Development of Complex Curricula for Molecular Bionics and Infobionics Programs within a consortial* framework**

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**Molekuláris bionika és Infobionika Szakok tananyagának komplex fejlesztése konzorciumi keretben

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MODELLING NEURONS AND NETWORKS

(Idegsejtek és neuronhálózatok modellezése)

Lecture 1
Basics of neural modeling

(A neurális modellezés alapjai)

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Overview

Since this is the first lecture of the course, we will start by reviewing the scope of Computational Neuroscience. Then you will learn about the basic electrophysiological properties of the neuronal membrane. We will begin with discussing the laws that describe the forces affecting the membrane potential. Then we construct a passive and isopotential cell model with the help of these equations.

Lesson topics:

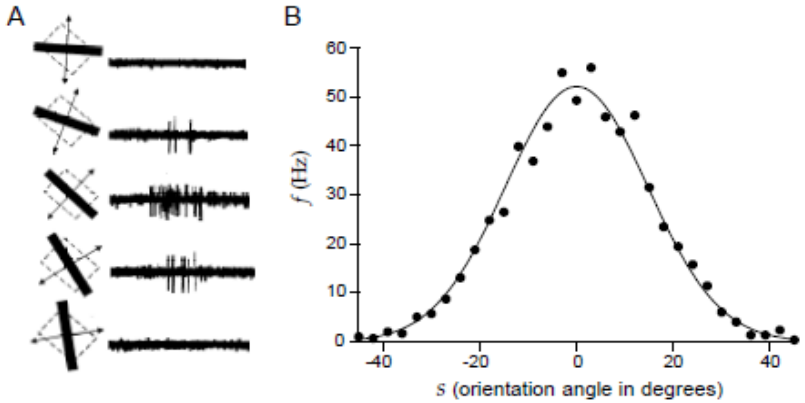
- Fundamental questions of neural modeling
- Elementary physical laws: Ohm's law, Fick's law, and the Einstein relation between diffusion and mobility.
- The Nernst equation, Donnan equilibrium, Goldman-Hodgkin-Katz equation
- Passive, isopotential cell model

Types of models:

- Descriptive – What is it like?
- Mechanistic – How does it function?
- Explanatory – Why is it like that?

How is information encoded by action potential trains?

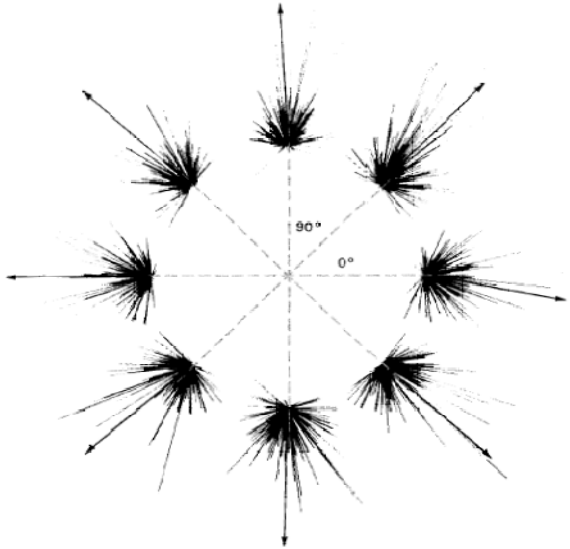
Neurons respond to input typically by producing complex spike sequences that reflect both the intrinsic dynamics of the neuron and the temporal characteristics of the stimulus.
Simple way: Count the action potentials fired during stimulus, repeat the stimulus and average the results:



Picture: Recordings from the visual cortex of a monkey. A bar of light was moved through the receptive field of the cell at different angles (figure A). The highest firing rate was observed for input oriented at 0 degrees (figure B).

How to decode information encoded by action potential trains?

