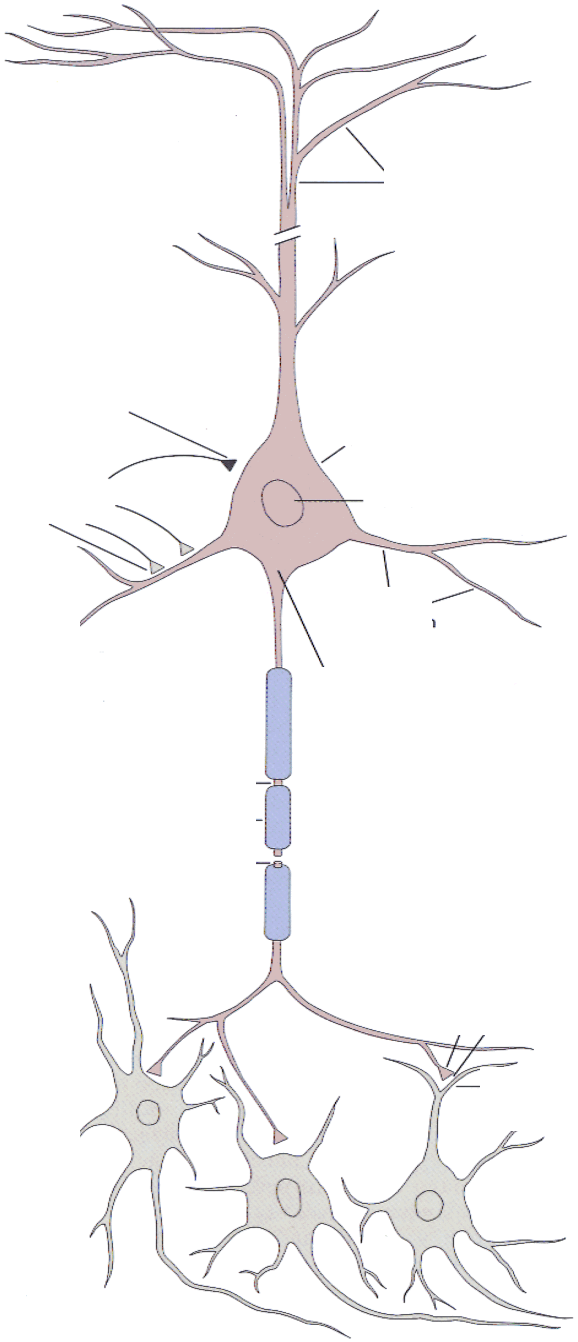
Neuroinformatics

Marcus Kaiser

Week 2: Neurons and conductance-based models
(textbook chapter 2)



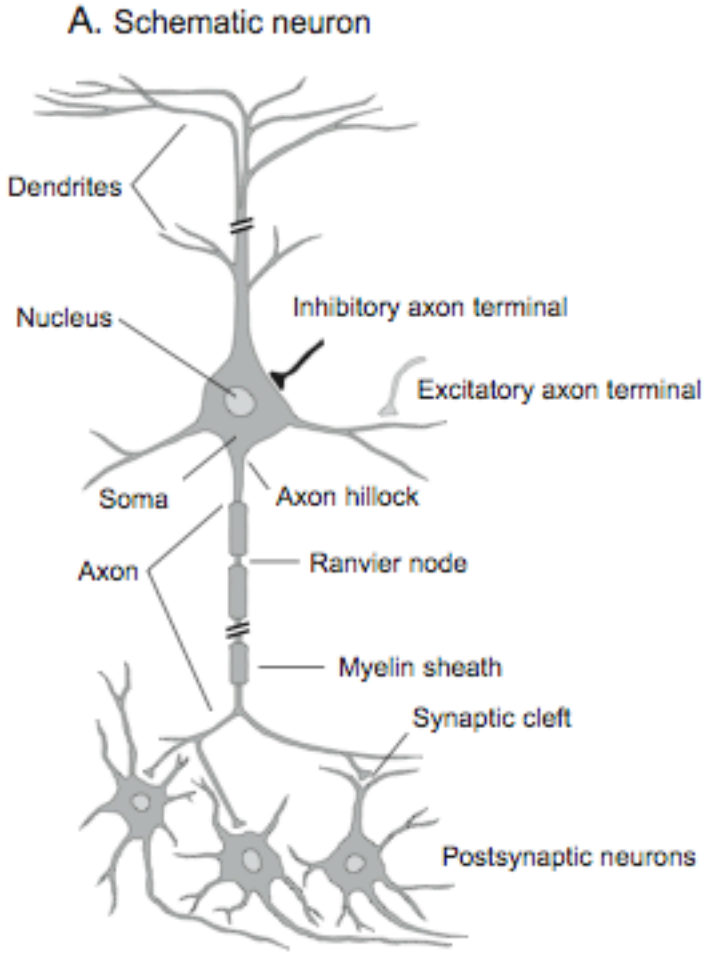
Single-Neuron simulation

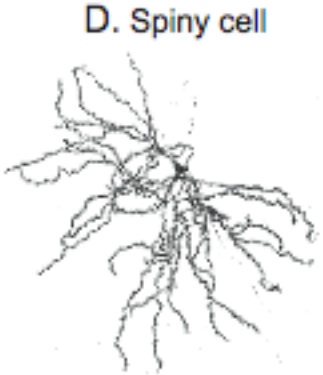
Passive propagation (dendrite and soma)

Active propagation (axon hillock and axon)
Hodgkin-Huxley

Neurotransmitter release -> Ion flow ->
change in Postsynaptic potential (PSP)

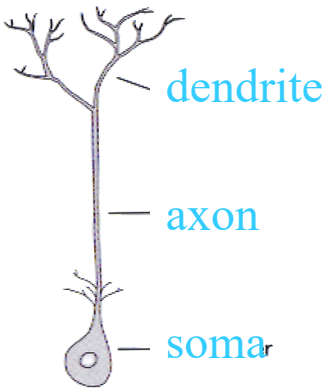
Biological background



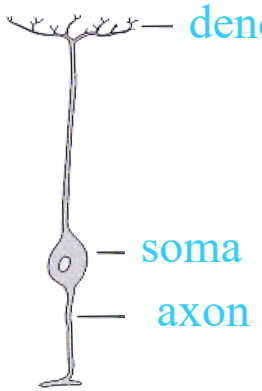


Different Types of Neurons:

Unipolar cell

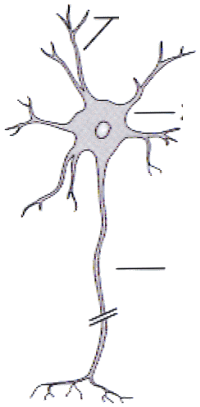


(Invertebrate N.)

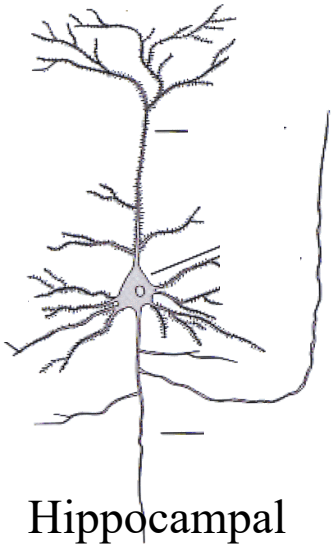


Retinal bipolar cell

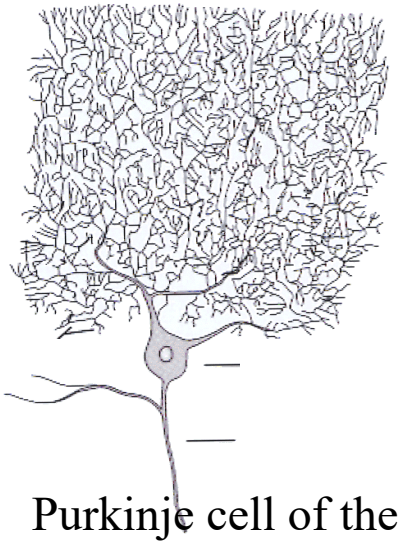
Bipolar cell



Spinal motoneuron



Hippocampal pyramidal cell

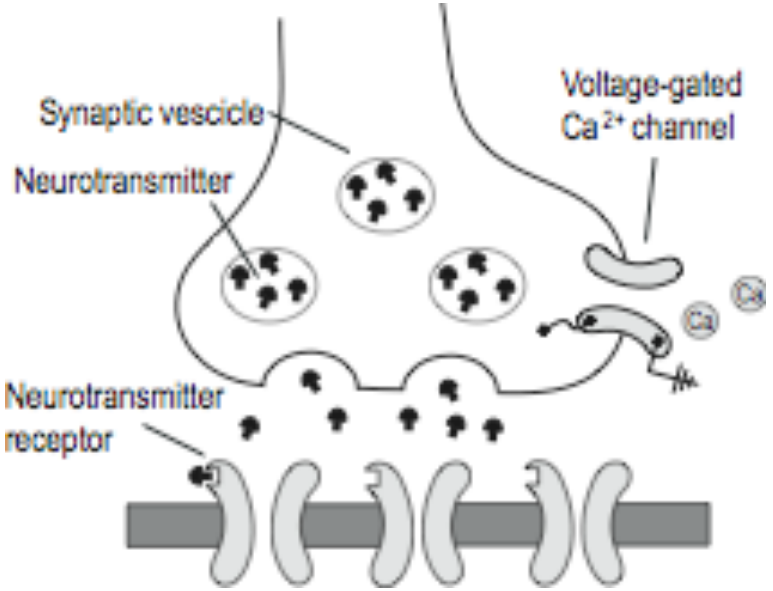


Purkinje cell of the cerebellum

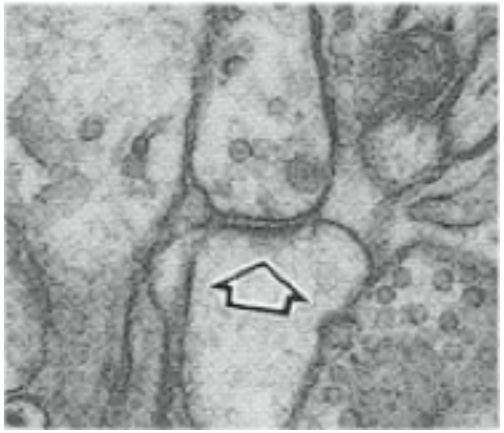
Different Types of Multi-polar Cells

(Chemical) Synapse

Motor Endplate
(Frog muscle)



Post-synaptic potential (PSP)

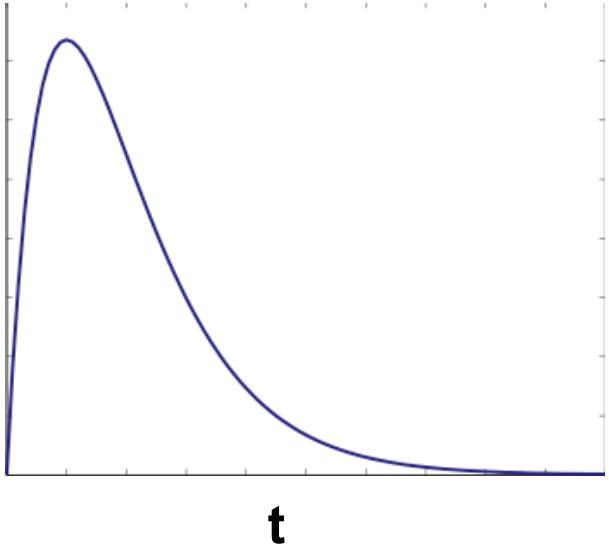


Neurotransmitters

Neurotransmitters can change the PSP either
exciting (depolarizing) or
inhibiting (subtractive = lowering the potential
divisive = modulating potential in combination with other signals;
e.g. synapse close to the cell body – shunting inhibition)

=> Effect (inhibition or excitation) depends on receptor and NOT on neurotransmitter!

