

# Bioelectric phenomena.

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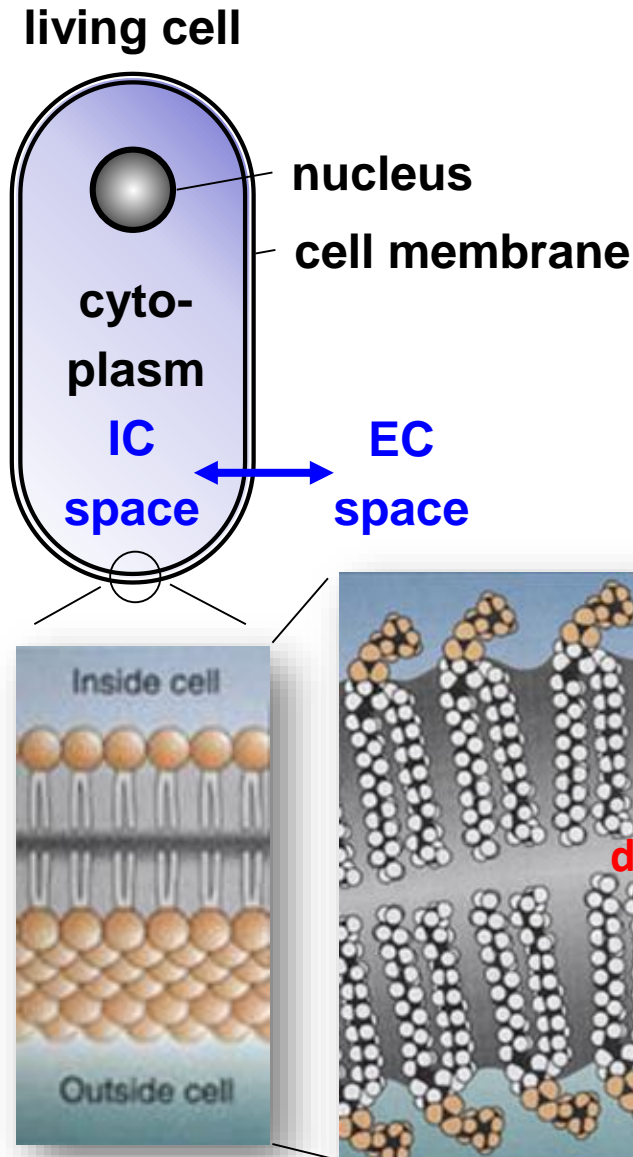
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**Institute of Biophysics and Radiation Biology,**

**Semmelweis University**

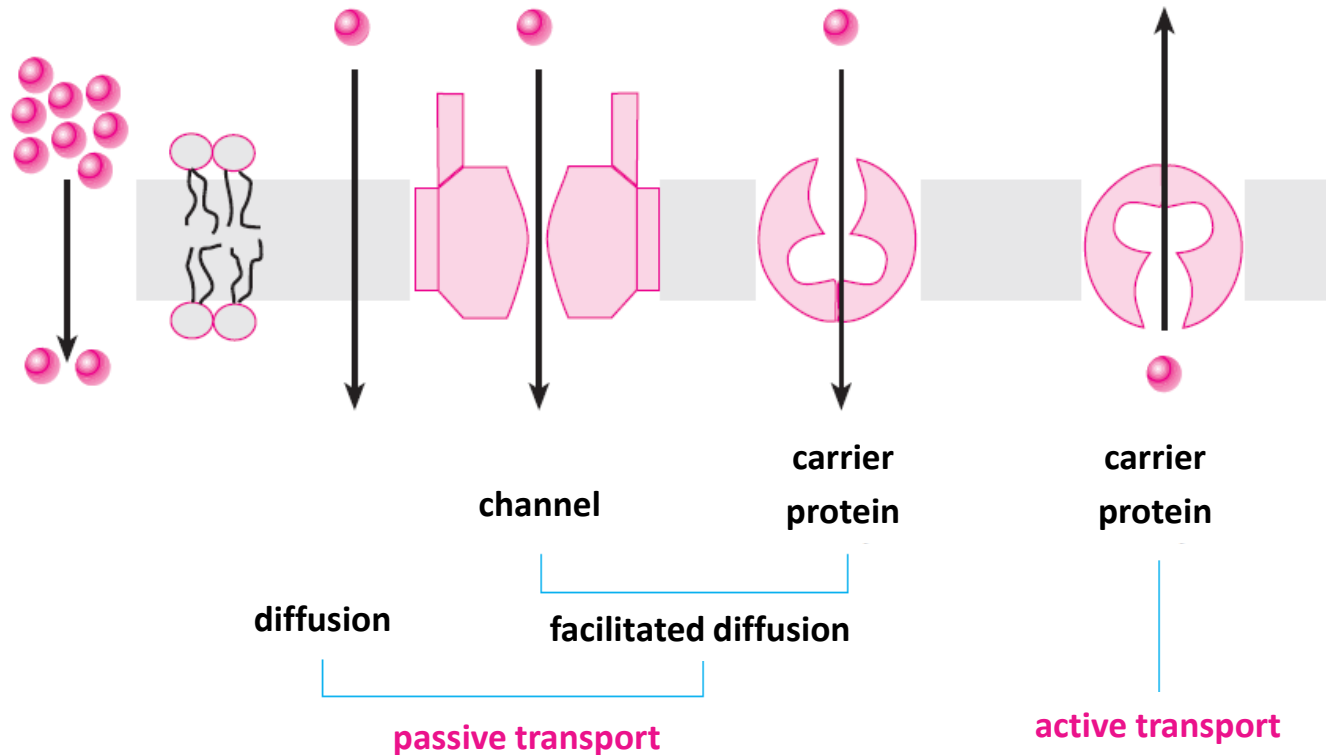
*20. March 2024.*

# Physical properties of the cell membrane



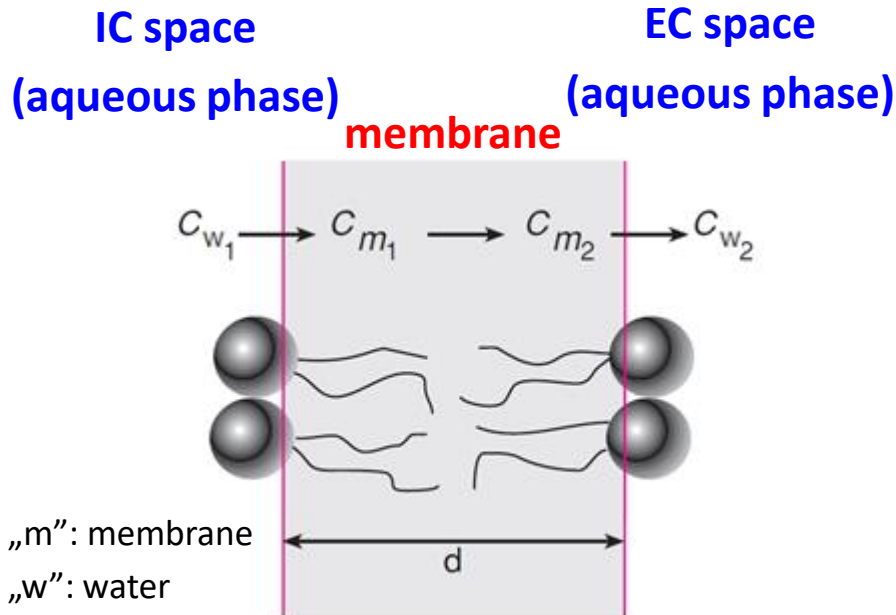
- **Noncovalent, cooperative structure:** phospholipid bilayer, vesicle formation, additional components (e.g. cholesterol, proteins)
- **Thin, layered:**  $d \sim 5 \text{ nm}$
- **Asymmetric:** the two sides of the membrane have different properties
- **Permeability:** impermeable to ions, permeable 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 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]

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

the thickness of the membrane is  
usually not precisely known

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

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

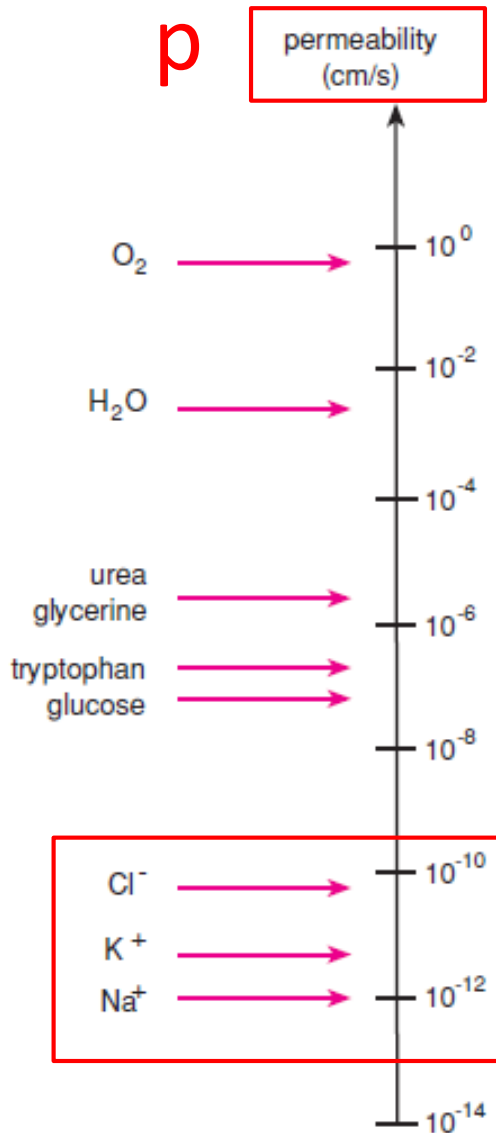
Aggregated permeability constant:  $p$ , [m/s]

$$p = K \cdot p_m$$

„permeability”

