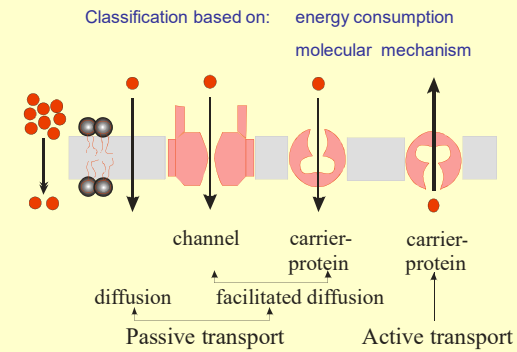


Transport across biological membranes

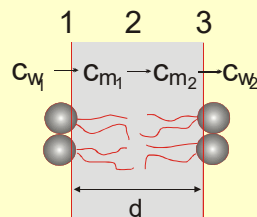
Transport in Resting Cell

Transport types across the membranes



Diffusion of neutral particles

Diffusion across the lipid bilayer



Assume that concentration changes linearly

Fick I.

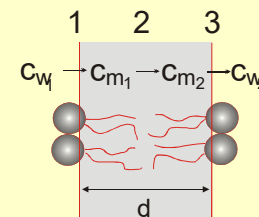
$$J_m = -D \frac{\Delta c}{\Delta x}$$

$$D_m \ll D$$

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

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

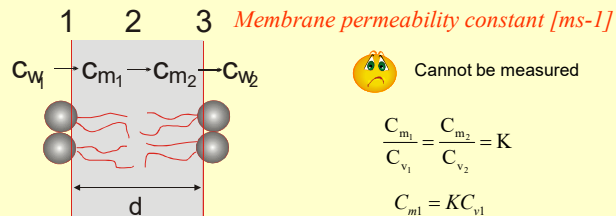
$$\frac{c_{m1}}{c_{v1}} = \frac{c_{m2}}{c_{v2}} = K$$

$$c_{m1} = K c_{v1}$$

Diffusion of neutral particles

Diffusion across the lipid bilayer

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



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

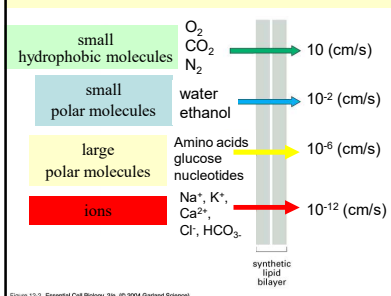
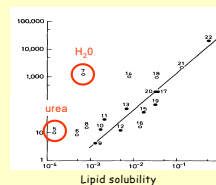


Figure 12-2 Essential Cell Biology, 2nd ed. (© 2004 Garland Science)

Lipid solubility v permeability



Diffusion of ions

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

chemical potential
and
electric potential
together

$$J_k = L_k X_k = -L_k \frac{\Delta \mu_{ek}}{\Delta x}$$

flux of k -th ion

Diffusion of ions

$$J_k = L_k X_k = -L_k \frac{\Delta \mu_{ek}}{\Delta x}$$

$$\frac{\Delta \mu_{ek}}{\Delta x} = \frac{\Delta \mu_k}{\Delta x} + Z_k F \frac{\Delta \phi}{\Delta x} \quad \text{és} \quad L_k = c_k \frac{D_k}{RT}$$

$$J_k = -D_k \left(\frac{\Delta c_k}{\Delta x} + c_k \frac{Z_k F}{RT} \frac{\Delta \phi}{\Delta x} \right) \quad D = u k T$$