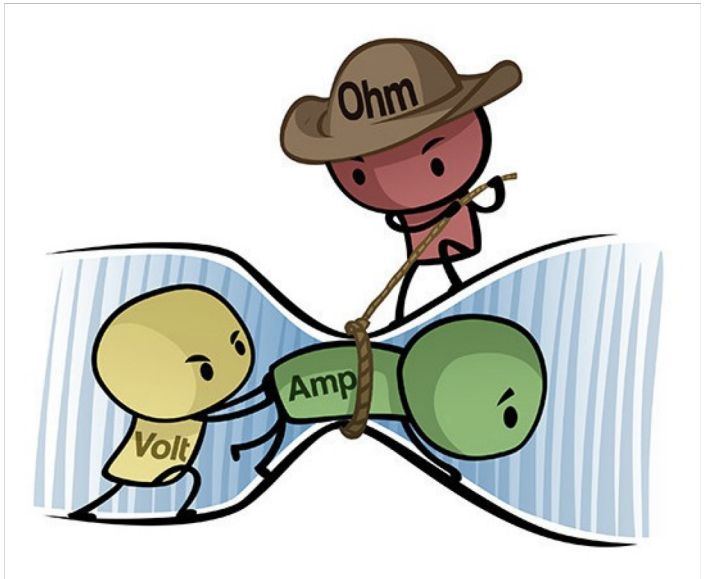
Non-NMDA: AMPA, GABA



Time course of response
(alpha-function)

$$\Delta V_{\mathrm{m}}^{\mathrm{non-NMDA}} \propto t\, \mathrm{e}^{-t/t^{\mathrm{peak}}}$$

Concept 1: Flow of charged particles



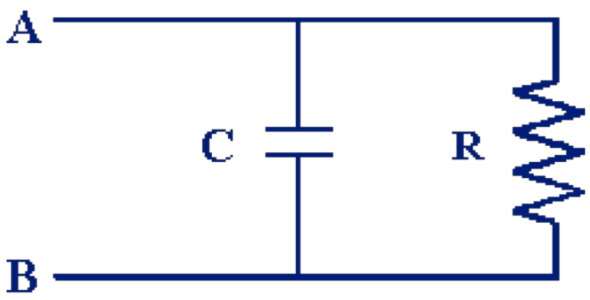
Potential difference (measured in Volt) drives movement of charged particles

Particle flow I is measured as current (in Ampere)

Resistors have the ability R (measured in Ohm) to slow down the flow of particles

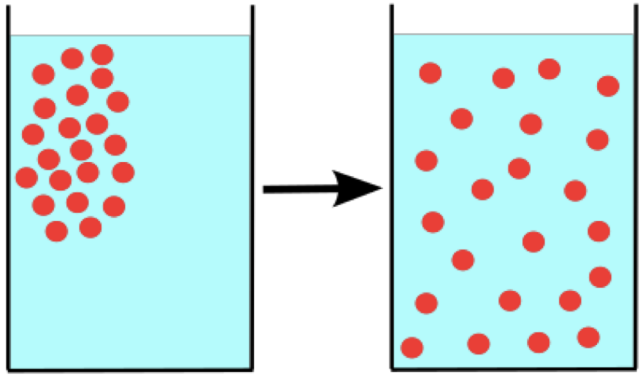
Conductance (measured in Siemens), the ability to move across a resistor, is the inverse of resistance R

A capacitor C can (almost) prevent the flow of particles



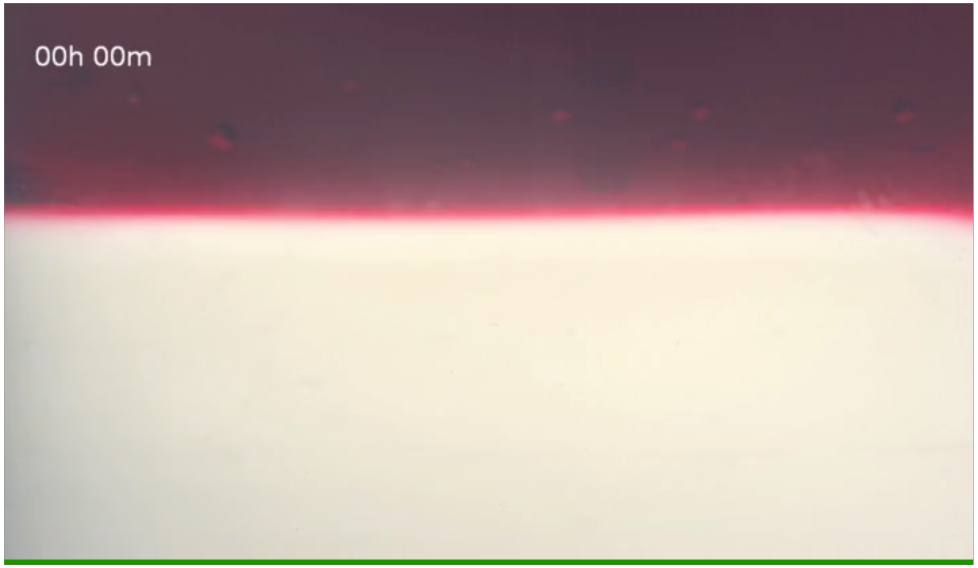
	Resistance	Current	Potential Difference	Conductance
Definition	Slows current down	The flow of electrons	Push of electrons or Energy per charges	How easily electrons flow
Symbol	R	I	V	G
Units	Ohms (Ω)	Amps (A)	Volts (V)	Siemens (S)
Formula (if applicable)	$R = \frac{V}{I}$	$I = \frac{V}{R}$ or $I = \frac{q}{t}$	$V = IR$ or $V = \frac{E}{q}$	$G = \frac{I}{V}$

Concept 2: Diffusion of particles (charged or non-charged)

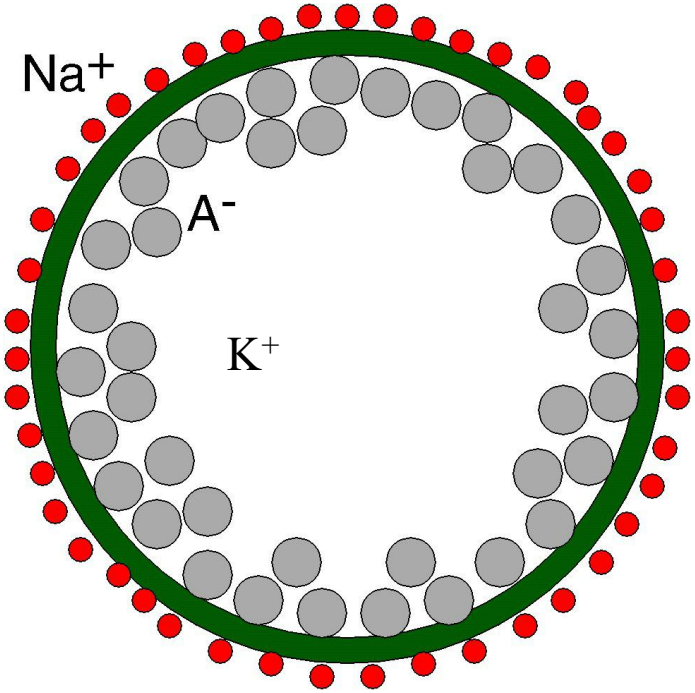


Difference in particle concentration

Speed of diffusion depends on temperature, viscosity, gradient



Cell membrane:



The cell membrane separates intra- from extra-cellular spaces

Extracellular there are many Na^+ and Cl^-, ions, intracellular there are many large (protein) negative ions (A^-) and plenty of K^+.

Due to differences in the ion-concenrations across the membrane a potential difference arises:

$$V_m$$

In addition, the membrane acts like a capacitor:

$$Q = CV_m$$

=> Current flow leads to voltage change:

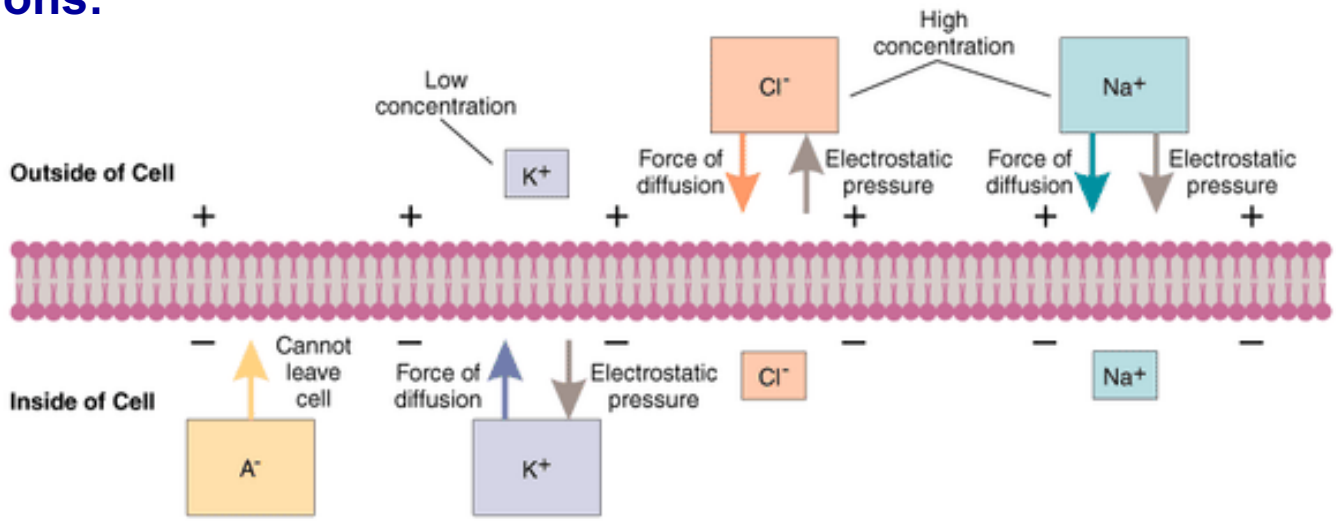
$$I_C = \frac{dQ}{dt} = C\frac{dV_m}{dt}$$

Membrane potential

What does causes the potential difference (more negative inside the cell)?