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

# Passive diffusion of particles



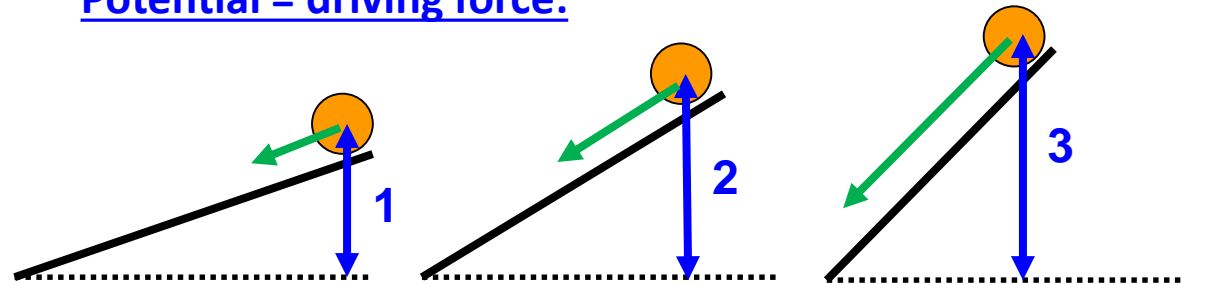
Onsanger equation:

$$J = L \cdot X$$

matter      conductivity      gradient of an  
flow density      coefficient      intensive quantity

**The driving force of transport is the chemical potential gradient.**

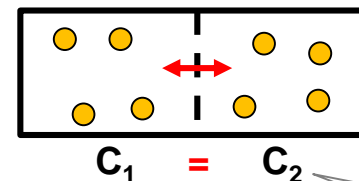
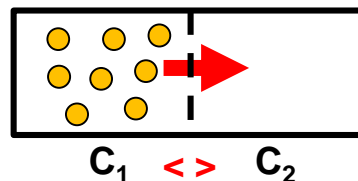
Potential = driving force:



also known as molar free enthalpy

Chemical potential:  $\mu$

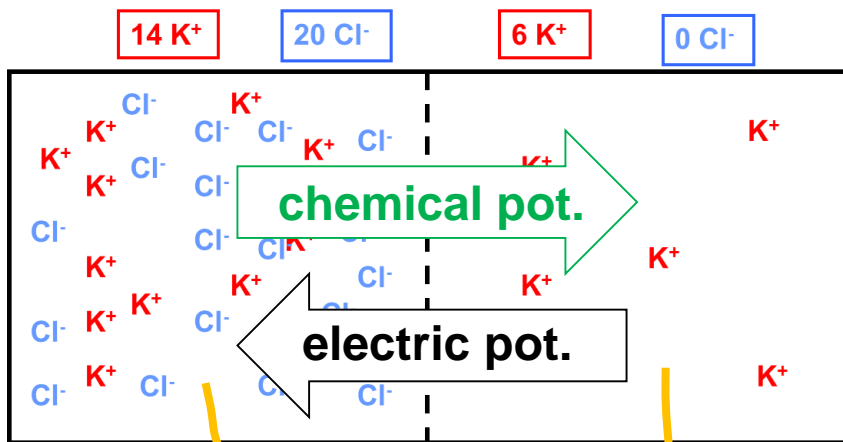
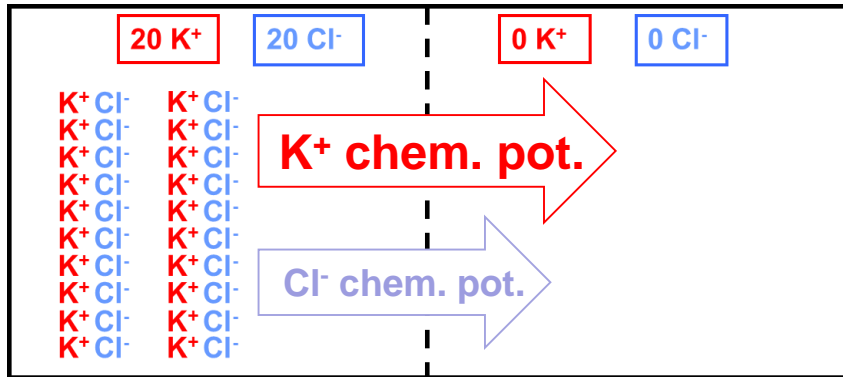
$$\mu = \mu_0 + RT \cdot \ln(c)$$



$\mu_0$ : standard  
chemical  
potential

in thermal equilibrium

# Passive diffusion of ions: electrochemical potential



$$J = -D \left( \frac{\Delta c}{\Delta x} + c \frac{z F}{RT} \frac{\Delta \phi}{\Delta x} \right)$$

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

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:  $\mu_e$ , [J/mol]

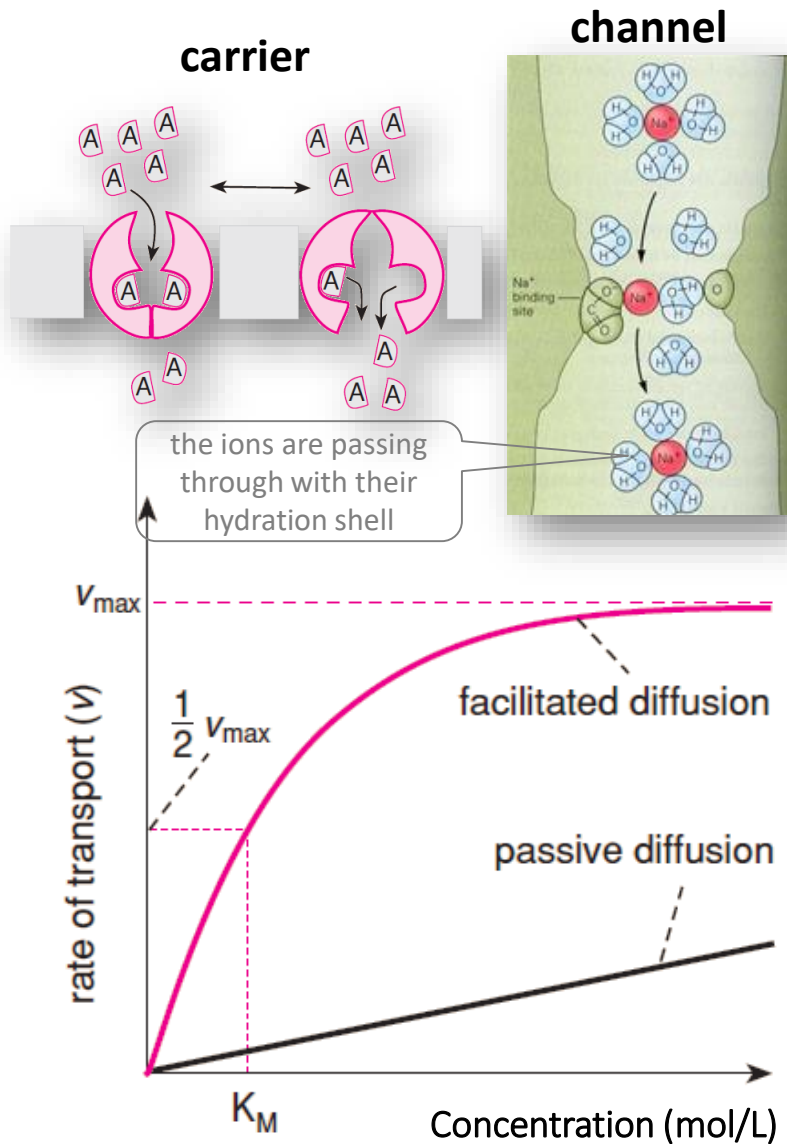
$$\mu_e = \underbrace{\mu}_{\text{chemical}} + \underbrace{zF\phi}_{\text{electric}}$$