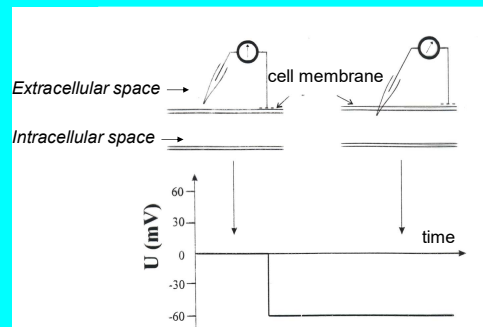
$$J_k = -u_k k T \left(\frac{\Delta c_k}{\Delta x} + c_k \frac{Z_k F}{RT} \frac{\Delta \phi}{\Delta x} \right)$$

flux of k -th ion

Basic principles of electrophysiology

Interpretation by transport phenomena

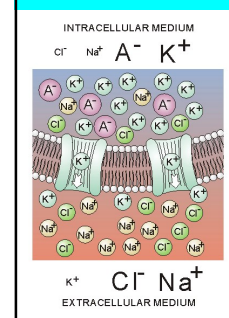
Observation 1: There is an electric potential difference between extra- and intracellular space



The intracellular side is negative with respect to the extracellular side

resting potential ~ 60 – 90 mV

Observation 2: Inhomogeneous ion distribution



Cell type	C _{Intracellular} (mmol/l)			C _{Extracellular} (mmol/l)		
	[Na ⁺] _i	[K ⁺] _i	[Cl ⁻] _i	[Na ⁺] _e	[K ⁺] _e	[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

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

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



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

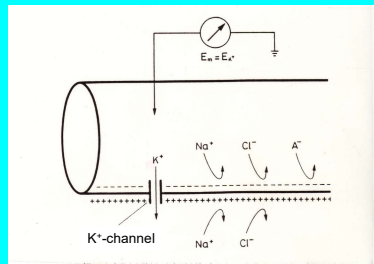


Equilibrium potential → $\phi_i^I - \phi_i^{II} = \frac{RT}{zF} \ln \frac{c_i^I}{c_i^{II}}$

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 ≡ 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

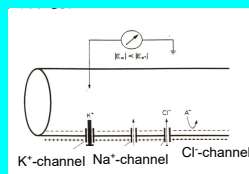
Model 2

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

$$\sum J_k = 0 \quad k: Na, K, Cl, \dots$$

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

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

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

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



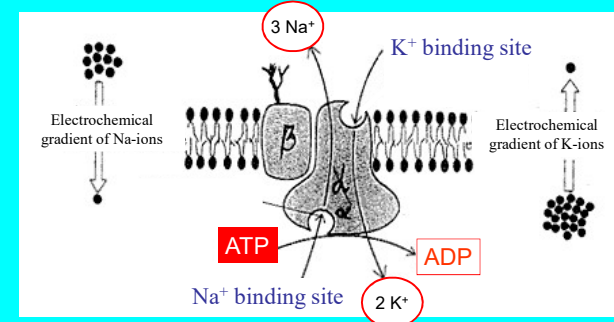
Electrodiffusion model

- 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.

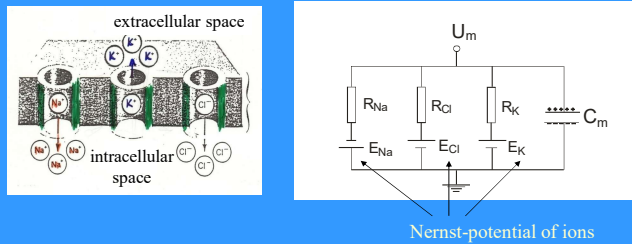
Na - K pump

antiporter

The condition for stationary flow is maintained by the active transport

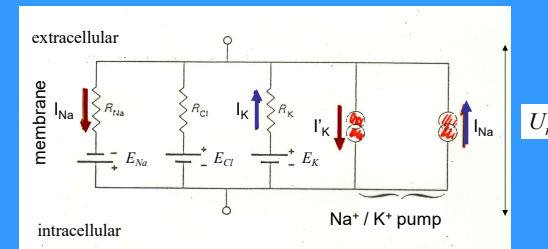


Equivalent circuit model



Ionselective channels modeled by electromotive force and conductivity

Na⁺/K⁺ pump restores the ion distribution

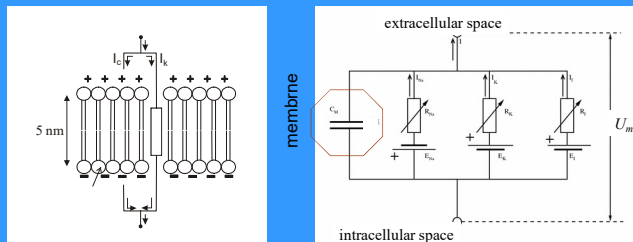


Ohm's law:

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

Capacitive property of the membrane

Capacitance $\sim 10^{-6}$ F/cm²



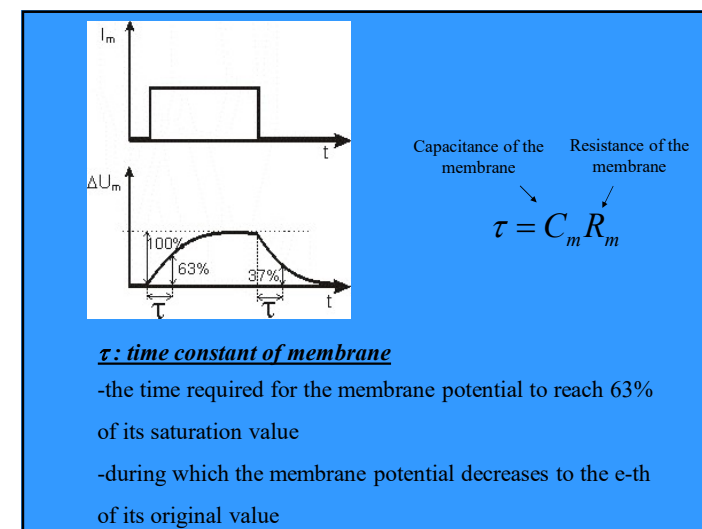
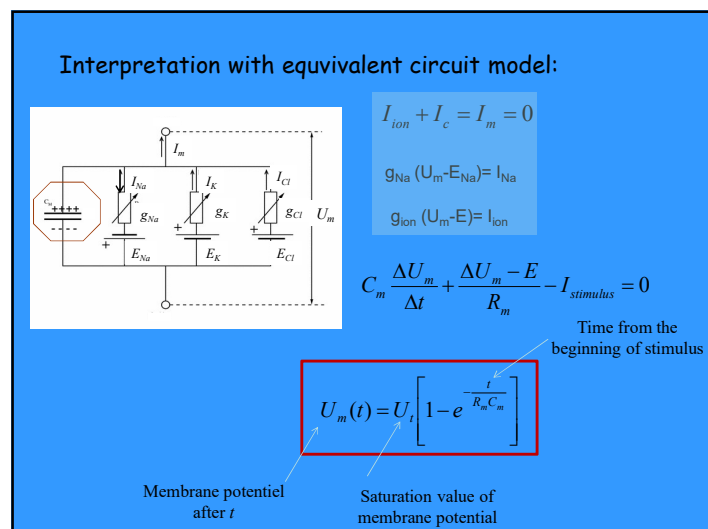
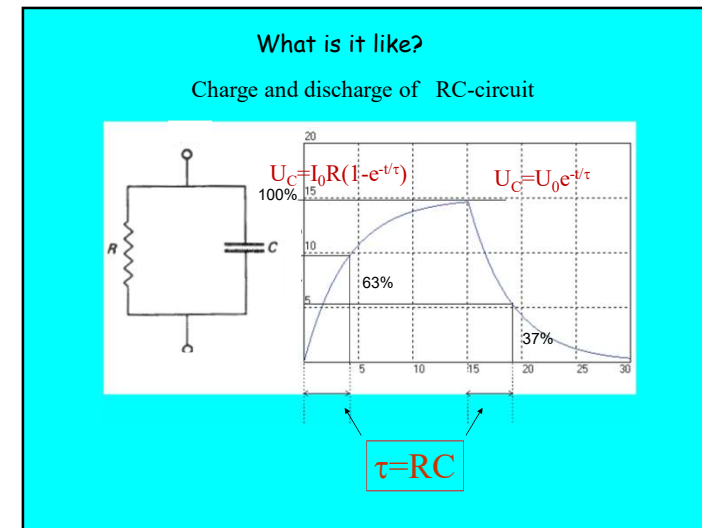
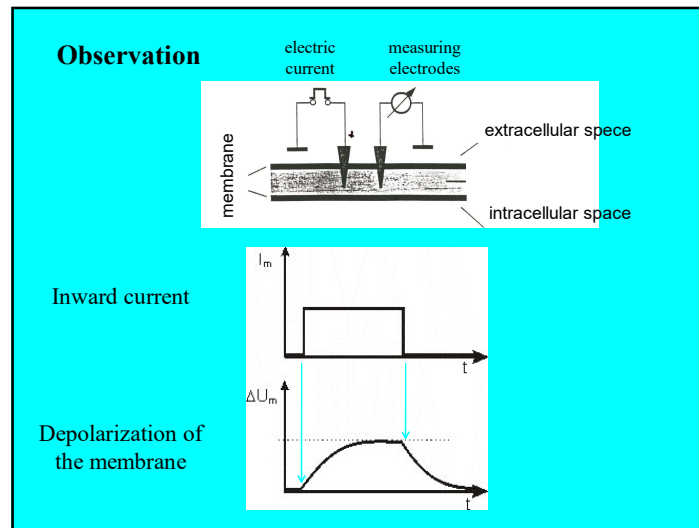
$$I_m = I_{ion} + I_c$$

