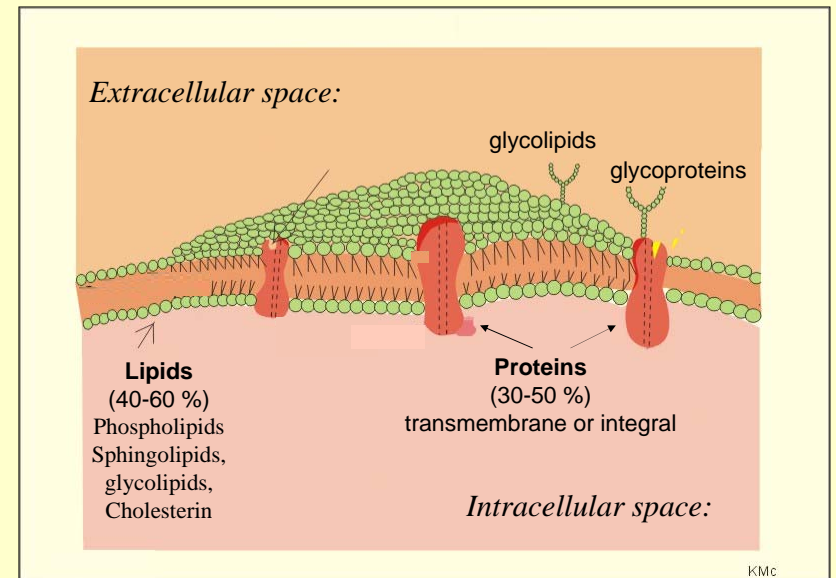


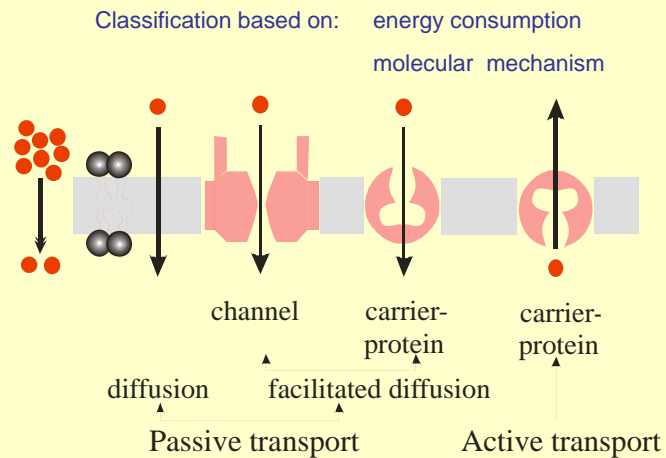
# Transport across biological membranes

Transport in Resting Cell

## Membrane structure



## Transport types across the membranes



## Diffusion of neutral particles

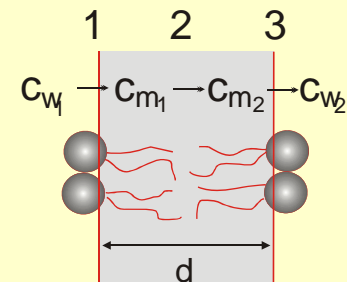
Diffusion across the lipid bilayer

Fick I.

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

$$D_m < D$$

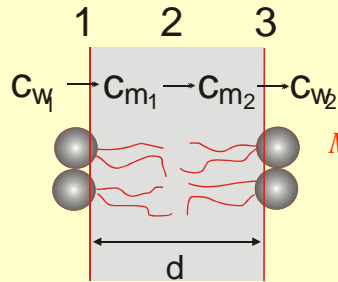
$$J_m = -D_m \frac{c_{m2} - c_{m1}}{d}$$



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 [ $ms^{-1}$ ]