$z$ : charge of the ion

$F$ : Faraday constant

$\phi$ : electric potential

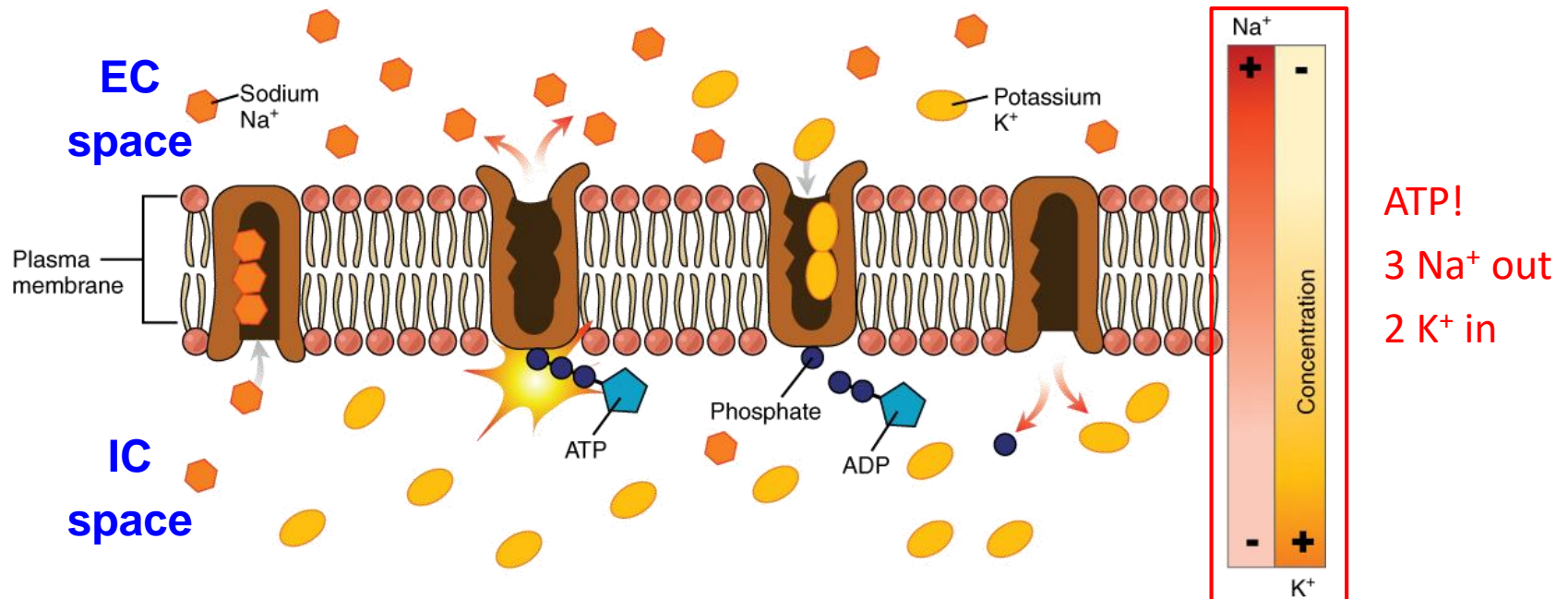
# Properties of the facilitated diffusion



- **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 (carriers or channels)
- **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<sup>+</sup>-K<sup>+</sup> ATP-ase**:

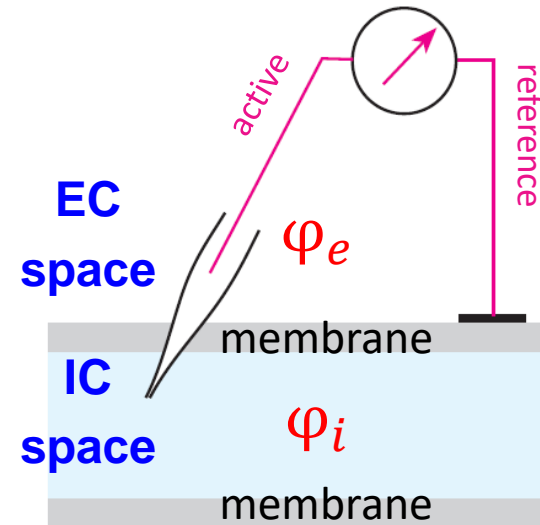
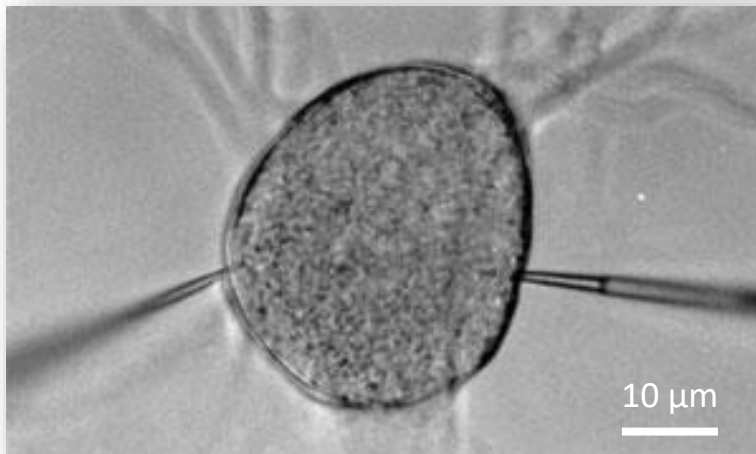




# Resting membrane potential

**Measurement:** with microelectrodes

- 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.

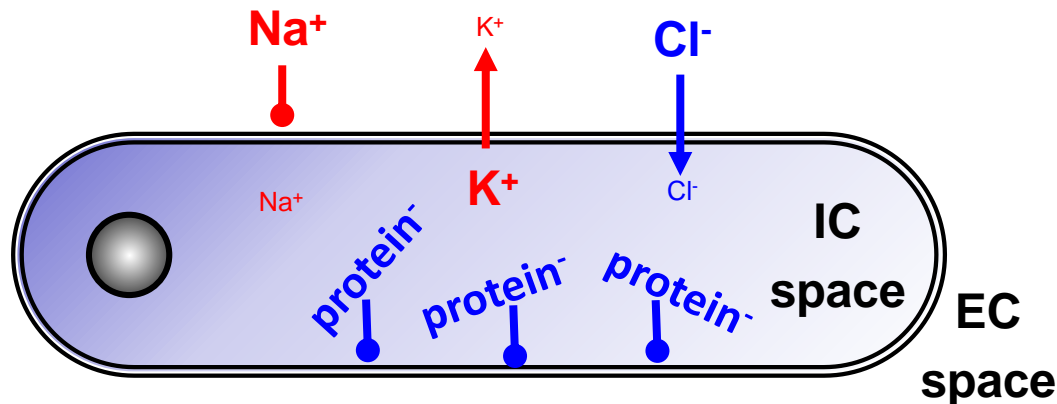
# Resting membrane potential

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

cell	intracellular concentration (mmol/l)			extracellular concentration (mmol/l)		
	Na <sup>+</sup>	K <sup>+</sup>	Cl <sup>-</sup>	Na <sup>+</sup>	K <sup>+</sup>	Cl <sup>-</sup>
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

This is done by applying the Nernst-equation...

**Equilibrium potential:** calculated based on the #1 Donnan-model...

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

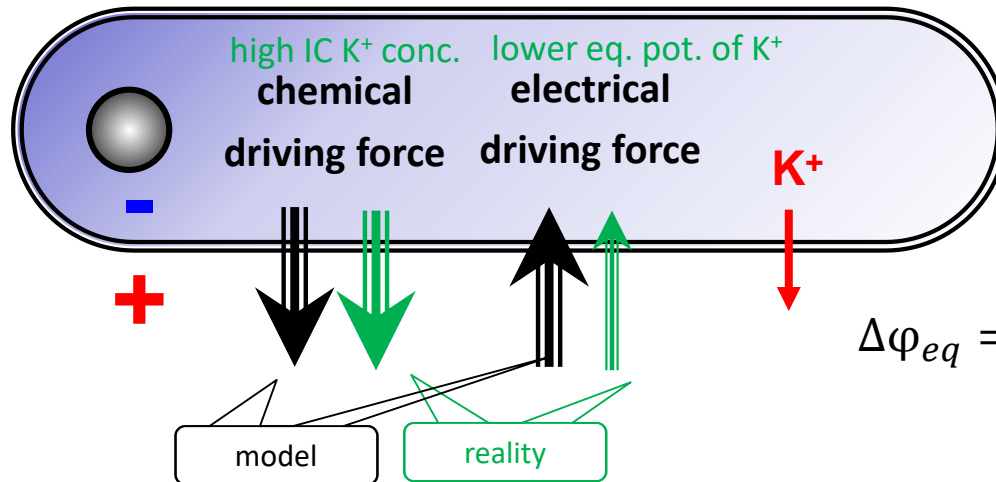
let's calculate it for the K<sup>+</sup> ions...

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

the Nernst-equation for the K<sup>+</sup> ions

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

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



**Measured membrane potential:** -62 mV

Outward flux of K<sup>+</sup> should happen at -62 mV

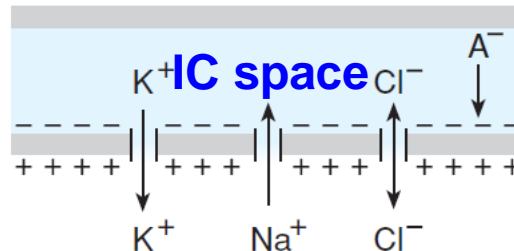
**The equilibrium model does not correctly describe the real situation!**

# The Goldman-Hodgkin-Katz (GHK) equation

Cell	$\Delta\phi_{\text{equilibrium}}$ (mV) using the Nernst equation			$\Delta\phi_{\text{membrane}}$ (mV)
	Na <sup>+</sup>	K <sup>+</sup>	Cl <sup>-</sup>	
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<sup>+</sup>
- inward flux of Na<sup>+</sup>
- minor outward flux of Cl<sup>-</sup>



