

Bioelectric phenomena.

- Related practices: Amplifier, Pulse generator, ECG
- Related book chapters: III/4 *Textbook: pp. 276-300.*

Balázs Kiss

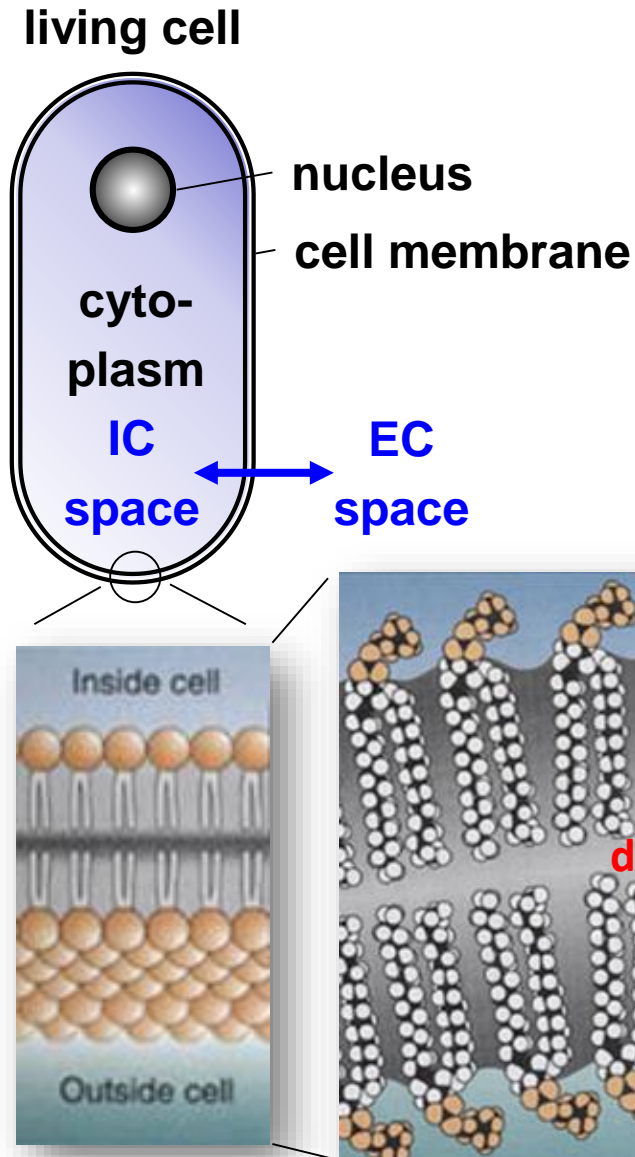
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Muscle Mechanobiophysics Group
Department of Biophysics and Radiation Biology,
Semmelweis University**

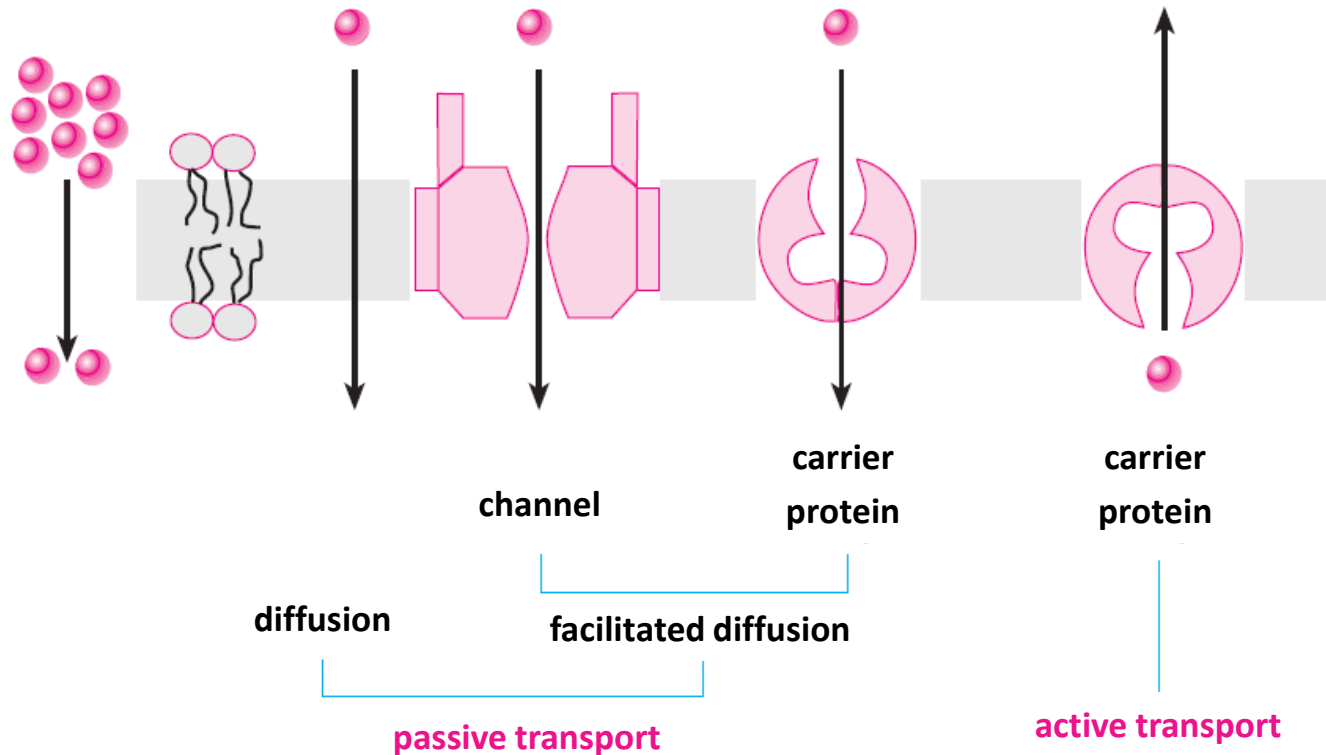
16. March 2022.

Physical properties of the cell membrane



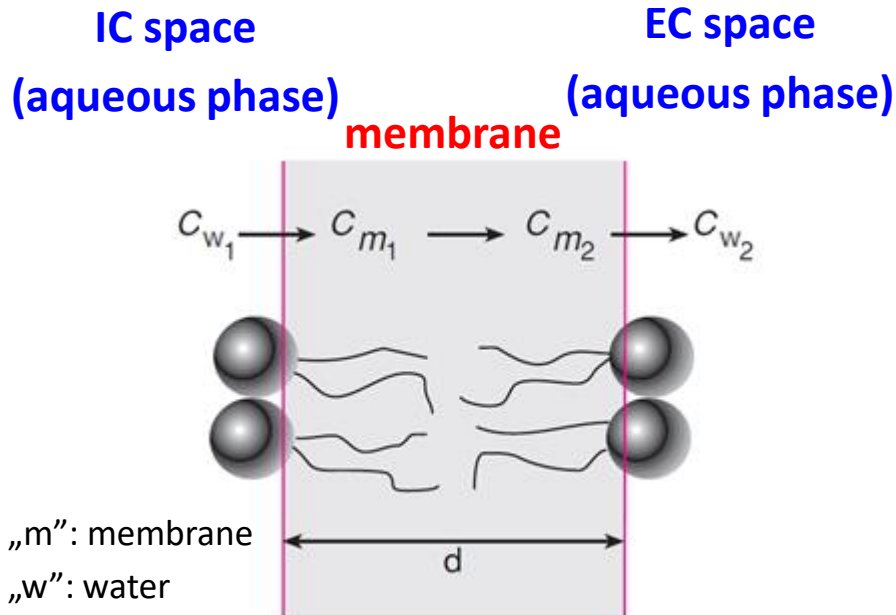
- **Noncovalent, cooperative structure:** phospholipid bilayer, vesicle formation, additional components (e.g. cholesterol, proteins)
- **Thin, layered:** $d \sim 5 \text{ nm}$
- **Asymmetric:** the two sides of the membrane have different properties
- **Permeability:** impermeable to ions, permeable to water
- **Fluidity:** melting temperature (T_m)
- **Lateral diffusion:** lateral movement of lipid-, and protein molecules
- **Flip-flop:** phospholipid translocation between the two layers (low probability)
- **Flexibility, elasticity:** see distortion / deformation of erythrocytes in the capillary

Transport across biological membranes



- **Passive diffusion:** „real”, classical diffusion (**Fick's first law**)
- **Facilitated or mediated diffusion:** through biological membranes, through/with protein(like) **mediator molecules** (carrier or channel proteins)
- **Active transport:** the particle is transported **against a gradient** (chemical/electrochem.)

