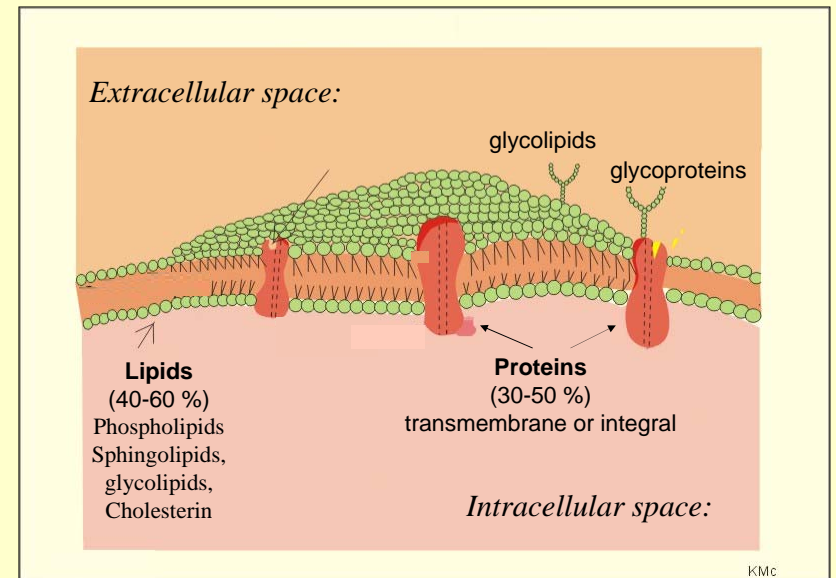


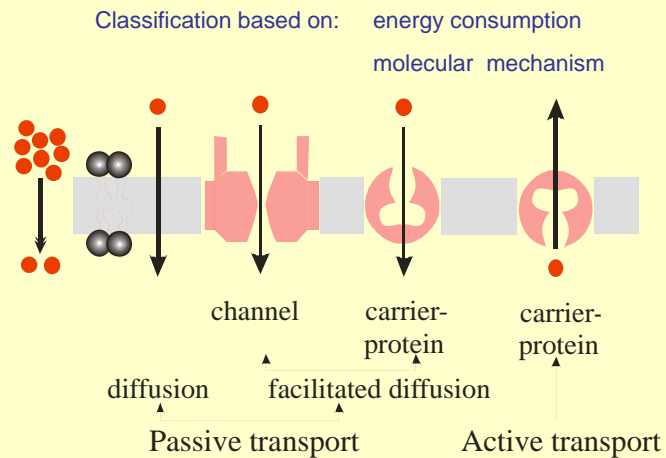
Transport across biological membranes

Transport in Resting Cell

Membrane structure



Transport types across the membranes



Diffusion of neutral particles

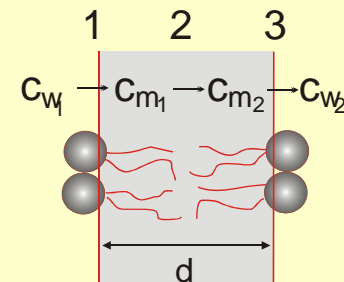
Diffusion across the lipid bilayer

Fick I.

$$J_m = -D \frac{\Delta c}{\Delta x}$$

$$D_m \ll D$$

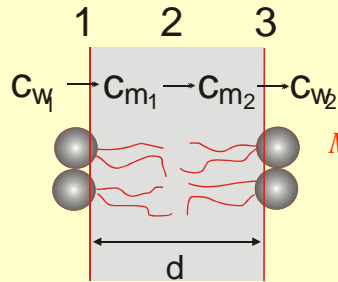
$$J_m = -D_m \frac{c_{m2} - c_{m1}}{d}$$



Assume that concentration changes linearly

Diffusion of neutral particles

Diffusion across the lipid bilayer



$$J_m = -D_m \frac{C_{m2} - C_{m1}}{d}$$

$$J_m = -p_m(C_{m2} - C_{m1})$$

Membrane permeability constant [ms^{-1}]



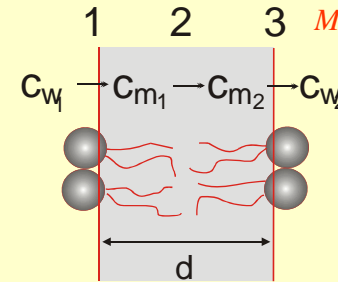
Cannot be measured

$$\frac{C_{m1}}{C_{v1}} = \frac{C_{m2}}{C_{v2}} = K$$

$$C_{m1} = KC_{v1}$$

Diffusion of neutral particles

Diffusion across the lipid bilayer



$$J_m = -p_m(C_{m2} - C_{m1})$$

Membrane permeability constant [ms^{-1}]