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

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

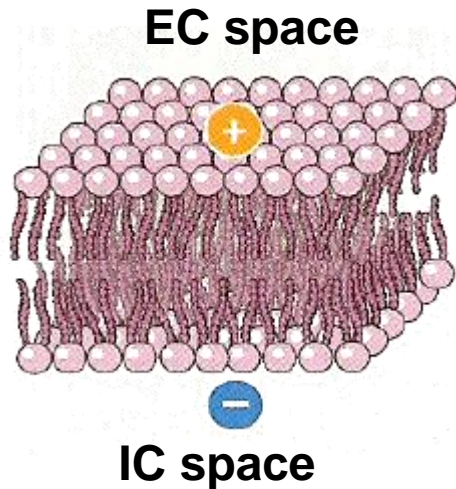
$$\Delta\phi = \phi_i - \phi_e = -\frac{RT}{F} \ln \frac{p_{Na}c_{Na}^i + p_Kc_K^i + p_{Cl}c_{Cl}^e}{p_{Na}c_{Na}^e + p_Kc_K^e + p_{Cl}c_{Cl}^i} = -91 \text{ mV}$$

in frog muscle

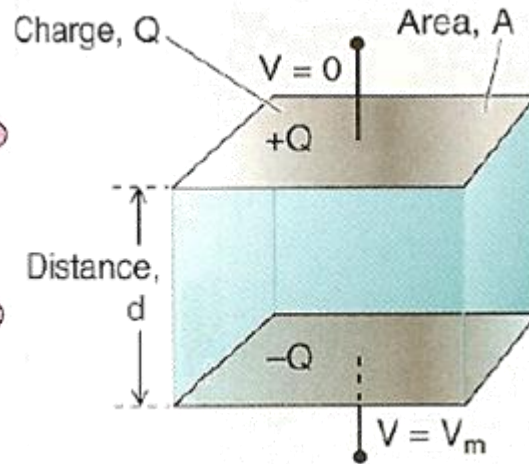
The calculation using the GHK equation is in agreement with the measurements.

# The electric model of the cell membrane

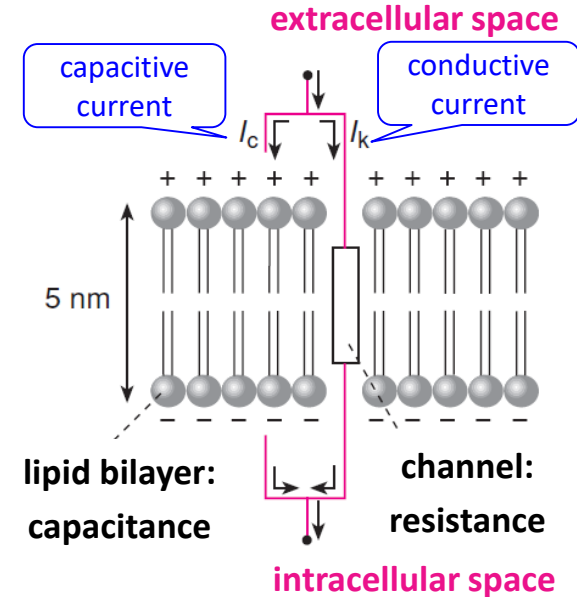
cell membrane



capacitor



electric model

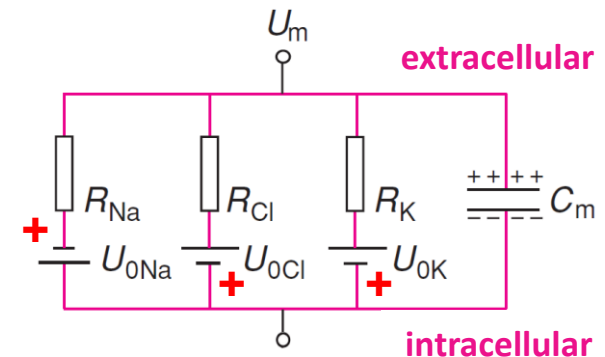


- different **transmembrane resistance (R)** in the case of the different ion channels

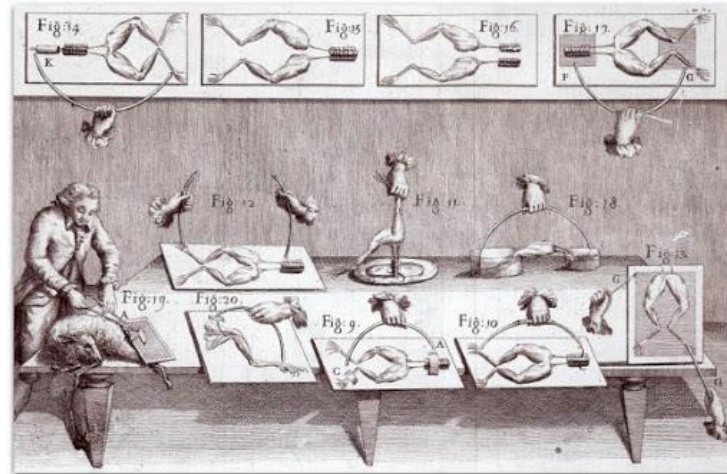
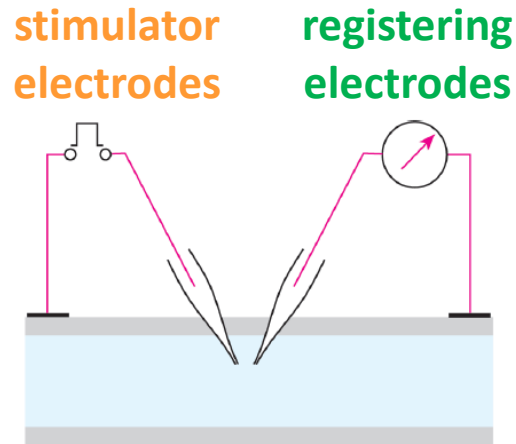
- electric conductivity:**  $G$  (unit: Siemens)  $G = \frac{1}{R}$

proportional to **permeability (p)**

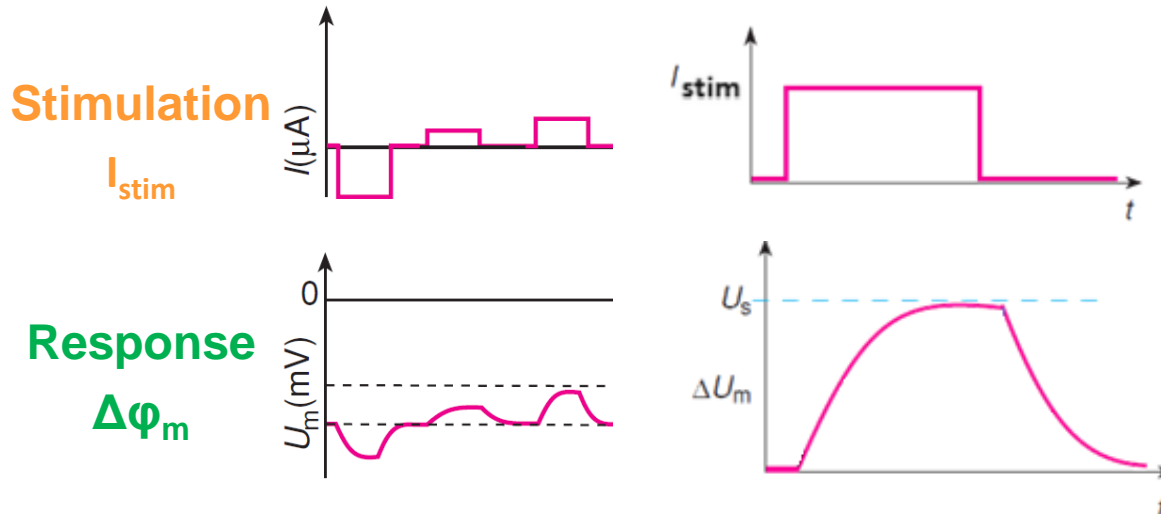
- specific conductivity:** sigma (unit:  $1/(\Omega \cdot m^2)$ )  $\sigma = \frac{1}{R \cdot A}$



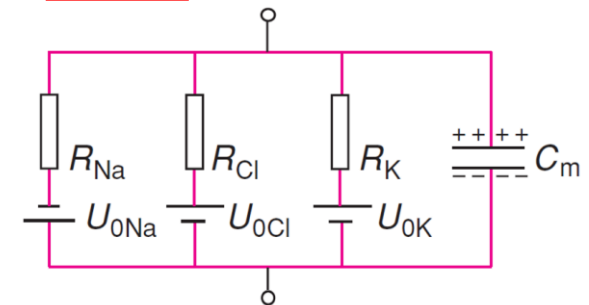
# The change of the resting potential in time



## Local (electrotonic) changes of the membrane potential:



### Model: RC-circuit

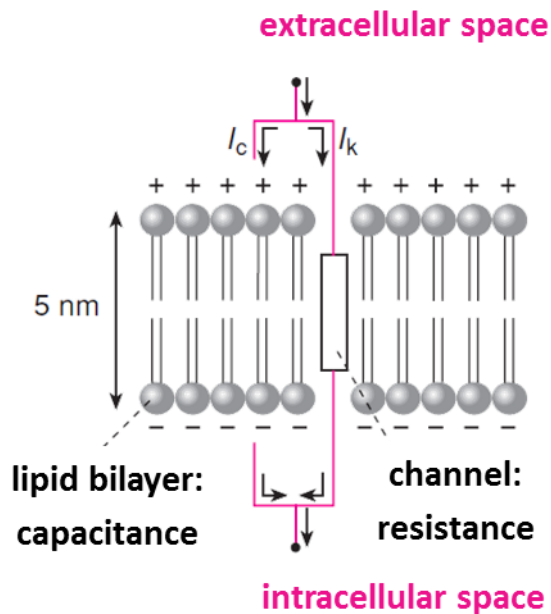


### Time-constant: tau: $\tau$ [s]

$$\tau = R_m \cdot C_m$$

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

# Electric properties of the membrane



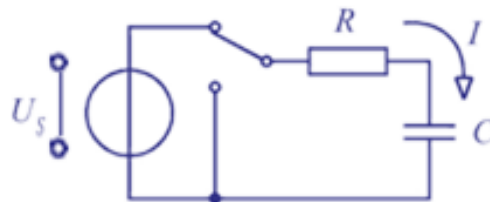
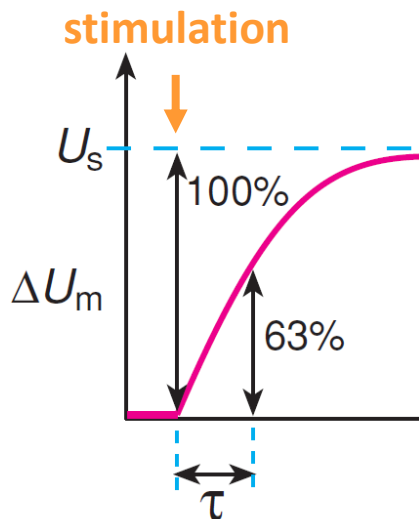
## Currents across the membrane:

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

## Based on the transport model for the resting state:

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

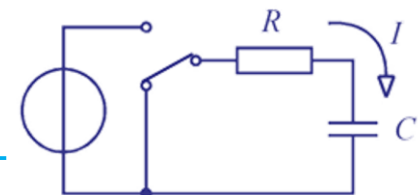
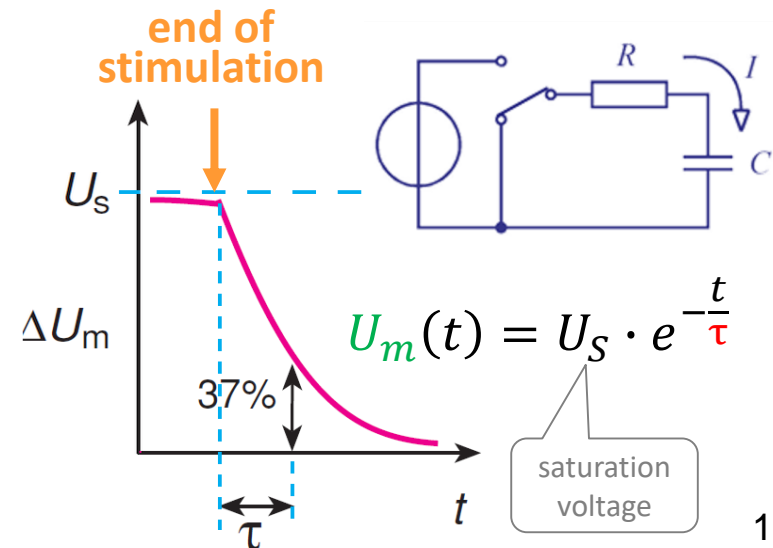
### RC: „charge”



$$U_m(t) = U_s \cdot (1 - e^{-\frac{t}{\tau}})$$

saturation voltage

### RC: „discharge”



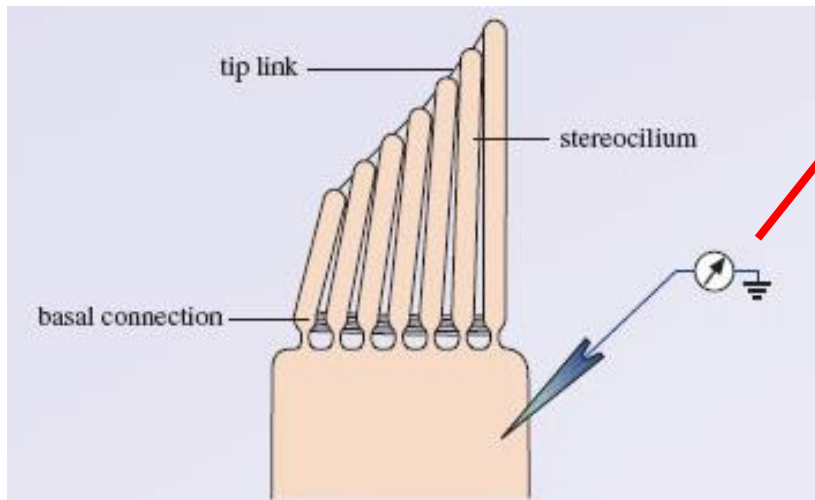
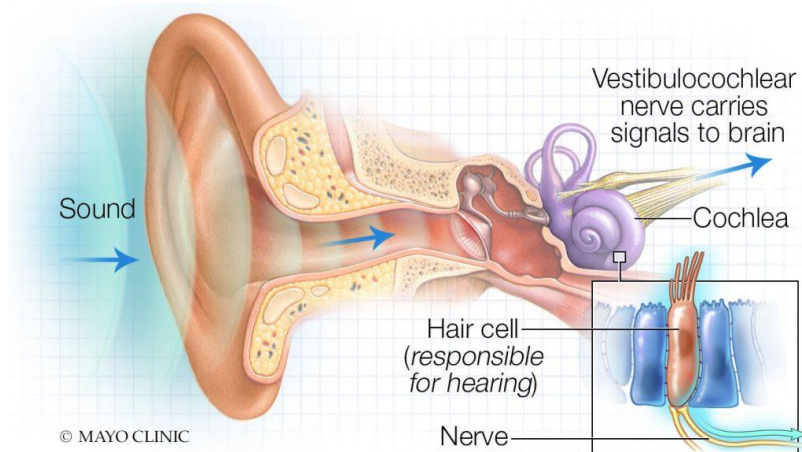
$$U_m(t) = U_s \cdot e^{-\frac{t}{\tau}}$$