Passive diffusion across the membrane



Fick's first law:

$$J_m = -D \cdot \frac{\Delta c}{\Delta x} = -D_m \frac{c_{m2} - c_{m1}}{d}$$

D_m : diffusion coefficient within the membrane

Permeability constant: p_m , [m/s]

$$p_m = \frac{D_m}{d}$$

Partition coefficient: K

(between the membrane and aqueous phases)

$$\frac{c_{m1}}{c_{w1}} = \frac{c_{m2}}{c_{w2}} = \text{const.} = K$$

in the case of stationary diffusion

$$J_m = -p_m \cdot K(c_{w2} - c_{w1}) = -p(c_{w2} - c_{w1})$$

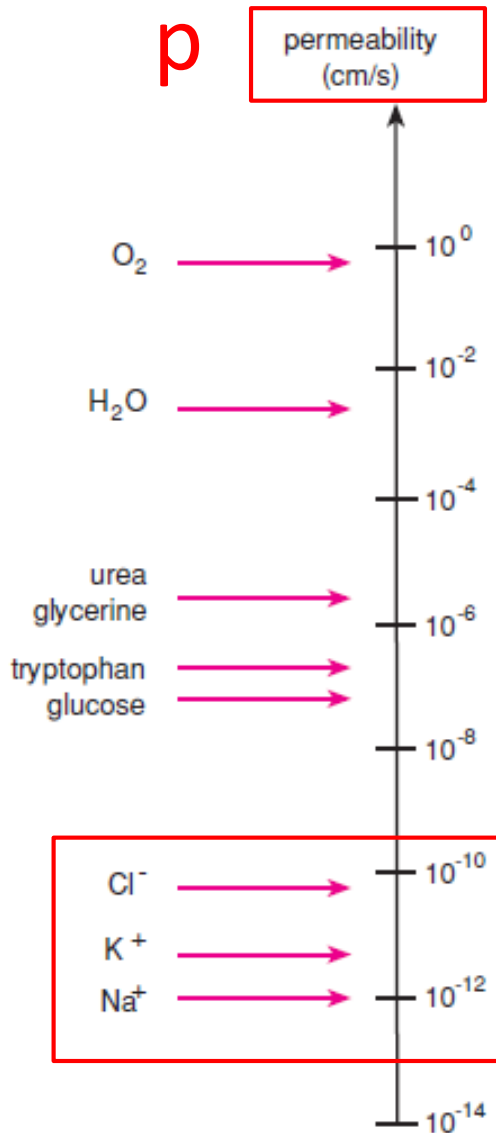
Aggregated permeability constant: p , [m/s]

$$p = K \cdot p_m$$

„permeability”

considers the diffusion coefficient, membrane thickness and concentrations inside and outside of the membrane

Passive diffusion of particles



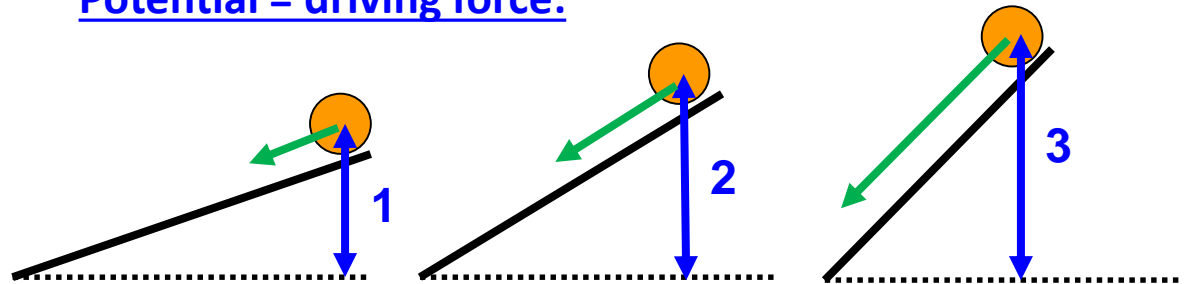
Onsanger equation:

$$J = L \cdot X$$

matter conductivity gradient of an
flow density coefficient intensive quantity

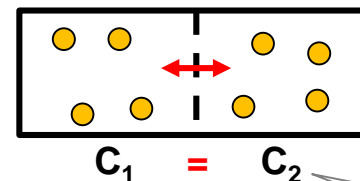
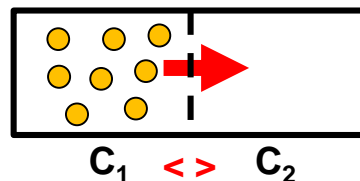
The driving force of transport is the chemical potential gradient.

Potential = driving force:



Chemical potential: μ

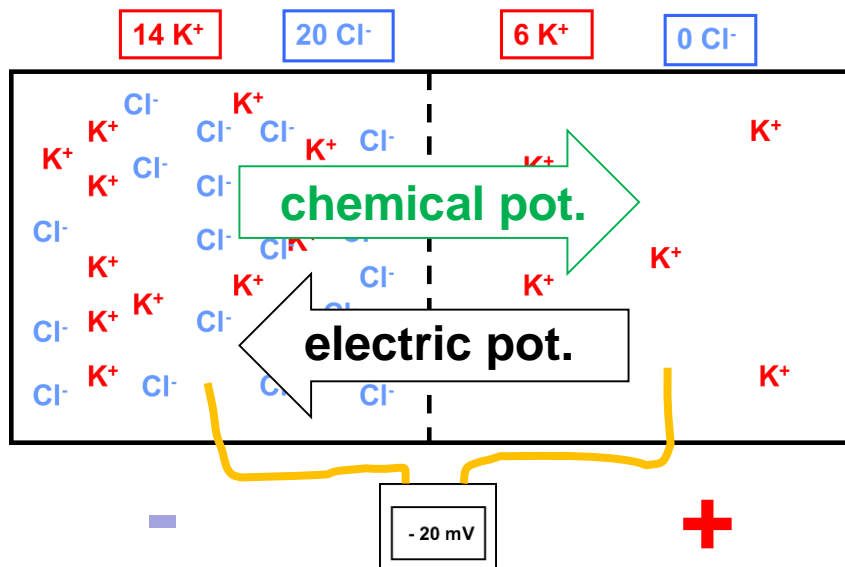
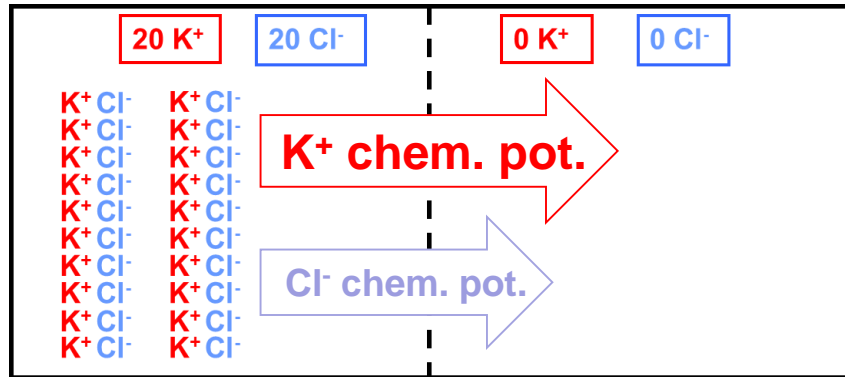
$$\mu = \mu_0 + RT \cdot \ln(c)$$



μ_0 : standard
chemical
potential

in thermal equilibrium

Passive diffusion of ions: electrochemical potential



Assume that the membrane is **only permeable to K⁺** ($p_{Cl^-}=0$).

In equilibrium:

- concentration difference
- electric potential difference exist between the two compartments.
- the chemical and electric potentials are of the same magnitude but oppositely directed.

Electrochemical potential: μ_e , [J/mol]

$$\mu_e = \underbrace{\mu}_{\text{chemical}} + \underbrace{zF\varphi}_{\text{electric}}$$

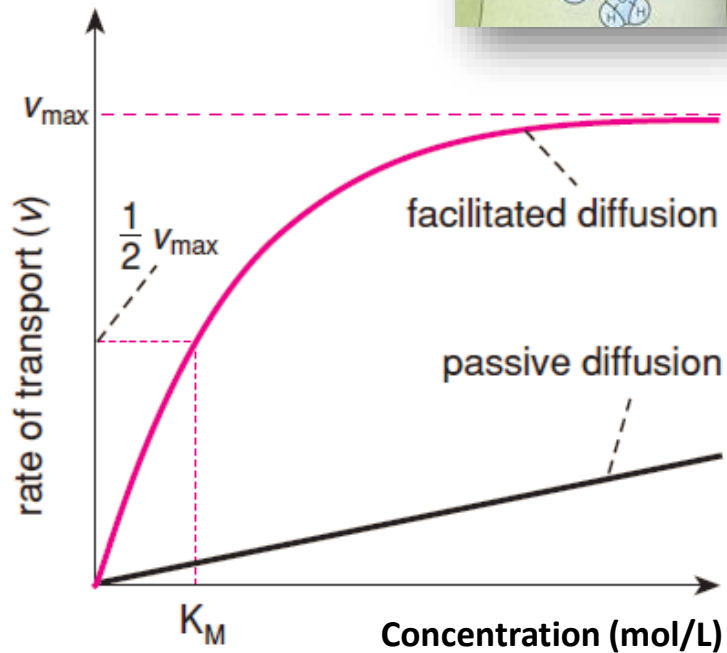
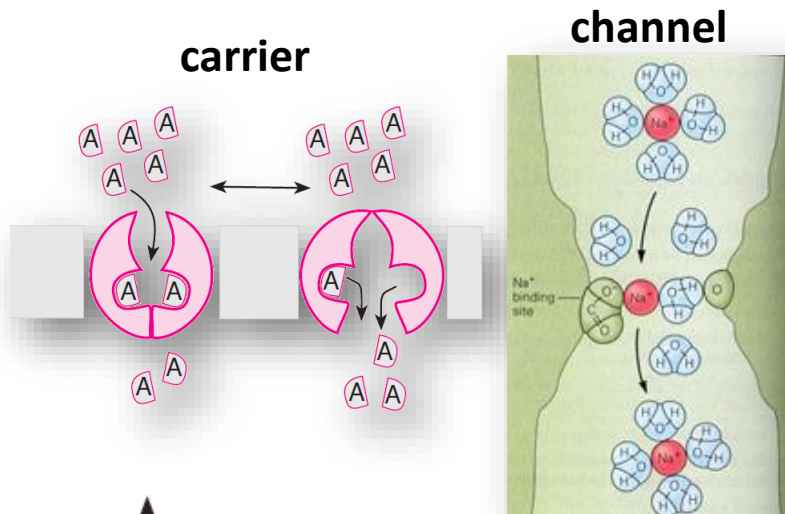
z : charge of the ion