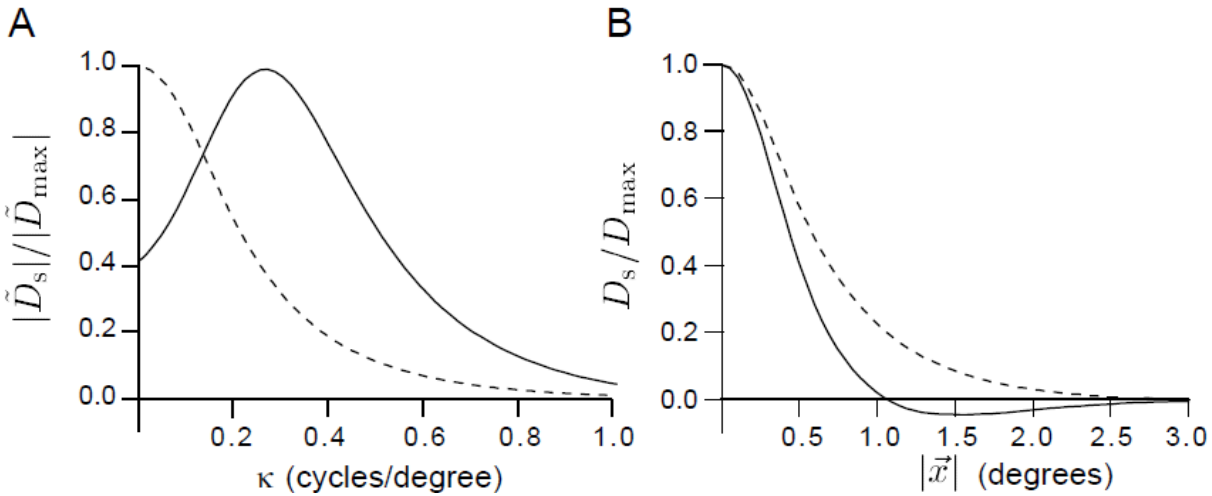
Example: Arm movement position decoding: If we take the average of the preferred directions of the neurons weighted by their firing rates, we get the arm movement direction vector.



Picture: Comparison of arm position and arm position-sensitive neurons. The population activity was recorded in 8 directions. Arrows indicate vector sums of preferred directions, which is approximately the arm movement direction.

Some fundamental questions

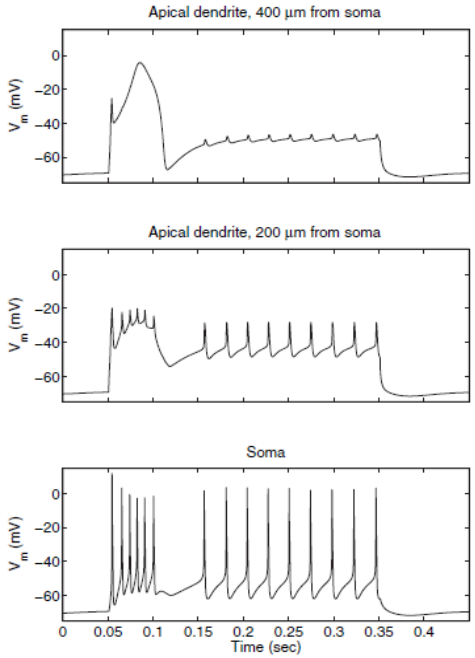
Why does a specific part of the brain use a specific type of coding? Example: Visual input noise filtering in a model of retinal ganglion cells: The structure of the receptive field changes according to the input signal-to noise ratio.



Solid curves are for low noise input (bright image), dashed lines are high noise input. Left: The amplitude of the predicted Fourier-transformed linear filters. Right: The linear kernel as a function of the distance from the center of the receptive field. Optimal kernels maximize the rate of information transmission.

How do neurons as information processing units function; specifically, what is the relation between the temporal and spatial pattern of the input and the spatial and temporal pattern of the output?

Example:

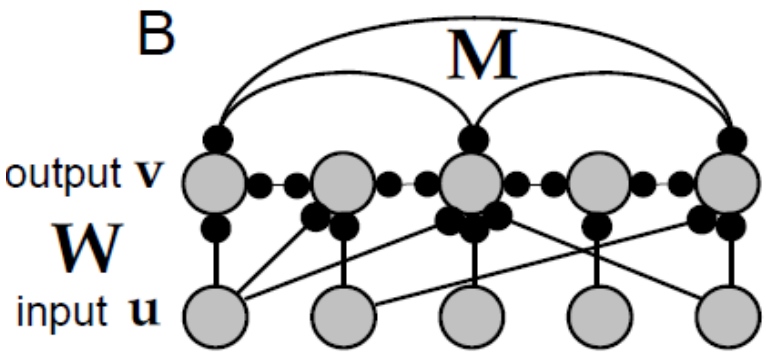


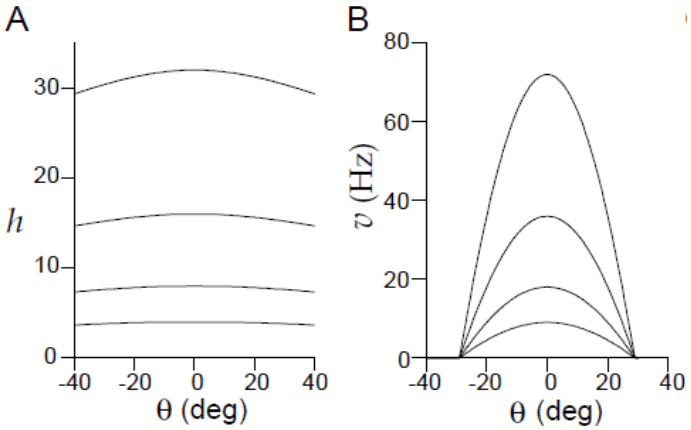
Picture: the effects of constant sustained dendritic current injection in a model of a hippocampal pyramidal cell. The cell responds with a burst of spikes, then sustained spiking. In distal regions only a slow, large-amplitude initial response is visible, corresponding to a dendritic calcium spike.

Some fundamental questions

How do neurons communicate, and what collective behaviors emerge in networks?

Example: Orientation selectivity and contrast invariance in the model of the primary visual cortex

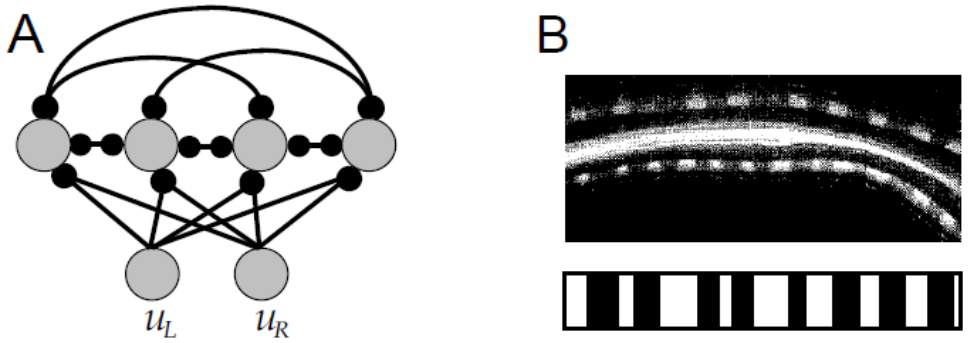




Left picture: schematics of a recurrent network with feedforward inputs.
Middle picture: The effect of contrast on orientation tuning. Figure A: orientation-tuned feedforward input curves for 80%,40%,20%,10% contrast ratios.
Right picture: The output firing rates for response to input in figure A.
The response of the network is much more strongly tuned to orientation as a result of selective amplification by the recurrent network, and tuning width is insensitive to contrast.

Some fundamental questions

How does cellular-level (synaptic) plasticity function? How can we understand behavioral-level learning? What is the connection between the two? Example: The development of ocular dominance patterns in the primary visual cortex



Left picture: schematics of the model network where right- and left-eye inputs from a single retinal location drive an array of cortical neurons.
Right picture: Ocular dominance maps, the light and dark areas along the cortical regions at the top and bottom indicate alternating right- and left-eye innervation. Top: In vitro measurements. Bottom: The pattern of innervation for the model after Hebbian development.