saturation voltage

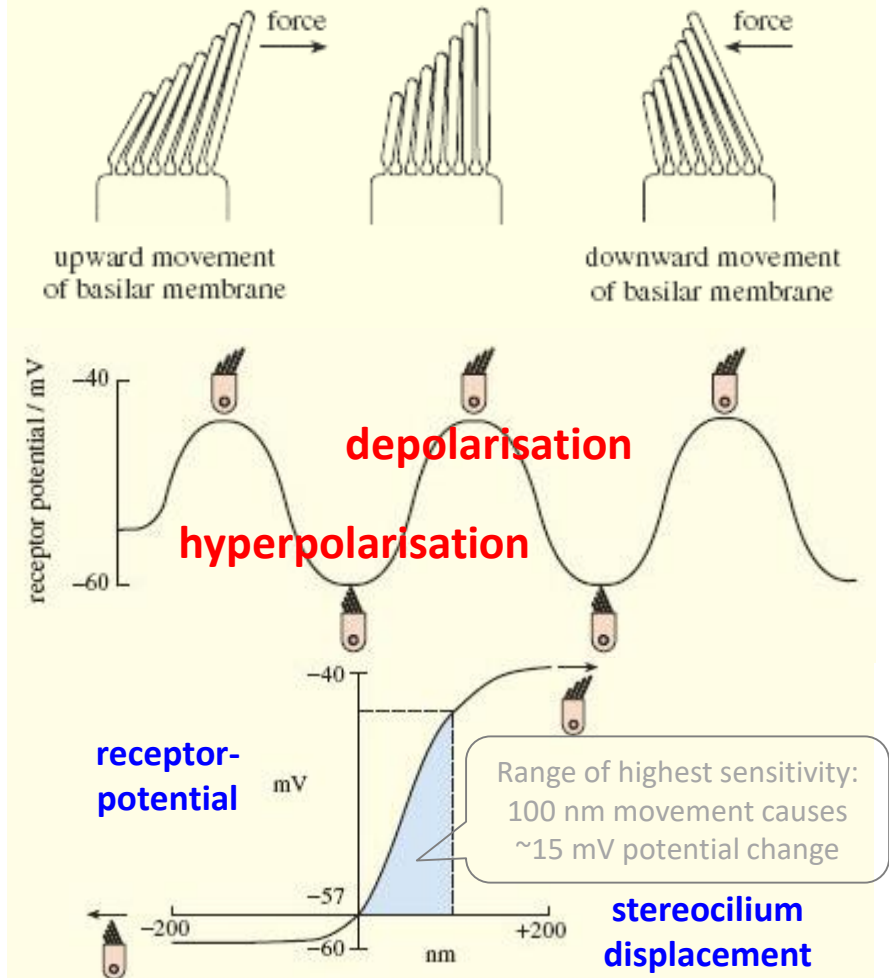


# Example: receptor potential

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



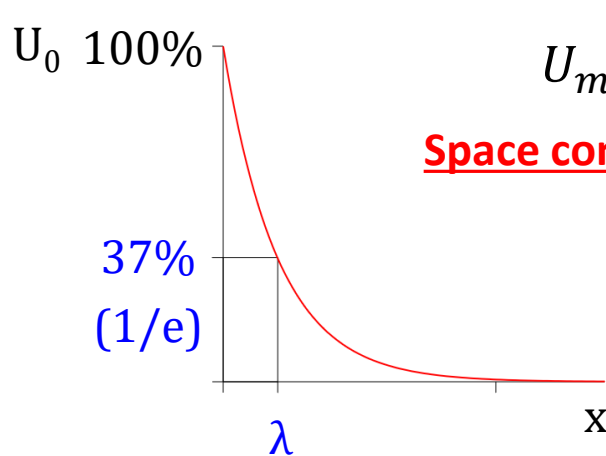
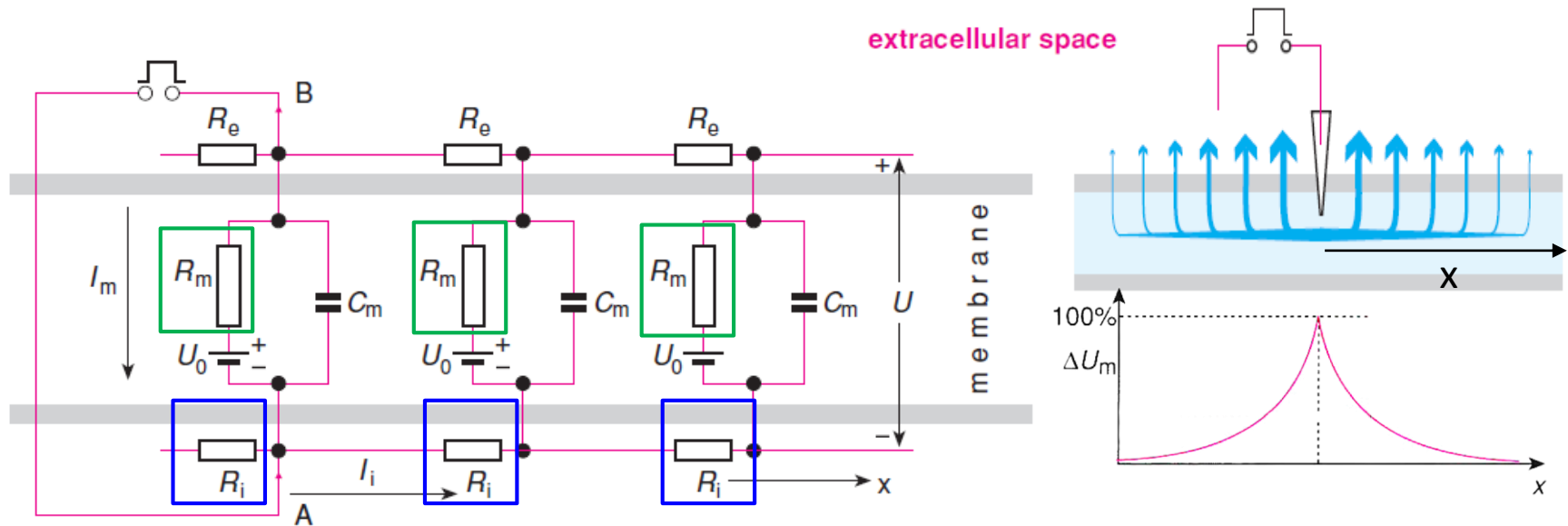
**mechanosensitive  $K^+$ -channel:  $K^+$  inward**





# Propagation of a local potential change in space

## Model of a larger membrane section:



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

**Space constant: lambda,  $\lambda$  [cm]**

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

$R_m$ : transmembrane resistance  
 $R_i$ : intracellular resistance

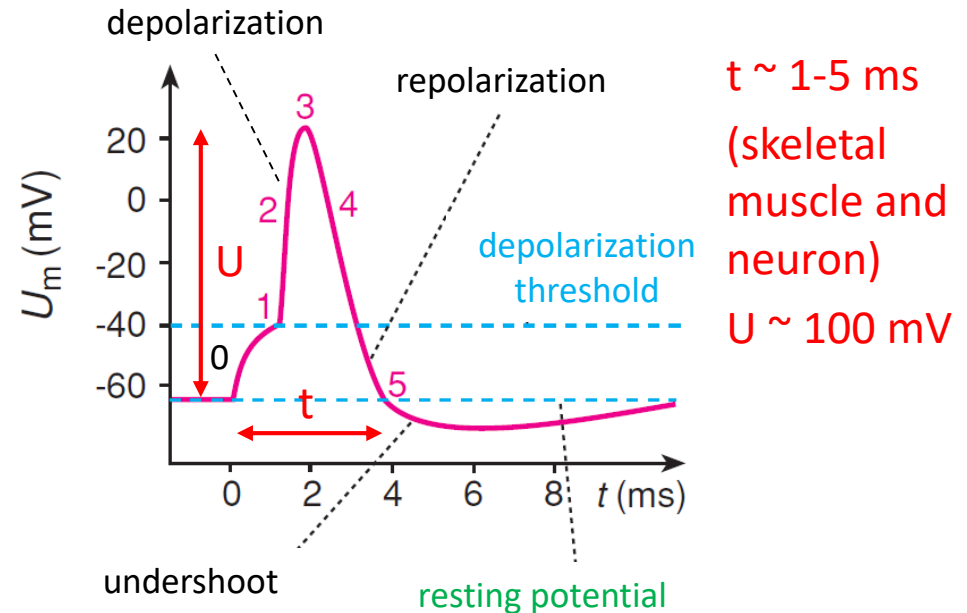
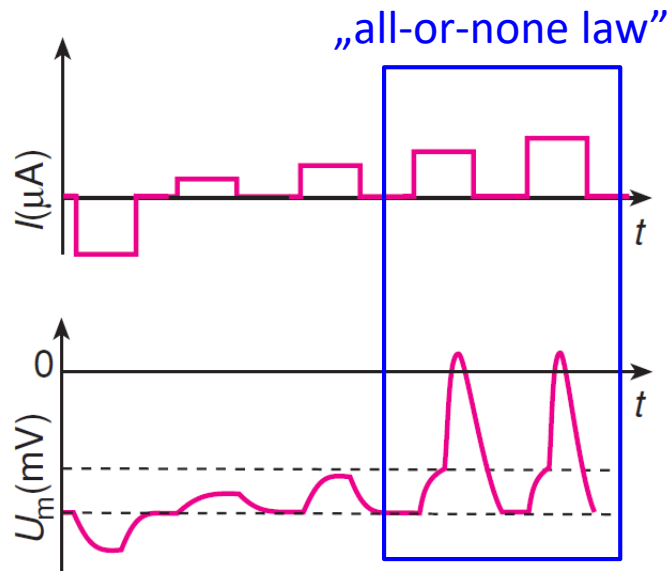
**Aim: to increase the value of  $\lambda$ .**

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

Examples: **myelin sheath** or **larger cell diameter**.

# Action potential

For stimuli above threshold: generalized change of the membrane potential



0: local change of membrane potential

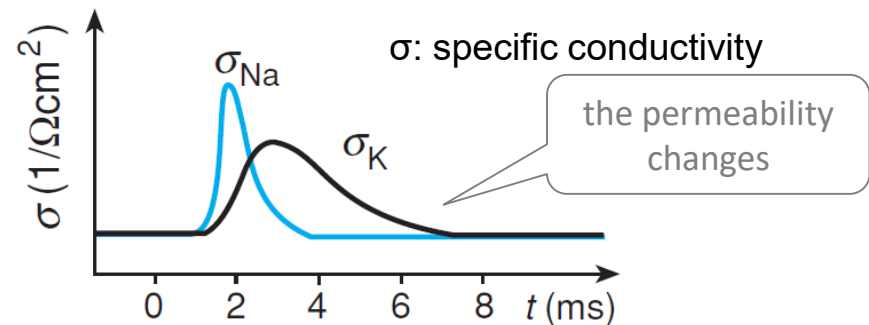
1: **volt. gated  $\text{Na}^+$  ch. open** ( $\text{Na}^+$ : in)

2: **volt. gated  $\text{K}^+$  ch. open** ( $\text{K}^+$ : out)

3:  **$\text{Na}^+$  ch. inactivation** (partial)

4:  **$\text{Na}^+$  channel closure**

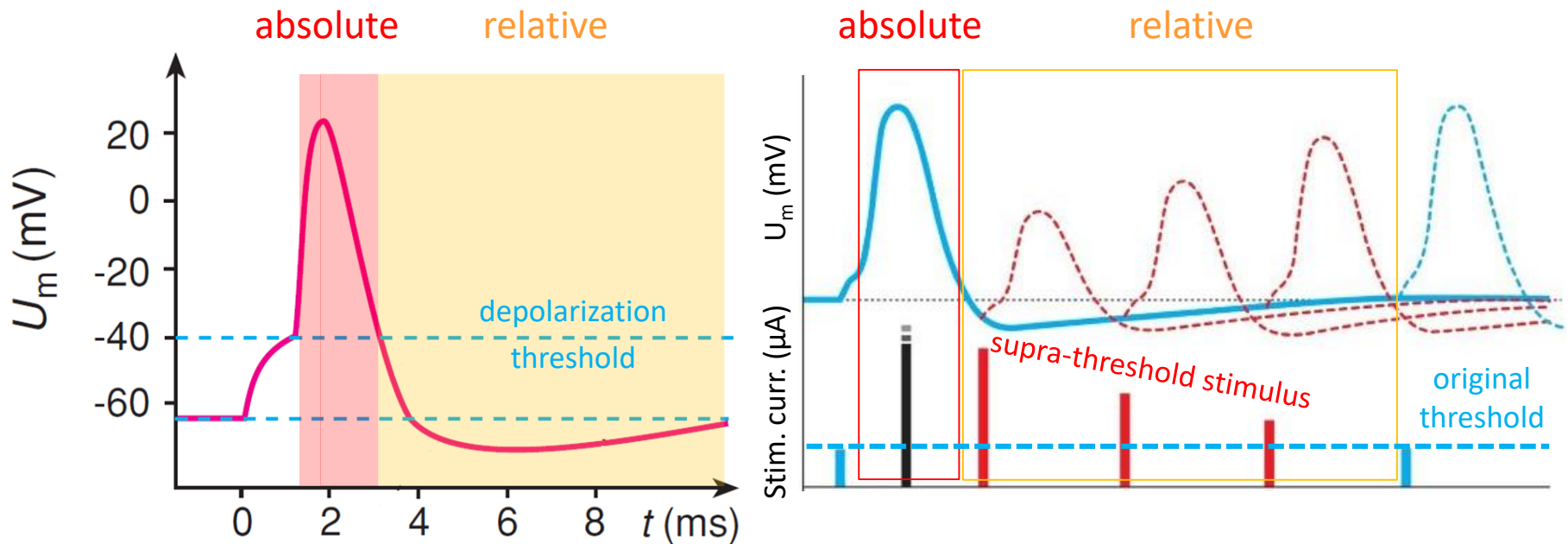
5:  **$\text{K}^+$  channel closure** (delayed)