F : Faraday constant

φ : electric potential

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

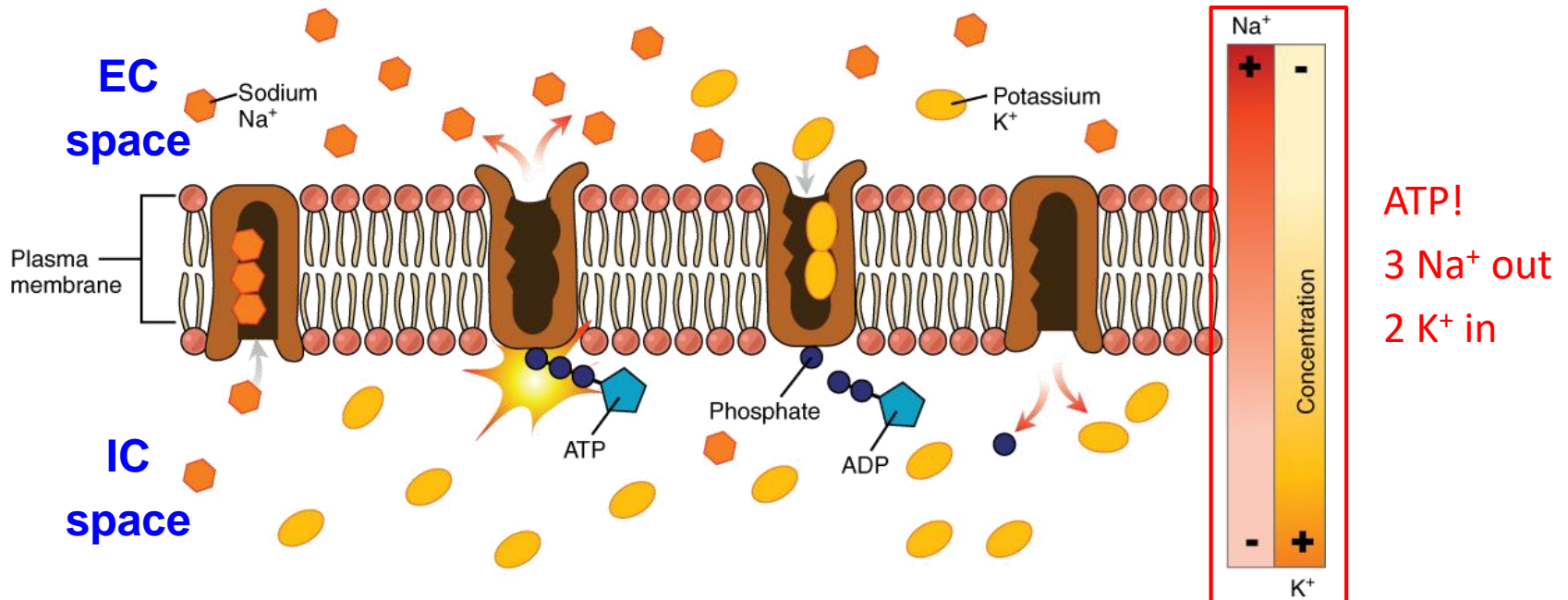
Properties of the facilitated diffusion



- **Faster, than the passive diffusion** (what is expected based on Fick's first law)
- **Selective:** works only for a given particle or for molecules sharing structural similarity
- **Can be saturated:** is realized through a limited number of mediator molecules (carrier or channel)
- **Can theoretically work in both directions:** the direction is determined by the sign or direction of the (electro)chemical potential gradient of the transported molecule
- **Can be selectively inhibited:** with inhibitors targeting the mediator molecules
- Ionophores: mobile ioncarriers or channel-forming molecules. Application: antibiotics

Active transport

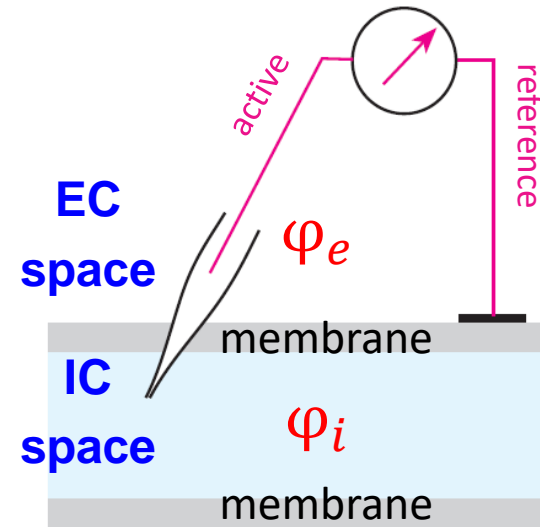
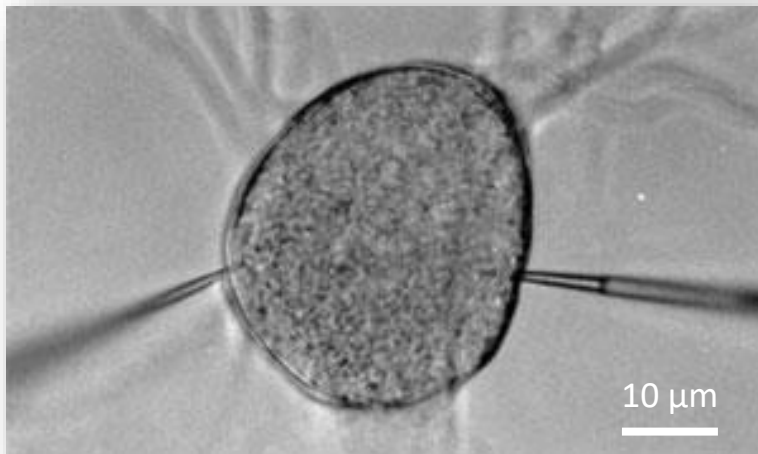
- **Transport of molecules against their (electro)chemical gradient, energetically:**
 - **ATP-driven:** ATP-ases, they hydrolyze ATP
 - **light-gated** (e.g. channelrhodopsin-2: non-selective cation channel)
 - **coupled transporter:** couples the transport of a substance with sufficient electrochemical gradient to the transport of another molecule against its gradient
- **According to the numbers of the transported molecules:**
 - **uniporter:** translocates only one molecule across the membrane
 - **symporter:** transport the particles in the same direction
 - **antiporter:** transport the particles in the opposite direction, e.g. **Na⁺-K⁺ ATP-ase**:



Resting membrane potential

Measurement: with microelectrode pairs

- active
- reference



voltage = potential difference = „potential“

Observation: $\Delta\varphi = \varphi_i - \varphi_e < 0$

Cell	$\Delta\varphi$ (mV)
squid giant axon	-62
frog muscle	-92
rat muscle	-92

The intracellular space is more negative.

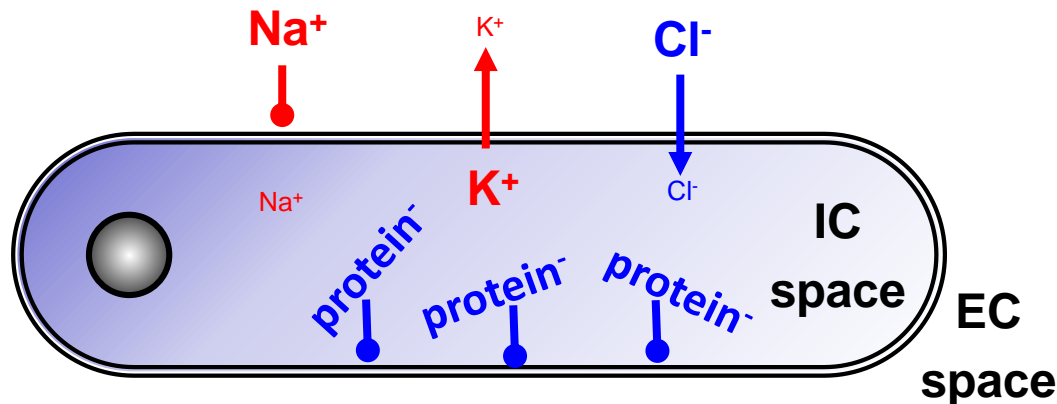
Resting membrane potential

Further observation: different ion concentrations on both sides of the membrane

cell	intracellular concentration (mmol/l)			extracellular concentration (mmol/l)		
	Na ⁺	K ⁺	Cl ⁻	Na ⁺	K ⁺	Cl ⁻
squid giant 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

Considering the ion distribution shown in the table above which physical model gives the best approximation of the resting membrane potential?

Model #1: Donnan-model: equilibrium ion distribution, additional protein anions (IC)



- The membrane is impermeable to certain ions ($p_{\text{protein}^-} = 0$).
- Electrochemical equilibrium is assumed.

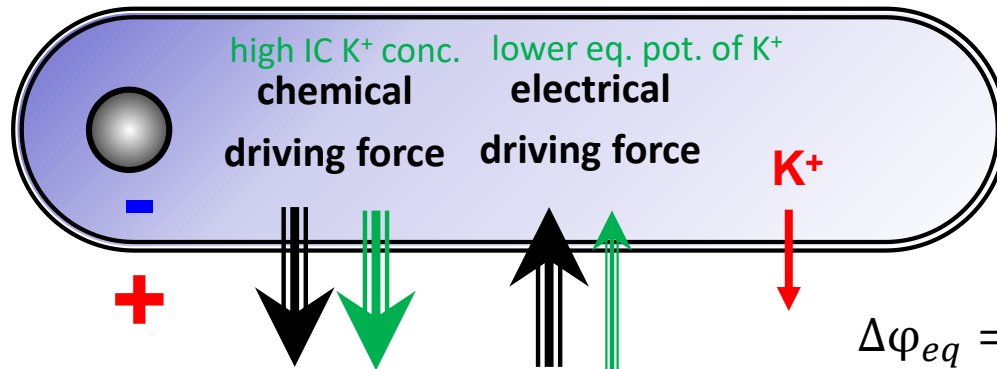
Resting membrane potential

Equilibrium potential: calculated based on the #1 Donnan-model... (book p. 287.)