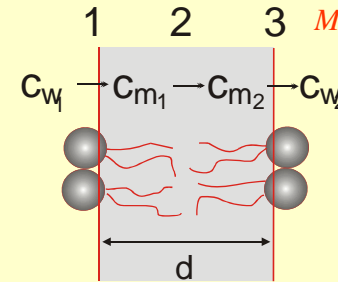
Cannot be measured

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

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

## 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

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

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

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

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

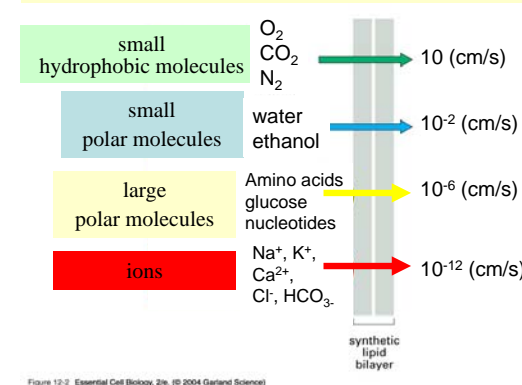
$$J_m = -p(C_{v2} - C_{v1})$$

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

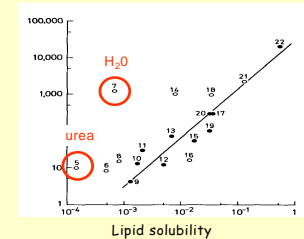


Figure 12-2 Essential Cell Biology, 2/e. (© 2004 Garland Science)

## Diffusion of ions

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

chemical potential  
and  
electric potential  
together

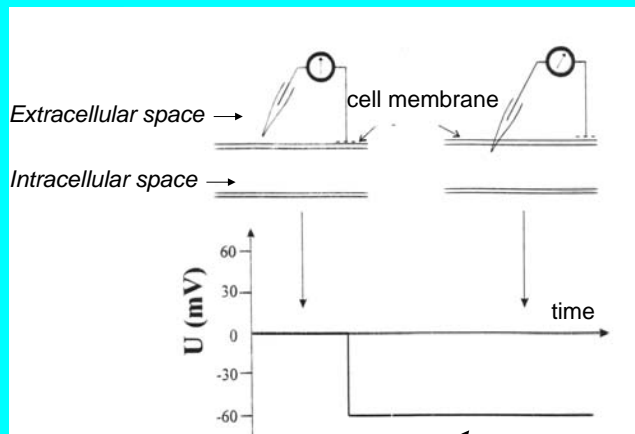
$$J_k = -D_k \left( \frac{\Delta c_k}{\Delta x} + c_k \frac{z_k F}{RT} \frac{\Delta \varphi}{\Delta x} \right)$$

flux of  $k$ -th ion

## Basic principles of electrophysiology

### Interpretation by transport phenomena

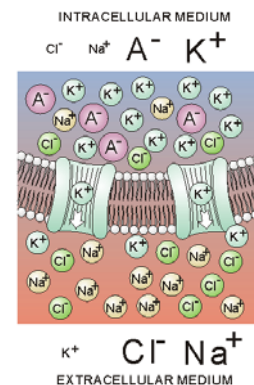
**Observation 1:** There is an electric potential difference between extra- and intracellular space



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	<b>345</b>	61	<b>455</b>	10	540
Frog muscle	20	<b>139</b>	3,8	<b>120</b>	2,5	120
Rat muscle	12	<b>180</b>	3,8	<b>150</b>	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*

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

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



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

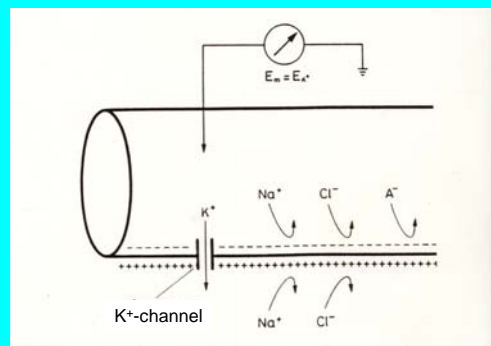


Equilibrium potential  $\rightarrow \phi_i^I - \phi_i^{II} = \frac{RT}{zF} \ln \frac{c_i^I}{c_i^{II}}$

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
$U_{\text{measured}}$	-62	-92
$U_{0K^+}$	-91	-103
$U_{0Na^+}$	+47	+46
$U_{0Cl^-}$	-56	-88



There is no good agreement

## Interpretation of the membrane potential

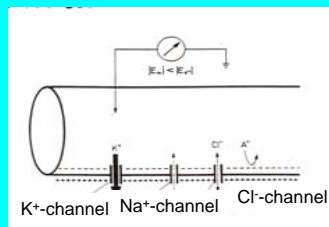
### Model 2

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
$U_{\text{measured}}$	<b>-62</b>	<b>-92</b>
$U_{\text{GHK}}$	-61,3	-89,2

