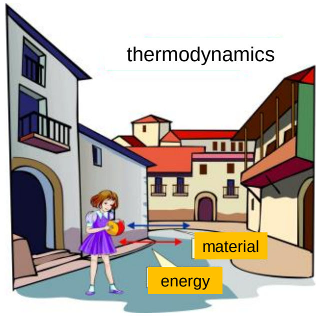


Interaction between living organism and the enviroment

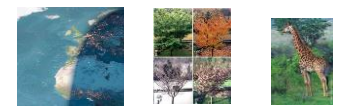
Open system: free material and energy exchange

Properties of the living organism

Separation from the enviroment:

Strictly controlled energy and material transport.

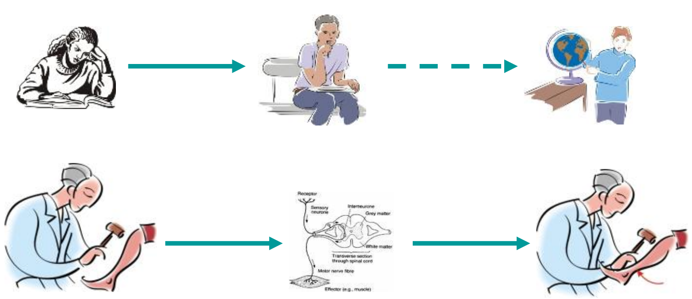
Changing in the enviroment: accomodation



Condition: information from the environment, right and fast processing and adequate response.

Processing informations

information — processing — answer

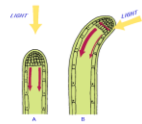


Definitions

- ***stimulus***: any effects on the organism (signal and noise)
- ***outer stimulus*** from the enviroment (e.g. light, sound etc.)
- ***inner stimulus***: from the organism (glucose concentration, pH of the blood etc.)

Simple responses in plants

phototropism



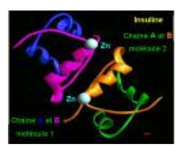
geotropism

„Fast” motion in plants

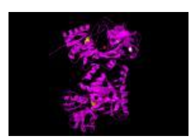
Sensitive plant

Simple responses in animals

insulin production



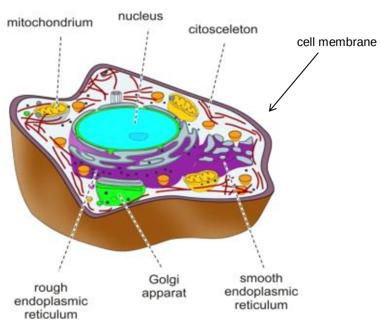
melanin production



Animals and the human beings

- Motion (requires fast processes)
- Chemical system : hormones
- More complex and faster system: nerves and muscles

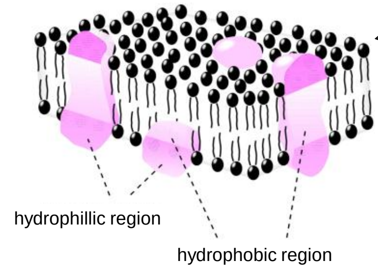
Membranes in the cell



Role of the cell membrane: separation and controlled interaction to the enviroment

Inner membranes: formation of intracellular spaces (compartments). Several base processes take place on the membrane.

Structure of the membranes

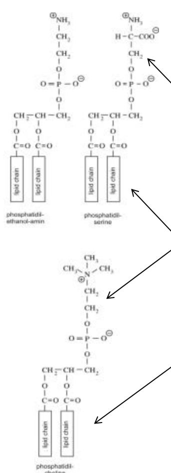


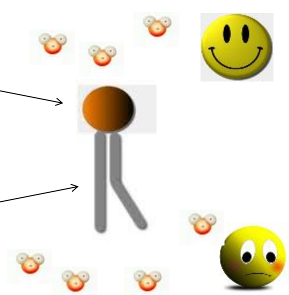
Base matrix: phospholipid bilayer.

