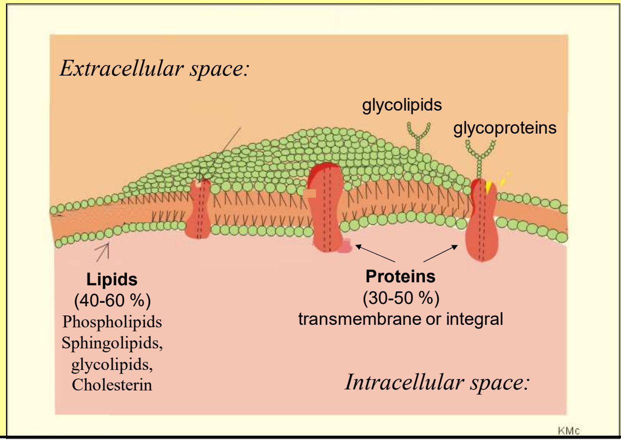
Transport across biological membranes

Transport in Resting Cell

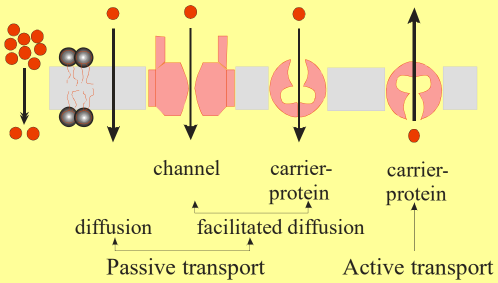
Membrane structure



Transport types across the memebranes

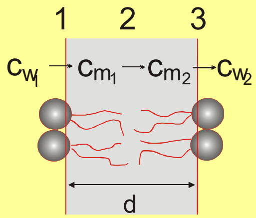
Classification based on: energy consumption

molecular mechanism



Diffusion of neutral particles

Diffusion across the lipid bilayer



Assume that concentration changes linearly

Fick I.

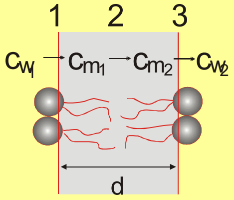
$$J_m = -D\frac{\Delta c}{\Delta x}$$

$$D_m << D$$

$$J_m = -D_m \frac{Cm_2 - Cm_1}{d}$$

Diffusion of neutral particles

Diffusion across the lipid bilayer



$$J_m = -D_m \frac{C_{m_2} - C_{m_1}}{d}$$

$$J_m = -p_m (c_{m_2} - c_{m_1})$$

Membrane permeability constant [ms-1]

Cannot be measured

$$\frac{C_{m_1}}{C_{w_1}} = \frac{C_{m_2}}{C_{w_2}} = K$$

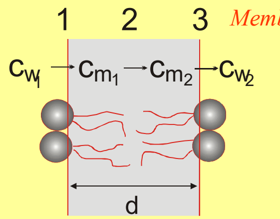
$$C_{m_1} = K C_{w_1}$$

K: partition coefficient

Diffusion of neutral particles

Diffusion across the lipid bilayer

$$J_m = -p_m (c_{m_2} - c_{m_1})$$



Membrane permeability constant [ms-1]

Cannot be measured

$$\frac{C_{m_1}}{C_{w_1}} = \frac{C_{m_2}}{C_{w_2}} = K$$

$$C_{m_1} = K C_{w_1}$$

$$J_m = -p_m K (c_{w_2} - c_{w_1})$$

$$J_m = -p (c_{w_2} - c_{w_1})$$

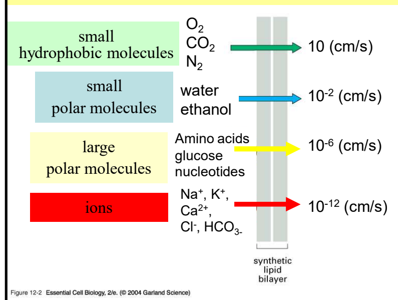
$$J_m = -\mathbf{p}(C_{w2} - C_{w1})$$

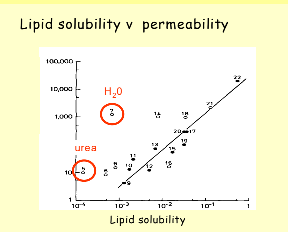
Permeability constant [ms-1]

It is influenced by:

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

Permeability vs hydrophobicity





Diffusion of ions

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

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

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

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

$$D = ukT$$

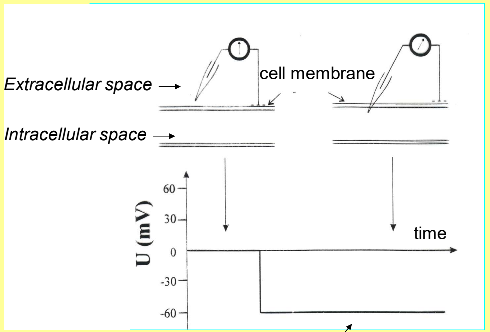
$$J_k = -u_k kT \left(\frac{\Delta c_k}{\Delta x} + c_k \frac{z_k F}{RT} \frac{\Delta \varphi}{\Delta x} \right)$$

flux of *k*-th ion

Basic principles of electrophysiology

Interpretation by transport phenomena

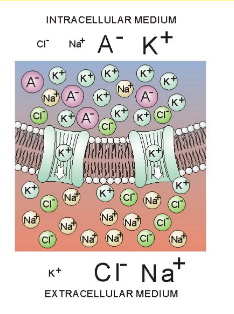
Observation 1: There is an electric potential difference between extra- and intracellular space



The intracellular side is negative with respect to the extracellular side

resting potential ~ 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

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

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

↓

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

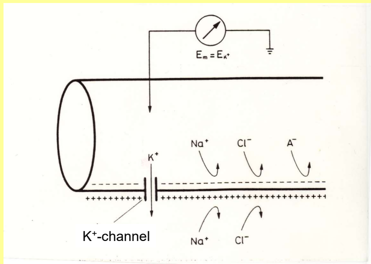
↓

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

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

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

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

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

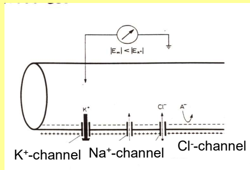
Model 2

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, ….

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

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

$$D_k = dp_k$$

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

Electrodiffusion model

Goldman – Hodgkin – Katz formula

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

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

Electrodiffusion model

Goldman – Hodgkin – Katz formula

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

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

Good agreement with experimental results

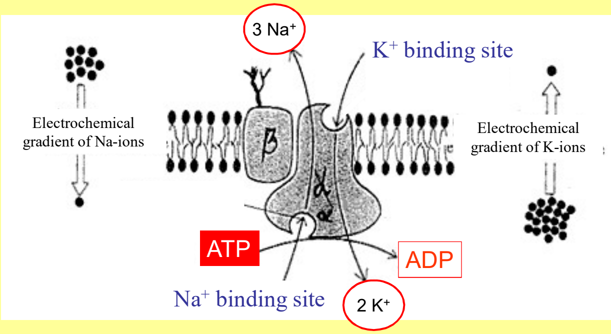
Electrodiffusion model

- 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.

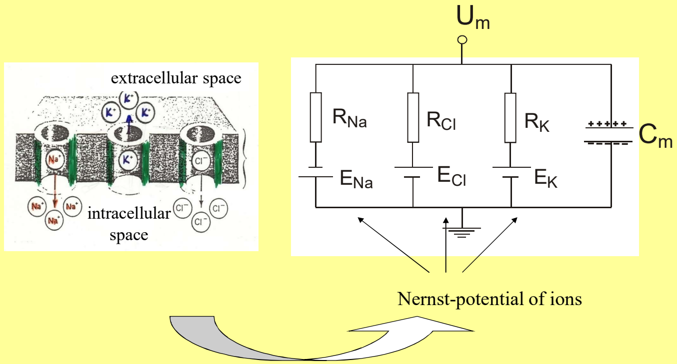
Na - K pump

antiporter

The condition for stationary flow is maintained by the active transport

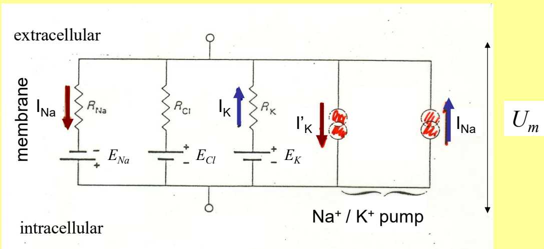


Interpretation of the membrane potential 2 Equivalent circuit model



Ionselective channels modeled by electromotive force and conductivity

Na^+ /K^+ pump restores the ion distribution



Ohm's law: $I_k=1/R_k(U_m-E_k)$

Calculation of resting potential according to the equivalent circuit model

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

E_k – Nernst-potential of ions

$\Sigma I_k=I_{ion}=0$

$\Sigma I_k=I_{Na}+I_K+I_{Cl}=0$

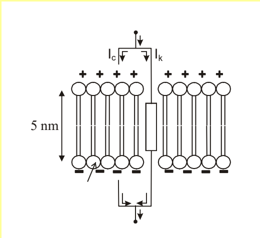
$g_K (U_m-E_K) + g_{Na} (U_m-E_{Na}) = 0$