Depends on a few ions:

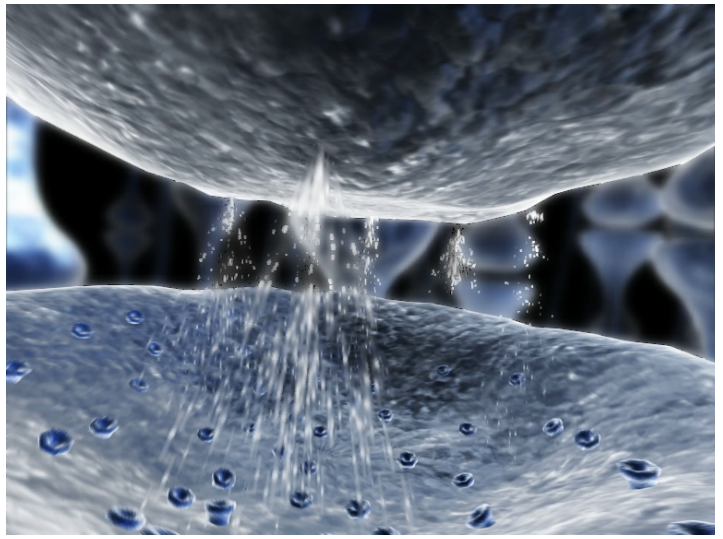
- **Potassium (K^+)**
- **Sodium (Na^+)**
- **Chloride (Cl^-)**
- **Calcium (Ca^{2+})**
- **Protein Anions (A^-)**

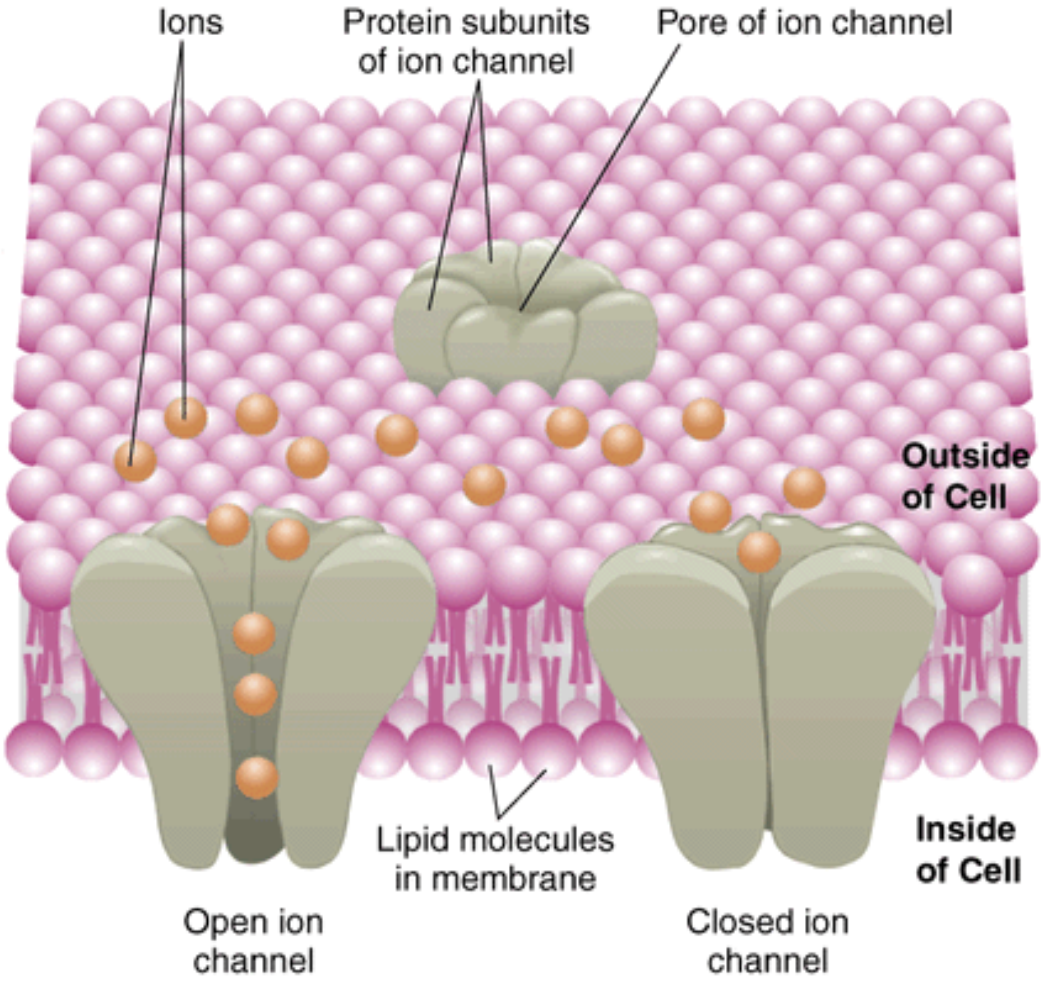


In the absence of active channels selective for ions, we find two forces:

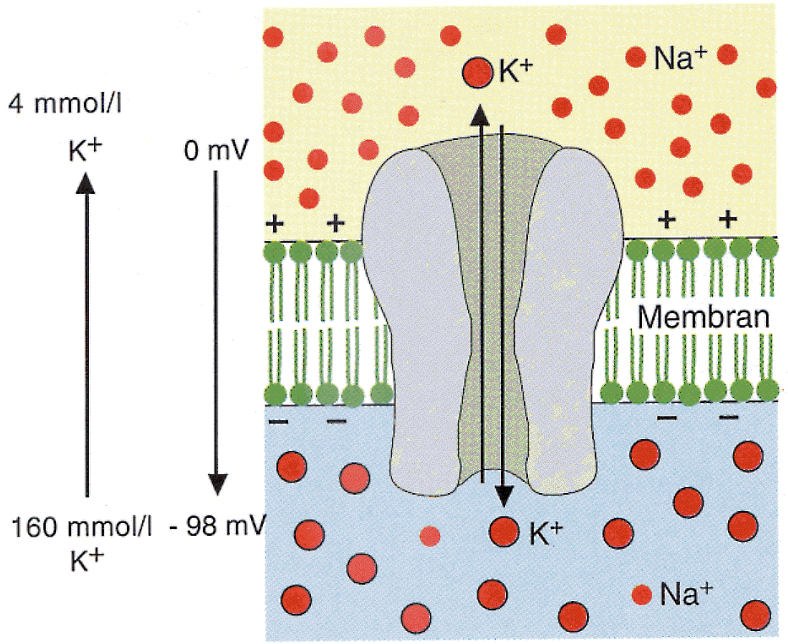
- **passive diffusion (from high to low concentrations)**
- **electric forces (charge balance)**

Selective ion channels





Ion channels:



By the way: What is the inside what is the outside of this cell ?

Ion channels consist of big (protein) molecules which are inserted into to the membrane and connect intra- and extracellular space.

Channels act as a restistance against the free flow of ions: Electrical resistor R:

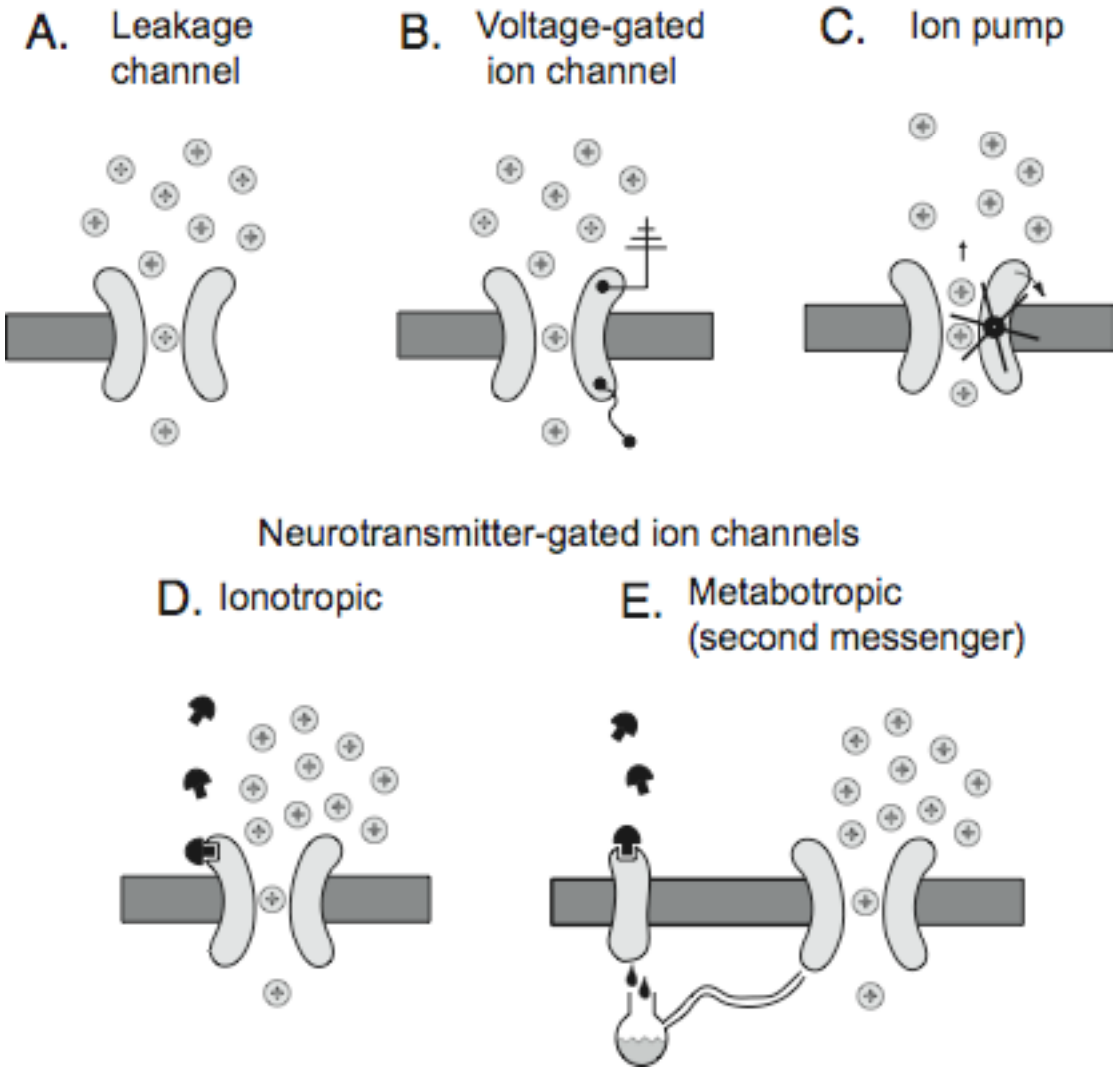
$$I_R = \frac{1}{R}(V_m - V_{rest}) = g(V_m - V_{rest})$$

If $V_m = V_{rest}$ (resting potential) there is no current flow. Electrical and chemical gradient are balanced (with opposite signs).