Proteins, polysacharids, etc.

location:
at the extracellular space
at the intracellular space
transmembrane molecules

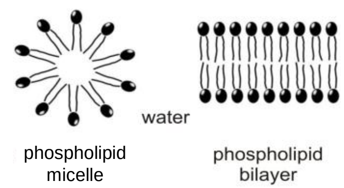
Phospholipids





phospholipids in water

Phospholipid structures in water



„Similis simili gaudet"
(similar likes similar)

From energetic viewpoint these arrangments are more favorite.

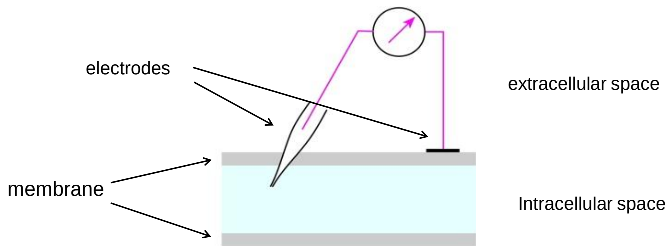
Lyotrop liquid crystals. (structure depends on the concentration)

Anisotropic, partially orederd structure, but liquid materials.

Resting membrane potential

observation

In resting state about -30 és -90 mV voltage may be measured between the extra- and intracellular space.



Typical ion distributions

observation → The ion concentration is different on the two sides of the membrane.

Intracellular space (mM/l)

	Na^+	K^+	Cl^-
Squid giant axon	**72**	**345**	**61**
Frog muscle	**20**	**139**	**3.8**
Rat muscle	**12**	**180**	**3.8**

Extracellular space(mM/l)

	Na^+	K^+	Cl^-
Squid giant axon	**455**	**10**	**540**
Frog muscle	**120**	**2.5**	**120**
Rat muscle	**150**	**4.5**	**110**

Diffusion of the ions

Diffusion of neutral particles. → Intensive quantity: chemical potential

In the case of charged particles the electric work must be taken into the consideration! → Intensive quantity: electrochemical potential

$$\mu^e = \mu + zF\varphi$$

z: no. of charges
F: Faraday constant.
φ: electric potential

equilibrium:

$$\mu_1^e = \mu_2^e \longrightarrow$$

Nernst-equation

$$\Delta\varphi = -\frac{RT}{zF}\ln\frac{c_1}{c_2}$$

Diffusion through the membrane

Use the permeability constant as characteristic quantity!

p = D/d

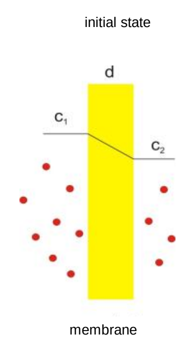
D – diffusion constant
d – thickness of the membrane

mobile ions (permeable membrane), final state equilibrium.

equilibrium:

c(1) = c(2)

Δφ = 0 !!!



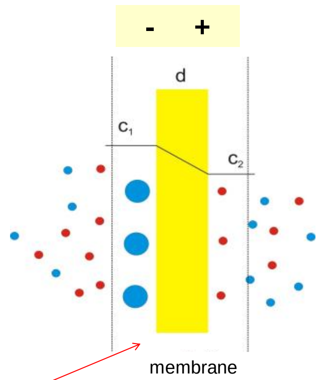
Donnan-equilibrium

Initial conditions:

There are non permeable ions. Electric neutrality both sides (the sum of the charges is zero)

c(1) ≠ c(2)

$\Delta\varphi \neq 0$



Right solution?

electric bilayer

Ratio of concentrations (extracell./intracell.)

Ion	Na^+	K^+	Cl^-
squid	6.3	0.029	8.9
frog	6.0	0.018	31.6
rat	12.5	0.025	29.0

Calculated potetials on the base of Nernst-equation for different ions and the measured potential (mV)

	membrane-potential (meas.)	Na^+	K^+	Cl^-
Squid giant axon	**-62**	**+46**	**-89**	**-55**
Frog muscle	**-92**	**+45**	**-101**	**-87**
Rat muscle	**-92**	**+64**	**-93**	**-85**

Significant differences between the measured and calculated values!
Main difference in the case of Na^+.