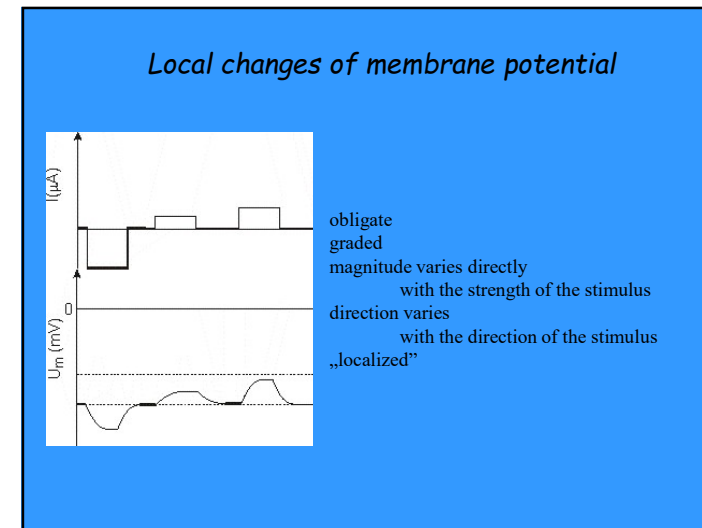
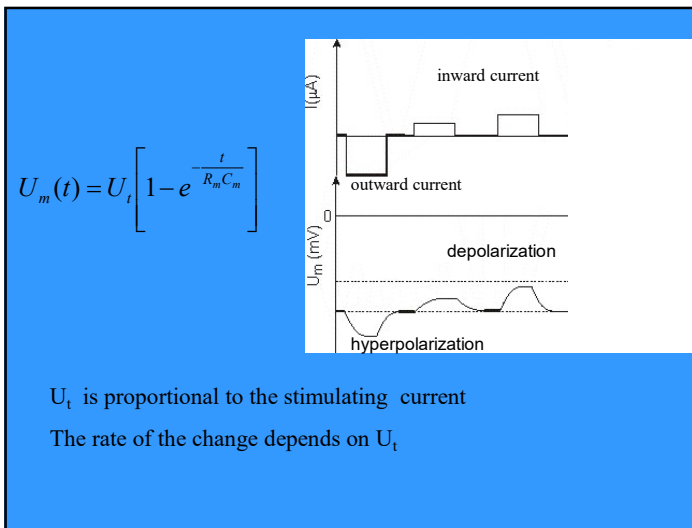
Ion current Capacitive current

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

Alteration of resting membrane potential

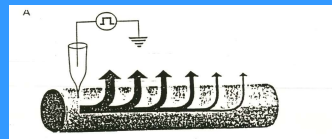
1. "passive" electric properties of the membrane