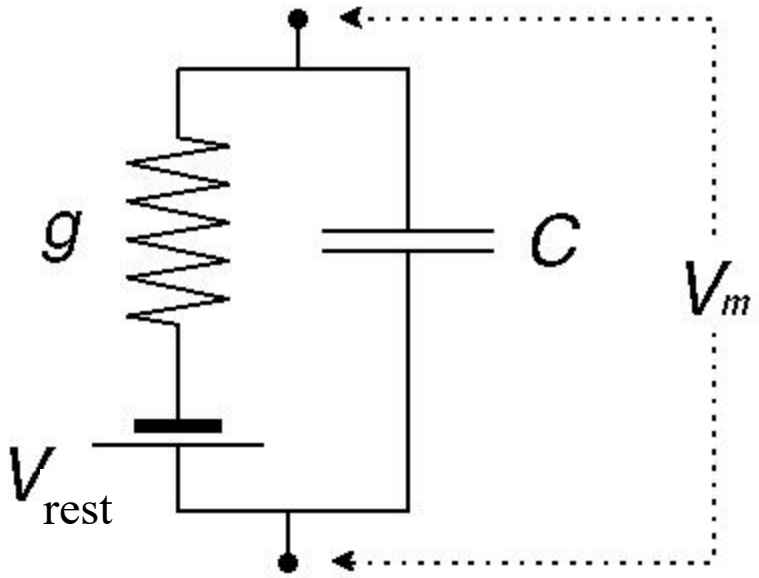
Channels are normally ion-selective and will open and close in dependence on the membrane potential (normal case) but also on (other) ions (e.g. NMDA channels).

Channels exists for: K^+, Na^+, Ca^{2+}, Cl^-

Ion channels



Membrane - Circuit diagram:



In order to decribe the electrical properties of a membrane you need the membrane capacitance C, the conductivity g=1/R and the resting potential V_{rest}.

Current across the membrane is given by:

$$I_{inj} = I_C + I_R = C\frac{dV_m}{dt} + g\,(V_m - V_{rest})$$

or:

$$C_m\frac{dV_m(t)}{dt} = -g(V_m - V_{rest}) + I_{inj}$$

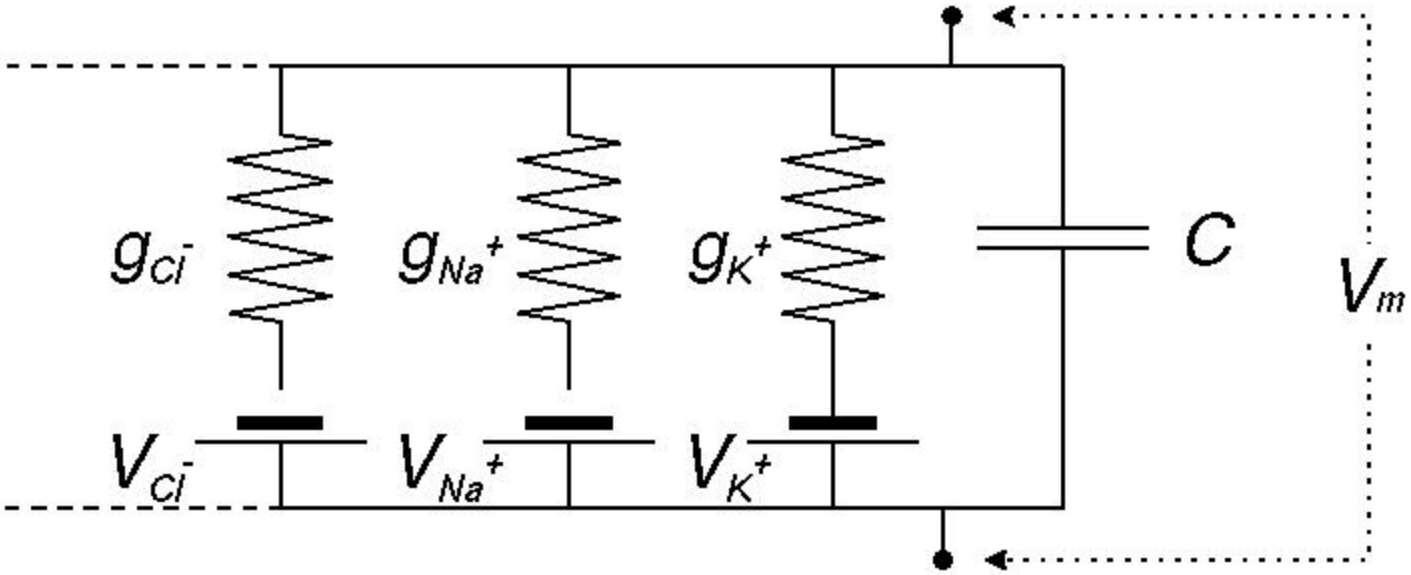
Using this equation you can calculate how the current changes depending on an experimentally injected current.

Membrane - Circuit Diagram (advanced version):

The whole thing gets more complicated due to the fact that there are many different ion channels all of which have their own characteristics depending on the momentarily existing state of the cell.

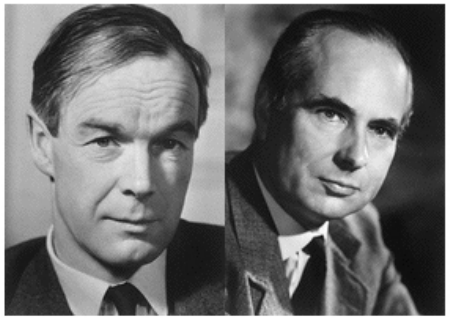
The conducitvity of a channel depends on the membrane potential and on the concentration difference between intra- and extracellular space (and sometimes also on other parameters).

One needs a computer simulation to describe this complex membrane behavior.



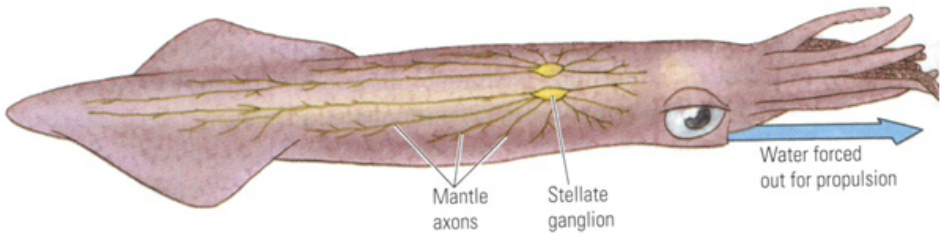
MATLAB program epsp.m

```
%% Synaptic conductance model to simulate an EPSP
 clear; clf; hold on;

%% Setting some constants and initial values
 c_m=1; g_L=1; tau_syn=1; E_syn=10; delta_t=0.01;
 g_syn(1)=0; I_syn(1)=0; v_m(1)=0; t(1)=0;

%% Numerical integration using Euler scheme
 for step=2:10/delta_t
   t(step)=t(step-1)+delta_t;
   if abs(t(step)-1)<0.001; g_syn(step-1)=1; end
   g_syn(step)= (1-delta_t/tau_syn) * g_syn(step-1);
   I_syn(step)= g_syn(step) * (v_m(step-1)-E_syn);
   v_m(step) = (1-delta_t/c_m*g_L) * v_m(step-1) ...
                    - delta_t/c_m * I_syn(step);
 end

%% Plotting results
 plot(t,v_m); plot(t,g_syn*5,'r--'); plot(t,I_syn/5,'k:')
```



Hodgkin and Huxley

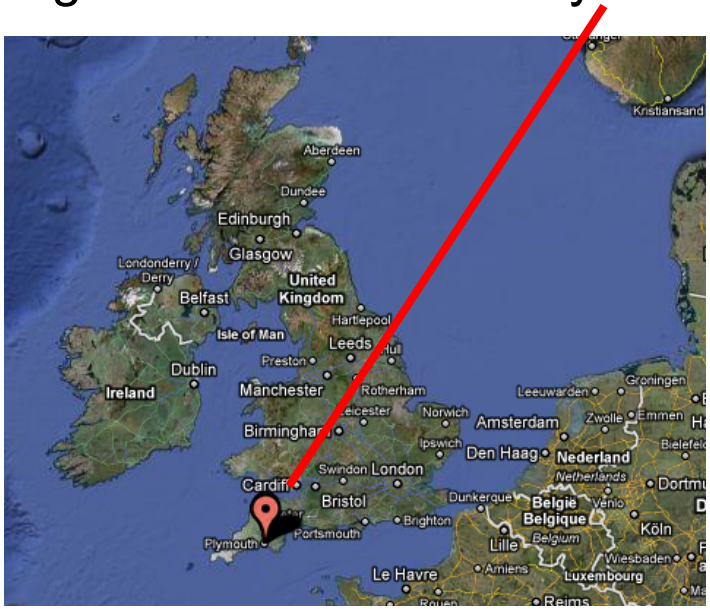
Nobel Prize, 1963



Squid length (10-14m incl. tentacles)

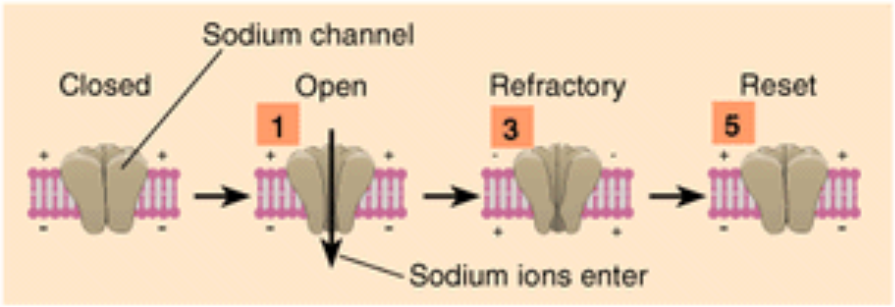
axon diameter: 0.5 mm

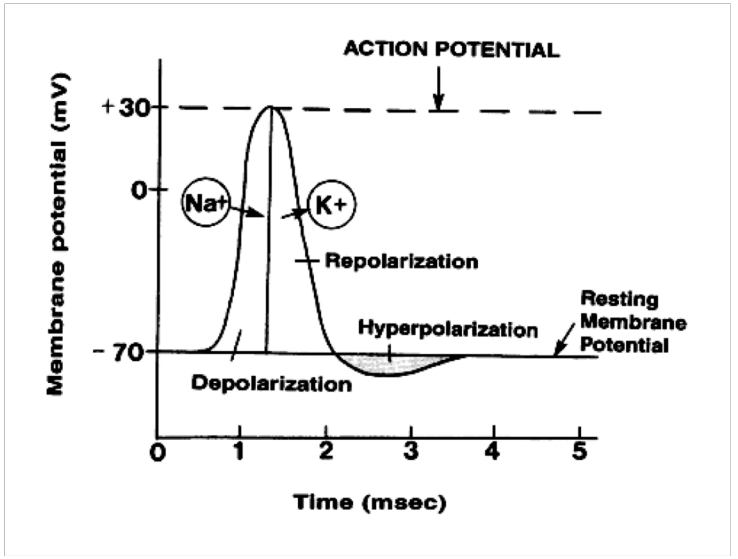
1939: Laboratory of the Marine Biological Association at Plymouth

