FRTF01 L8—Electrophysiology

Lecture

- Electrophysiology in general
- Recap: Linear Time Invariant systems (LTI)
  - Examples of 1 and 2-dimensional systems
  - Stability analysis
- The need for non-linear descriptions of systems
  - Stability analysis of equilibrium points via linearization
  - Examples in Electrophysiology:
    - the Van der Pol heartbeat-model
    - the Hodgkin and Huxley model of the action potential
- Summary

Definition of Electrophysiology

Merriam Webster's definition of **Electrophysiology**:

Physiology that is concerned with the electrical aspects of physiological phenomena.

Electrophysiological systems

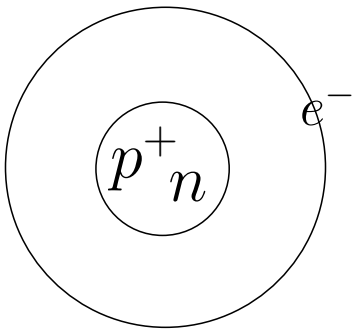
Can you give an example of a physiological system with electrical properties?

Electrophysiological systems

The heart (cardiac cells), muscle cells, neurons, endocrine cells (releasing hormones due to electrical stimuli).

What is electricity?

- Atom: protons (+), neutrons and electrons (-).
- Ions: charges are out of balance, either negatively or positively charged.
- Flow of electrons, or a negative charge, is electricity.



Physiological example: The flow of ions over the cell membrane gives rise to an electric potential.

Electricity in the body

For what purpose is electricity used in the body?

- To send information

Why aren't we sending information with diffusing chemicals instead?

- **Speed**. With electricity, nearly instantaneous response to control messages.

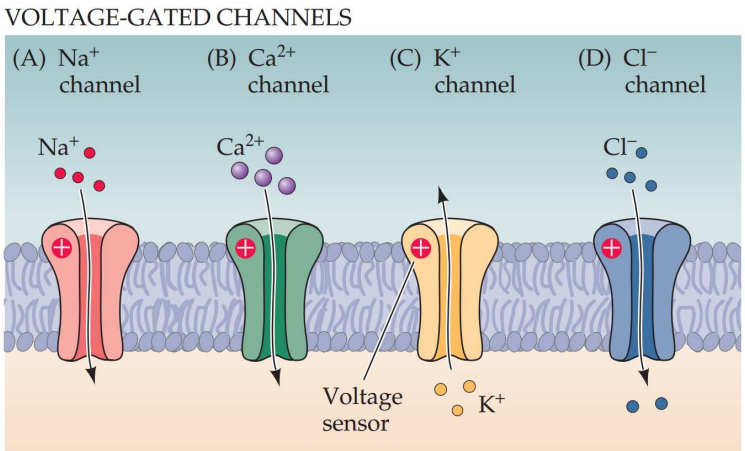
How do we send information with electricity?

- The natural resting potential of the cell membrane is negative due to imbalance between ions
- The cell is capable of depolarizing its membrane and creating an **action potential** (either through external stimuli or by itself)
- The electrical information is "jumping" from one cell to another until it reaches its destination

Note: only excitable cells are able to create action potentials. In the majority of cells the membrane potential stays relatively constant over time.

Reminder: Membrane potential

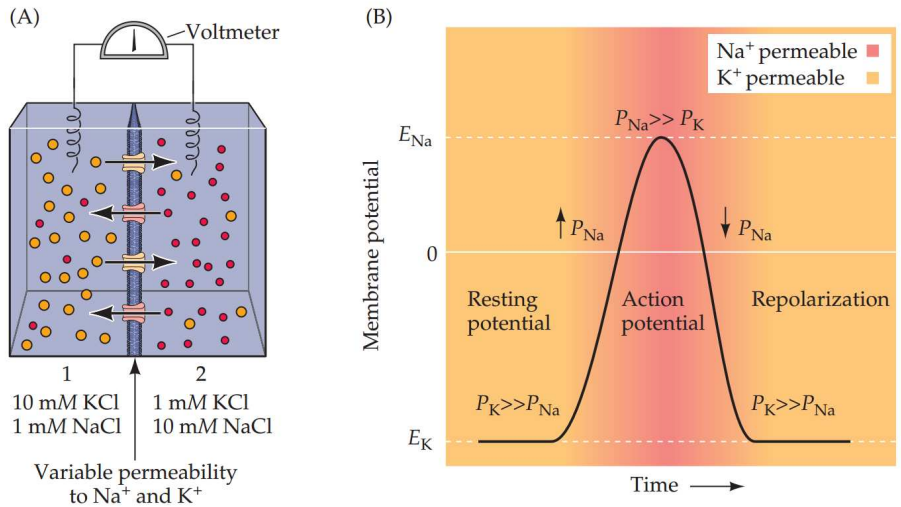
- The membrane is selectively permeable to different ions
- Membrane potential measured as the difference between intra- and extracellular potential
- Non-uniform distribution of ions across membrane
- $\rightarrow$ Resting potential is negative



Ref: Purves et al., Neuroscience p. 76, 2004

Reminder: Action potential

- Voltage-gated ion channels can describe the change in permeability of different ions
- Permeability dependent on membrane potential and time



Ref: Purves et al., Neuroscience p. 39, 2004

More on this later...