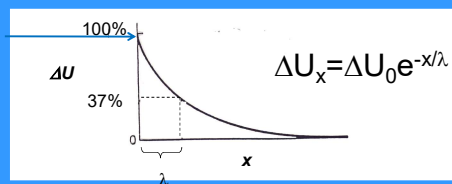


The local changes are not isolated from the neighborhood

Observation



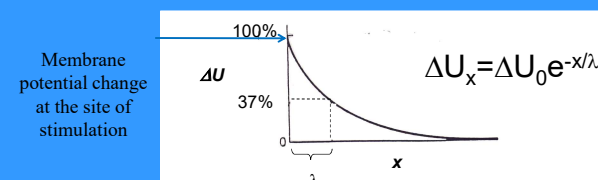
Membrane potential change at the site of stimulation



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



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

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

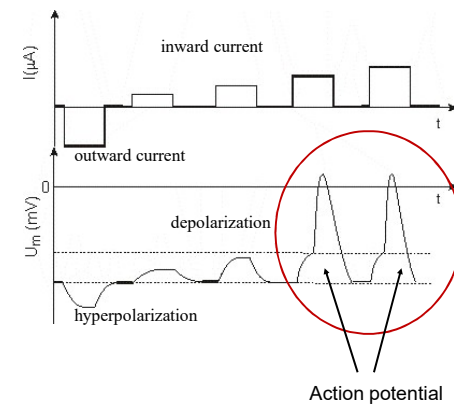
Significance of the local changes of resting membrane potential

Sensory function
Impulse conduction
Signal transduction

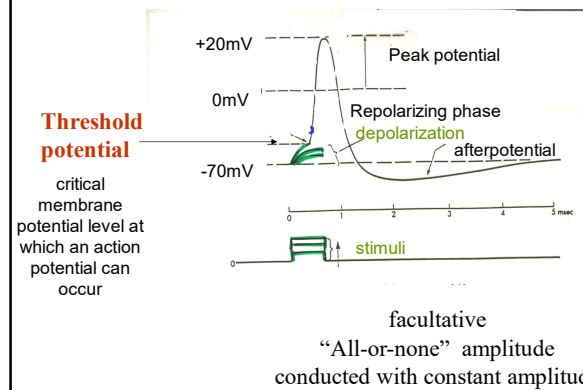
Alteration of resting membrane potential

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

Observation



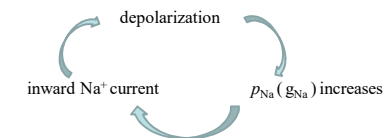
Phases and landmark of the action potential



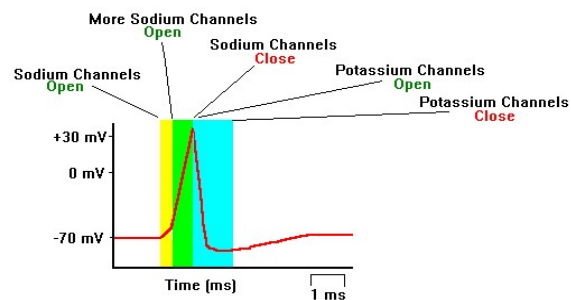
Hodgkin-Katz hypothesis of action potential generation