Nernst equation: $\Delta\varphi = \varphi_2 - \varphi_1 = -\frac{RT}{F} \ln \frac{c_2}{c_1}$

- let's calculate it for the K⁺ ion...

	intracellular concentration (mmol/l)			extracellular concentration (mmol/l)		
cell	Na ⁺	K ⁺	Cl ⁻	Na ⁺	K ⁺	Cl ⁻
squid giant axon	72	345	61	455	10	540



$$\Delta\varphi_{eq} = -\frac{RT}{F} \ln \frac{c_i}{c_e}$$

$$\Delta\varphi_{eq} = -\frac{8,31 \cdot 293}{96500} \ln \frac{345}{10} = -0,089 \text{ V} = \boxed{-89 \text{ mV}}$$

Measured membrane potential: -62 mV

The equilibrium model does not correctly describe the real situation!

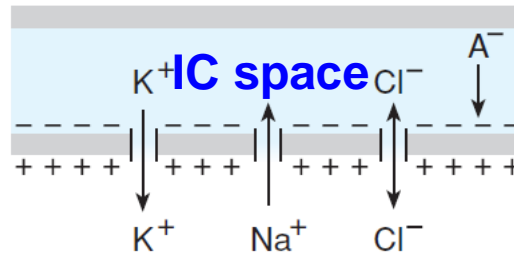
Outward flux of K⁺ should happen at -62 mV.

The Goldman-Hodgkin-Katz (GHK) equation

Cell	$\Delta\varphi_{\text{equilibrium}}$ (mV) using the Nernst equation			$\Delta\varphi_{\text{membrane}}$ (mV)
	Na ⁺	K ⁺	Cl ⁻	
squid giant axon	+46	-89	-55	-62
frog muscle	+45	-101	-87	-92
rat muscle	+64	-93	-85	-92

No equilibrium at rest but the transport processes continue:

- outward flux of K⁺
- inward flux of Na⁺
- minor outward flux of Cl⁻



- **active transport: requires energy (ATP)**

Transport model #2: continuous diffusion of different ions with different permeability (p)

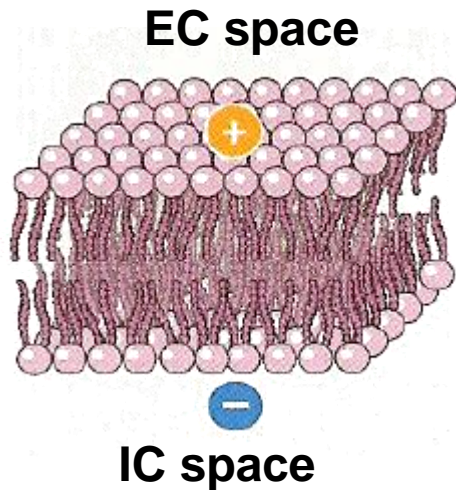
$$\Delta\varphi = \varphi_i - \varphi_e = -\frac{RT}{F} \ln \frac{p_{Na}c_{Na}^i + p_Kc_K^i + p_{Cl}c_{Cl}^e}{p_{Na}c_{Na}^e + p_Kc_K^e + p_{Cl}c_{Cl}^i} = -91 \text{ mV}$$

in frog muscle

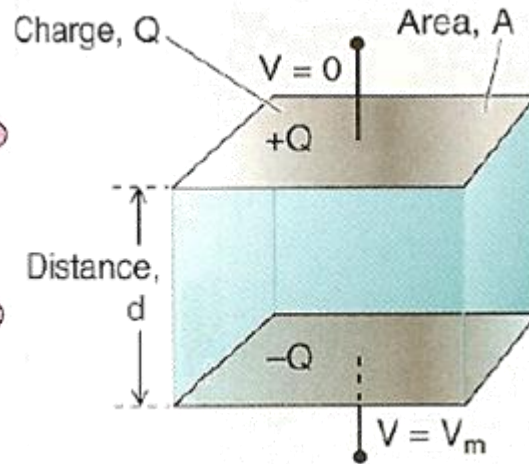
The calculation using the GHK equation is in agreement with the measurements.

The electric model of the cell membrane

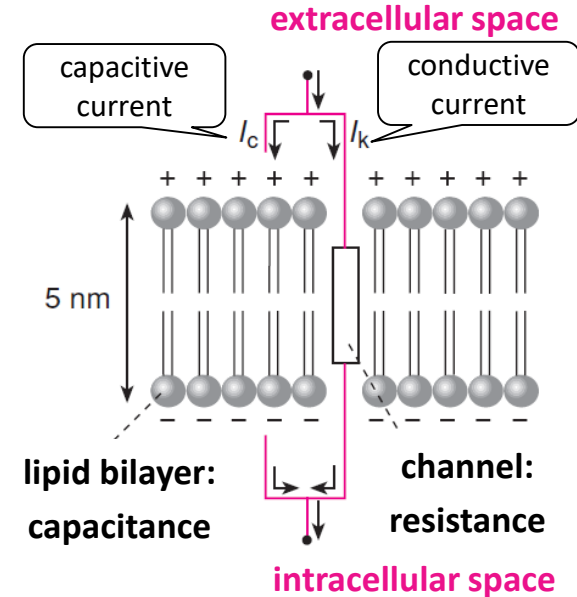
cell membrane



capacitor



electric model

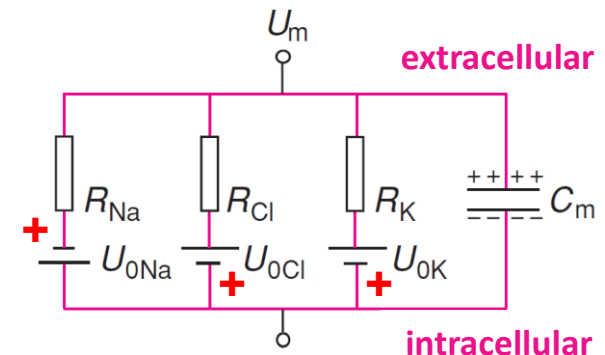


- different **transmembrane resistance (R)** in the case of the different ion channels

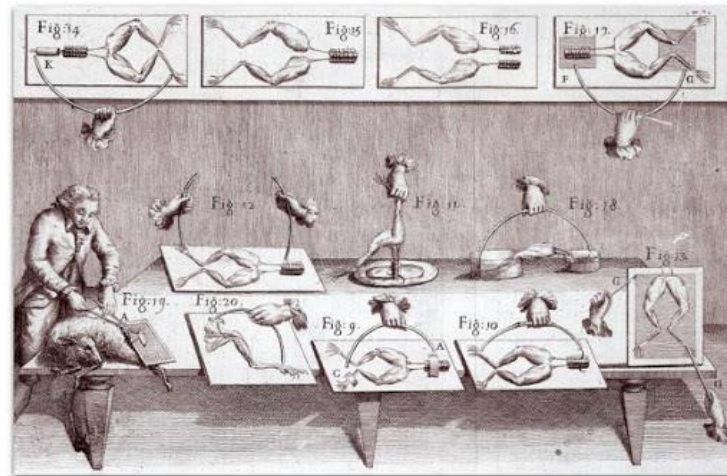
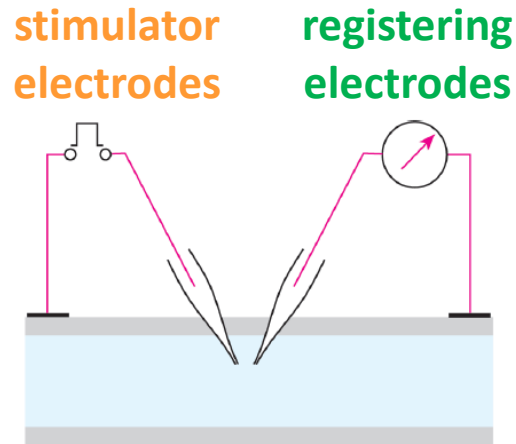
- electric conductivity:** G (unit: Siemens) $G = \frac{1}{R}$

proportional to **permeability (p)**

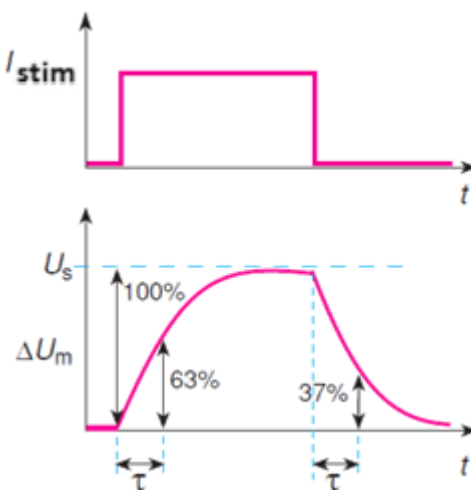
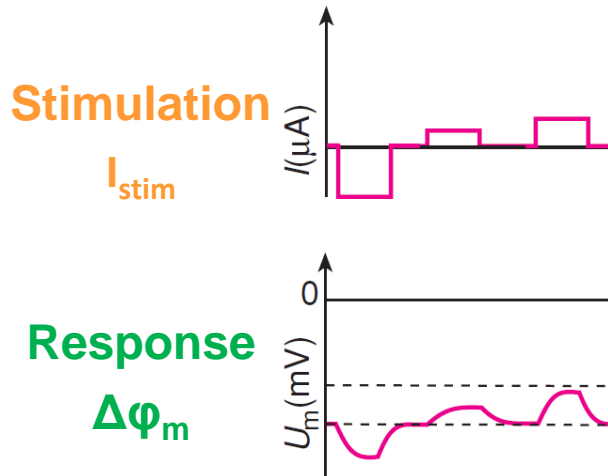
- specific conductivity:** sigma (unit: $1/(\Omega \cdot m^2)$) $\sigma = \frac{1}{R \cdot A}$