Basics

Neuronal membrane:

•Lipid bilayer (insulator)

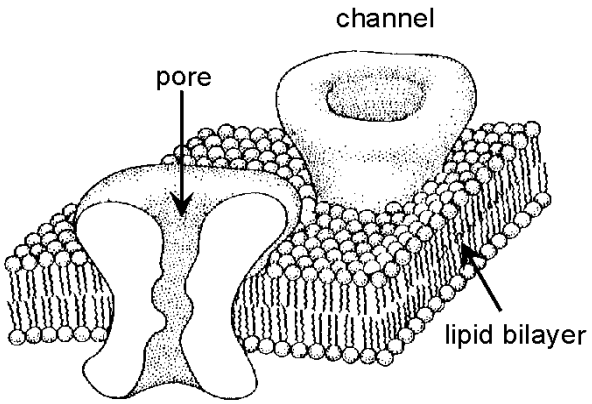
•Ion channels

- Selectivity
- Modulation:
  - Membrane potential
  - Intracellular messengers (for example Ca^{2+})
  - Neurotransmitters and -modulators

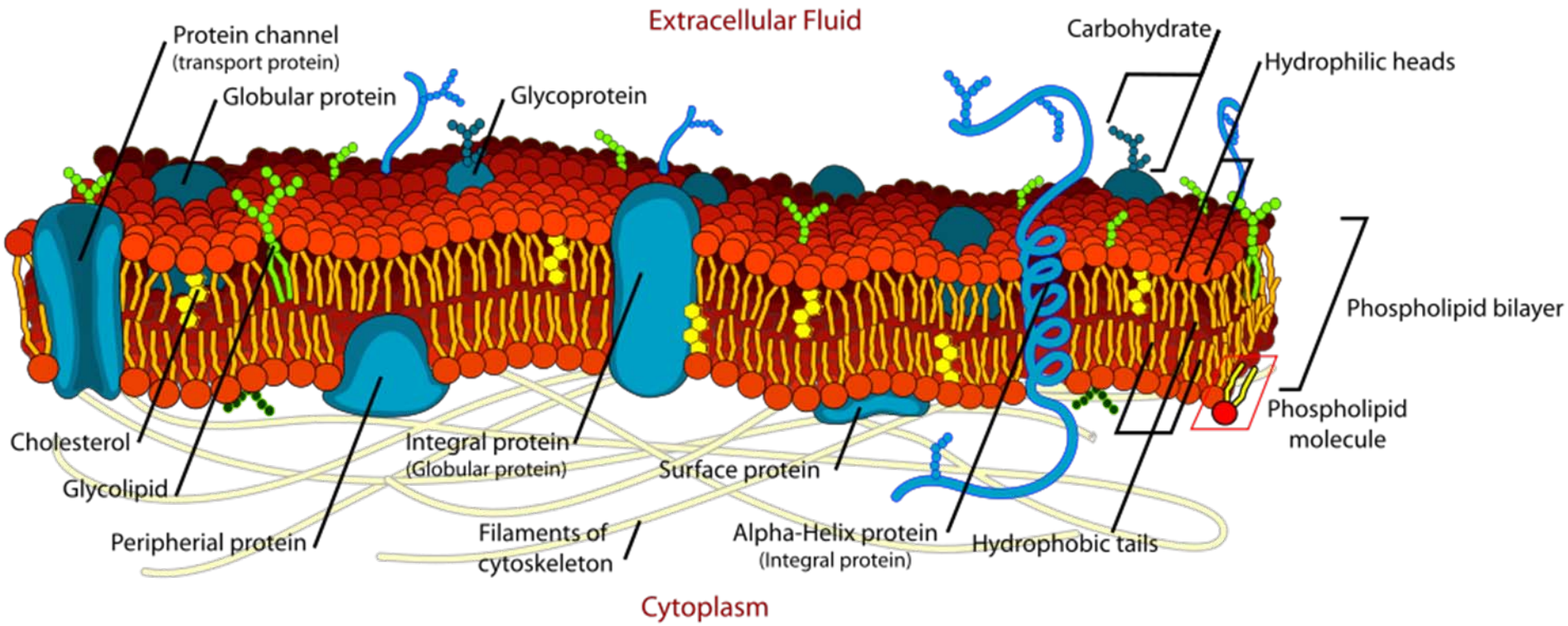
•Ion pumps

•Receptors not bound to ion channels

•Others



The neuronal membrane is an insulating lipid bilayer with embedded proteins



Elementary physical laws 1: Ohm's law for drift

$$J_{drift} = -\mu z\,[C]\,\frac{\partial V}{\partial x}$$

J_{drift} : Drift flux $(molecules/sec \cdot cm^2)$

μ : Mobility $(cm^2/V \cdot sec)$

Z : Valence of the ion

$[C]$: Concentration of ions $(molecules/cm^3)$

Charged particles (e.g., ions) in a fluid (e.g., cell plasma or extracellular fluid) experience a force resulting from the interaction of their electric charges and the electric field in the environment.
This equation states that drift of positively charged particles takes place down the electric potential gradient and is everywhere directly proportional to the magnitude of that gradient.