Cannot be measured

$$\frac{C_{m1}}{C_{v1}} = \frac{C_{m2}}{C_{v2}} = K$$

$$C_{m1} = KC_{v1}$$

$$J_m = -p_m K (C_{v2} - C_{v1})$$

$$J_m = -p(C_{v2} - C_{v1})$$

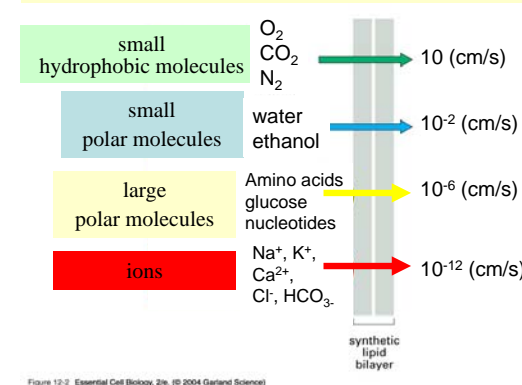
$$J_m = -p(C_{v2} - C_{v1})$$

Permeability constant [ms^{-1}]

It is influenced by:

- diffusion coefficient within the membrane
- thickness of the membrane
- partition coefficient

Permeability vs hydrophobicity



Lipid solubility v permeability

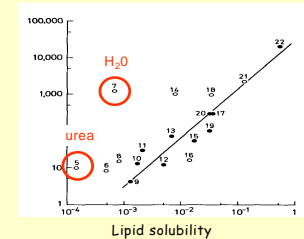


Figure 12-2 Essential Cell Biology, 2/e. (© 2004 Garland Science)

Diffusion of ions

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

chemical potential
and
electric potential
together

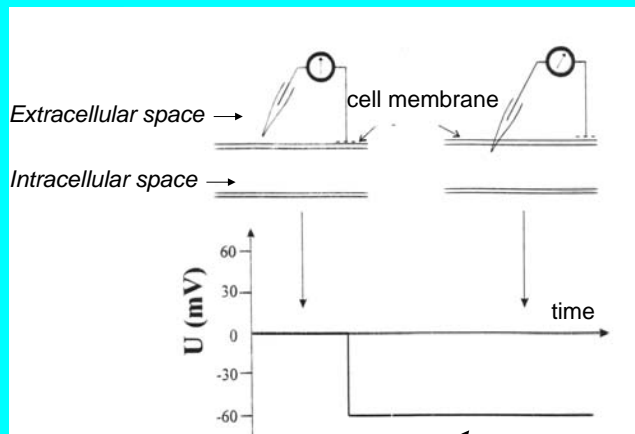
$$J_k = -D_k \left(\frac{\Delta c_k}{\Delta x} + c_k \frac{z_k F}{RT} \frac{\Delta \varphi}{\Delta x} \right)$$

flux of k -th ion

Basic principles of electrophysiology

Interpretation by transport phenomena

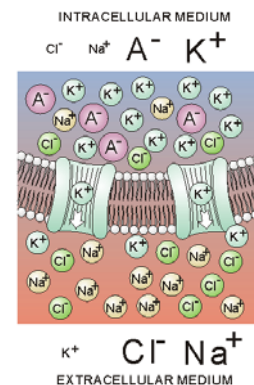
Observation 1: There is an electric potential difference between extra- and intracellular space



The intracellular side is negative with respect to the extracellular side

resting potential $\sim 60 - 90 \text{ mV}$

Observation 2: Inhomogeneous ion distribution



Cell type	$C_{\text{Intracellular}}$ (mmol/l)			$C_{\text{Extracellular}}$ (mmol/l)		
	$[\text{Na}^+]_i$	$[\text{K}^+]_i$	$[\text{Cl}^-]_i$	$[\text{Na}^+]_e$	$[\text{K}^+]_e$	$[\text{Cl}^-]_e$
Squid axon	72	345	61	455	10	540
Frog muscle	20	139	3,8	120	2,5	120
Rat muscle	12	180	3,8	150	4,5	110

Interpretation of the membrane potential

Model 1

Constant ion distribution in resting state



No transport (?)



Assume that (1) the system is in *equilibrium*

that is

no electrochemical potential difference

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

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



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

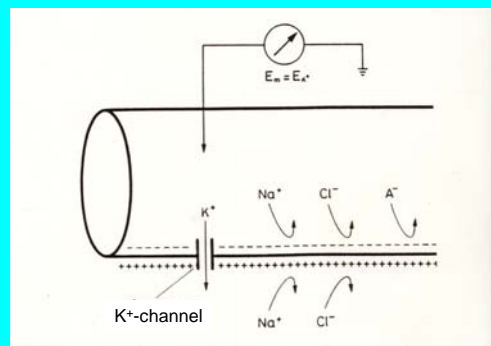


Equilibrium potential $\rightarrow \phi_i^I - \phi_i^{II} = \frac{RT}{zF} \ln \frac{c_i^I}{c_i^{II}}$

Nernst-equation

Assume (2) unlimited K^+ permeability

(3) zero Na^+ permeability



Donnan model – Equilibrium model

- No electrochemical potential difference between extra- and intracellular medium
- The membrane is permeable only for K^+ (and Cl^-)
- The cell with its extracellular region is thermodynamically closed system



equilibrium potential \equiv resting potential

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

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

Data from the equilibrium approach do not agree with the experiments

Tissue	Resting potential (mV)	
	calculated	measured
Squid axon	91	62
Frog muscle	103	92
Rat muscle	92,9	92