# Properties of the action potential #1

**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

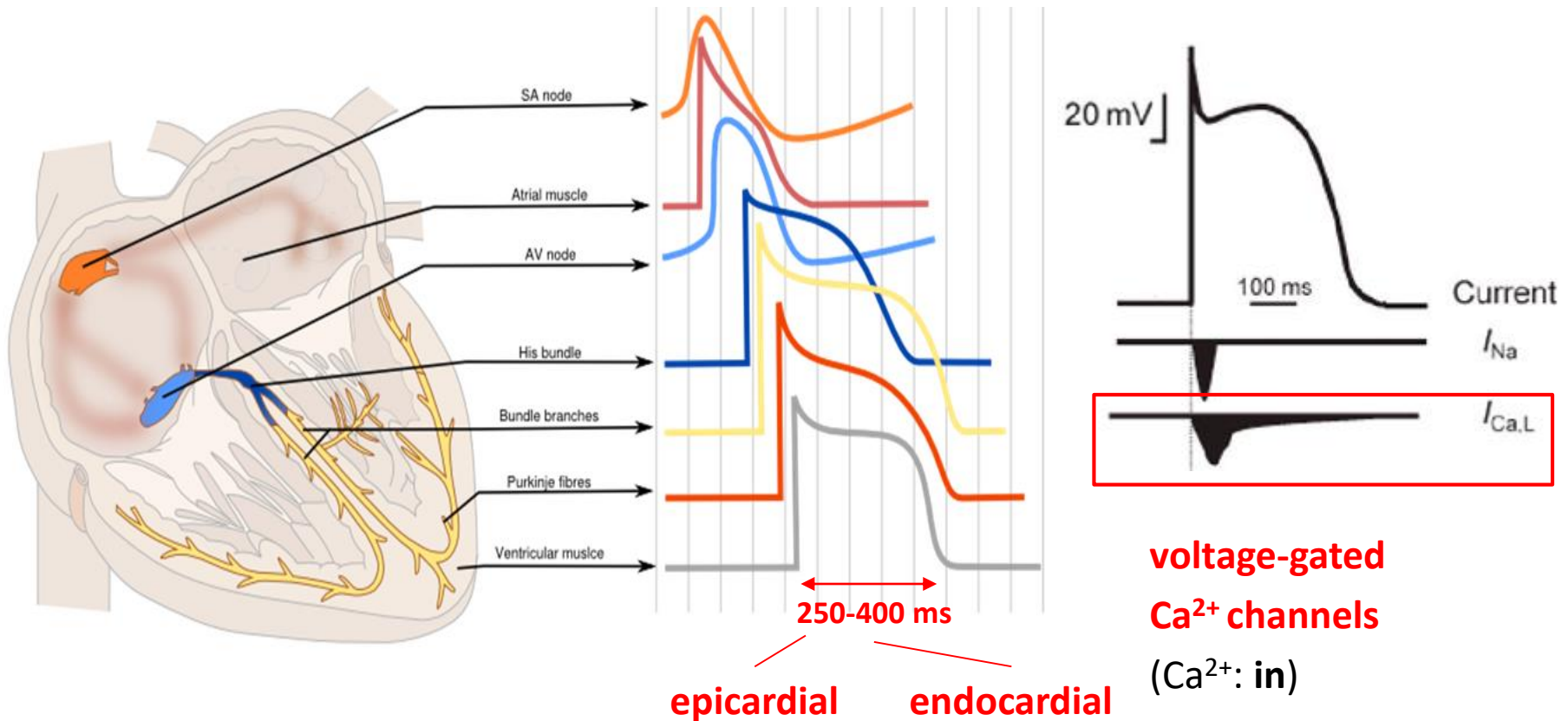


- **absolute:** voltage-gated  $\text{Na}^+$  channels are inactivated
- **relative:** AP with supra-threshold stimulus  
Reopening of the closed voltage-gated  $\text{Na}^+$  channels.

prevents the  
backpropagation  
of action  
potential

# Properties of the action potential #2

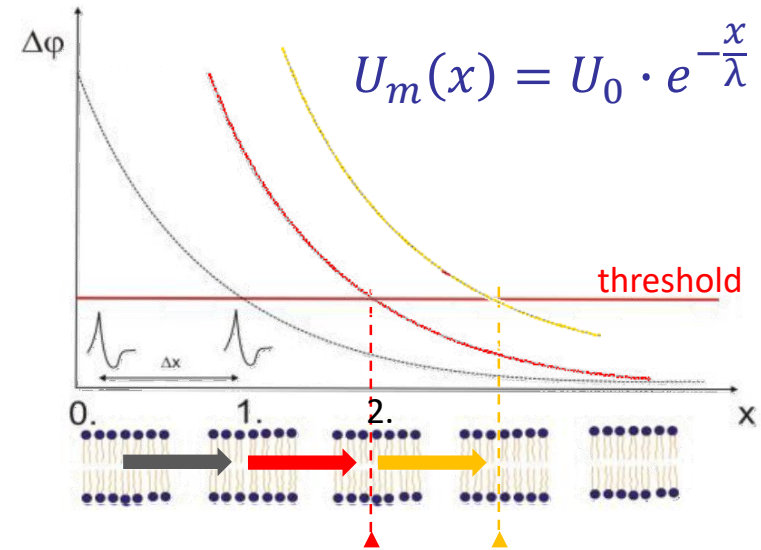
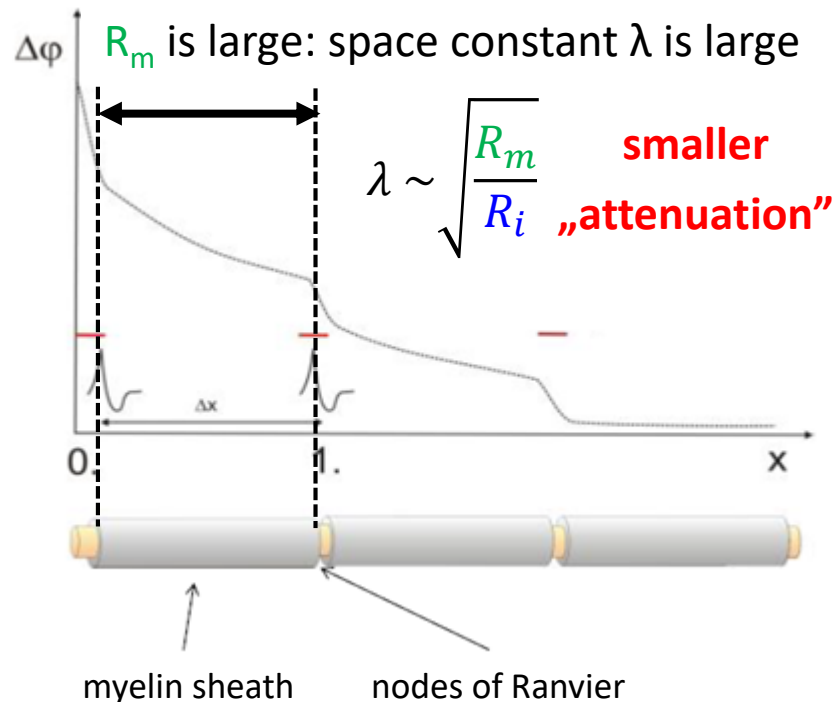
Special action potential: ventricular cardiomyocytes



# 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

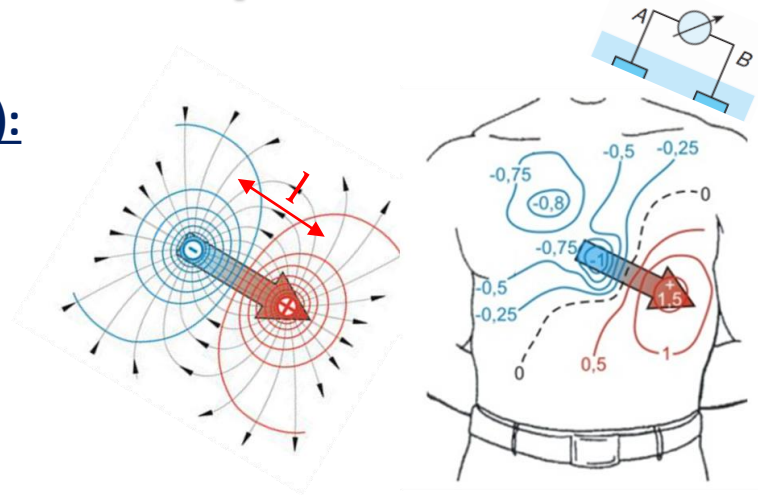
# Medical application of bioelectric phenomena