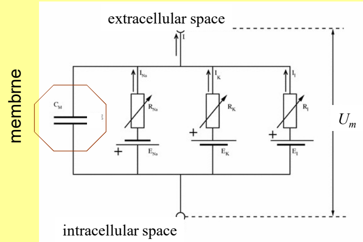
$$U_m = \frac{(U_{0K} x g_K) + (U_{0Na} x g_{Na})}{g_K + g_{Na}}$$

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

Capacitive property of the membrane

Capacitance ~10^{-6} F/cm^2





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

Ion current

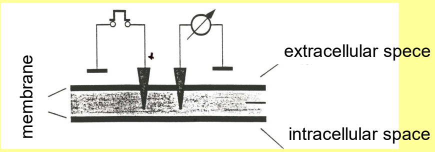
Capacitive current

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

Alteration of resting membrane potential

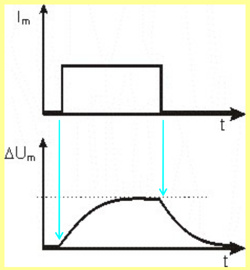
1. “passive” electric properties of the membrane

Observation



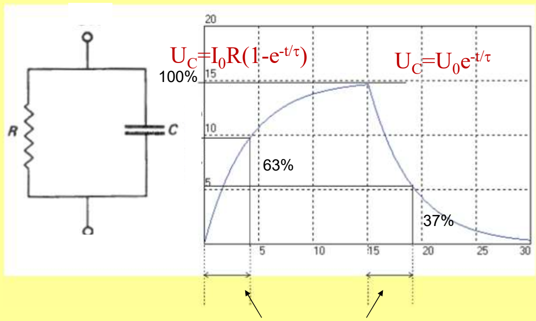
Inward current

Depolarization of the membrane



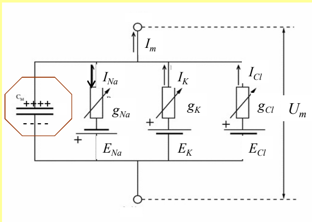
What is it like?

Charge and discharge of RC-circuit



τ=RC

Interpretation with equivalent circuit model:



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

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

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

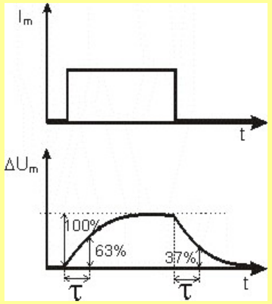
$$C_m \frac{\Delta U_m}{\Delta t} + \frac{\Delta U_m - E}{R_m} - I_{stimulus} = 0$$

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

Time from the beginning of stimulus

Membrane potentiel after t

Saturation value of membrane potential



Capacitance of the membrane

Resistance of the membrane

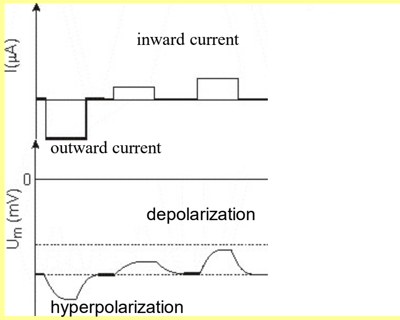
$$\tau = C_m R_m$$

***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

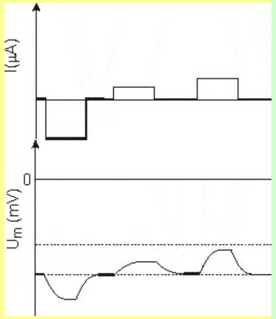
$$U_m(t) = U_t \left[1 - e^{-\frac{t}{R_m C_m}} \right]$$



U_t is proportional to the stimulating current

The rate of the change depends on U_t

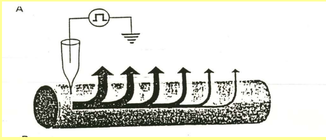
Local changes of membrane potential



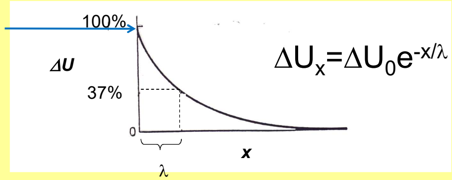
obligate
graded
magnitude varies directly
with the strength of the stimulus
direction varies
with the direction of the stimulus
„localized"

The local changes are not isolated from the neighborhood

Observation



Membrane potential change at the site of stimulation

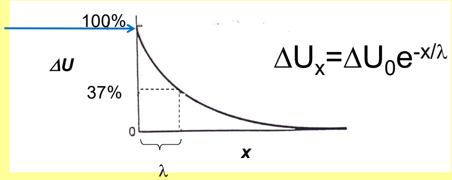


Decrease in amplitude with distance due to leaky membranes

λ: space constant of the membrane:

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

Membrane potential change at the site of stimulation



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

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