Calculations based on other ions

potential (mV)	Squid axon	Rat muscle
U_{measured}	-62	-92
U_{0K^+}	-91	-103
U_{0Na^+}	+47	+46
U_{0Cl^-}	-56	-88



There is no good agreement

Interpretation of the membrane potential

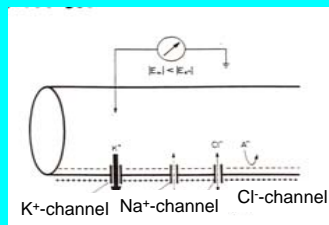
Model 2

1. Assume that the system is *not in equilibrium*

that is

transport is forced across the membrane

2. Take into consideration the real permeability of the membrane



the membrane is represented by specific ion-permeabilities

Electrodiffusion model - transport across the membrane

$$\sum J_k = 0$$

k : Na, K, Cl,

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

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

$$D_k = dp_k$$

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

Electrodiffusion model

Goldman – Hodgkin – Katz formula

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

c_k : ion-concentration
 p_k : permeability constant
 e : extracellular
 i : intracellular

Electrodiffusion model

Goldman – Hodgkin – Katz formula

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

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

Good agreement with experimental results



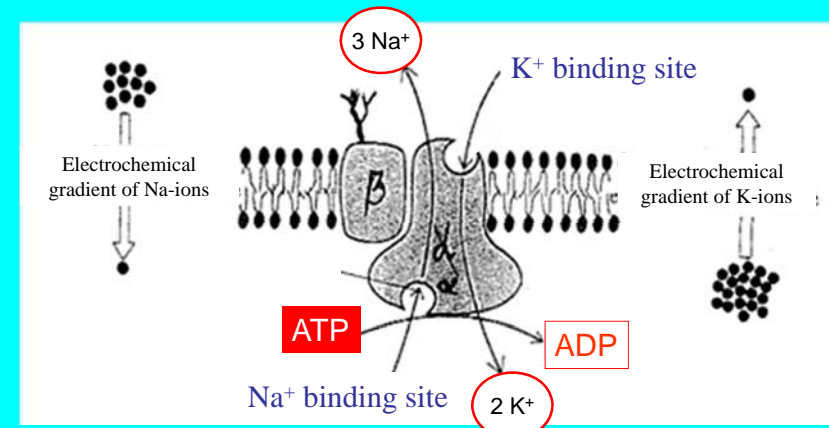
Electrodiffusion model

- Resting U_m depends on the concentration gradients and on the relative permeabilities to Na, K and Cl.
- The GHK equation describes a steady-state condition, not electrochemical equilibrium.
- There is net flux of individual ions, but no net charge movement.
- The cell must supply energy to maintain its ionic gradients.

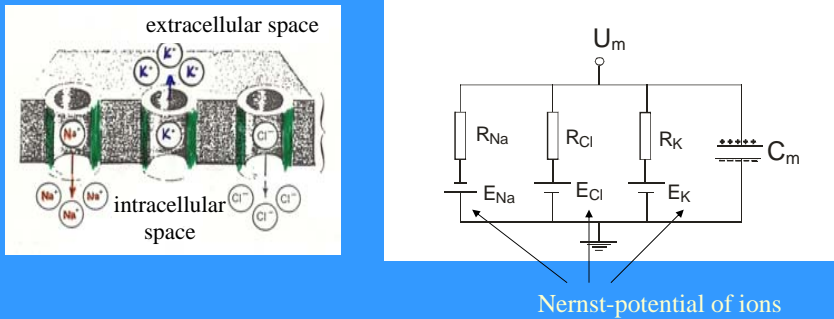
Na - K pump

antiporter

The condition for stationary flow is maintained by the active transport



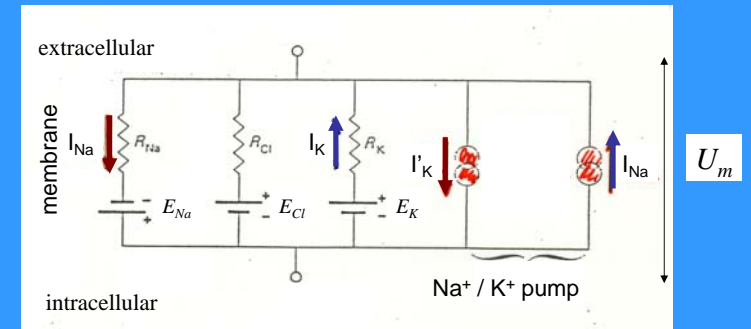
Equivalent circuit model



Nernst-potential of ions

Ionselective channels modeled by electromotive force and conductivity

Na⁺ /K⁺ pump restores the ion distribution



Ohm's law:

$$I_k = 1/R_k(U_m - E_k)$$

Calculation of resting potential according to the equivalent circuit model

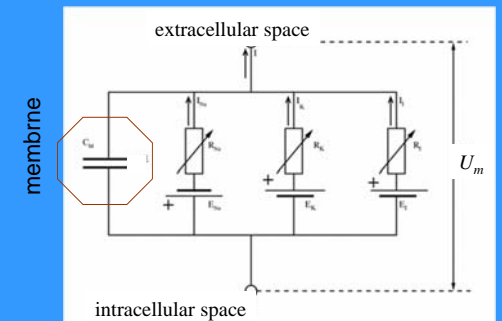
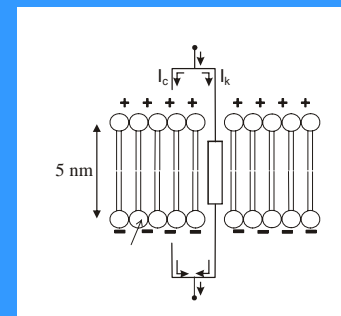
$$\left. \begin{aligned} I_k &= 1/R_k(U_m - E_k) \\ E_k &= \text{Nernst-potential of ions} \\ \sum I_k &= I_{\text{ion}} = 0 \\ \sum I_k &= I_{Na} + I_K + I_{Cl} = 0 \end{aligned} \right\} \begin{aligned} g_K(U_m - E_K) + g_{Na}(U_m - E_{Na}) &= 0 \\ \downarrow \\ U_m &= \frac{(U_{0K} \cdot x g_K) + (U_{0Na} \cdot x g_{Na})}{g_K + g_{Na}} \end{aligned}$$

Calculation:
$$U_m = \frac{(-100 \times 5) + (50 \times 1)}{5 + 1} = -75 \text{ [mV]}$$



Capacitive property of the membrane

Capacitance $\sim 10^{-6} \text{ F/cm}^2$



$$I_m = I_{\text{ion}} + I_c$$

Ion current

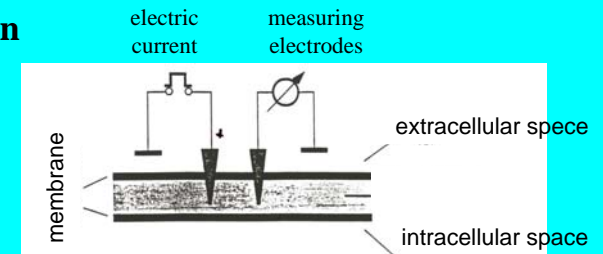
Capacitive current

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

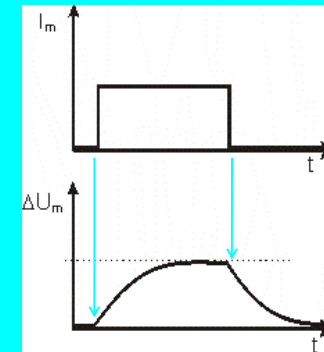
Alteration of resting membrane potential

1. “passive” electric properties of the membrane

Observation



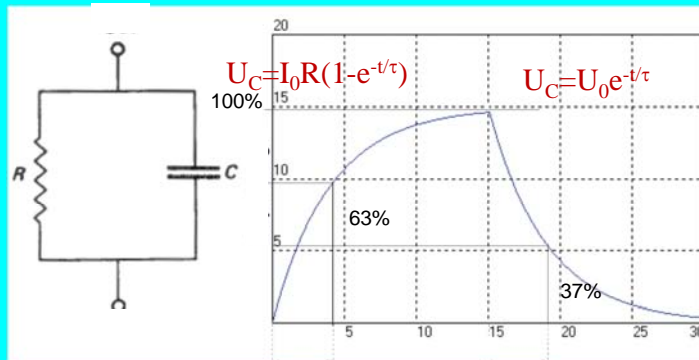
Inward current



Depolarization of the membrane

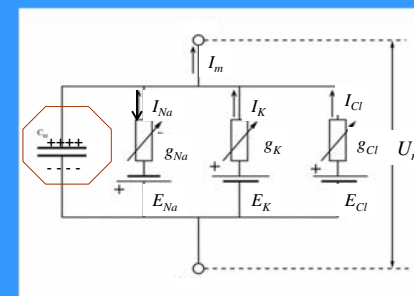
What is it like?

Charge and discharge of RC-circuit



$$\tau = RC$$

Interpretation with equivalent circuit model:



$$I_{ion} + I_c = I_m = 0$$

$$g_{Na} (U_m - E_{Na}) = I_{Na}$$

$$g_{ion} (U_m - E) = I_{ion}$$

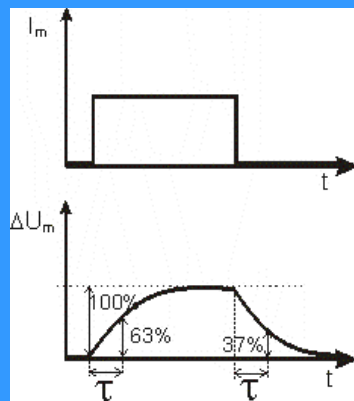
$$C_m \frac{\Delta U_m}{\Delta t} + \frac{\Delta U_m - E}{R_m} - I_{stimulus} = 0$$