Reminder: Muscle contraction

- Action potential travels along **motor neuron** and terminates on a **muscle fiber**.
- Acetylcholine, **ACh**, is released into the **synaptic cleft** (the space separating the axon terminal and the motor end plate) and changes the permeability of the cells of the muscle fiber.
- An action potential is created and propagates across the surface of the sarcolemma. ACh is removed from synaptic cleft so the effect is brief.

In this lecture

We will consider two non-linear models that describe

- the electrical potential during a heartbeat
- the action potential of a neuron

Recap: Linear Time invariant systems

LTI: the differential equation can be written as a linear combination of the variable and its derivatives. Time-invariant parameters.

Example in 1D: Homogeneous differential equation (right-hand side only contains terms involving the unknown variable x)

$$\frac{\mathrm{d}x}{\mathrm{d}t} = -\frac{1}{k} \cdot x$$

With some initial condition $x(0)$. Rate coefficient $1/k$ (k is a constant).

Solution: $x(t) = x(0) \cdot e^{-t/k}$

Physiological relevance: Describes a process of growth or decay.

Recap: LTI systems

Example in 1D: Inhomogeneous differential equation (right-hand side contains additional term which is independent of x)

$$\frac{\mathrm{d}x}{\mathrm{d}t} = \frac{1}{k}\left(-x + u(t)\right)$$

With some initial condition $x(0)$ and input $u(t)$. Rate coefficient $1/k$ (k is a constant).

Solution: $x(t) = x(0) \cdot e^{-t/k} + \frac{1}{k}\int_0^t e^{-(t-\tau)/k} u(\tau)\,\mathrm{d}\tau$.

Physiological relevance: Describes a process of growth or decay when stimulated by a time-varying stimuli $u(t)$.

Recap: 1D LTI - Stability analysis

State space representation

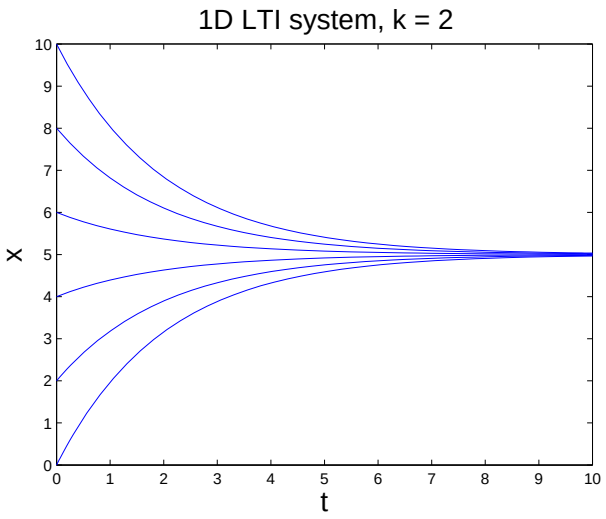
$$\dot{x} = -\frac{1}{k}x + \frac{1}{k}u$$

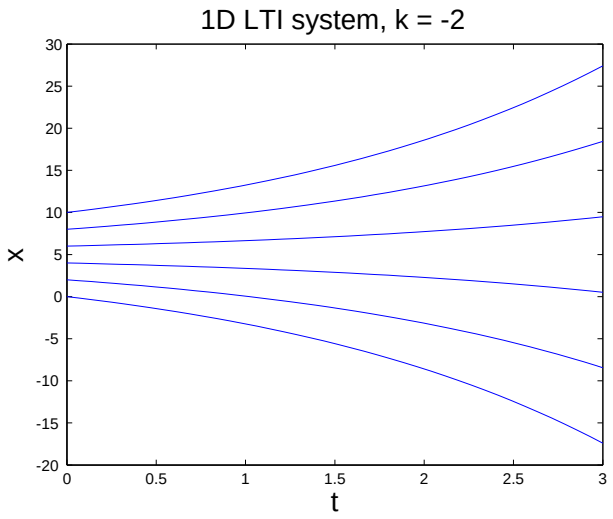
Is the system stable if $k > 0$? If $k < 0$?