Elementary physical laws 2: Fick's law, diffusion of particles caused by concentration differences

$$J_{diff} = -D\frac{\partial [C]}{\partial x}$$

J	: Diffusion flux $(molecules/sec \cdot cm^2)$
D	: Diffusion coefficient (cm^2/sec)
[C]	: Concentration of ions $(molecules/cm^3)$

Fick's law states that diffusion takes place down the concentration gradient and is everywhere directly proportional to the magnitude of that gradient, with proportionality constant D.

Elementary physical laws 3: The Einstein relation between diffusion and mobility

$$D = \frac{kT}{q}\mu$$

μ	: Mobility $(cm^2/V \cdot sec)$
D	: Diffusion coefficient (cm^2/sec)
k	: Boltzmann constant
T	: Temperature (Kelvin)
q	: Charge of the molecule

This relationship states that diffusion and drift processes in the same medium are additive, because the resistances presented by the medium to the two processes are the same. This equation enables us to convert the diffusion coefficient to mobility.

Nernst-Planck equation

From Ohm's law, Fick's law, the Einstein relation and the space-charge neutrality principle the total current density is:

$$J = J_{drift} + J_{diff} = -\left(uz[C]\frac{\partial V}{\partial x} + u\frac{RT}{F}\frac{\partial [C]}{\partial x}\right)$$

Which is the **Nernst-Planck equation** (in molar form, J is in $mol/sec{\cdot}cm^2$, and $u=\mu/N_A$, where N_A is Avogadro's number ($6x10^{23}$/mol)).
The current density form of the equation can be obtained by multiplying the molar flux (J) by the molar charge (zF):

$$I = J \cdot zF = -\left(uz^2F[C]\frac{\partial V}{\partial x} + uzRT\frac{\partial [C]}{\partial x}\right)$$

where I is A/cm^2. The Nernst-Planck equation describes the ionic current flow driven by electrochemical potentials (concentration gradient and electric field). This equation describes the passive behavior of ions in biological systems.

Nernst-equation

If the total electric current across the membrane is zero (*I=0*),

$$\frac{\partial V}{\partial x} = -\frac{RT}{zF}\frac{1}{[C]}\frac{\partial [C]}{\partial x}$$

The membrane potential of a cell is defined as $V_m = V_{in} - V_{out}$

The reversal potential of ion *i*, defined as the membrane potential where the membrane current carried by ion *i* is zero, can be expressed as:

$$E_i = V_m(I_i = 0) = \frac{RT}{zF} ln \frac{[C]_{out}}{[C]_{in}}$$

This is called the **Nernst-equation**.

The Nernst-equation also implies that when the membrane is at the reversal potential of an ion species, the cross-membrane voltage (drift force) and concentration gradient (diffusion force) exert equal and opposite forces.

Donnan-equilibrium

Without active transport (ion pumps) in equilibrium $V_m = E_i$ for each ion. Therefore for every pair of ions *i,j*:

$$\left(\frac{[C]_{i,out}}{[C]_{i,in}}\right)^{1/m_i} = \left(\frac{[C]_{j,out}}{[C]_{j,in}}\right)^{1/m_j}$$

where m_i denotes the valence of ion *i.*

This equation is called the **Donnan-equilibrium**.

From the Donnan-equilibria and the neutral space charge we can calculate the equilibrium concentration for every ion and the resting membrane potential in various situations.

Goldman-Hodgkin-Katz equation

In a typical neuron $[K^+]_{in} > [K^+]_{out}$ but $[Na^+]_{in} < [Na^+]_{out}$ $[Ca^{2+}]_{in} < [Ca^{2+}]_{out}$ and $[Cl^-]_{in} < [Cl^-]_{out}$

The anions inside the cell, which cannot pass through the membrane, must be taken into account in the calculation, too.