Time from the beginning of stimulus

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

Membrane potential after t

Saturation value of membrane potential



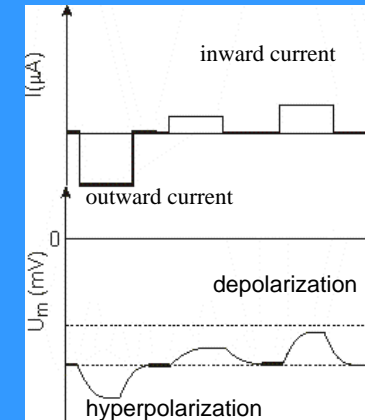
Capacitance of the membrane Resistance of the membrane

$$\tau = C_m R_m$$

τ : time constant of membrane

- the time required for the membrane potential to reach 63% of its saturation value
- during which the membrane potential decreases to the e-th of its original value

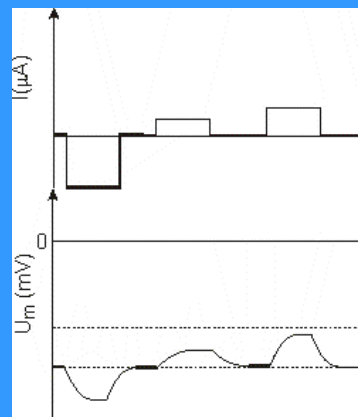
$$U_m(t) = U_i \left[1 - e^{-\frac{t}{R_m C_m}} \right]$$



U_i is proportional to the stimulating current

The rate of the change depends on U_i

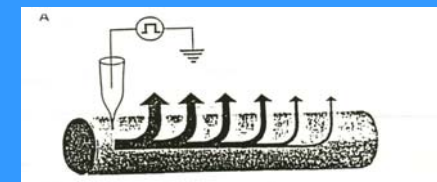
Local changes of membrane potential



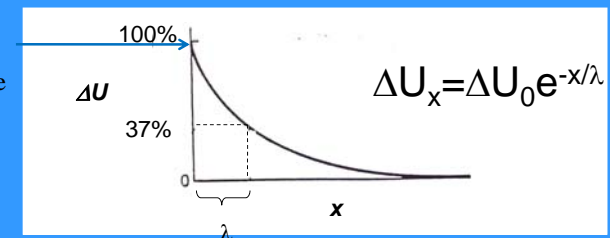
obligate
graded
magnitude varies directly
with the strength of the stimulus
direction varies
with the direction of the stimulus
„localized”

The local changes are not isolated from the neighborhood

Observation



Membrane potential change at the site of stimulation

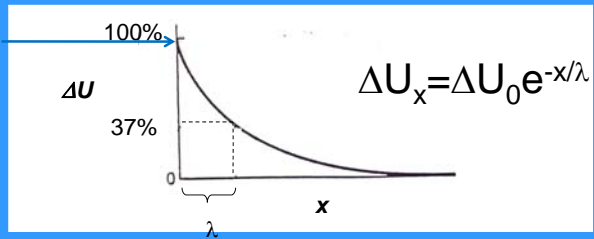


Decrease in amplitude with distance due to leaky membranes

λ : space constant of the membrane:

distance in which the maximal value of induced membrane potential change decreases to its e-th value

Membrane potential change at the site of stimulation



$$\lambda \sim \sqrt{\frac{R_m}{R_i}} \leftarrow \text{Resistance of intracellular space}$$

Local changes of resting membrane potential can be induced

- by electric current pulses
- by adequate stimulus at receptor cells
- by neurotransmitters at postsynaptic membrane
 - excitatory inhibitory postsynaptic potential - depolarization
 - inhibitory postsynaptic potential - hyperpolarization

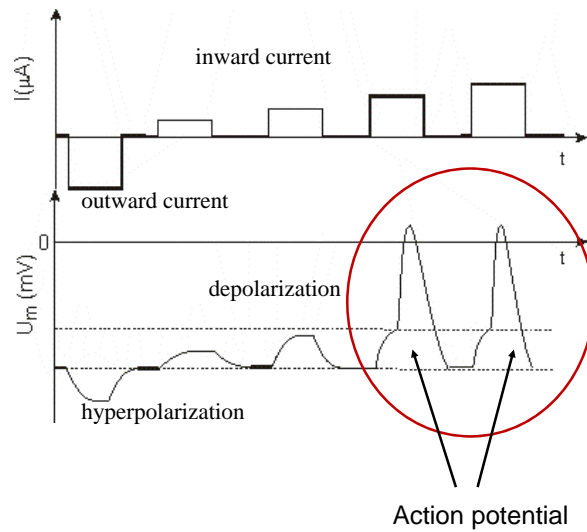
Significance of the local changes of resting membrane potential