Good agreement with experimental results



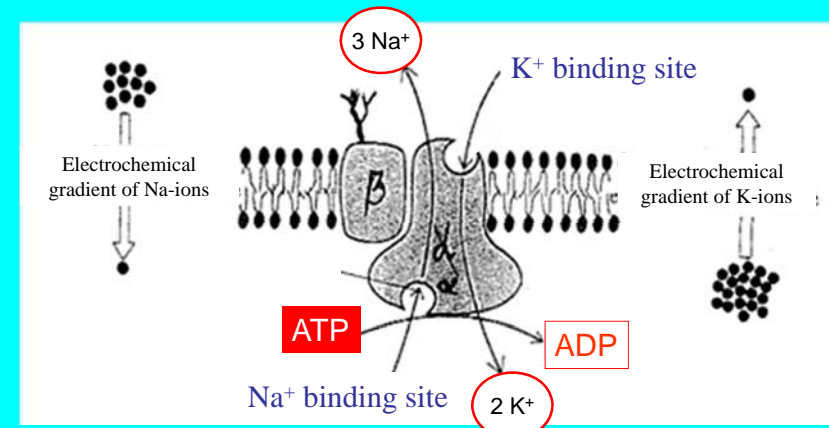
## Electrodiffusion model

- 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.

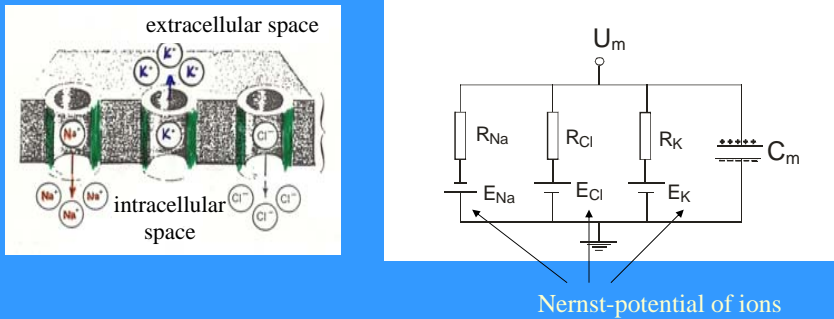
## Na - K pump

antiporter

The condition for stationary flow is maintained by the active transport



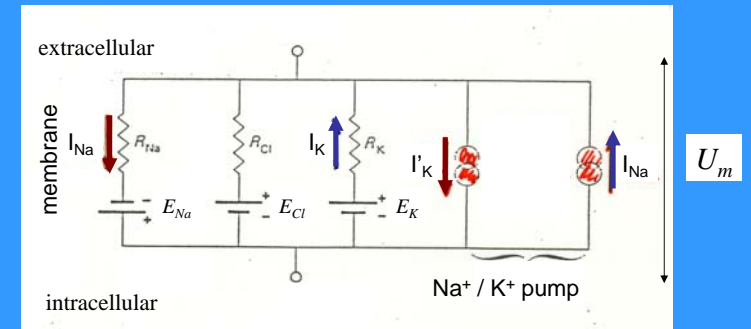
## Equivalent circuit model



Nernst-potential of ions

Ionselective channels modeled by electromotive force and conductivity

## Na<sup>+</sup> /K<sup>+</sup> 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

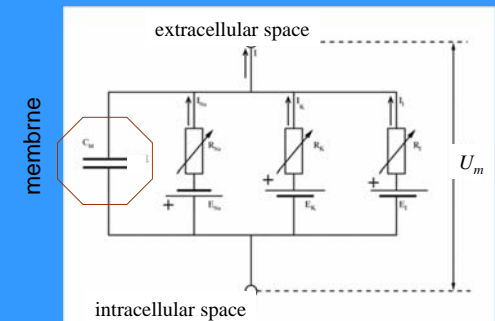
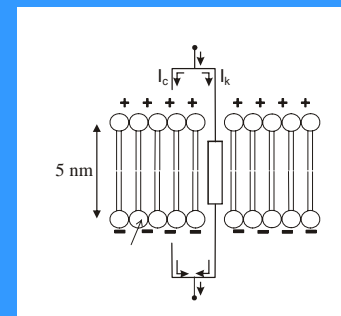
$$\left. \begin{array}{l} I_k = 1/R_k(U_m - E_k) \\ E_k - \text{Nernst-potential of ions} \\ \Sigma I_k = I_{\text{ion}} = 0 \\ \Sigma I_k = I_{Na} + I_K + I_{Cl} = 0 \end{array} \right\} \begin{array}{l} g_K(U_m - E_K) + g_{Na}(U_m - E_{Na}) = 0 \\ \downarrow \\ U_m = \frac{(U_{0K} \cdot x g_K) + (U_{0Na}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