Typical values for the heart

ion	Extracell. space (mM)	Intracell. space (mM)	ratio (extra/intra)
Na^+	145	15	9.7
K^+	4	150	0.027
Cl^-	120	5-30	4-24
Ca^{2+}	2	10^{-7}	$2 \cdot 10^4$

Calculated membrane potential

ion	Na^+	K^+	Cl^-	Ca^{2+}
Membrane potential (mV)	61	-96	-(37-85)	

Donnan-equilibrium

- In the case of the phenomenon described by Donnan constant potential difference may be observed between two sides of the membrane.
- There are mobile and immobile ions.
- In the case of equilibrium the electrochemical potential is same.

Conclusion

On the base of the measured values there is no Donnan-equilibrium between two sides of the membrane. (The concentration difference of the Na^+ is too high for example!)

- The biological system is not in equilibrium!
- Passive process (diffusion) may change the state to the equilibrium.
- Active (energy consumption) processes are necessary to keep steady state.

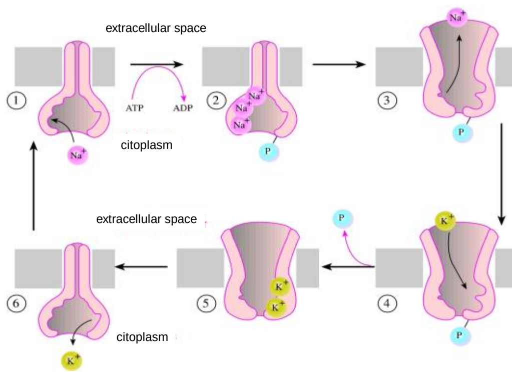
The role of active transport

- Charge and material transport exist, the concentration were not constant, e.g. slow inflow of Na^+ into the cell.
- Different, energy consumer mechanisms, so-colled pumps ensure the steady state.
- (e.g. Na^+-K^+ pump, Na^+-Ca^{++} etc.)

Na-K pump

3 Na^+ ion and 2 K^+ exchange

requires ATP!



Ion flow in the membrane

neutral particles

$$J = -p \cdot \Delta c$$

J – flux
p – permeability constant
Δc- concentration gradient

(single) charged particles

$$J = -p\left(\Delta c + c\frac{F}{RT}\Delta\varphi\right)$$

J – flux
p – permeability constant
Δc- concentration gradient
F – Faraday constant
T – temperature
Δφ – potential difference
R - gas constant

The base of the transport-model

- The membrane is in rest but there is no equilibrium between two sides.
- The membrane potential is constant ⇒ the net ion flow through the membrane is zero.
- The potential gradient in the membrane is constant ⇒ dφ/dx = const.

Goldman-Hodgkin-Katz (GHK) potential equation

condition of steady state:

(the net flux is zero)

$$\sum_k J_k = 0$$

$$\Delta\varphi = -\frac{RT}{F}\ln\frac{p_{Na}c_{Na}^{e} + p_{K}c_{K}^{e} + p_{Cl}c_{Cl}^{i}}{p_{Na}c_{Na}^{i} + p_{K}c_{K}^{i} + p_{Cl}c_{Cl}^{e}}$$

p –permeability constant of an ion
e – extracellular space
i – intracellular space

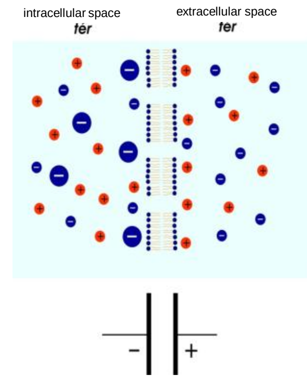
Simplified GHK equation

$$\varphi = -\frac{RT}{F}\ln\frac{pc_{Na}^{e} + c_{K}^{e}}{pc_{Na}^{i} + c_{K}^{i}}$$