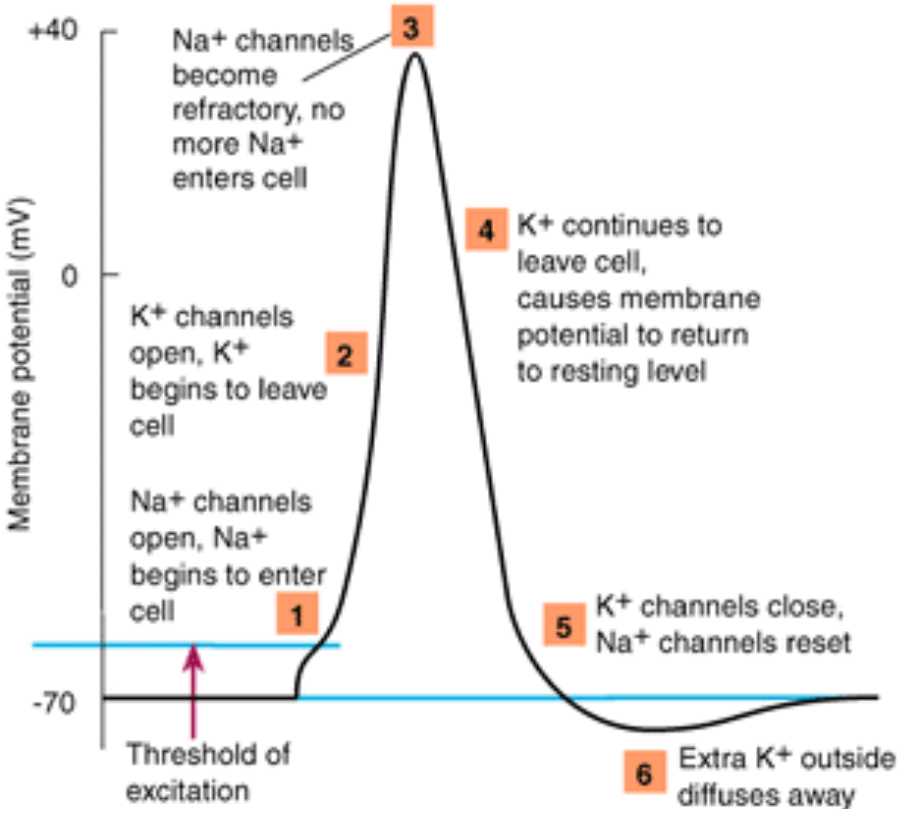


Age at the time of these experiments:
Huxley: 22
Hodgkin: 25

A. L. Hodgkin and A. F. Huxley. A quantitative description of membrane current and its application to conduction and excitation in nerve. J Physiol, 117(4):500-544, Aug 1952


Sodium channel
Closed
Open
Refractory
Reset
1
3
5
Sodium ions enter


ACTION POTENTIAL
+30
0
-70
Na+
K+
Repolarization
Hyperpolarization
Resting Membrane Potential
Depolarization
Membrane potential (mV)
0
1
2
3
4
5
Time (msec)

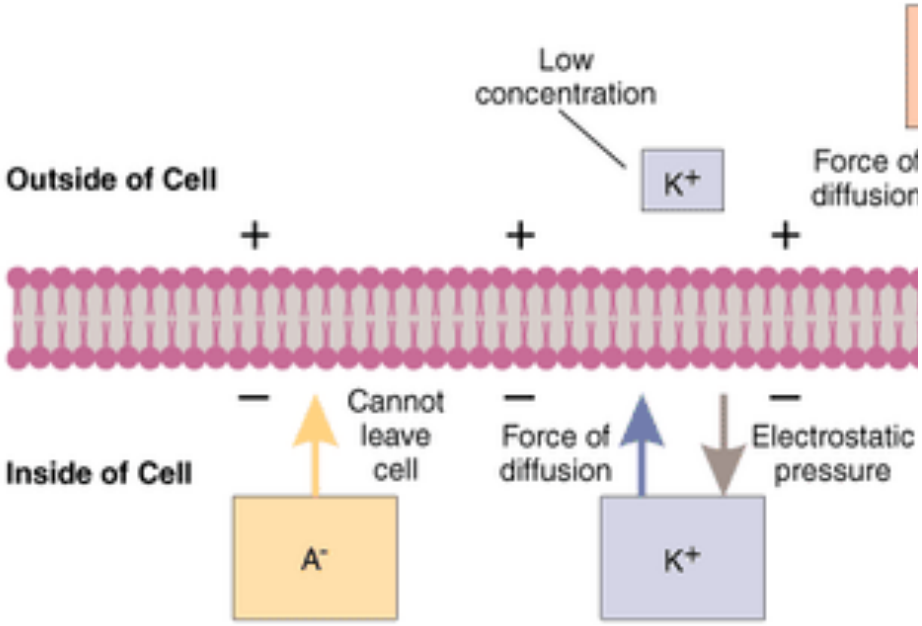

+40
0
-70
Membrane potential (mV)
Na+ channels become refractory, no more Na+ enters cell
3
4
K+ continues to leave cell, causes membrane potential to return to resting level
K+ channels open, K+ begins to leave cell
2
Na+ channels open, Na+ begins to enter cell
1
5
K+ channels close, Na+ channels reset
Threshold of excitation
6
Extra K+ outside diffuses away

Nernst equation (equilibrium potential; not considering active ionically selective channels):

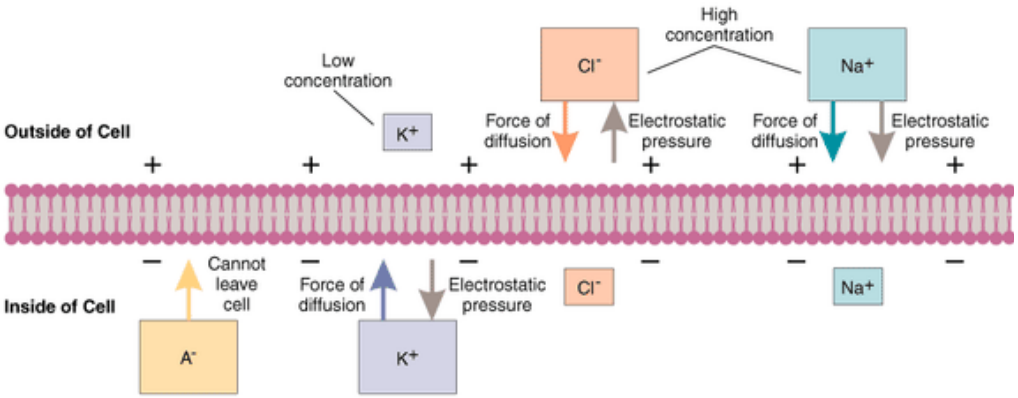
$$V_x = \frac{RT}{zF} \ln \frac{[X]_o}{[X]_i}$$

For T=25° C:

$$V_x = -\frac{60}{z} \log \frac{[X]_i}{[X]_o} [mV]$$



Goldman-Hodgkin-Katz equation (equilibrium potential):



$$V_m = \frac{RT}{F} \ln \frac{P_K[K^+]_o + P_{Na}[Na^+]_o + P_{Cl}[Cl^-]_i}{P_K[K^+]_i + P_{Na}[Na^+]_i + P_{Cl}[Cl^-]_o}$$

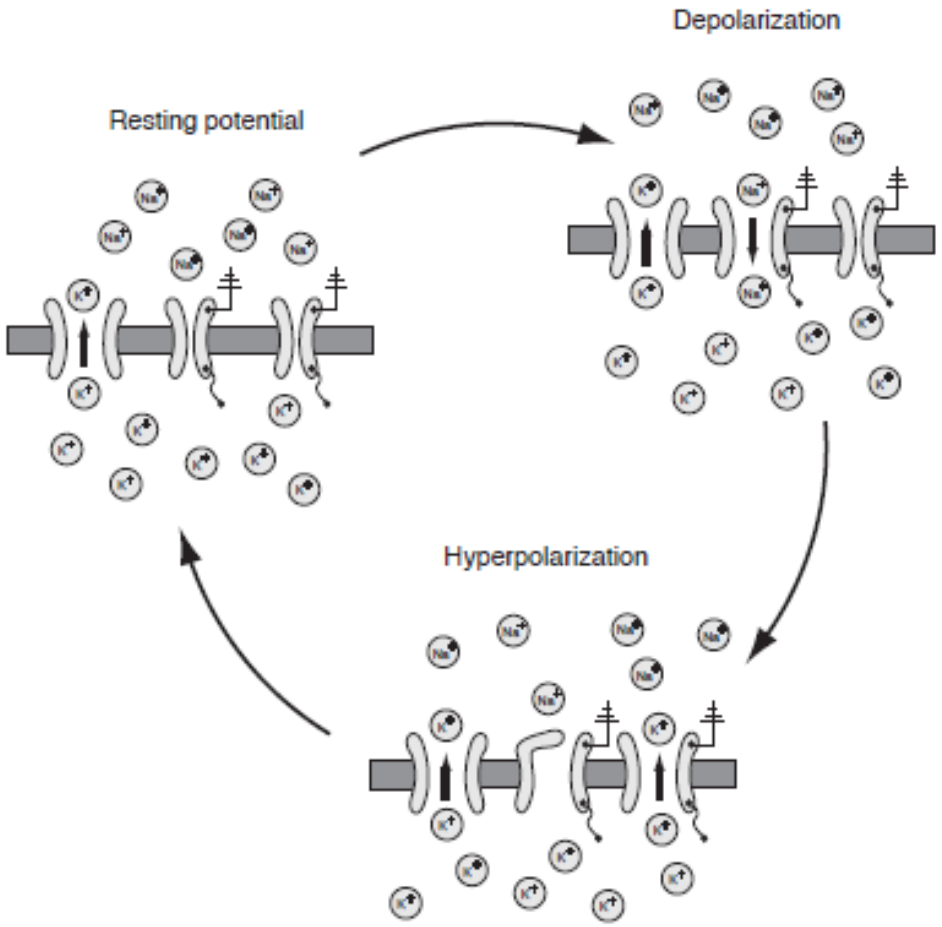
P: permeability for that Ion

Applies only when V_m is not changing!