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

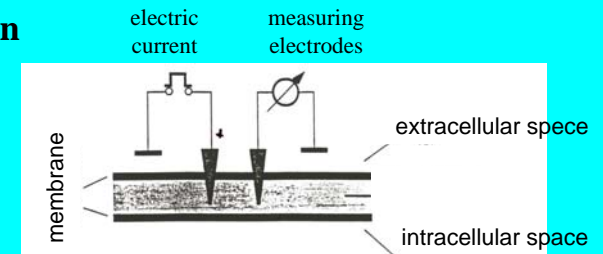
Capacitive current

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

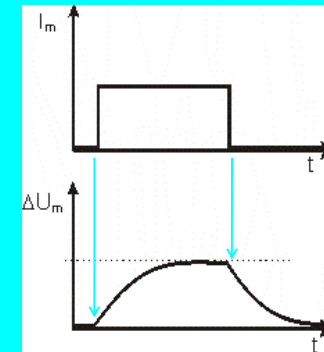
## Alteration of resting membrane potential

1. “passive” electric properties of the membrane

## Observation



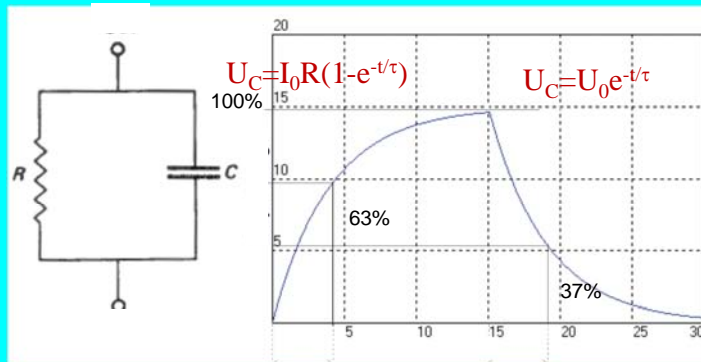
Inward current



Depolarization of the membrane

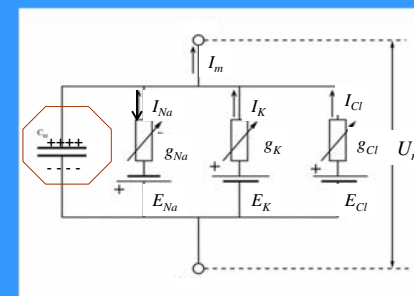
What is it like?

Charge and discharge of RC-circuit



$$\tau = RC$$

Interpretation with equivalent circuit model:



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

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

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

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

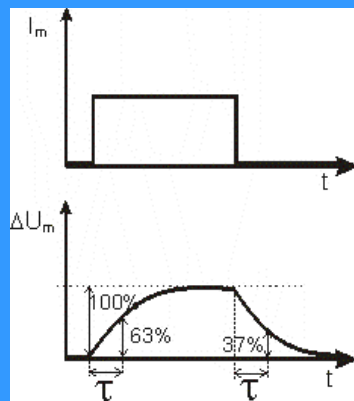
Time from the beginning of stimulus

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

Membrane potential after  $t$

Saturation value of membrane potential





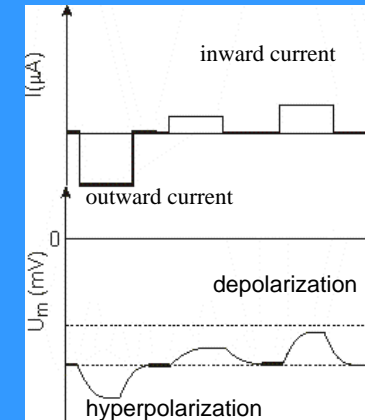
Capacitance of the membrane  $C_m$  Resistance of the membrane  $R_m$

$$\tau = C_m R_m$$

### $\tau$ : 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

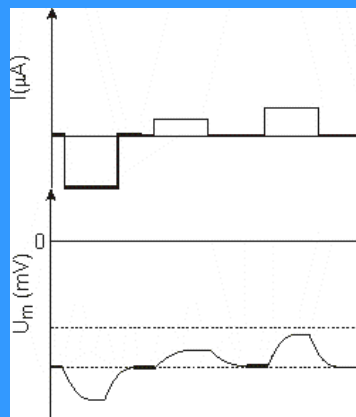
$$U_m(t) = U_i \left[ 1 - e^{-\frac{t}{R_m C_m}} \right]$$