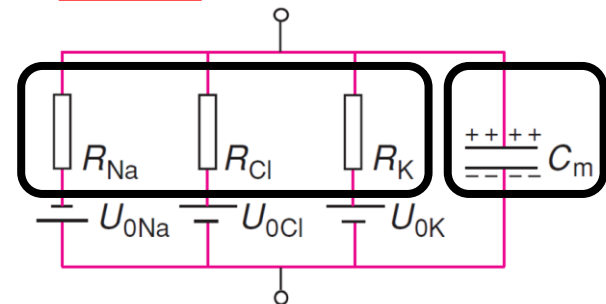
The change of the resting potential



Local (electrotonic) changes of the membrane potential:



Model: RC-circuit

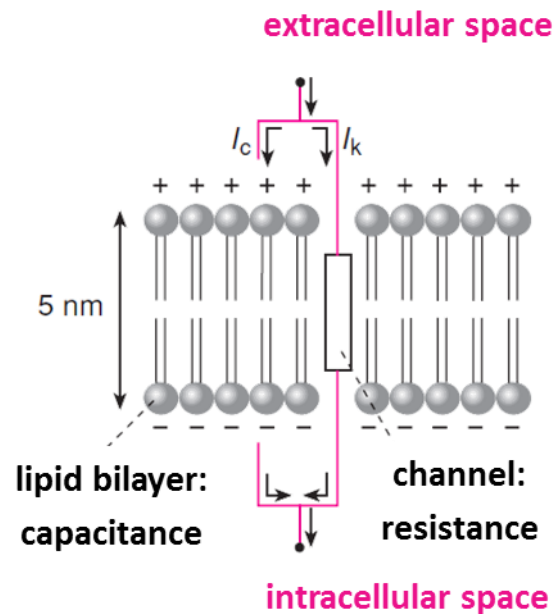


Time-constant: tau: τ [s]

$$\tau = R_m \cdot C_m$$

The amplitude of the response is proportional to the stimulating current, but shows a characteristic delay.

Electric properties of the membrane

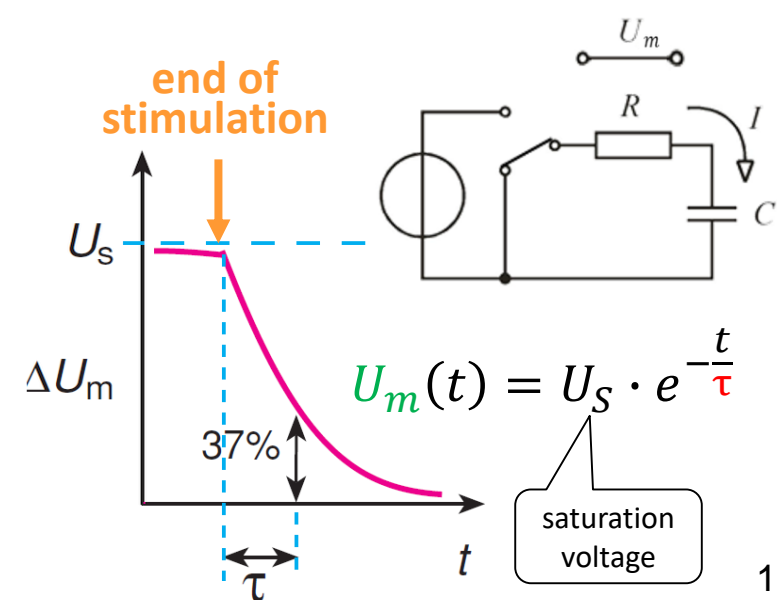
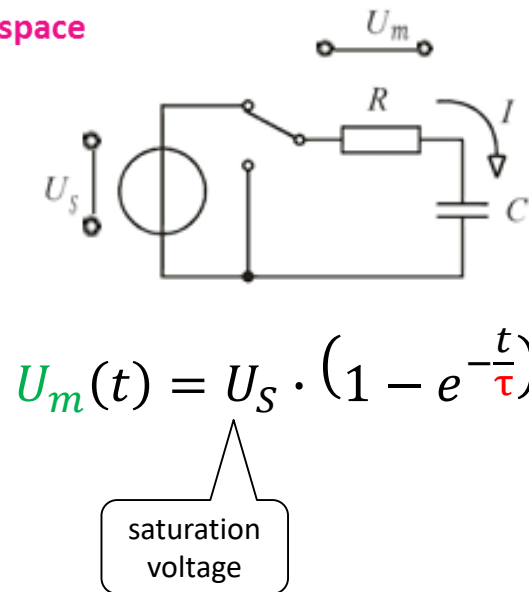
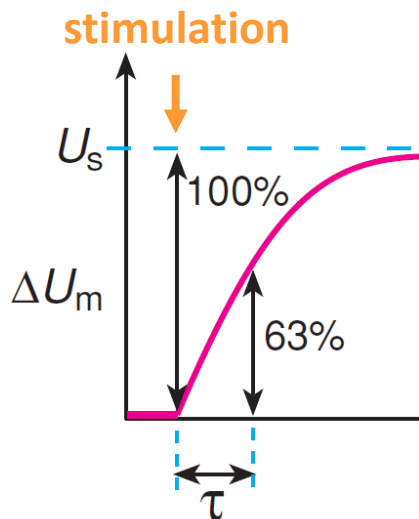


Currents across the membrane:

- conductive: I_k
- capacitive: I_c
- **stimulating: I_{stim}** negative with the influx of + charges

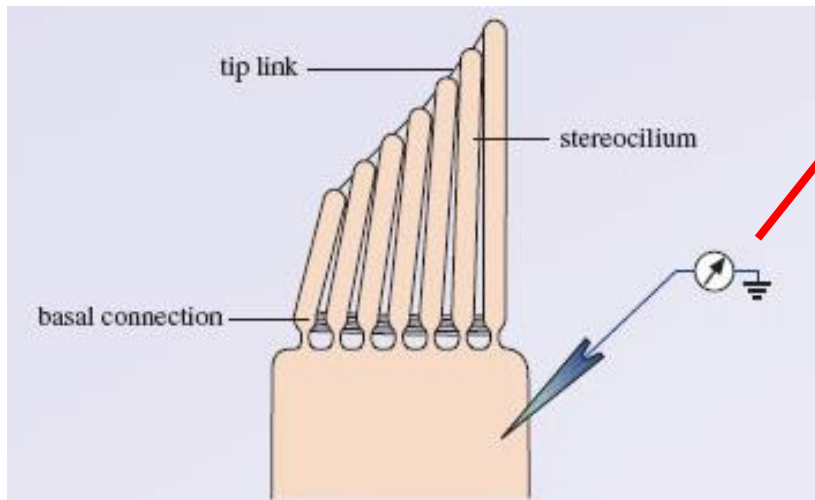
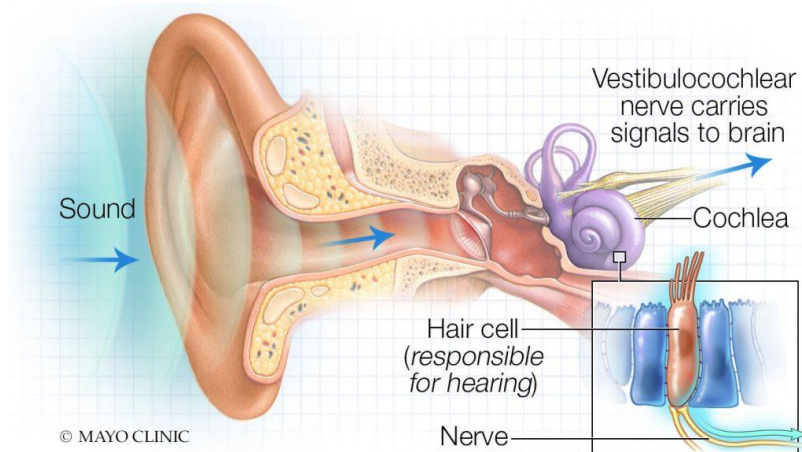
Based on the transport model for the resting state:

$$I_c + I_k - I_{stim} = 0$$

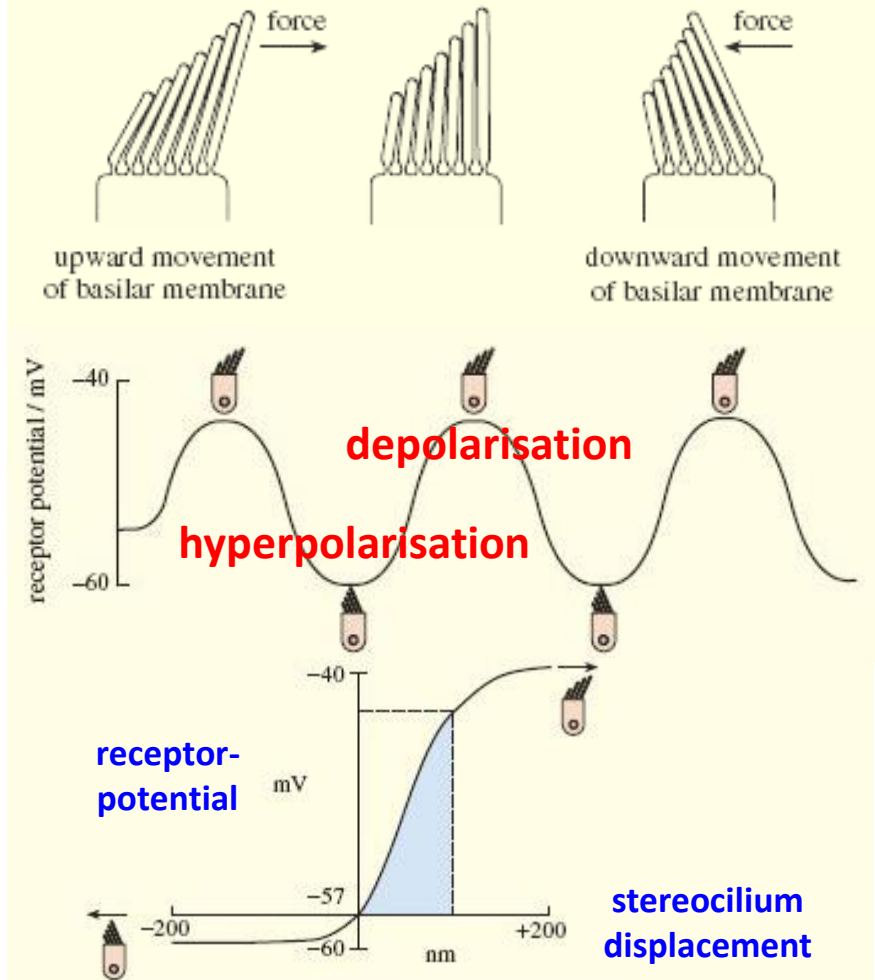


Example: receptor potential

Example for the local change of the membrane potential: hair cells as mechanoreceptors

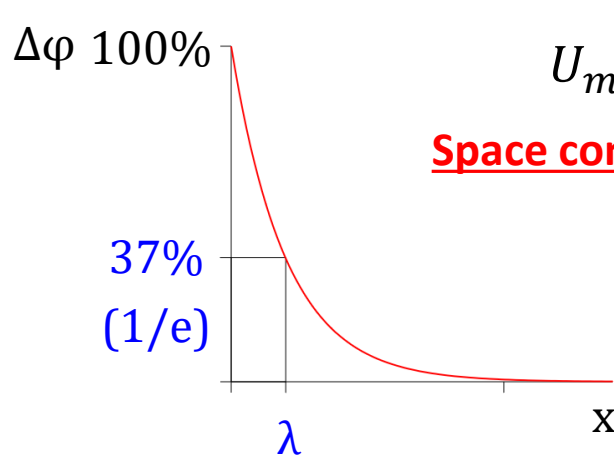
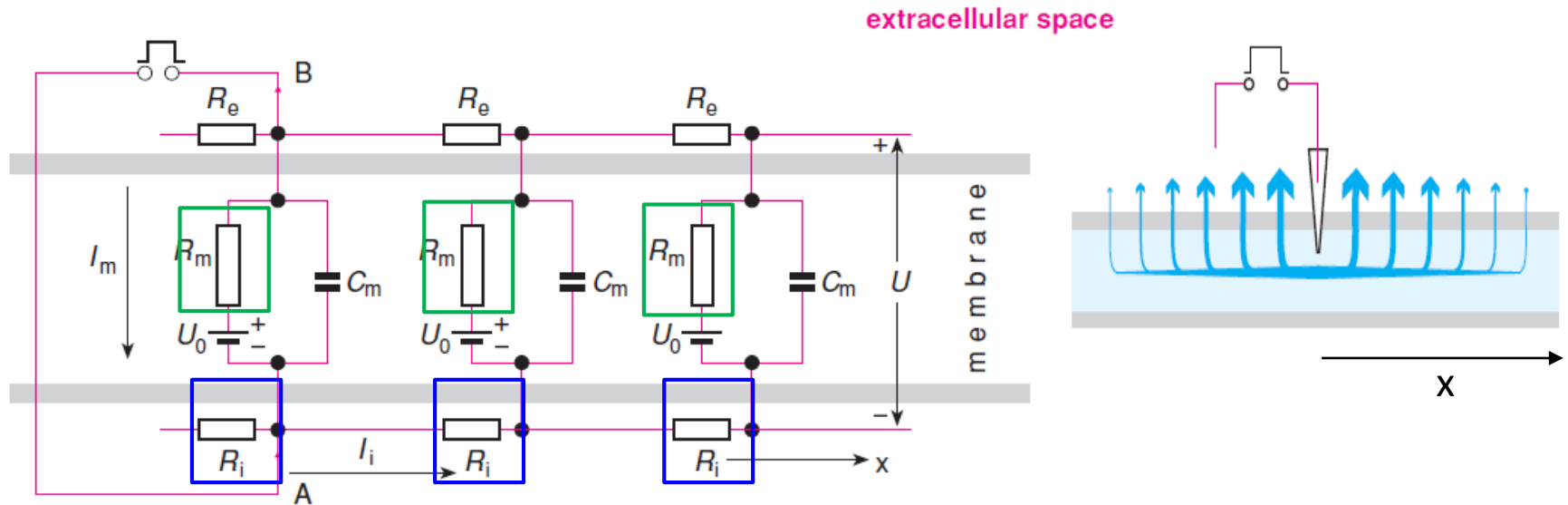


mechanosensitive K^+ -channel: K^+ in



The propagation of a local potential change

Model of a larger membrane section:



$$U_m(x) = U_0 e^{-\frac{x}{\lambda}}$$

Space constant: lambda, λ [cm]

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

R_m : transmembrane resistance
 R_i : intracellular resistance

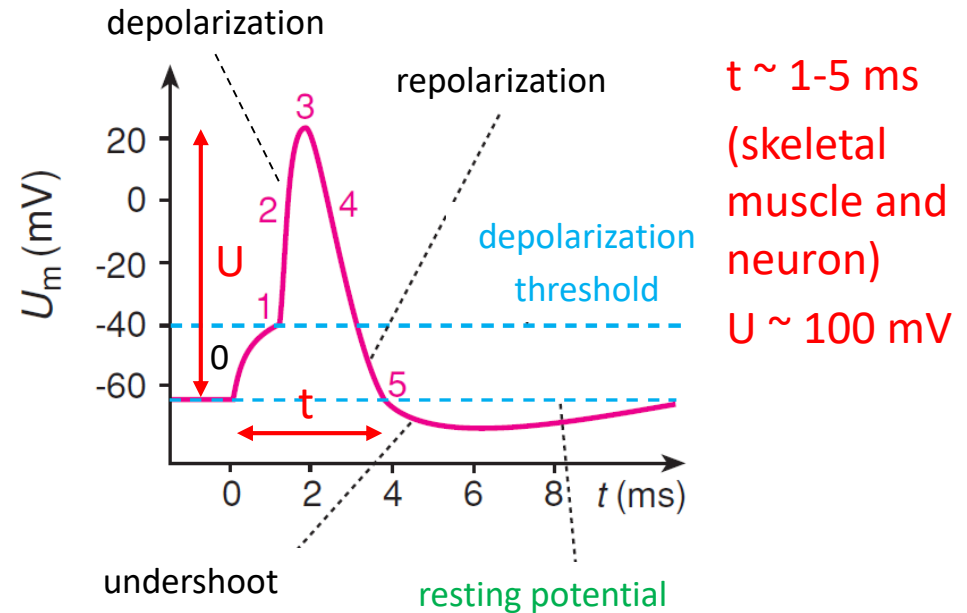
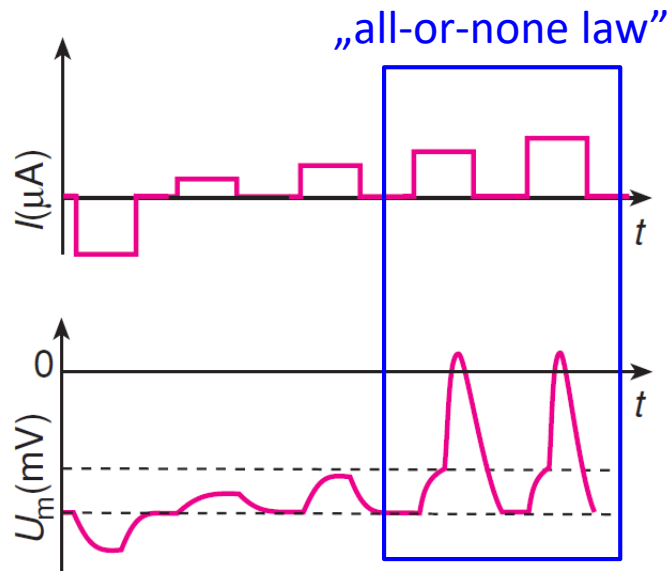
Aim: to increase the value of λ .

When $R_m \uparrow$ or $R_i \downarrow$: potential propagation improved.

Example: myelin sheath or larger cell diameter.