For T=37° C:

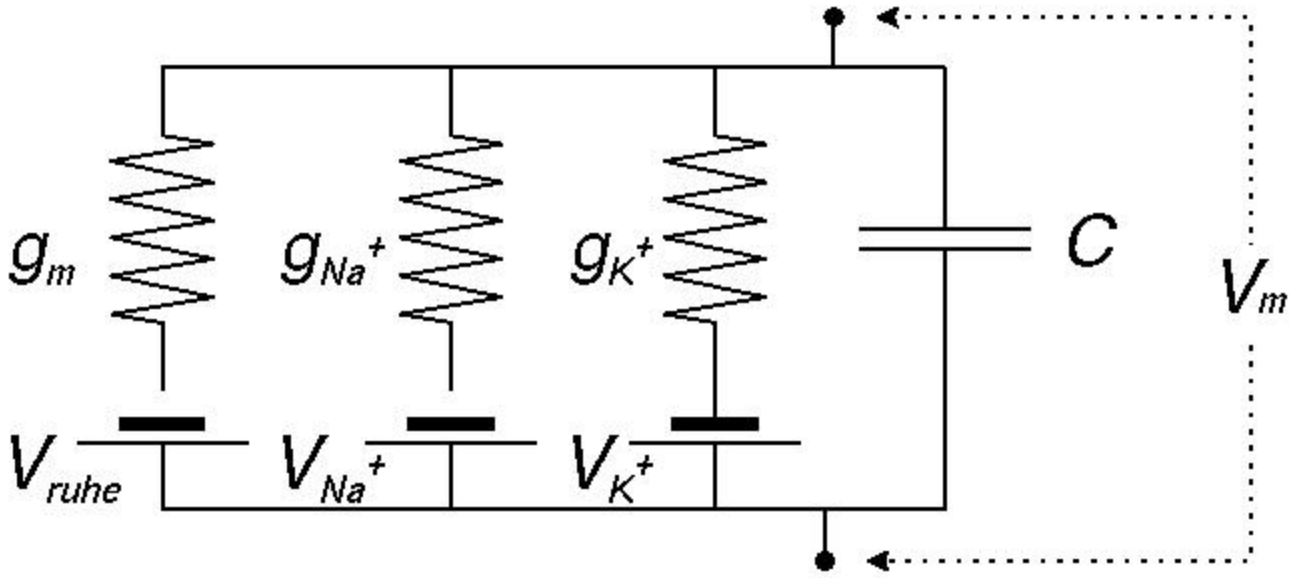
$$V_m = -61 \cdot \log \frac{P_K[K^+]_i + P_{Na}[Na^+]_i + P_{Cl}[Cl^-]_o}{P_K[K^+]_o + P_{Na}[Na^+]_o + P_{Cl}[Cl^-]_i}$$

The minimal mechanism



Hodgkin Huxley Model:

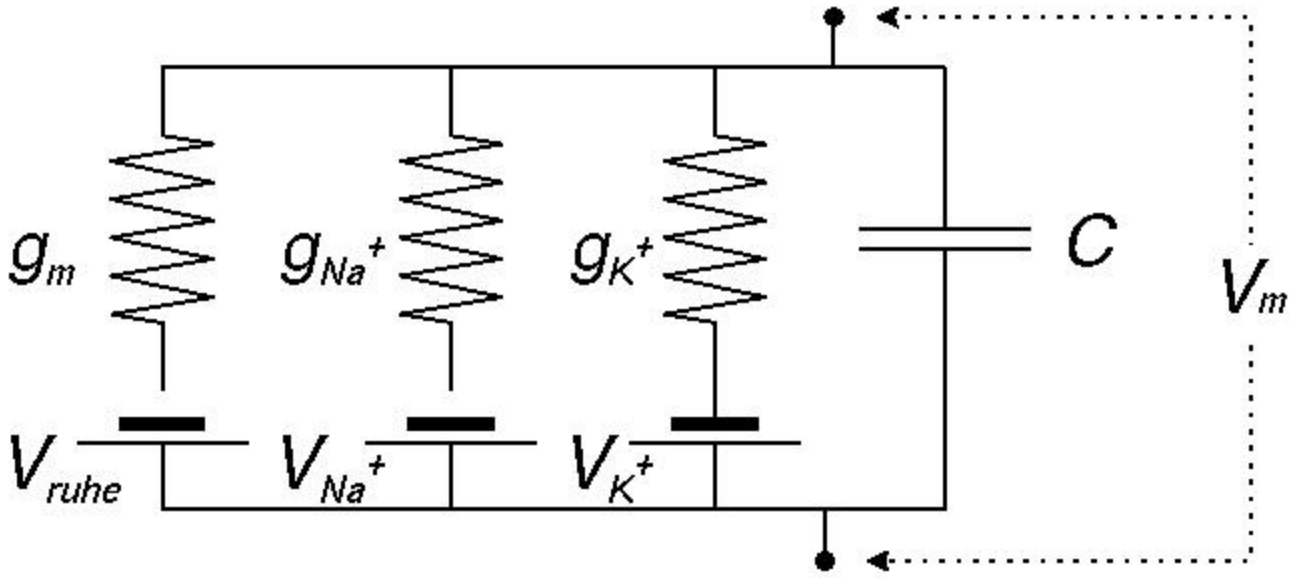
$$C_m \frac{dV_m(t)}{dt} = \text{Na-Current + K-Current + Leakage Current + injec. Current}$$



Hodgkin Huxley Model:

$$C_m \frac{dV_m(t)}{dt} = -\bar{g}_{Na} m^3 h (V_m - V_{Na})$$ **+ K-Current + Leakage Current + injec. Strom**

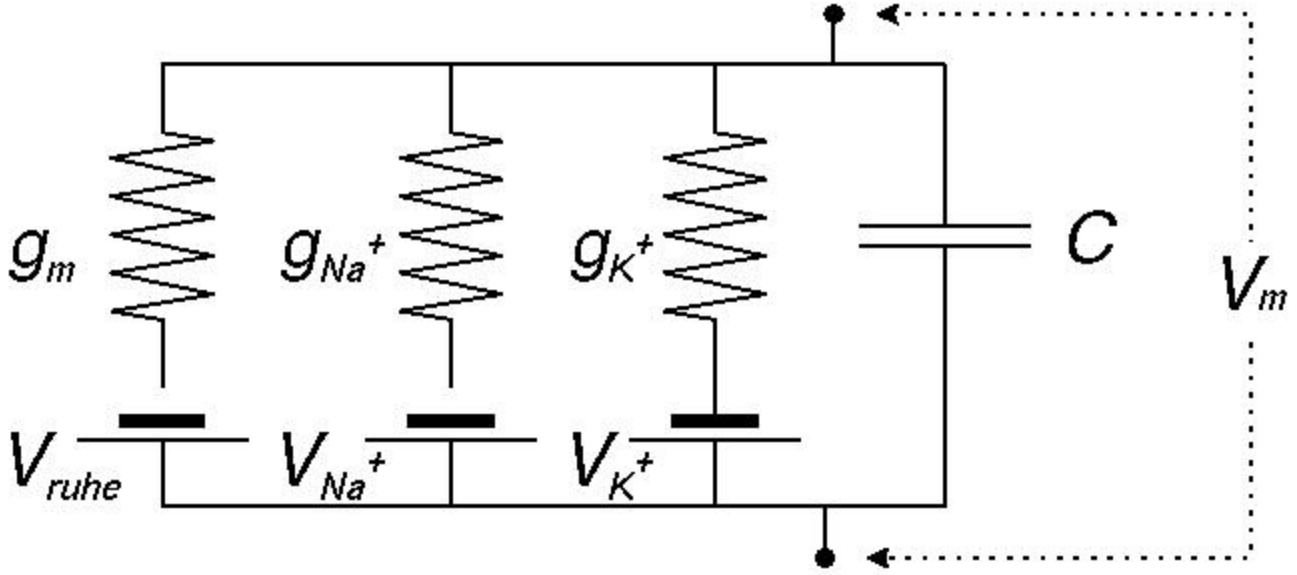
plus Equations for *m* and *h*



Hodgkin Huxley Model:

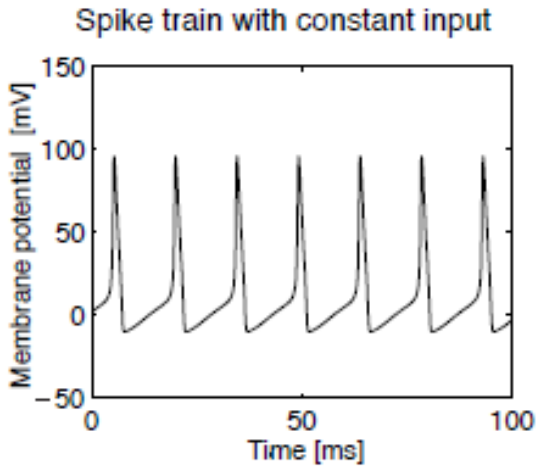
$$C_m \frac{dV_m(t)}{dt} = -\bar{g}_{Na} m^3 h (V_m - V_{Na}) - \bar{g}_K n^4 (V_m - V_K)$$ **+ Leakage Current + injec. Current**