$U_i$  is proportional to the stimulating current

The rate of the change depends on  $U_i$

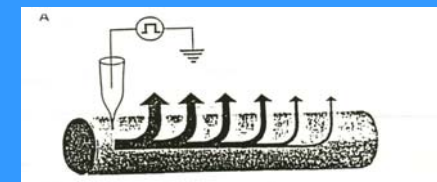
### *Local changes of membrane potential*



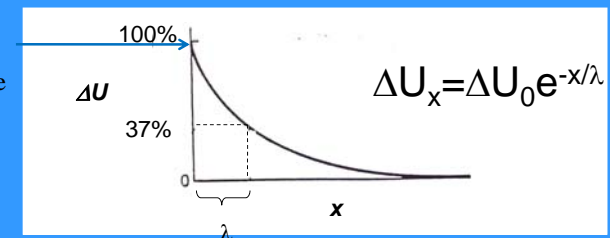
obligate  
graded  
magnitude varies directly  
with the strength of the stimulus  
direction varies  
with the direction of the stimulus  
„localized”

### *The local changes are not isolated from the neighborhood*

#### Observation



Membrane potential change at the site of stimulation

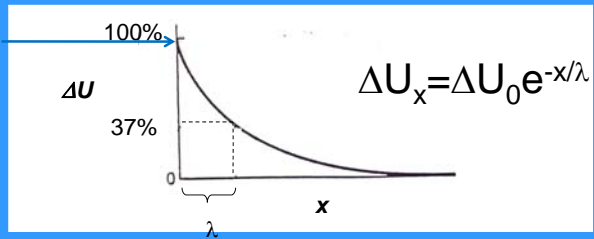


Decrease in amplitude with distance due to leaky membranes

**$\lambda$ : 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

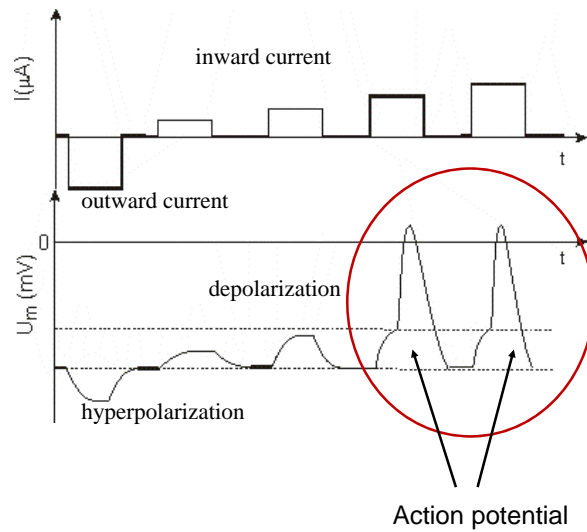
***Significance of the local changes of resting membrane potential***

Sensory function  
Impulse conduction  
Signal transduction

***Alteration of resting membrane potential***

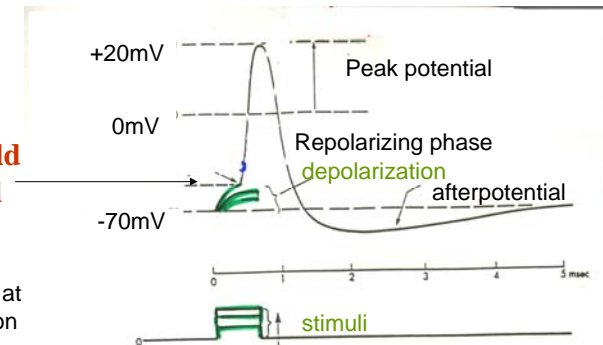
2. “active” electric properties of the membrane in excited state

## Observation



## Phases and landmark of the action potential

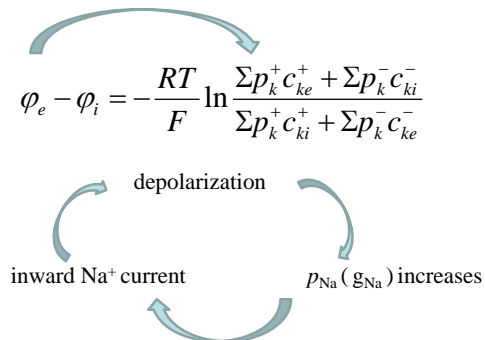
**Threshold potential**  
critical membrane potential level at which an action potential can occur