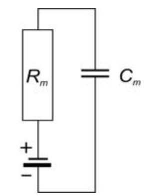
(p = relative permeability constant, compared to the K^+)

	p	φ(calc.) (mV)	φ(meas.) (mV)
Squid giant axon	**0,04**	**-63**	**-62**
Frog muscle	**0,01**	**-91**	**-92**

Electric model of the membrane

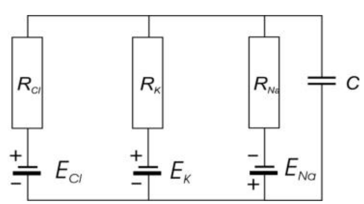


The model describing the resting potential and the ion current:



According to the main ions

model for resting potential

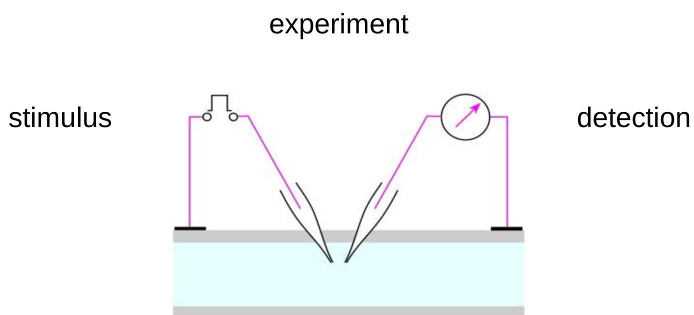


C – represents the membrane capacity,
R - characterizes the resistance against the flow of the given ion,
E – voltage source representing the membrane potential

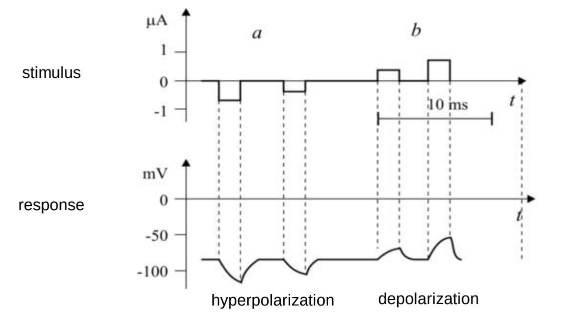
Changing of the membrane potential

- The definition of the stimulus: changing of the membrane potential transmits the information.
- Changing of the resting potential is due to the specific ion flow though the membrane.

Changing the membrane potential



Depolarization, hyperpolarization

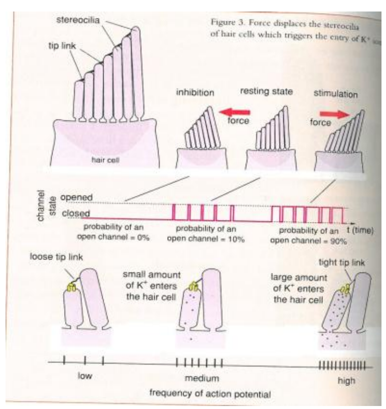


exponential increasing and decreasing.

Depolarization (example)

hair cells in the ear:

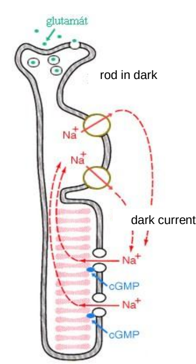
Mechanical effect - membrane depolarization.

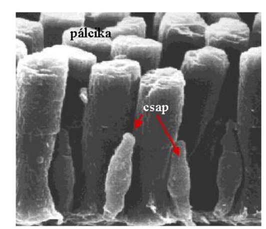


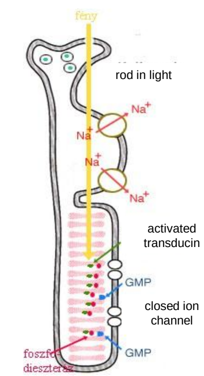
Hyperpolarization

rods in the eye:

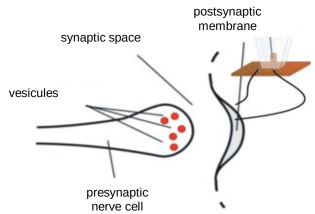
photochemical effect results the hyperpolarization of the membrane.