Action potential

For stimuli above threshold: generalized change of the membrane potential



0: local change of membrane potential

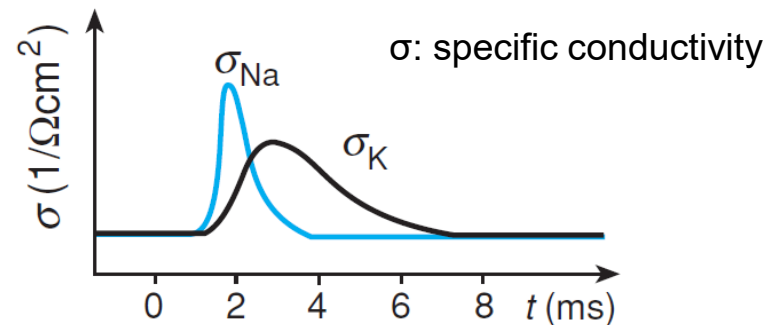
1: **volt. gated Na^+ ch. open (Na^+ : in)**

2: **volt. gated K^+ ch. open (K^+ : out)**

3: **Na^+ ch. inactivation** (partial)

4: **Na^+ channel closure**

5: **K^+ channel closure** (delayed)

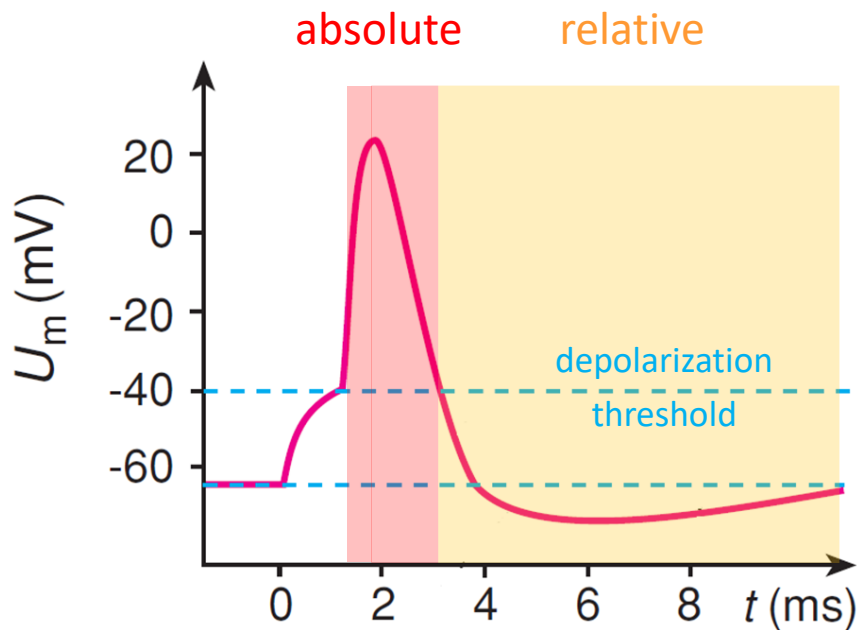


Properties of the action potential

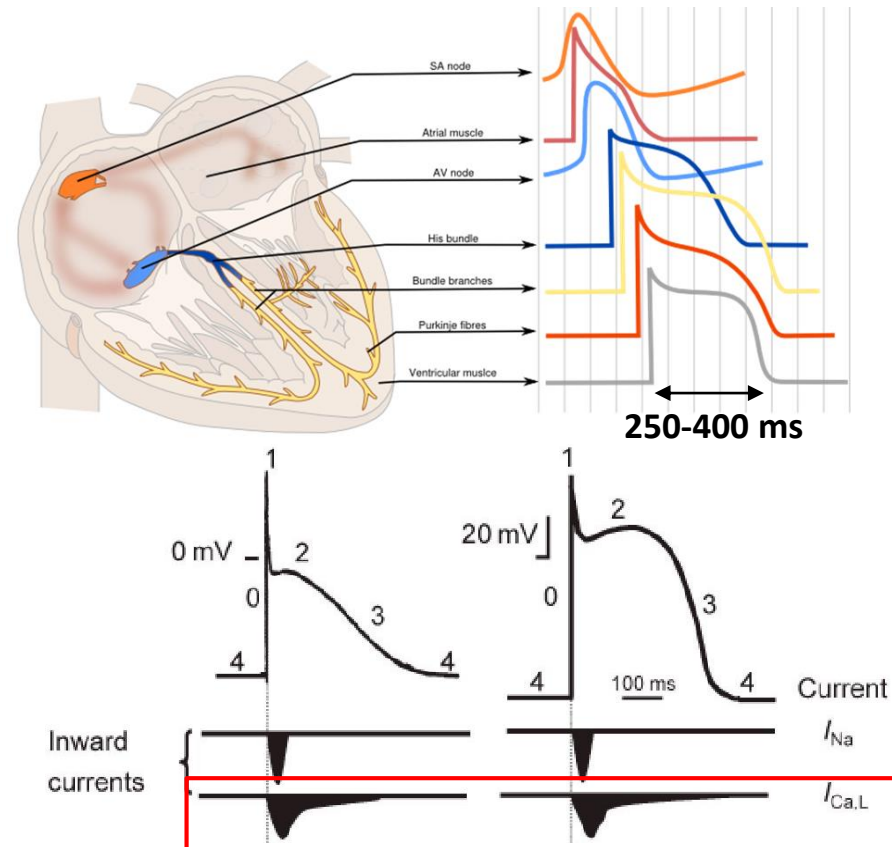
Unaltered ion concentration: the transported ions diffuse away far from the membrane. During the AP only the permeability changes (GHK).

Refractory period: the cell is not excitable

Special AP: e.g. ventricular cardiomyocytes



- **absolute:** voltage-gated Na^+ channels are inactivated
- **relative:** AP with supra-threshold stimulus prevents the backpropagation of AP

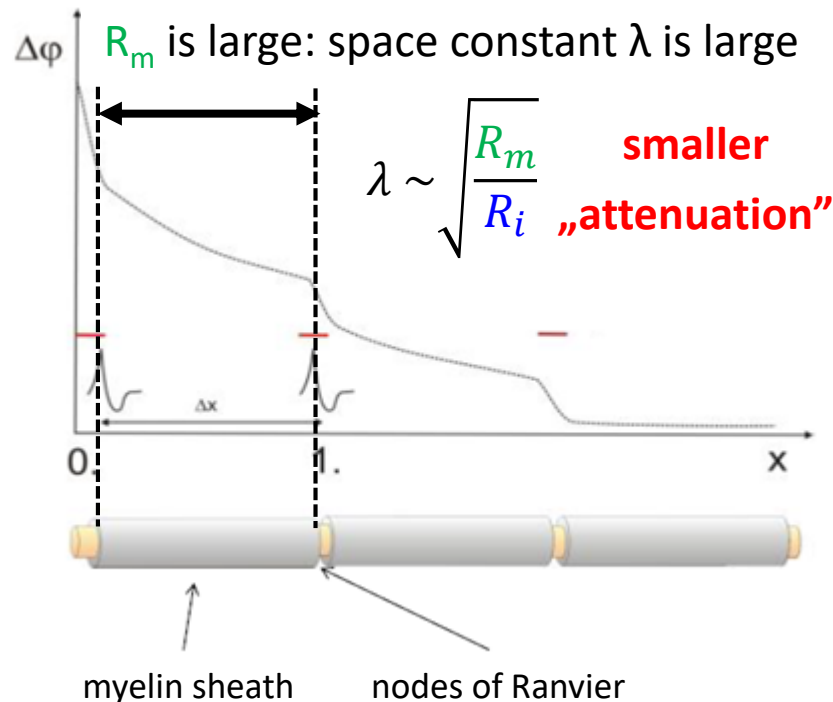
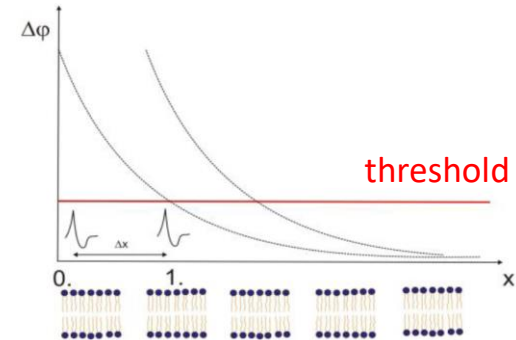


- **voltage-gated Ca^{2+} channels**

The propagation of the action potential

Properties:

- AP shape is independent from stimulus
- propagates far without attenuation
- much faster than hormonal response

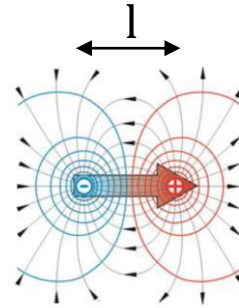


fiber	diameter (μm)	Speed (m/s)
α	15	70-120
β	8	30-70
γ	5	15-30
δ	<3	12-30
No sheath	<1	0.5-2

Medical application of bioelectric phenomena

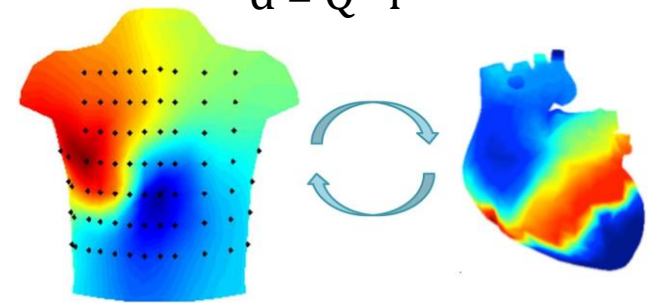
Electric signals on the body surface (diagnostics):

- Electrocardiography (EKG)
- Electroencephalography (EEG)
- Electromyography (EMG)
- Electrooculography (EOG)
- Electroretinography (ERG)