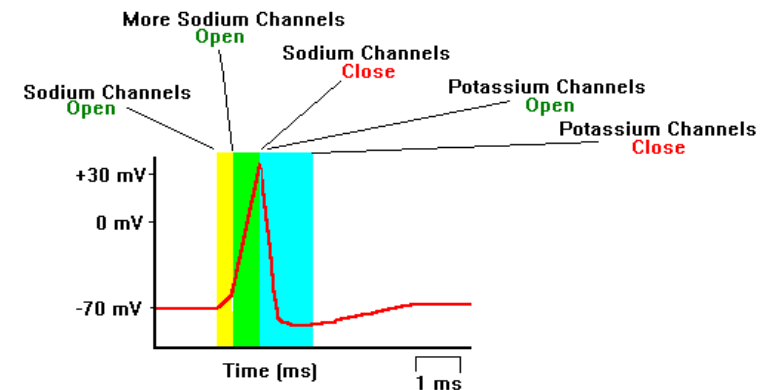
facultative  
“All-or-none” amplitude  
conducted with constant amplitude

## Hodgkin-Katz hypothesis of action potential generation

Voltage-gated, potential sensitive ion channels



## Hodgkin-Katz hypothesis of action potential sequence





**Andrew Fielding Huxley**  
(1917- )

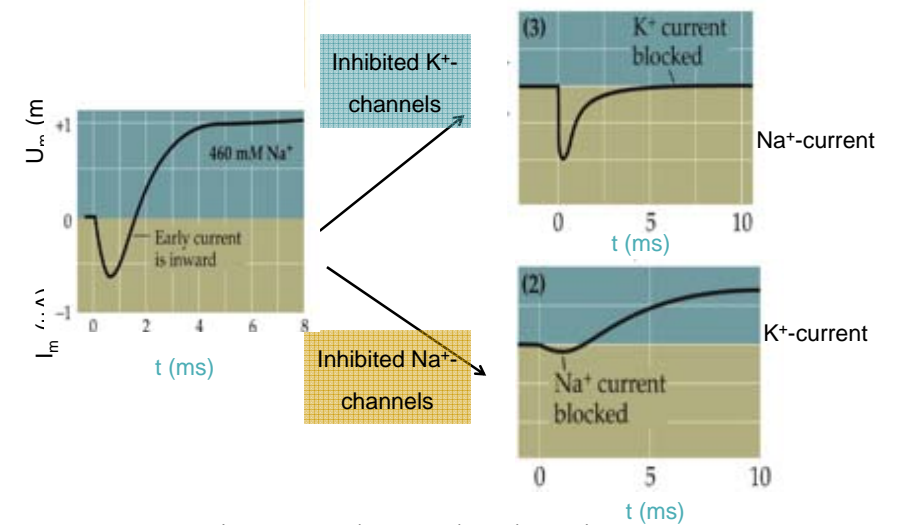


**Alan Loyd Hodgkin**  
(1914-1998)

The Nobel Prize in Physiology or Medicine  
1963

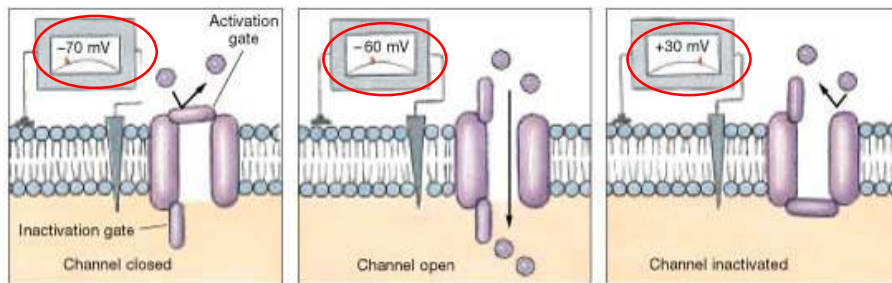
"for their discoveries concerning the ionic mechanisms involved in excitation and inhibition in the peripheral and central portions of the nerve cell membrane"