Sensory function
Impulse conduction
Signal transduction

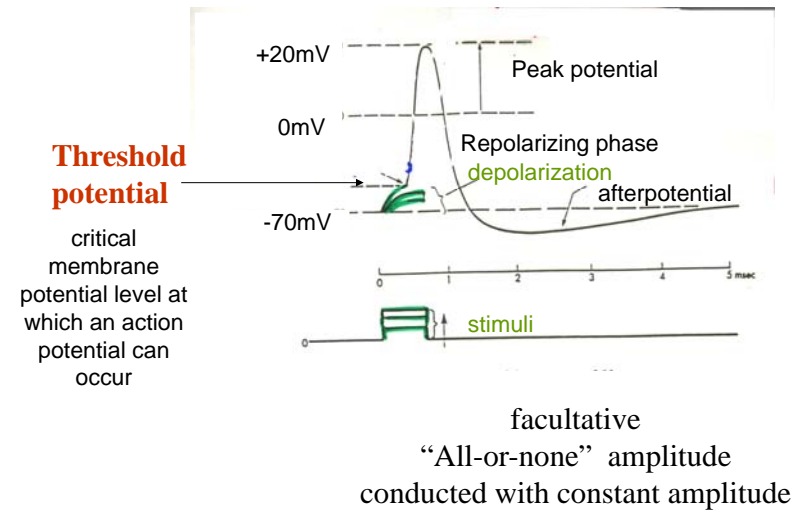
Alteration of resting membrane potential

2. “active” electric properties of the membrane in excited state

Observation

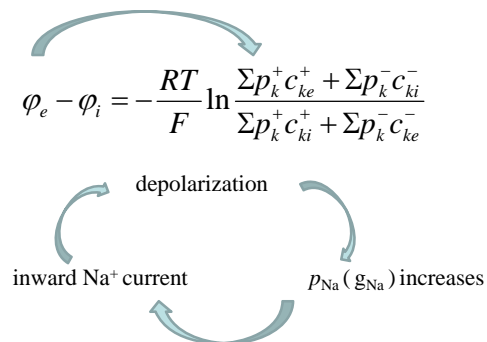


Phases and landmark of the action potential

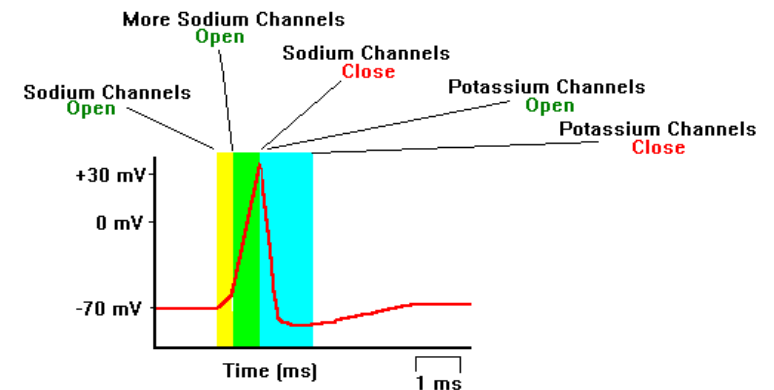


Hodgkin-Katz hypothesis of action potential generation

Voltage-gated, potential sensitive ion channels



Hodgkin-Katz hypothesis of action potential sequence





Andrew Fielding Huxley
(1917-)

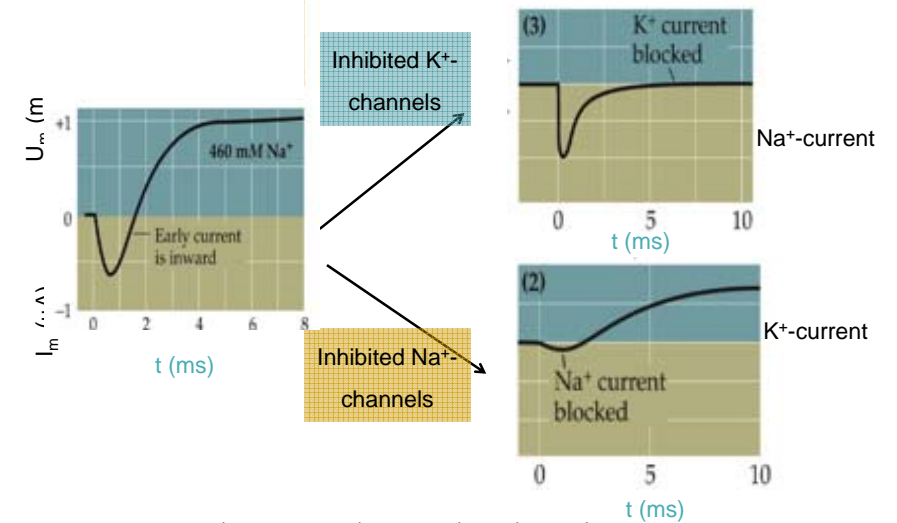


Alan Loyd Hodgkin
(1914-1998)

The Nobel Prize in Physiology or Medicine
1963

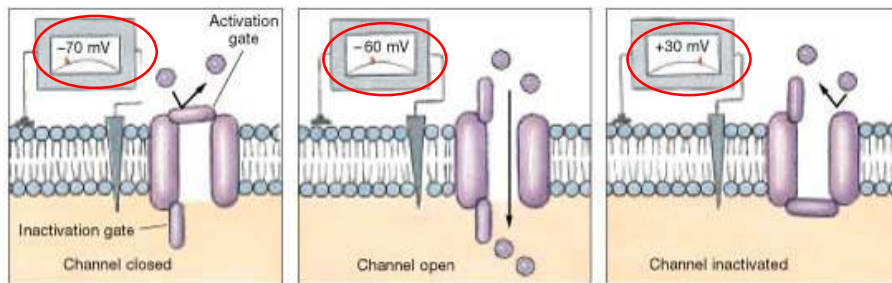
"for their discoveries concerning the ionic mechanisms involved in excitation and inhibition in the peripheral and central portions of the nerve cell membrane"