## Electric signals on the body surface (diagnostics):

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

Origin:

**dipole-**  
**moment:**  
 $\mathbf{d} = Q \cdot \mathbf{l}$



## Electric stimulation (therapy):

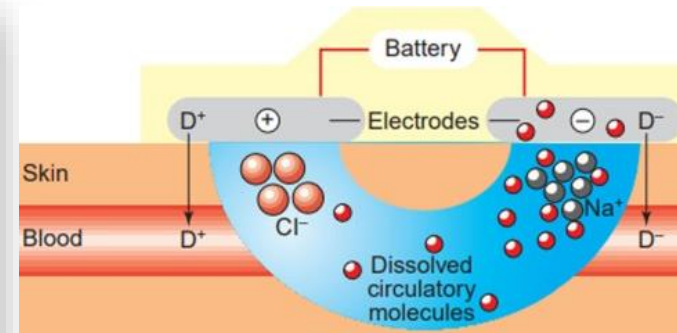
- Galvanic treatment (DC)
- Iontophoresis (DC)
- HF-thermotherapy (AC)
- Electric surgery (AC)
- Electric stimulus therapy (pulse)
- Defibrillator (pulse)
- Pacemaker (pulse)

## Galvanic treatment



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

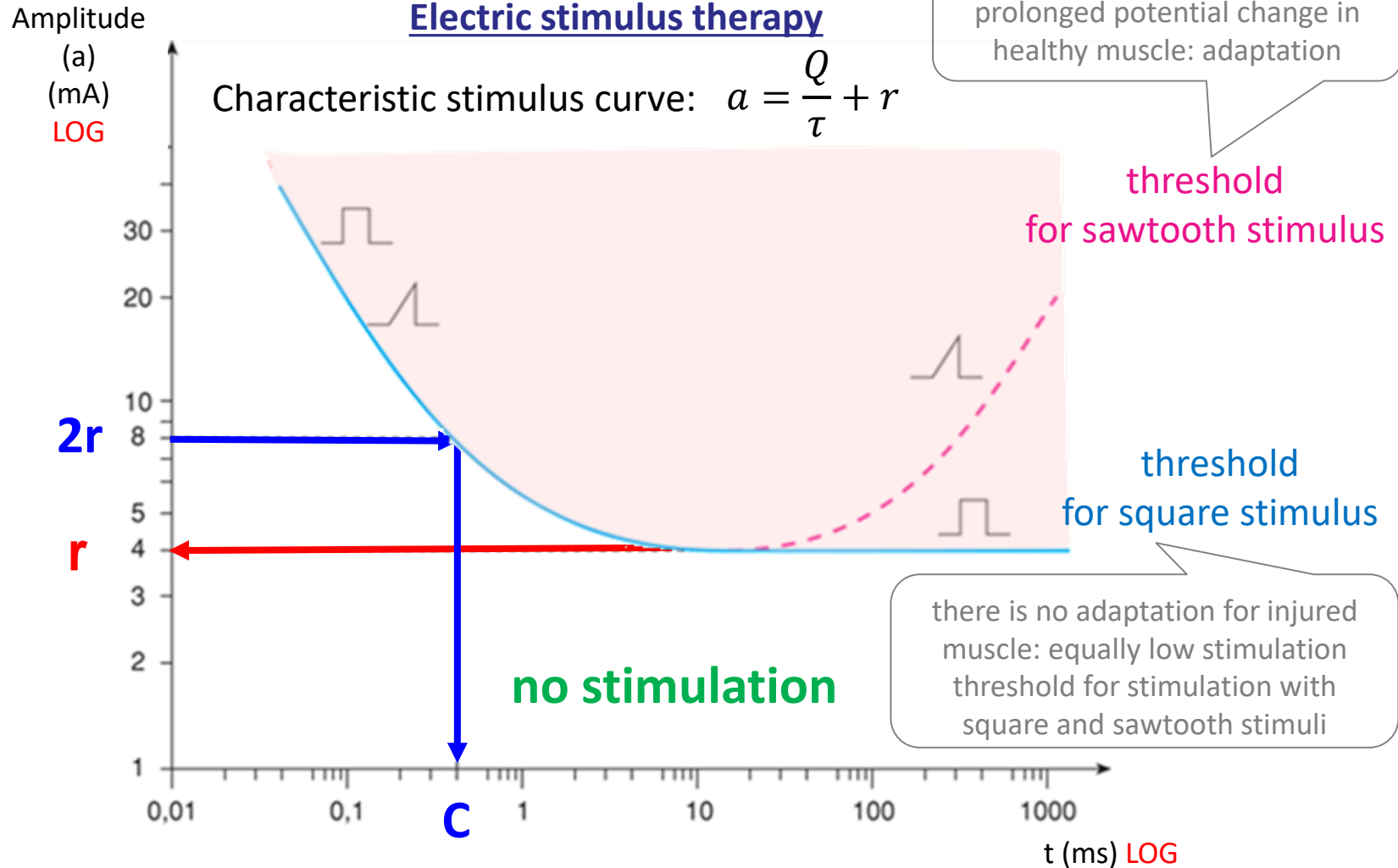
## Iontophoresis



- $I \sim \text{mA}$ ,  $t \sim 10 \text{ min}$
- a charged substance is propelled through the dermis into the blood
- the polarity of the electrode should match the charge of the substance
- indifferent „counterion” (e.g.  $\text{Cl}^-$ )

# Pulse therapy

## Electric stimulus therapy

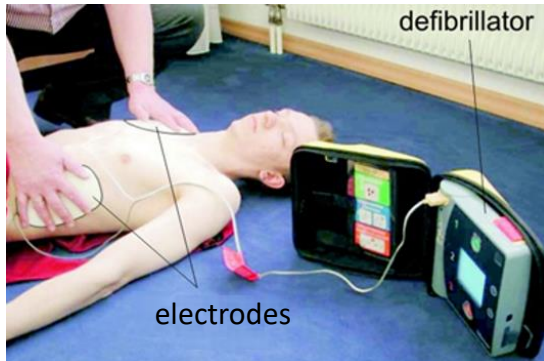


- **rheobase (r)**: minimal electric current that elicits (muscle) stimulation
- **chronaxie (C)**: time to 2x rheobase

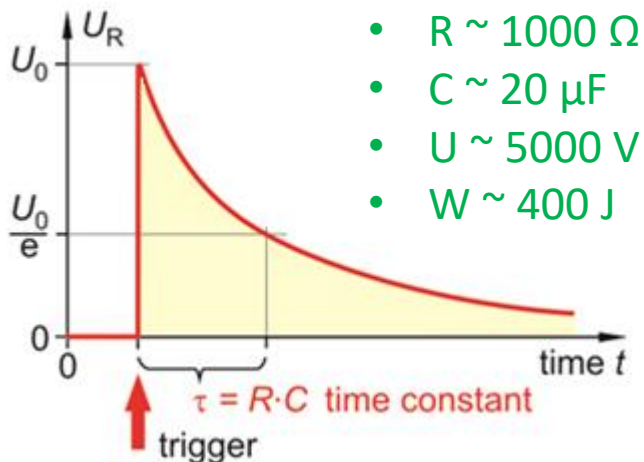
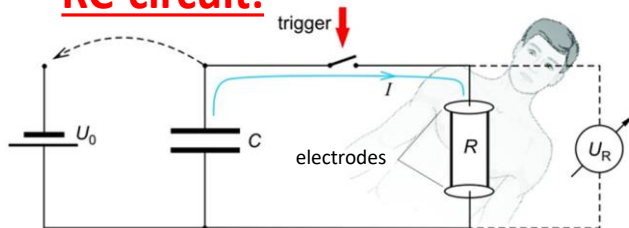


# Therapy with electric stimuli

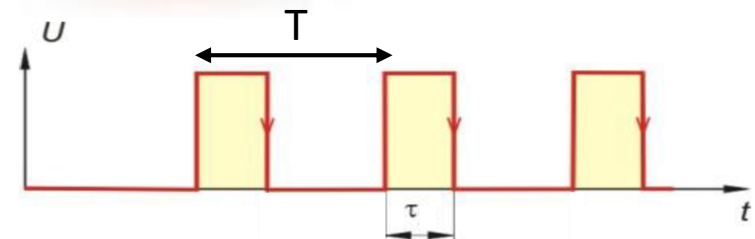
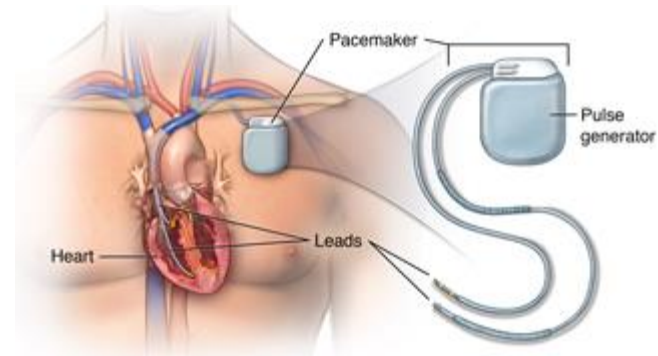
## Defibrillator



### RC-circuit:



## Pacemaker



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