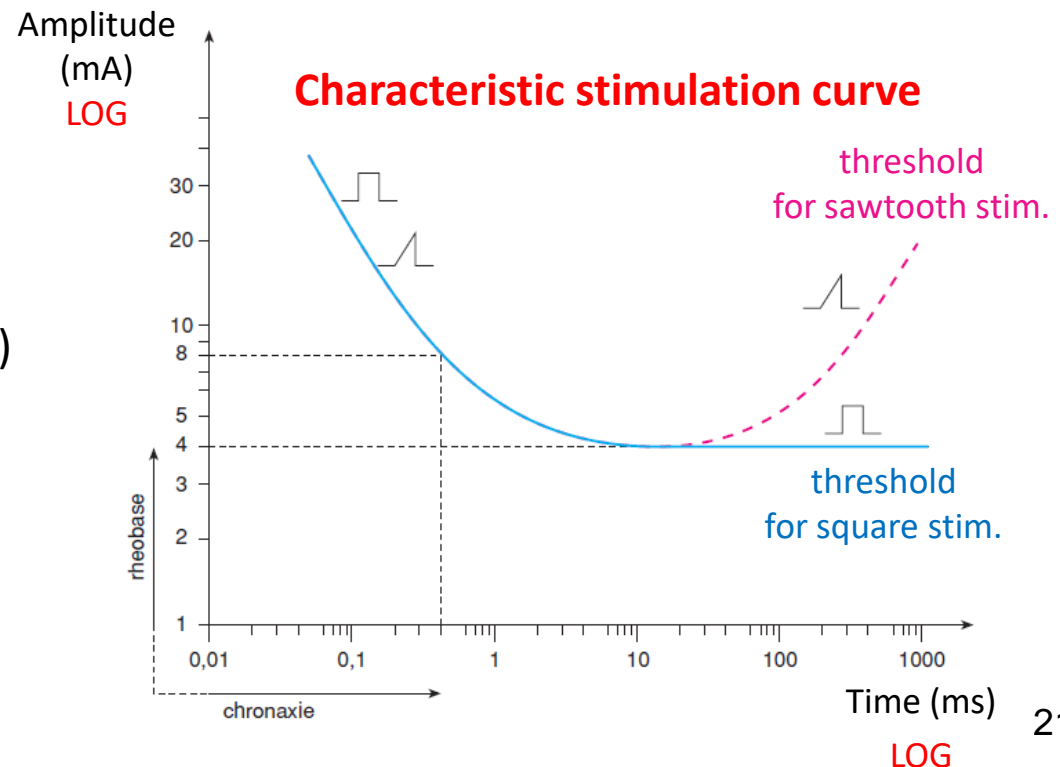
origin: dipole moment, d

$$d = Q \cdot l$$



Electric stimulation (therapy):

- Galvanic treatment (DC)
- Iontophoresis (DC)
- HF-thermotherapy (AC)
- Electric stimulus therapy (pulse)
- Defibrillator (pulse)
- Pacemaker (pulse)
- **rheobase**: minimal electric current that elicits stimulation
- **chronaxie**: time to 2x rheobase



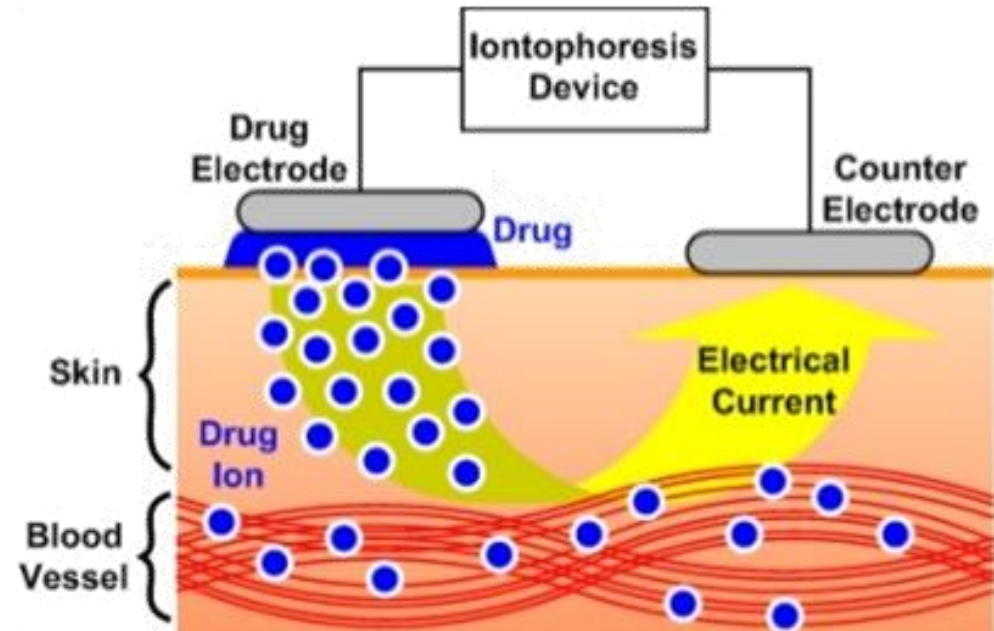
The Application of Direct Current (DC)

Galvanic treatment



- $I \sim \text{mA}$, $t \sim 10 \text{ min}$
- analgesia
- improving circulation
- improving metabolism

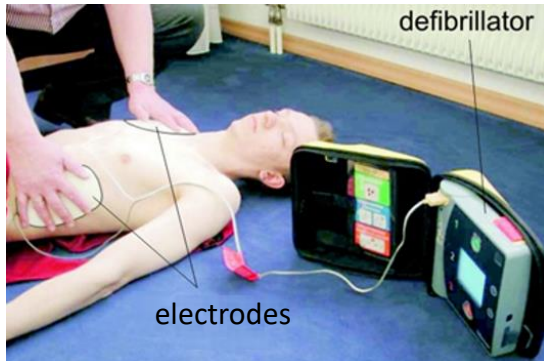
Iontophoresis



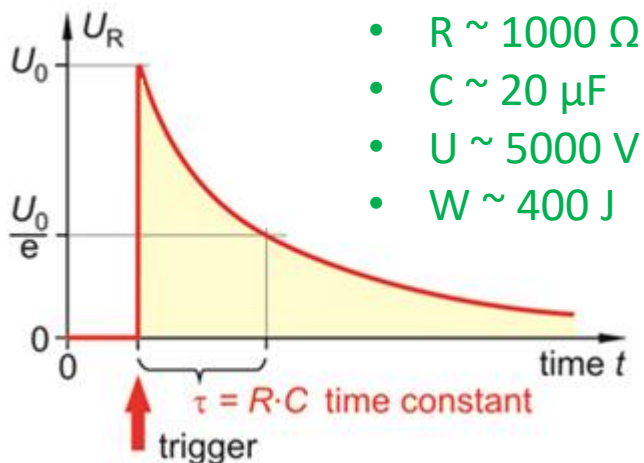
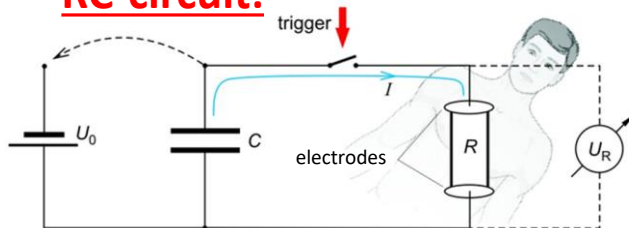
- $I \sim \text{mA}$, $t \sim 10 \text{ min}$
- a charged substance (e.g. medication) propelled rapidly through the dermis
- the polarity of the drug electrode should match the charge of the substance

Therapy with electric stimuli

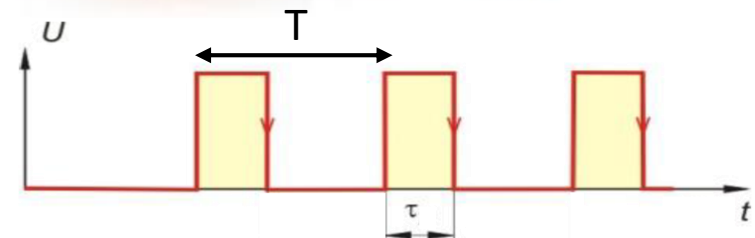
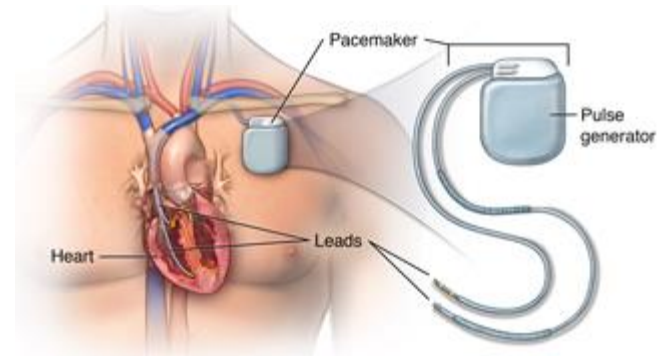
Defibrillator



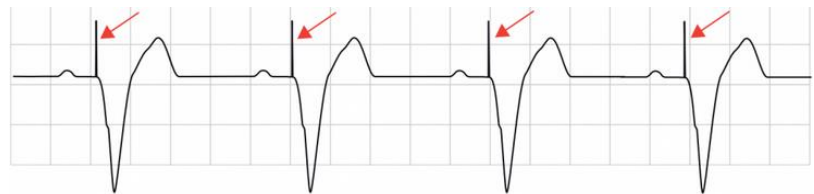
RC-circuit:



Pacemaker



- $\tau \sim \text{ms}$
- $T \sim \text{s}$
- $U \sim 1 \, \text{V}$
- $R \sim 200 \, \Omega$
- $I \sim 5 \, \text{mA}$



**Electrophysiology:
Phases of the Cardiac Cycle**

**Thank you
for your
attention!**