Most of the ions are not in equilibrium:

E_{Na}: 50 mV E_K: -90 mV
E_{Ca}: 150 mV E_{Cl}: -70 mV

Thus, ionic currents start to flow as soon as ion channels open, and ion concentrations must be maintained by active transport (ion pumps).

Goldman-Hodgkin-Katz equation

The equilibrium membrane potential is determined by the ion permeabilities of the membrane (**Goldman-Hodgkin-Katz** equation):

$$V = \frac{RT}{F} \ln \frac{P_K[K^+]_{out} + P_{Na}[Na^+]_{out} + P_{Cl}[Cl^-]_{in} + \dots}{P_K[K^+]_{in} + P_{Na}[Na^+]_{in} + P_{Cl}[Cl^-]_{out} + \dots}$$

Where
P_{ion} is the permeability for that ion (in meters per second)
V is the membrane potential
[ion] is the concentration of that ion (in moles per cubic meter)

The Goldman-Hodgkin-Katz equation is used in cell membrane physiology to determine the equilibrium potential of the cell's membrane taking into account all of the ions that are permeant through that membrane.

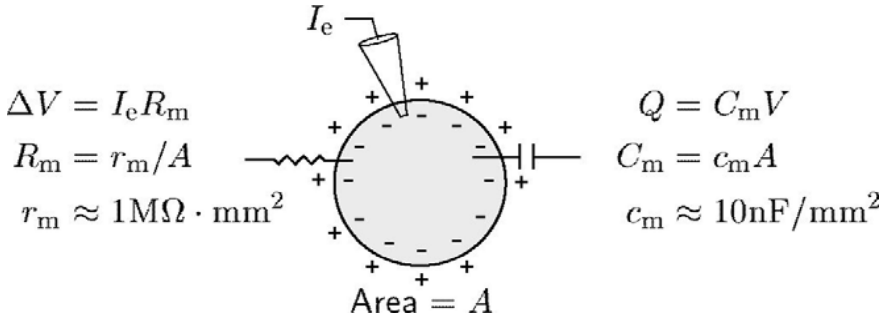
Resting potential

The resting potential (V_{rest}) is between -80 and -50mV, and with the change of the permeabilities the membrane potential can take up values between -90mV and +50mV.

The following processes influence the membrane potential:

- Depolarizing and hyperpolarizing voltage-gated conductances
- Excitatory and inhibitory synapses
- Shunting effect: Conductances with reversal potentials near the resting potential (for example Cl^-), may pass little net current. Instead, their primary impact is to change the membrane resistance of the cell. Such conductances are called shunting, because they increase the total conductance of a neuron.

Passive, isopotential (single compartment) neuron model



V : Membrane potential [V].
I_e : Current injected into the cell, with an electrode for example [A].
Q : Excess internal charge [C].
R_m : Membrane resistance, treated as a constant in the equations (specific membrane resistance, r_m) [Ohm].
C_m : Membrane capacitance, treated as a constant in the equations (specific membrane capacitance, c_m) [F].

The cell membrane is represented by a resistance and a battery in parallel with a capacitance.

Calculating the membrane current 1

From the definition of capacitance, the amount of current (charge per unit time) needed to change the membrane potential of a neuron with a total capacitance C_m at a rate *dV/dt* is:

$$\frac{dQ}{dt} = C_m \frac{dV}{dt}$$

Because of the principle of conservation of charge, the time derivative of the charge *dQ/dt* is equal to the current passing into the cell, so

$$\frac{dQ}{dt} = -\frac{V - E_r}{R_m} + I_e$$

Where E_r is the resting potential of the cell. In most equations membrane conductance (g_m) is used instead of resistance ($g_m = 1/r_m$), because it is directly related to biophysical properties of the neuron:

$$\frac{dQ}{dt} = -g_m(V - E_r) + I_e$$

Calculating the membrane current 2 : The membrane time constant

The product of the membrane capacitance and the membrane resistance is
a quantity with the units of time called the membrane time constant, denoted by *tau*:

$$\tau = R_m C_m$$

The membrane time constant sets the basic time scale for changes in the membrane potential and typically falls in the range between 10 and 100 milliseconds.