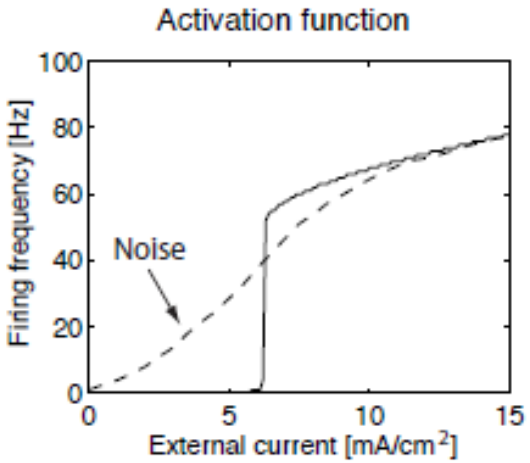
plus Equ. for *m*, *h* and *n*

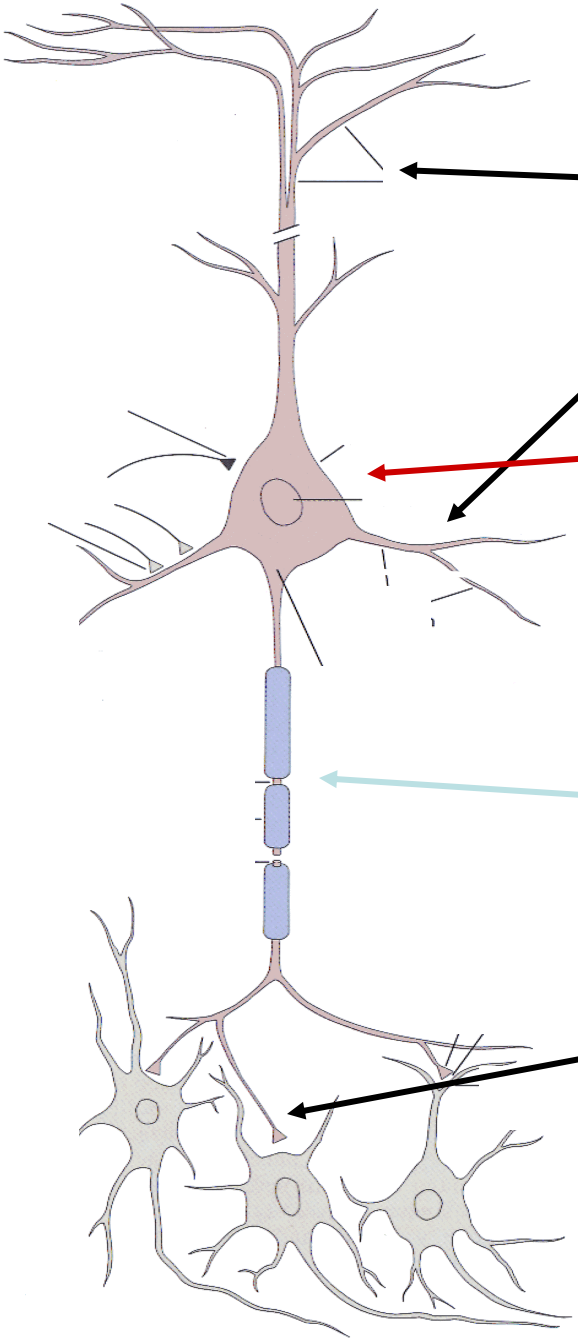


Hodgkin-Huxley equations and simulation

$$
\begin{aligned}
C\frac{dV}{dt} &= -g_K n^4 (V - E_K) - g_{Na} m^3 h (V - E_{Na}) - g_L (V - E_L) + I(t) \\
\tau_n(V)\frac{dn}{dt} &= -[n - n_0(V)] \\
\tau_m(V)\frac{dm}{dt} &= -[m - m_0(V)] \\
\tau_h(V)\frac{dh}{dt} &= -[h - h_0(V)]
\end{aligned}
$$







At the dendrite the incoming signals arrive (incoming currents)

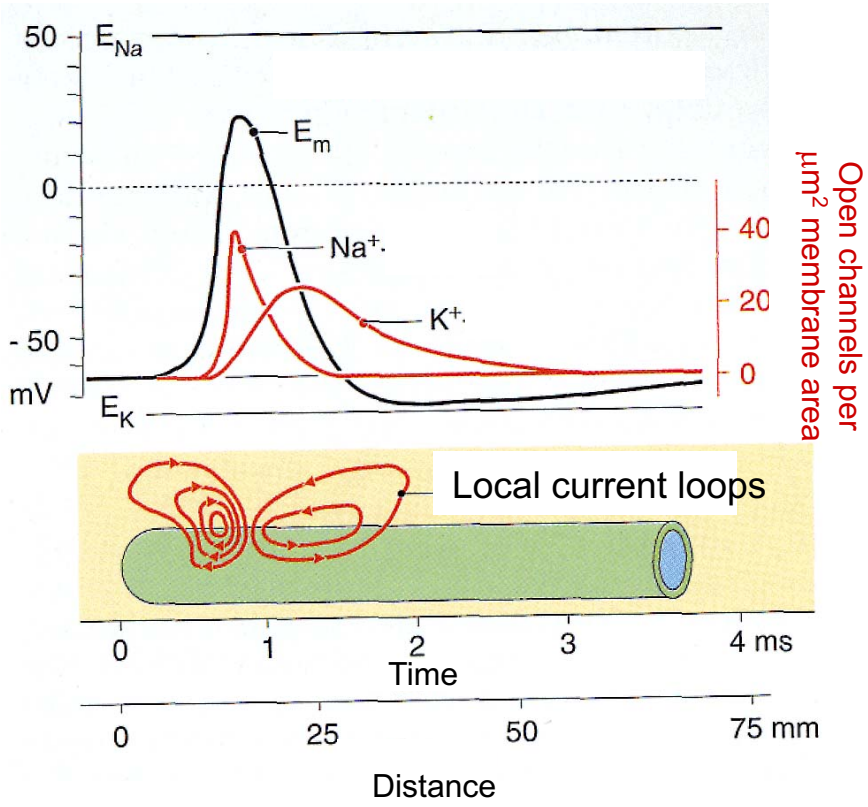
At the soma current are finally integrated.

At the axon hillock action potential are generated if the potential crosses the membrane threshold.

The axon transmits (transports) the action potential to distant sites

At the synapses are the outgoing signals transmitted onto the dendrites of the target neurons

Propagation of an Action Potential:



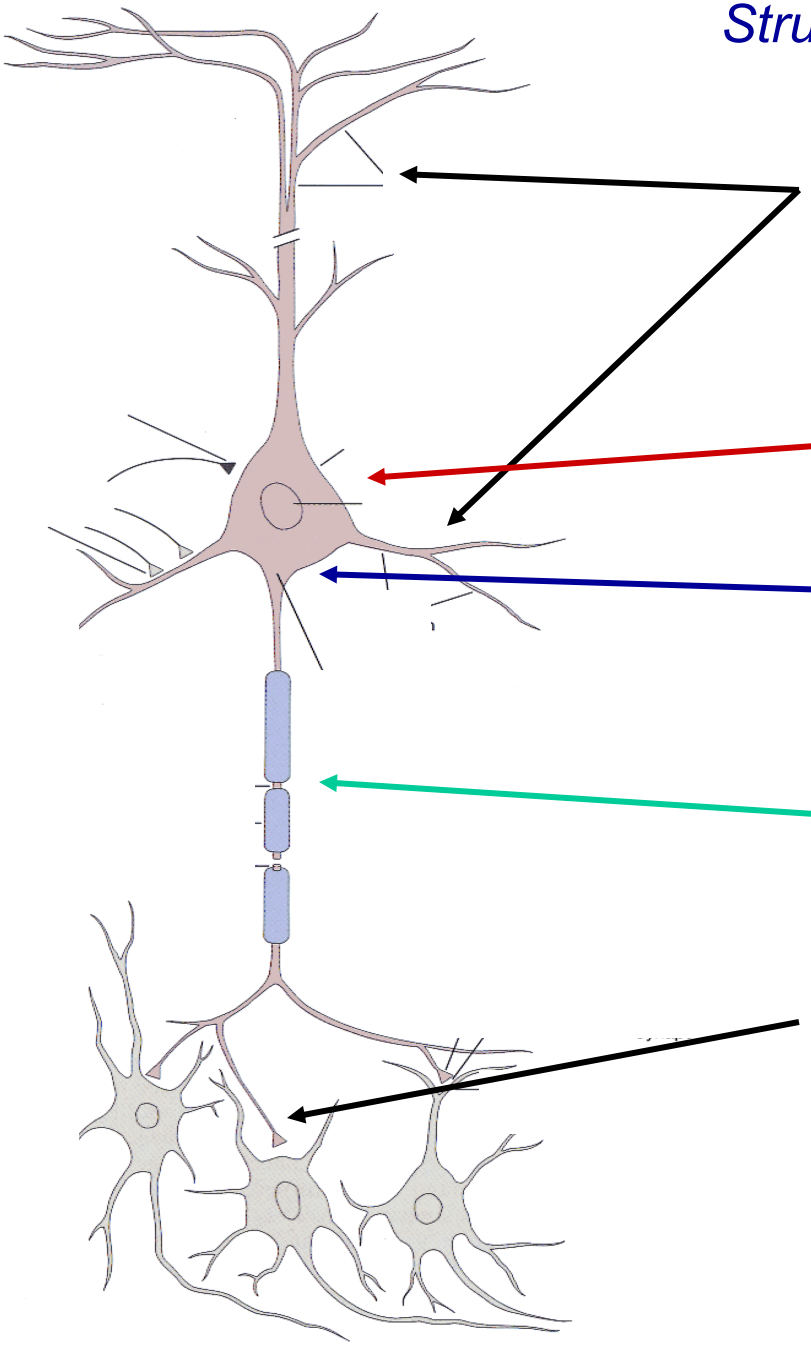
Action potentials propagate without being diminished (active process).

All sites along a nerve fiber will be depolarized until the potential passes threshold. As soon as this happens a new AP will be elicited at some distance to the old one.

Main current flow is across the fiber.

Why is the action potential not flowing backwards to the neuron?

Structure of a Neuron:



At the dendrite the incoming signals arrive (incoming currents). Signals propagate (normally) in a passive, electrotonic way towards the soma

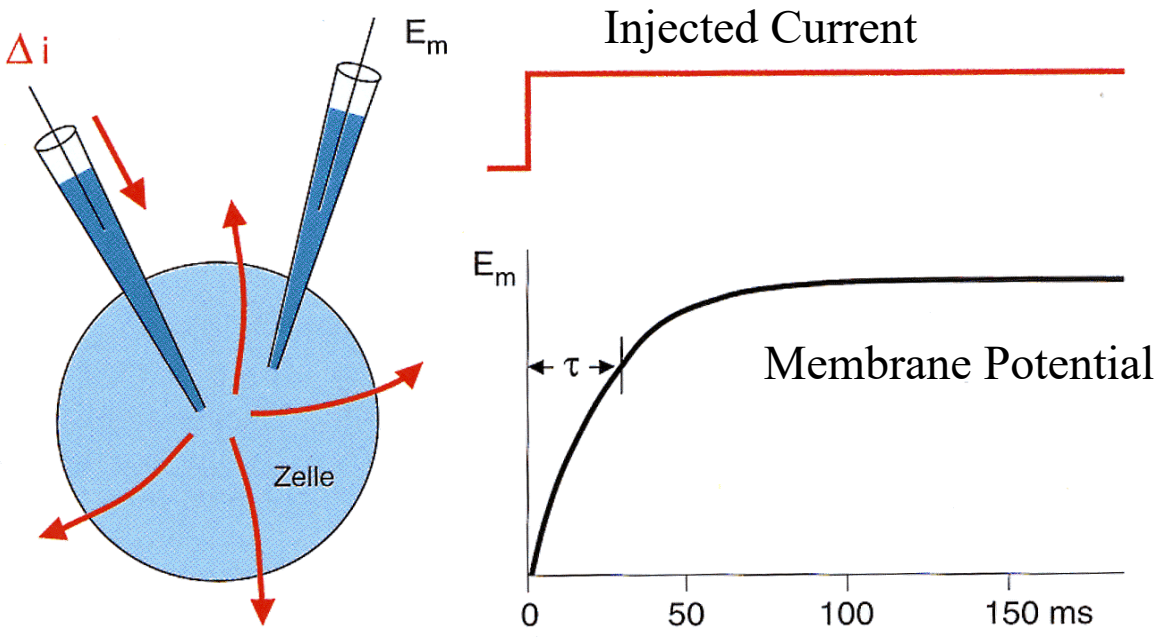
At the soma current are finally integrated.