Voltage-gated, potential sensitive ion channels

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



Hodgkin-Katz hypothesis of action potential sequence



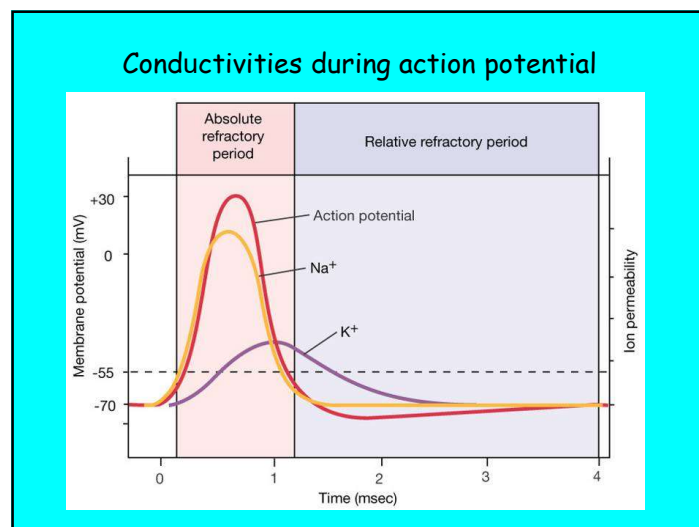
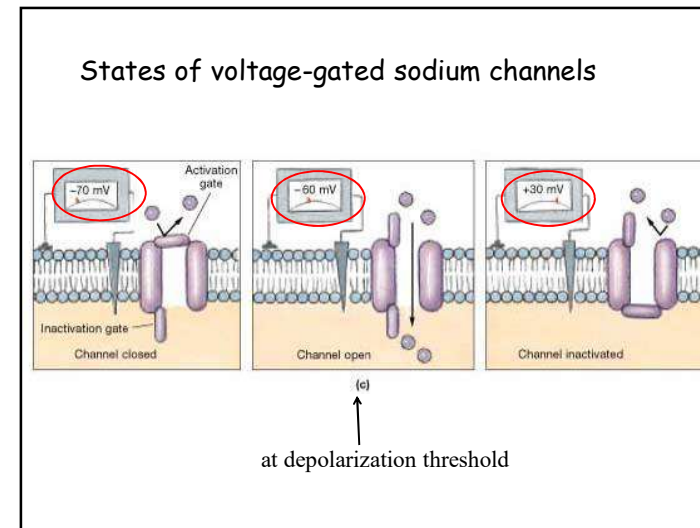
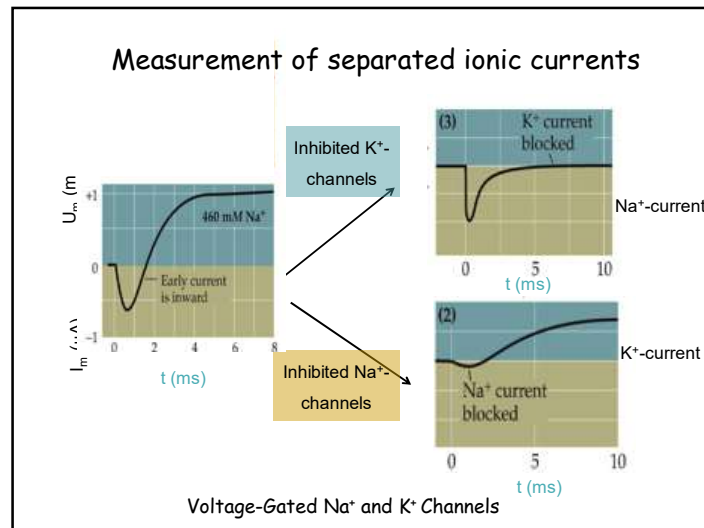
Andrew Fielding Huxley
(1917-)



Alan Loyd Hodgkin
(1914-1998)

The Nobel Prize in Physiology or Medicine
1963

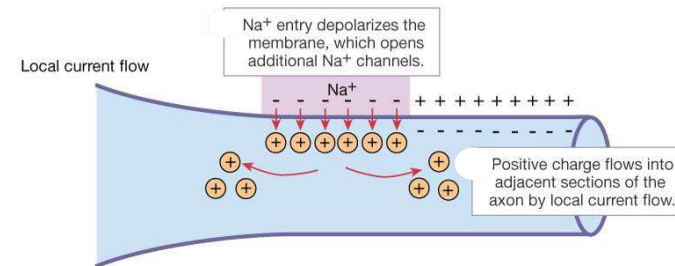
"for their discoveries concerning the ionic mechanisms involved in excitation and inhibition in the peripheral and central portions of the nerve cell membrane"



Factors Influencing Conduction Direction and Velocity

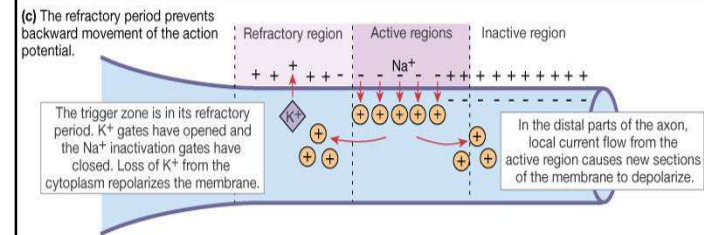
The evolutionary need for the fast and efficient transduction of electrical signals

Propagation of action potential (1)



based on local current flow and depolarization of adjacent membrane area

Propagation of action potential (2)

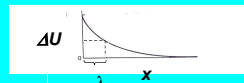


Speed and distance of propagation?