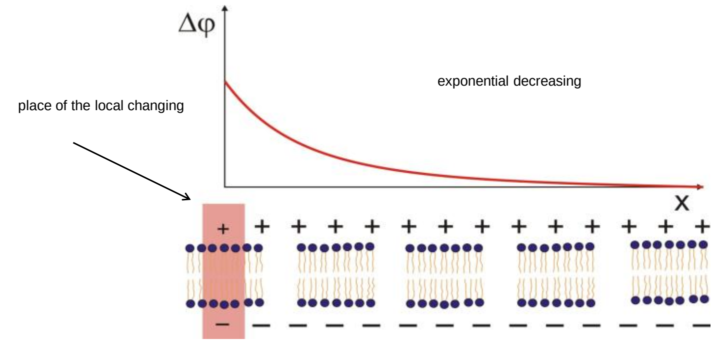


Synaps (example)

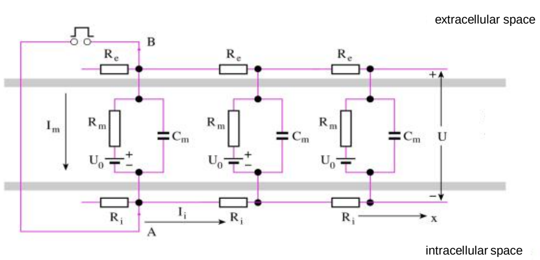


A possible mechanism: the released acetyl choline bonding to the receptor opens an ion-channel.

Propagation of the changing along the membrane



Extension of the electric model: cable model



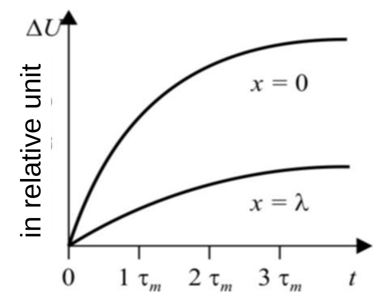
R_e - longitudinal resistance of the extracellular space.
R_i - longitudinal resistance of the intracellular space.
These elements connect to each other the different parts of the membrane.

Electric properties: time constant

on the base of the exponential answer of the membrane:

(responses according to the distance of the place of the stimulus)

$$\tau_m = R_m \cdot C_m$$



the time, while the changing decreases or increases by factor e.

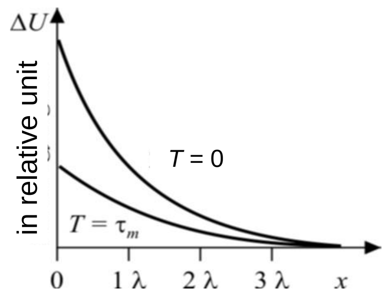
Electric properties: space constant

on the base of the propagation of the changing along the membrane:

(responses according to the time)

$$\lambda \approx \sqrt{\frac{R_m}{R_i + R_e}} \approx \sqrt{\frac{R_m}{R_i}}$$

the distance, where the changing decreases by factor e.



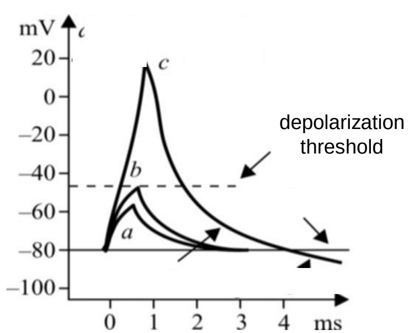
$R_i >> R_e$

Propagation of the depolarization

	ρ_m (Ω cm^2)	ρ_i (Ω cm^2)	τ (ms)	diameter (μm)	λ (cm)
Squid nerve	700	30	0,7	500	0,5
Crawfish nerve	2000	22	5	30	0,25
Frog muscle	4000	87	24	75	0,2

Both the time constant and the space constant depend on the diameter.
The value of the space constant shows that these are **local phenomena** they are not able to propagate too far.