## Measurement of separated ionic currents



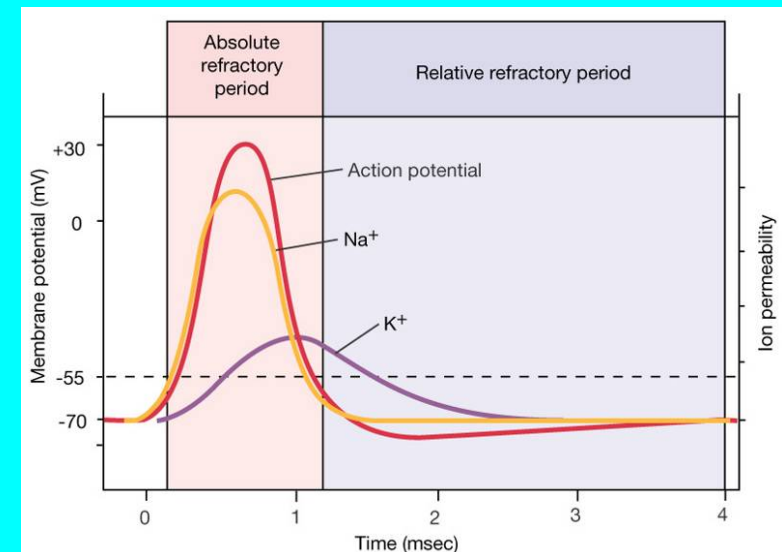
Voltage-Gated Na<sup>+</sup> and K<sup>+</sup> Channels

## States of voltage-gated sodium channels



(c)  
↑  
at depolarization threshold

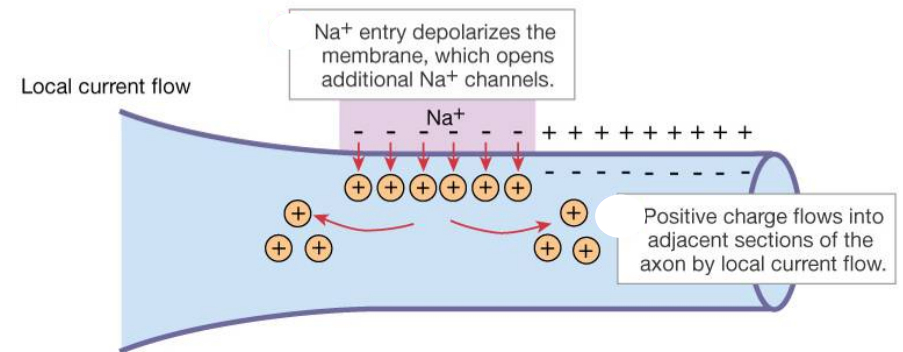
## Conductivities during action potential



## Factors Influencing Conduction Direction and Velocity

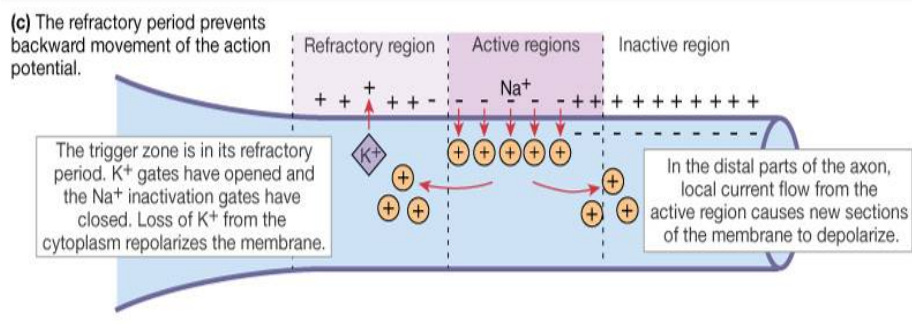
The evolutionary need for the fast and efficient transduction of electrical signals

### Propagation of action potential (1)



based on local current flow and depolarization of adjacent membrane area

### Propagation of action potential (2)

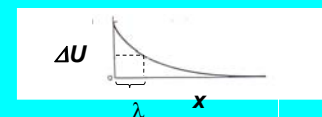


Speed and distance of propagation?

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

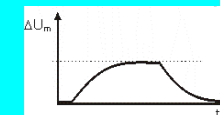
Generation of the next peak potential

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 –  $\tau$  and  $\lambda$  – of membranes**

### Effect of axon diameter:

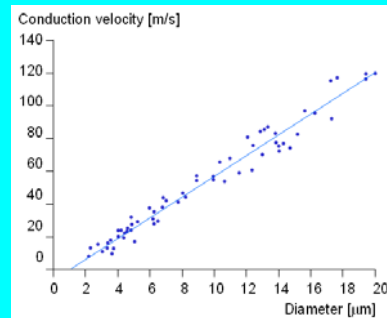
$$r \uparrow \Rightarrow \begin{matrix} R_i \downarrow (\sim 1/r^2) \\ R_m \downarrow (\sim 1/r) \end{matrix} \Rightarrow \begin{matrix} \tau \downarrow \\ \lambda \uparrow \end{matrix}$$

$$\tau = C_m R_m$$

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

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

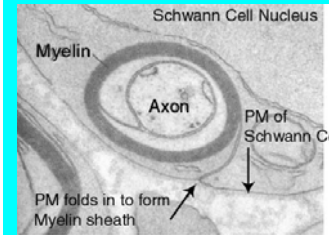
human nerve cell  $r=10\mu\text{m}$   
 $v \approx 0.5\text{m/s}$  ?