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

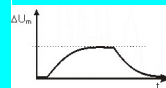
Generation of the next peak potential

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:

$$r \uparrow \Rightarrow R_i \downarrow (\sim 1/r^2) \Rightarrow \tau \downarrow$$

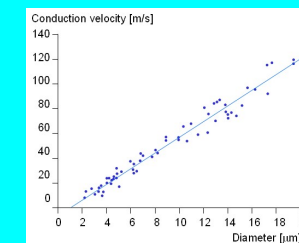
$$R_m \downarrow (\sim 1/r) \Rightarrow \lambda \uparrow$$

$$\tau = C_m R_m$$

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

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

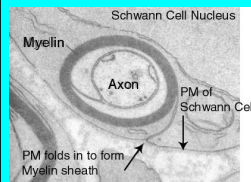
human nerve cell $r=10\mu\text{m}$
 $v \approx 0.5\text{m/s}$?



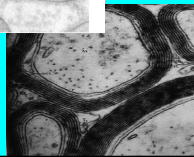
Myelination!

R_m – very high \Rightarrow big space constant

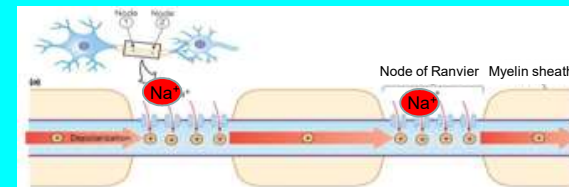
C_m – very small \Rightarrow small time constant



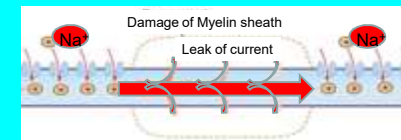
human nerve cell $r = 10 \mu\text{m}$
 $v \sim 100 \text{ m/s}$



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.

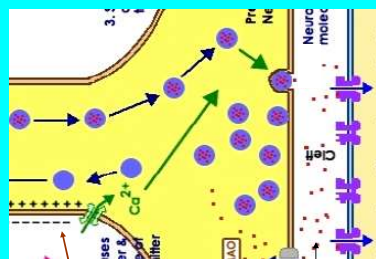
Fiber type	Average axon diameter (μm)	Conduction velocity ($\text{m} \cdot \text{s}^{-1}$)
Myelinated fibers		
A α	18.5	42
A β	14.0	25
A γ	11.0	17
B	Approximately 3.0	4.2
Unmyelinated fibers		
C	2.5	0.4–0.5

Effect of passive electric properties on signal transduction in synapses

Signal transmission in synapses

presynaptic terminal

postsynaptic terminal

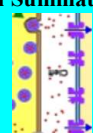


Action potential

neurotransmitter

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

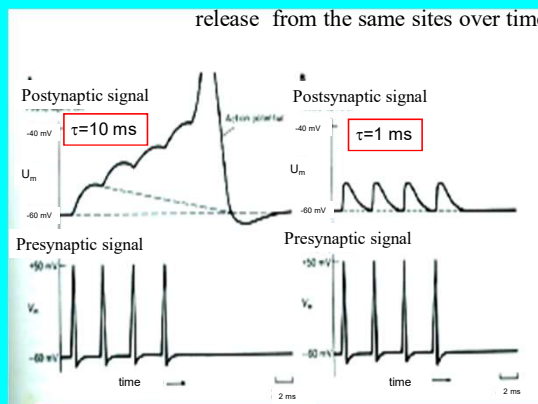
Spatial Summation : combined influences at the same cell at a particular moment in time



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