Processes in nerves and muscles



a – depolarization below the threshold (local response)

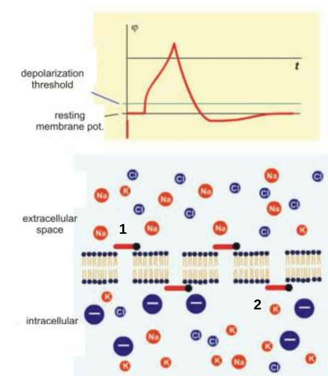
b – depolarization below the threshold (local response)

c – depolarization above the threshold - action potential

Action potential

1 – voltage sensitive Na^+-channels

2 - voltage sensitive K^+-channels

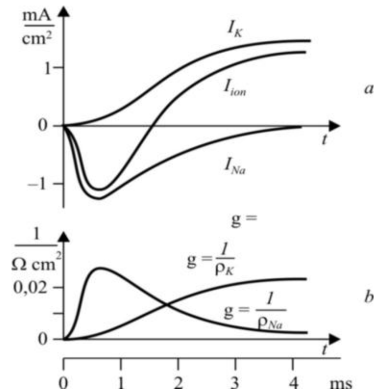


Ion flow during action potential

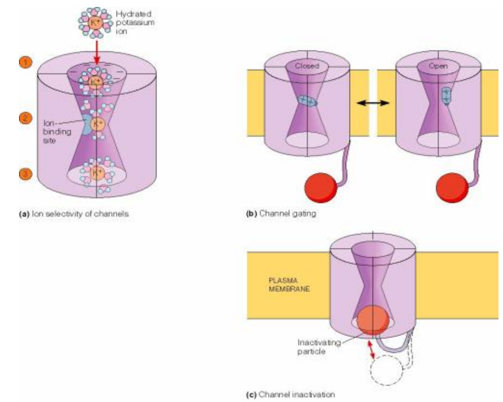
the inflow of the Na^+ is fast at the beginning according to the non-equilibrium state.

g = (1/ρ)

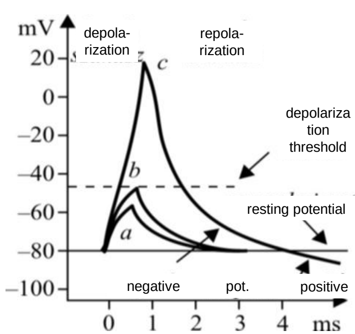
conductivity



K^+ channel



Properties of the action potential



The first step is fast!

(slow, long process is not suitable for fast response.)

Why is it fast?

ratio of ion concentration (extra/intracellular space)

ion	Na^+	K^+	ΔU (mV)
Squid	6.3	0.029	-62
Frog	6.0	0,018	-92
rat	12.5	0.025	-92

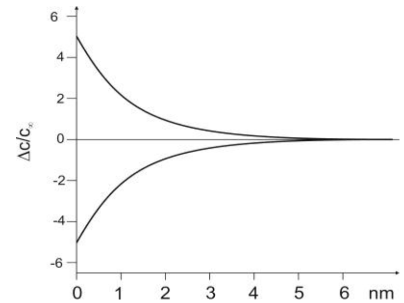
Simple calculation

- Let the radius of a cell 20 μm!
- The volume is: ~$3 \cdot 10^{-11}$ l.
- amount of the K^+ : **~$6 \cdot 10^{-12}$ mol.**
- surface of the cell: ~$5 \cdot 10^{-5}$ cm^2.
- capacity of the membrane: ~$5 \cdot 10^{-5}$ μF.
  (specific capacity: ~1 μF/cm^2)
- on the base of resting potential:
  ~$5 \cdot 10^{-12}$ C ⇒ **~$5 \cdot 10^{-17}$ mol** ion.