Measurement of separated ionic currents



Voltage-Gated Na^+ and K^+ Channels

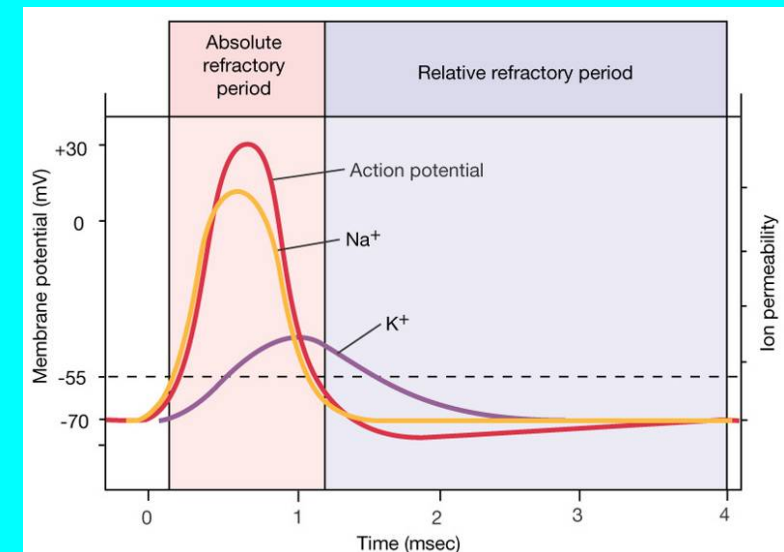
States of voltage-gated sodium channels



(c)

at depolarization threshold

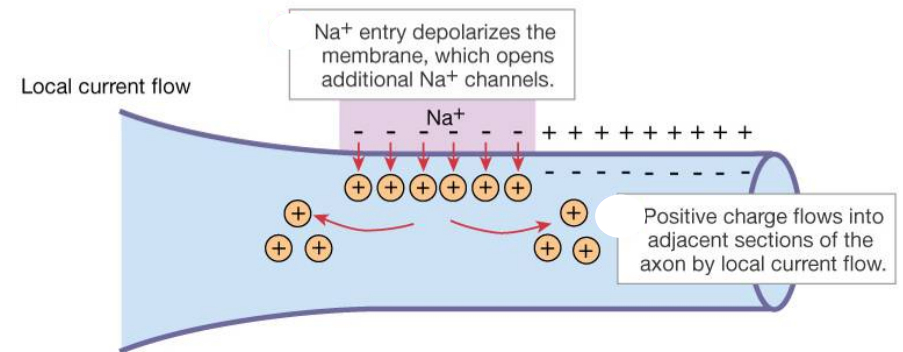
Conductivities during action potential



Factors Influencing Conduction Direction and Velocity

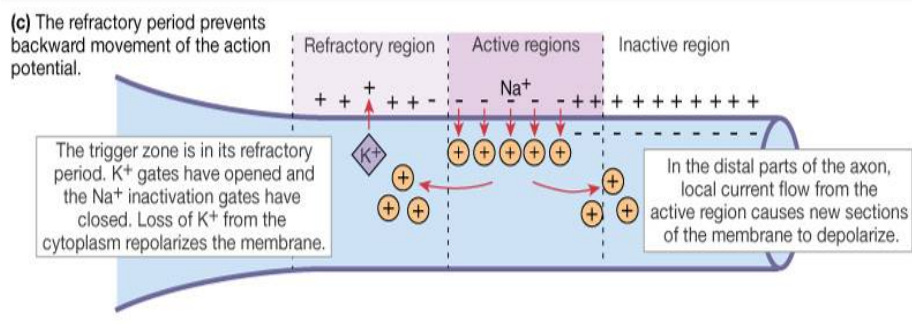
The evolutionary need for the fast and efficient transduction of electrical signals

Propagation of action potential (1)



based on local current flow and depolarization of adjacent membrane area

Propagation of action potential (2)

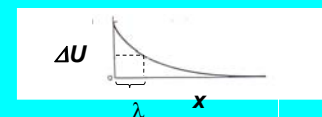


Speed and distance of propagation?

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

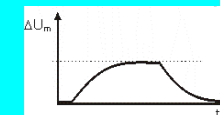
Generation of the next peak potential

Where?



The greater the space constant, the more rapidly distant regions will be brought to threshold and the more rapid will be the propagation velocity

When?



The smaller the time constant, the more rapidly a depolarization will affect the adjacent region.