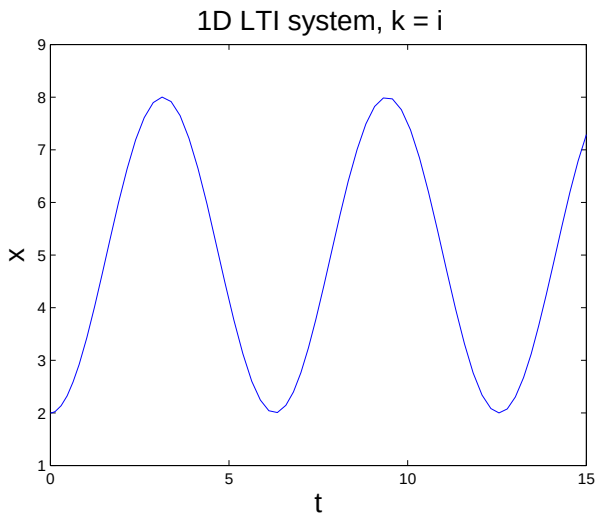
Example in MATLAB

```
% Parameter
k = 2;

% Input function
u = @(t) 5;

% Differential Equation
dxdt = @(t,x) 1/k*(-x+u(t));

% Solution
init_value = 0;
[t X] = ode45(dxdt,[0 10],init_value);
```

Example in MATLAB







Stability analysis of the equilibrium point

Trajectory: the entire time course of the solution of the differential equation from $t = 0$ to $t = \infty$.

Stability of the equilibrium point:

- **Asymptotically stable**: all trajectories starting within a region containing the equilibrium point decays to that point exponentially as $t \to \infty$.
- **Unstable**: at least one trajectory in the region leaves that region permanently.
- **Stable/Neutrally stable**: if nearby trajectories remain nearby as $t \to \infty$ but do not approach asymptotically.

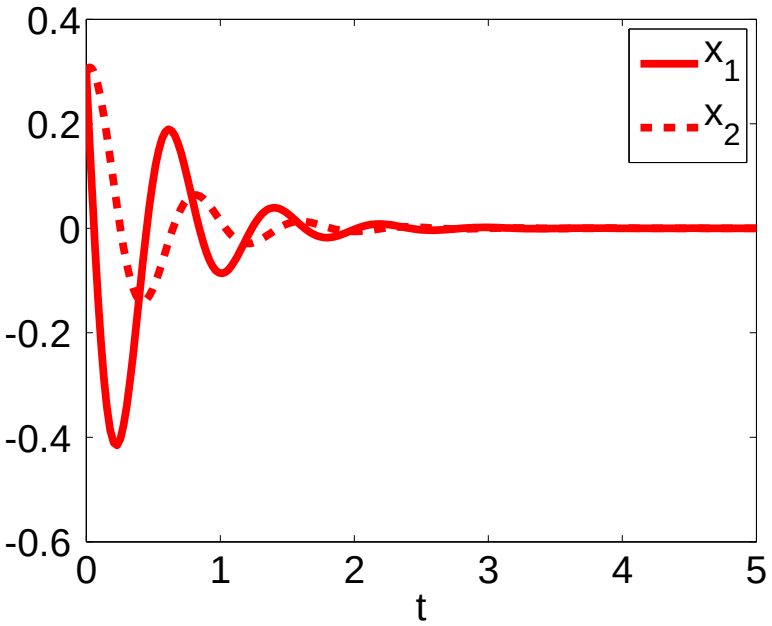
2D LTI: Spiral

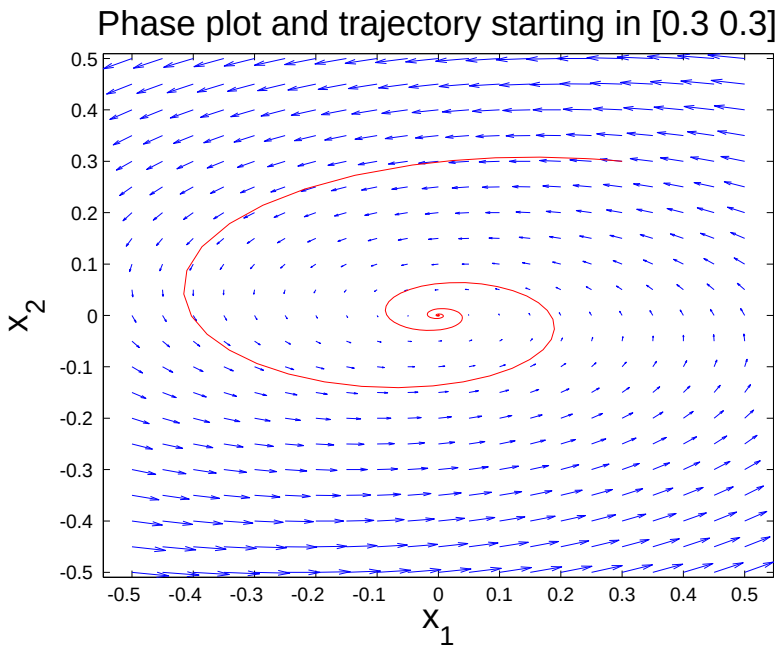
$$\begin{pmatrix} \dot{x}_1 \\ \dot{x}_2 \end{pmatrix} = \begin{pmatrix} -2 & -16 \\ 4 & -2 \end{pmatrix} \begin{pmatrix} x_1 \\ x_2 \end{pmatrix}$$