The changing affects only the small environment of the membrane and transports a small amount of ions.

Debye-length and diffusion

the ion concentration close to the membrane



Speed of the diffusion

$$d = \sqrt{3Dt}$$

example:

D ~ 10^{-9} m^2/s, t = 0,1 ms

d ~ 100-200 nm

(Compare d, the average distance, to the Debye length!)

The diffusion transports the ions far from the membrane.

Electrochemical potential (rat muscle)

$$\Delta\mu^e = -RT \ln\frac{c_2}{c_1} + zF\Delta\varphi$$

Na^+ $\Delta\mu^e_{Na} = -8.31 \times 310 \times \ln 12.5 + 96500 \cdot (-0.092)$ ~ -15.4 kJ/mol

K^+ $\Delta\mu^e_K = -8.31 \times 310 \times \ln 0.025 + 96500 \cdot (-0.092)$ ~ - 0.625 kJ/mol

In rest there is a large thermodynamic force for Na^+!

K^+ $\Delta\mu^e_K = -8.31 \cdot 310 \cdot \ln 0.025 + 96500 \cdot (+0.02)$ ~ - 11.4 kJ/mol

After reversing the polarity this force is high for K^+!

Comparison

membrane

Large force acts on Na-ions. Fast passive inflow.

No energy consumption.

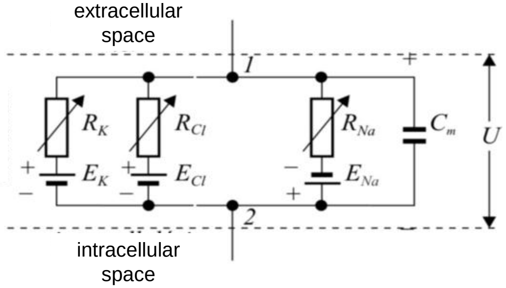
Changing of the membrane potential result the outflow of the K^+.

If were equilibrium.

(Donnan-equilibrium)

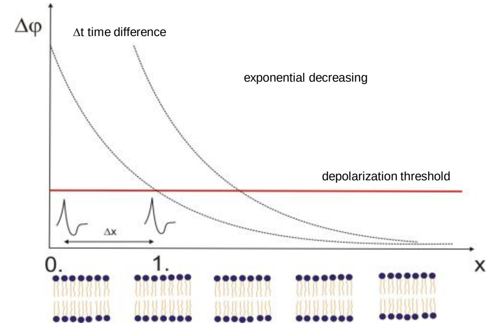
Changing of the membrane potential: requires energy and were slower!

Modified electric model



The transmembrane rseistance is represented by variable resistors, that makes possiblechanging the speed of the ion flow.

Propagation of the action potential (ap)



at Δx the local changing is enough large to produce a new ap.

speed ~ Δx/Δt

Advantage

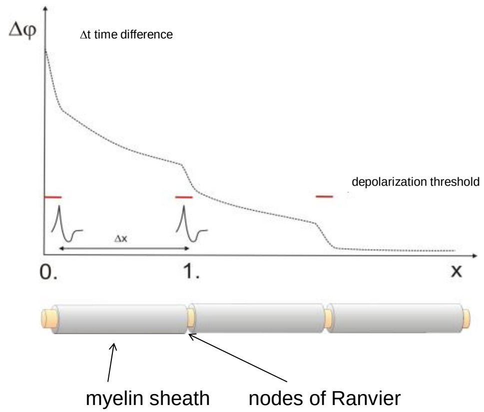
- Shape is independent from the stimulus: not sensitive to the external effects, noises.
- propagates far without any attenuation.
- Fast makes possible fast responses.

Speed of the propagation

space constant depends on: diameter, R_m, R_i

	ρ_m (Ω cm²)	τ (ms)	diameter (μm)	λ (cm)
Squid	700	0.7	500	0.5
Crawfish	2000	5	30	0.25
frog	4000	24	75	0.2

Saltatoric propagation



Δx larger!
Larger speed.