Velocity is the function of passive properties – τ and λ – of membranes

Effect of axon diameter:

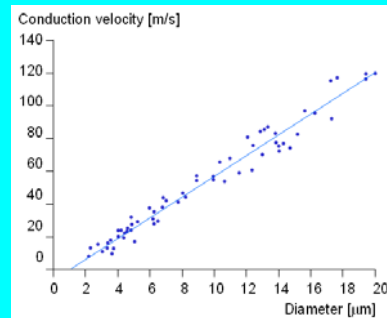
$$r \uparrow \Rightarrow \begin{matrix} R_i \downarrow (\sim 1/r^2) \\ R_m \downarrow (\sim 1/r) \end{matrix} \Rightarrow \begin{matrix} \tau \downarrow \\ \lambda \uparrow \end{matrix}$$

$$\tau = C_m R_m$$

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

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

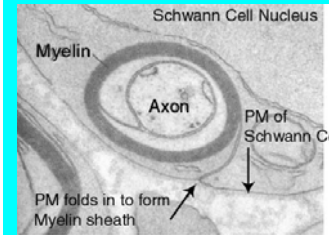
human nerve cell $r=10\mu\text{m}$
 $v \approx 0.5\text{m/s}$?



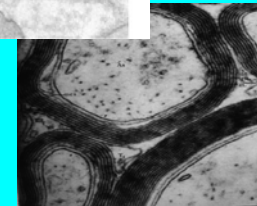
Myelination!

R_m – very high \Rightarrow big space constant

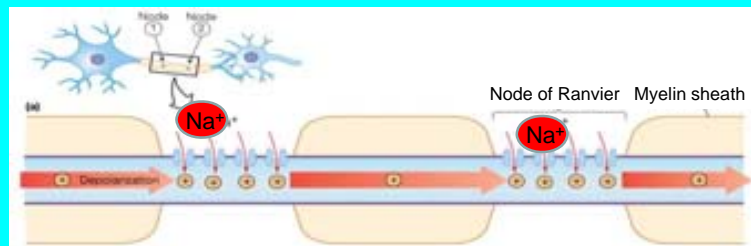
C_m – very small \Rightarrow small time constant



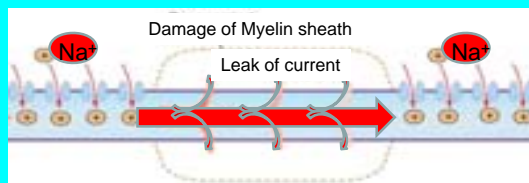
human nerve cell $r=10\mu\text{m}$
 $v \sim 100\text{m/s}$



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.

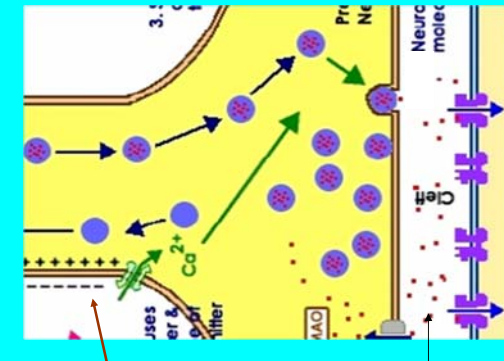
Fiber type	Average axon diameter (μm)	Conduction velocity ($\text{m} \cdot \text{s}^{-1}$)
Myelinated fibers		
A α	18.5	42
A β	14.0	25
A γ	11.0	17
B	Approximately 3.0	4.2
Unmyelinated fibers		
C	2.5	0.4–0.5

Effect of passive electric properties on signal transduction in synapses

Signal transmission in synapses

presynaptic terminal

postsynaptic terminal

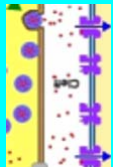


Action potential

neurotransmitter

How can neurons transmit information from presynaptic to postsynaptic cells **if most synaptic effects are subthreshold?**

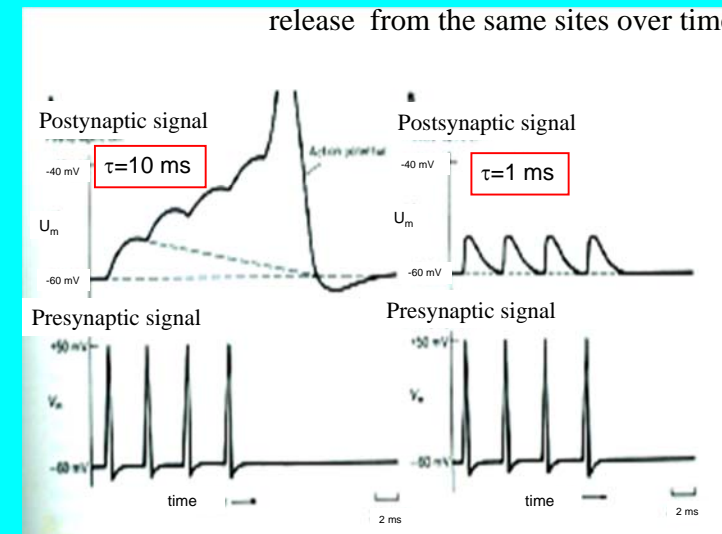
Spatial Summation : combined influences at the same cell at a particular moment in time



Temporal Summation : combined effects of neurotransmitter release from the same sites over time



Temporal Summation : combined effects of neurotransmitter release from the same sites over time



Temporal and spatial summation