Poles of the system: $-2 + 8i$, $-2 - 8i$

```
% Differential Equation
dxdt = @(t,x) [-2 -16; 4 -2]*x;

% Solution
init_value = [0.3 0.3];
[t X] = ode45(dxdt,[0 10],init_value);
```

2D LTI: Spiral





Stability possibilities for spiral: Asymptotically stable or unstable.

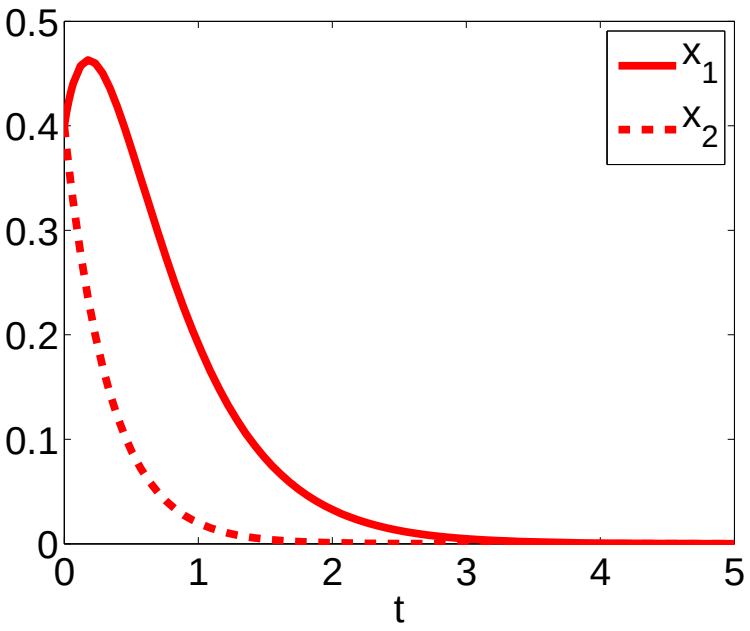
2D LTI: Node

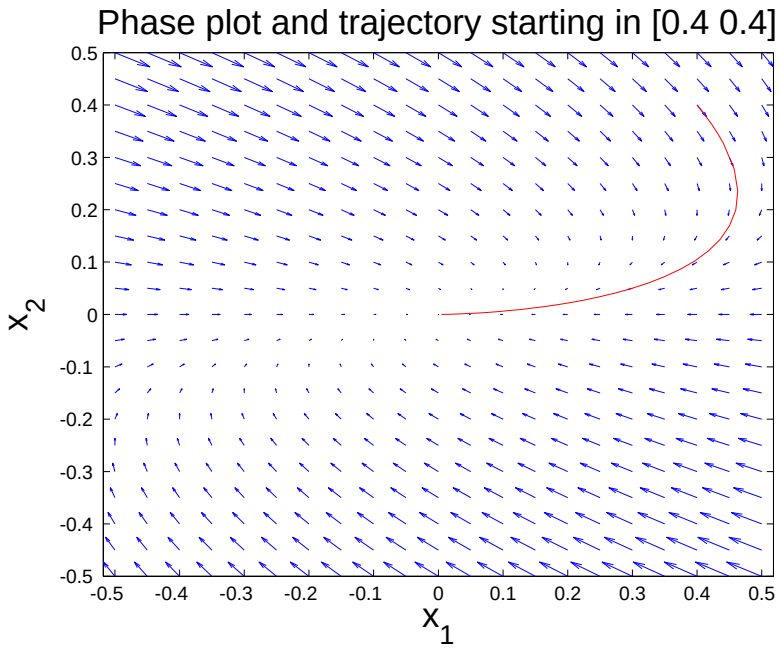
$$\begin{pmatrix} \dot{x}_1 \\ \dot{x}_2 \end{pmatrix} = \begin{pmatrix} -2 & 4 \\ 0 & -3 \end{pmatrix} \begin{pmatrix} x_1 \\ x_2 \end{pmatrix}$$

Poles of the system: -2, -3

```
% Differential Equation
dxdt = @(t,x) [-2 4; 0 -3]*x;

% Solution
init_value = [0.4 0.4];
[t X] = ode45(dxdt,[0 3],init_value);
```

2D LTI: Node





Stability possibilities for node: Asymptotically stable or unstable.