(due to the myelin R_m is large)

Role of the myelin sheath

R_m very large, space constant is large too

At the nodes of Ranvier:

$R_m \sim 50\ \Omega\ \mathrm{cm}^2$

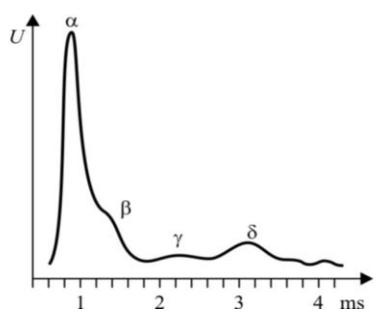
about 10^4 Na^+-channel/μm

Speed

large space constant: about 10-20 m/s

cat
n. saphaneus

the time that is necessary to cover 6 cm



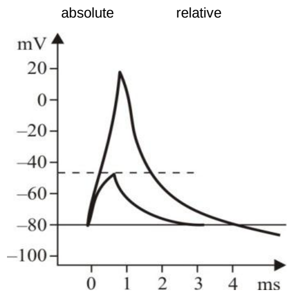
Speed of the propagation

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

$$\lambda \approx \sqrt{\frac{R_m}{R_i + R_e}} \approx \sqrt{\frac{R_m}{R_i}}$$

increasing diameter – increasing R_m and decreasing R_i.

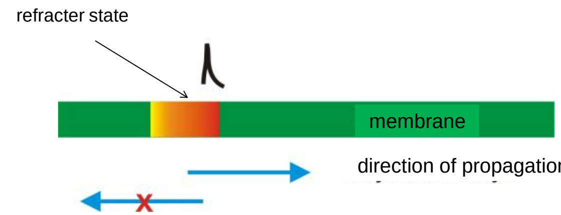
Refracter state



absolute: Na-channels are open, no new ap.

relative: only larger stimulus is able to produce new ap.

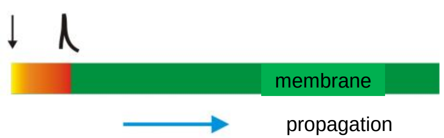
Role of the refracter state



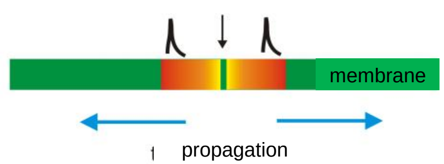
the refracter state prevents the back propagation of the ap.

When is it not true

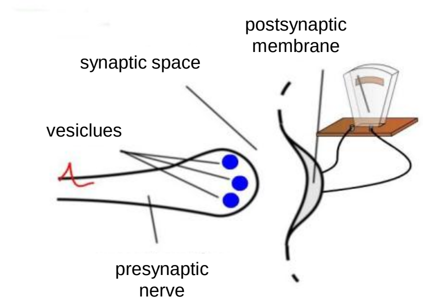
initiated at the end



initiated at the center



Rectification: synaps



neuro-transmitters emitted by the vesicules depolarize the postsynaptic membrane and result action potential after the synapse.
The structure makes impossible the back propagation.

Unidirectional step!

Not a whitdrawal?

remember: speed of the diffusion

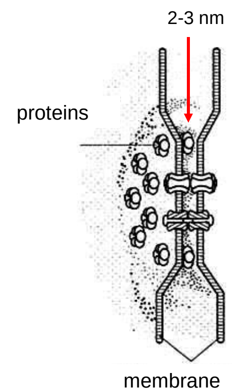
$$d = \sqrt{3Dt}$$

the size of the synaptic space is about a few 10 nm!

the diffusion is very fast if the distance is small!

the delay is not more than a few hundred μs!

Electric synaps



bidirectional, no rectification.

More characteristics for the invertebrates.

man: e.g. heart muscle.

Conclusion

Developed a fast system based on electric phenomena of the membrane.

The charges are ions, so this system is slower than equipment s used by us.

The stimulus (signal) is able to propagate far without any attenuation.