$$\tau \frac{dV}{dt} = -V(t) + E_r + R_m I_e$$

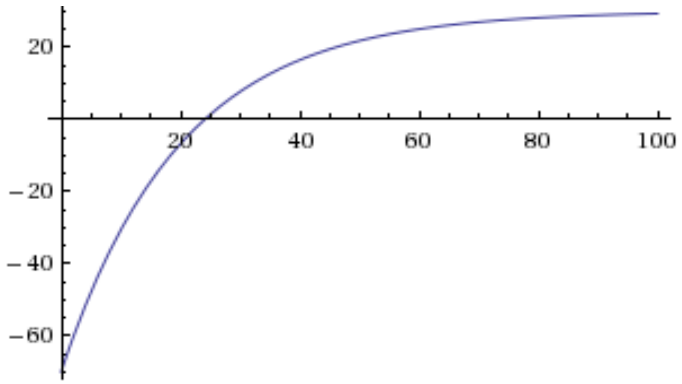
The total membrane conductance can change dynamically, causing the membrane time constant to change, too.

Response to current step at t=0

$$(\Delta V = R_m I_e,\ V_0 = E_r,\ V_\infty = R_m I_e + E_r)$$

$$V(t) = \Delta V(1 - e^{-t/\tau}) + V_0 = V_\infty(1 - e^{-t/\tau}) + V_0 e^{-t/\tau}$$

Example:



(ΔV = 100 mV, *tau* = 20msec, V_0 = -70 mV)

The passive membrane behaves as a low-pass filter.

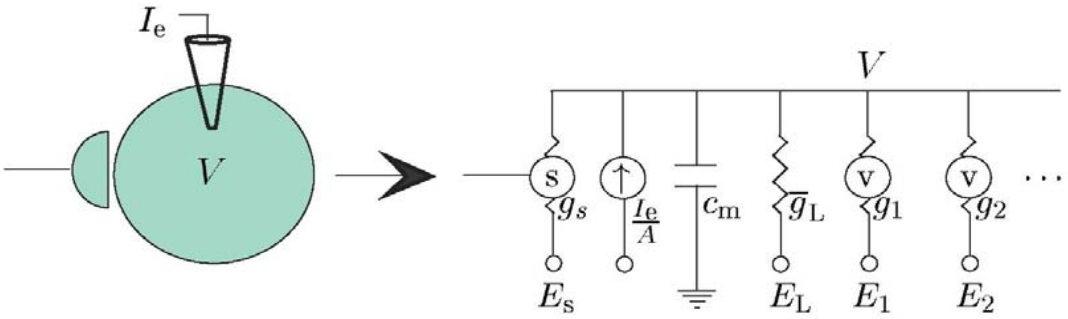
Total current flowing through the membrane

If there are multiple conductances (ion channels):

$$I_{\mathrm{m}} = C_m \frac{dV}{dt} + \sum_i g_i(V - E_i) = I_e$$

Where $g_i(V\text{-}E_i)$ is the current flowing through ion channel *i*.

Equivalent electric circuit:



Ion channels and synaptic channels can be represented as variable conductances.

Summary

In this lesson we learned that:

- The goals of Computational Neuroscience are to understand how neurons and neural networks function. The methodology to accomplish this is to build and analyze mathematical models, which faithfully represent the relevant properties of the examined biological phenomena.
- The basic electrophysiological properties of the neuronal membrane can be described by the following laws: Ohm's law for drift, Fick's law for diffusion, The Einstein relation between diffusion and mobility, the Nernst-equation, the Donnan equilibrium, and finally the Goldman-Hodgkin-Katz equation. With these it is possible to describe the dynamics of the neuronal cell membrane.
- We introduced two important concepts: The membrane current, which is the total current flowing trough the membrane and the membrane time constant, which describes the basic time scale for changes in the state of the neuron.

Suggested reading

Books:

•Christof Koch: *Biophysics of computation* (Oxford University Press), chapter 2

•Peter Dayan and L.F. Abbott: *Theoretical Neuroscience* (MIT Press), chapter 5

•Daniel Johnston, Samuel Miao-Sin Wu: Foundations of Cellular Neurophysiology (MIT Press)