At the axon hillock action potential are generated if the potential crosses the membrane threshold

The axon transmits (transports) the action potential to distant sites

At the synapses are the outgoing signals transmitted onto the dendrites of the target neurons

Electrotonic Signal Propagation:

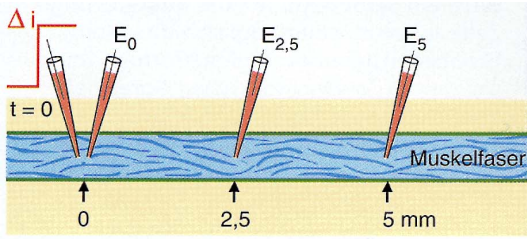


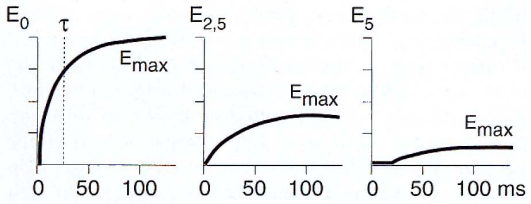
Injected current flows out from the cell evenly across the membrane.

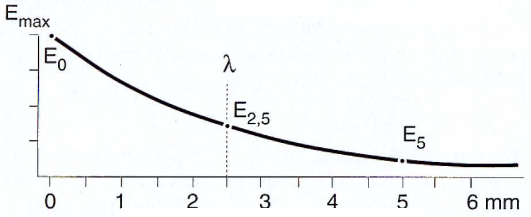
The cell membrane has everywhere the same potential.

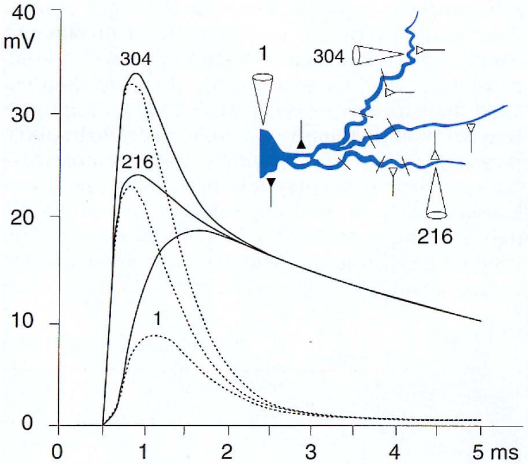
The change in membrane potention follows an exponential with time constant: $\tau = RC$

Electrotonic Signal Propagation:









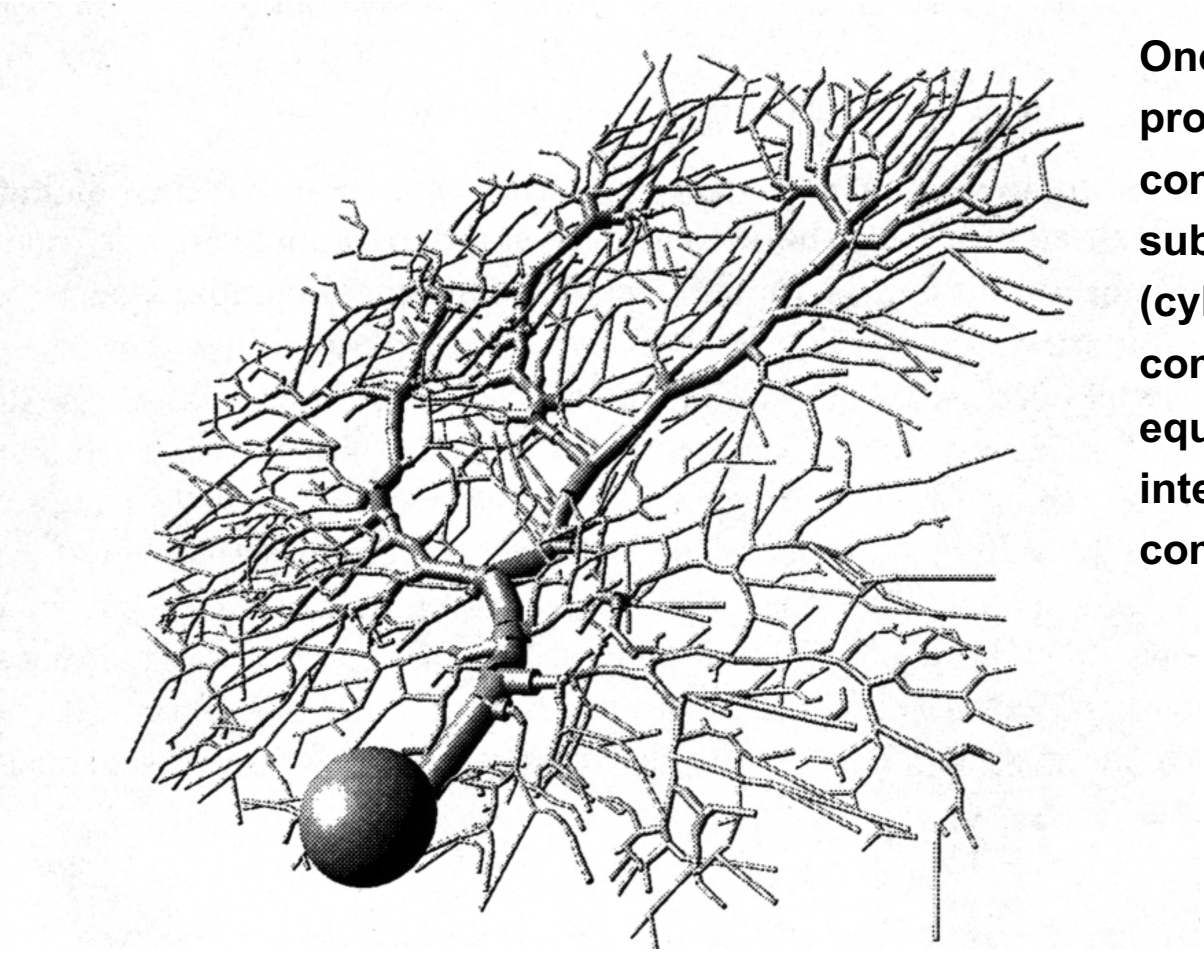
The potential decays along a dendrite (or axon) according to the distance from the current injection site.

At every location the temporal response follows an exponential but with ever decreasing amplitude.

If plotting only the maxima against the distance then you will get another exponential.

Different shape of the potentials in the dendrite and the soma of a motoneuron.

Compartment-Model:

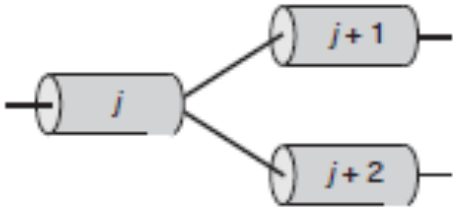


One can model the electrotonic propagation of potentials in the complex dendritic tree by subdividing the tree into small (cylindrical) compartments. For each compartment the membrane equations can then be solved and integrated. (All this is tedious and complicated.)

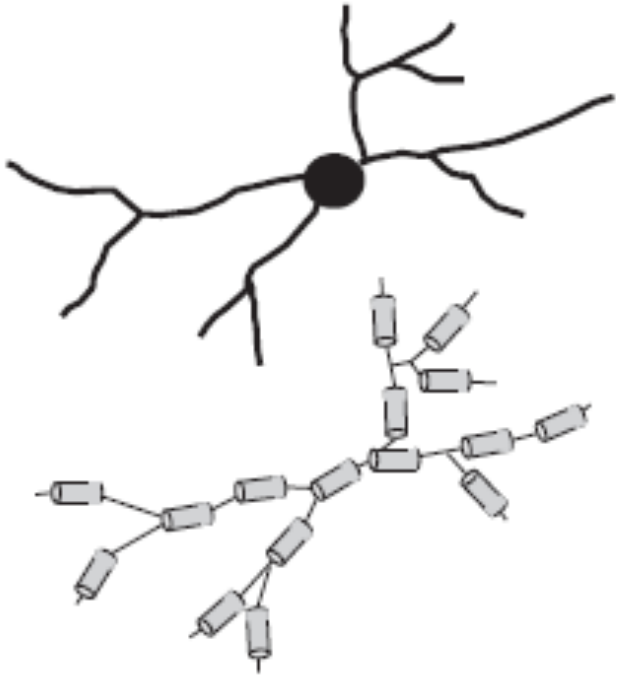
Compartmental models

A. Chain of compartments

B. Branching compartments



C. Compartmental reconstruction

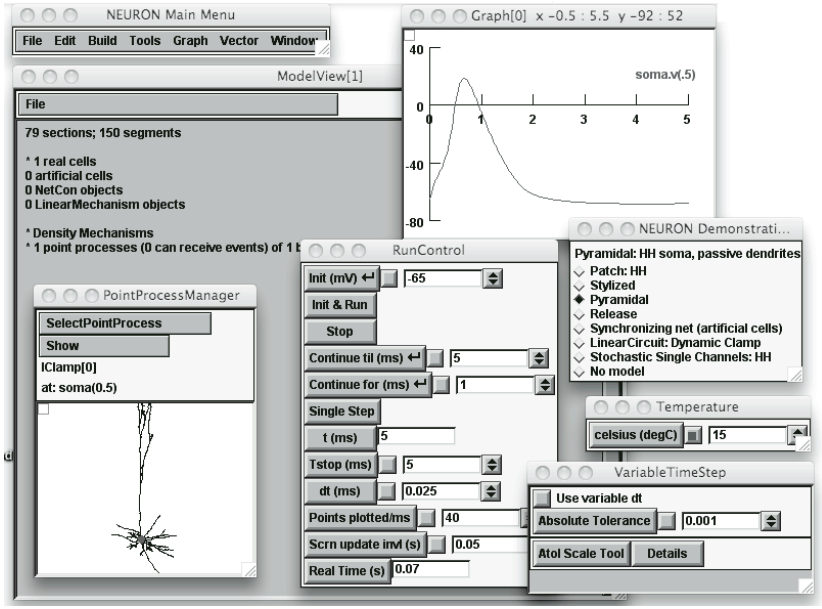


Simulators

- **Online:**
  http://jackterwilliger.com/biological-neural-networks-part-i-spiking-neurons/

- **Nernst / Goldman Simulator:**
  http://www.nernstgoldman.physiology.arizona.edu/

- **Neuron**
  http://www.neuron.yale.edu/neuron/
- **Genesis**
  http://genesis-sim.org/



Further readings

Mark F. Bear, Barry W. Connors, and Michael A. Paradiso (2006), **Neuroscience: exploring the brain**, Lippincott Williams & Wilkins , 3rd edition.

Eric R. Kandel, James H. Schwartz, and Thomas M. Jessell (2000), **Principles of neural science**, McGraw-Hill, 4th edition

Gordon M. Shepherd (1994), **Neurobiology**, Oxford University Press, 3rd edition.

Christof Koch (1999), **Biophysics of computation; information processing in single neurons**, Oxford University Press

Christof Koch and Idan Segev (eds.) (1998), **Methods in neural modelling**, MIT Press, 2nd edition.

C. T. Tuckwell (1988), **Introduction to theoretical neurobiology**, Cambridge University Press.

Hugh R. Wilson (1999) **Spikes, decisions and actions: dynamical foundations of neuroscience**, Oxford University Press. See also his paper in J. Theor. Biol. 200: 375–88, 1999.