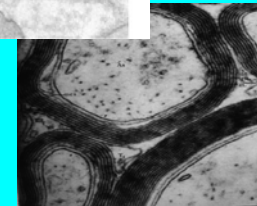
### Myelination!

$R_m$  – very high  $\Rightarrow$  big space constant

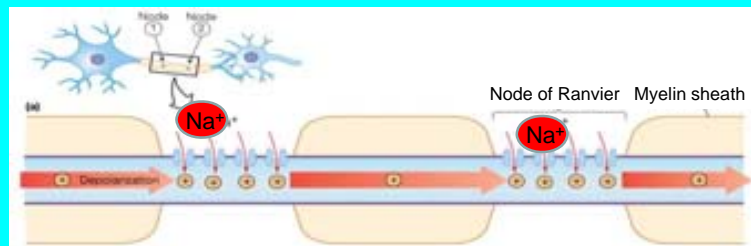
$C_m$  – very small  $\Rightarrow$  small time constant



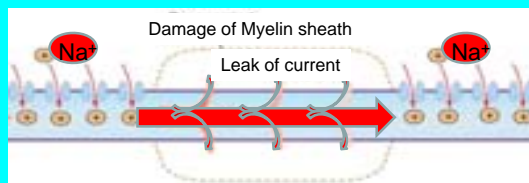
human nerve cell  $r=10\mu\text{m}$   
 $v \sim 100\text{m/s}$



### 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.

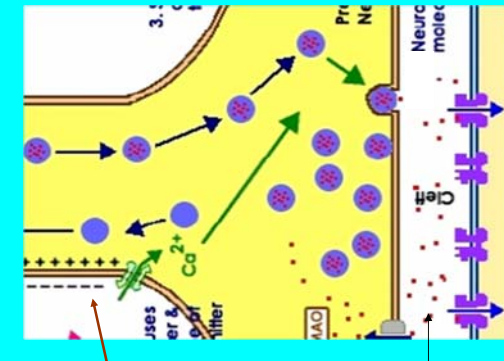
Fiber type	Average axon diameter ( $\mu\text{m}$ )	Conduction velocity ( $\text{m} \cdot \text{s}^{-1}$ )
<b>Myelinated fibers</b>		
A $\alpha$	18.5	42
A $\beta$	14.0	25
A $\gamma$	11.0	17
B	Approximately 3.0	4.2
<b>Unmyelinated fibers</b>		
C	2.5	0.4–0.5

## Effect of passive electric properties on signal transduction in synapses

## Signal transmission in synapses

presynaptic terminal

postsynaptic terminal

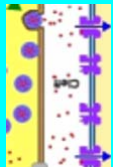


Action potential

neurotransmitter

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

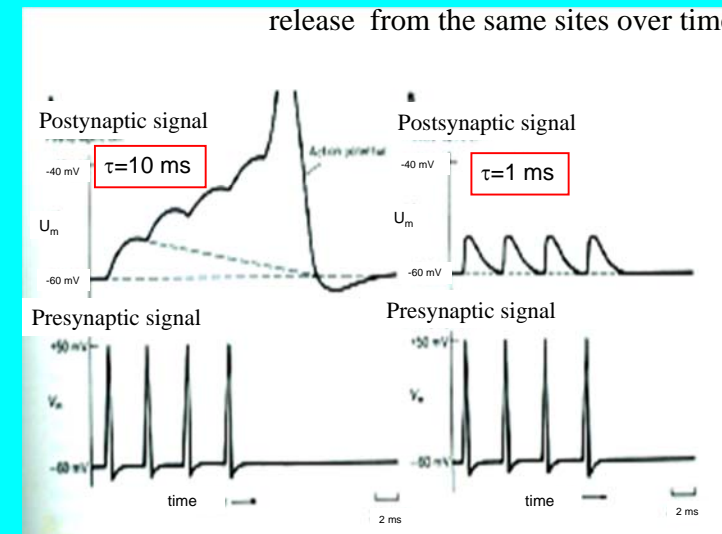
**Spatial Summation** : combined influences at the same cell at a particular moment in time



**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