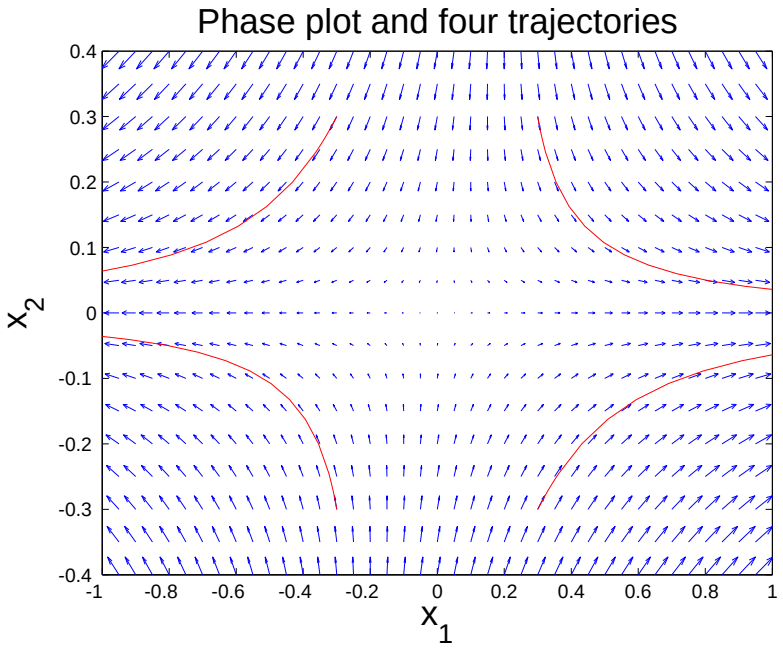
2D LTI: Saddle Point

$$\begin{pmatrix} \dot{x}_1 \\ \dot{x}_2 \end{pmatrix} = \begin{pmatrix} 2 & -1 \\ 0 & -3 \end{pmatrix} \begin{pmatrix} x_1 \\ x_2 \end{pmatrix}$$

Poles of the system: $2, -3$

```
% Differential Equation
dxdt = @(t,x) [2 -1; 0 -3]*x;

% Solution
init_value = [0.3 0.3];
[t X] = ode45(dxdt,[0 5],init_value);
```

2D LTI: Saddle Point



Stability possibilities for saddle point: Unstable.

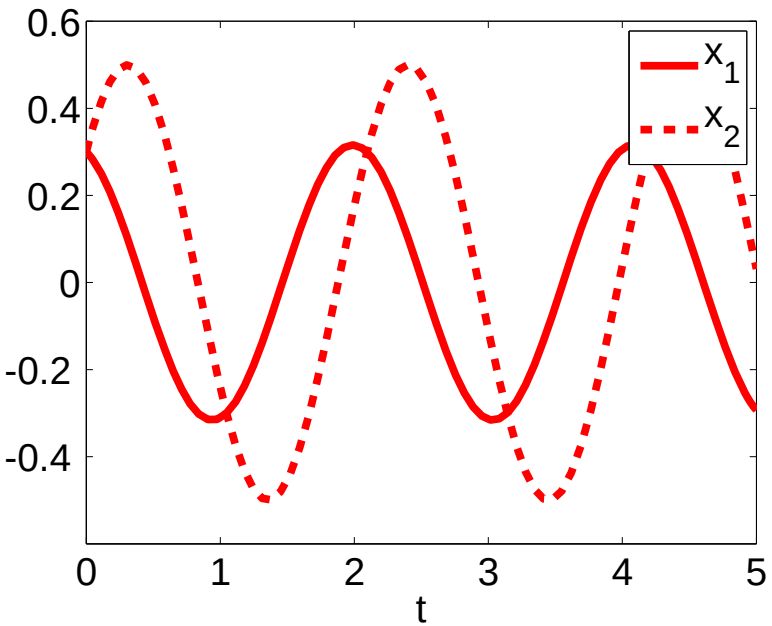
2D LTI: Center

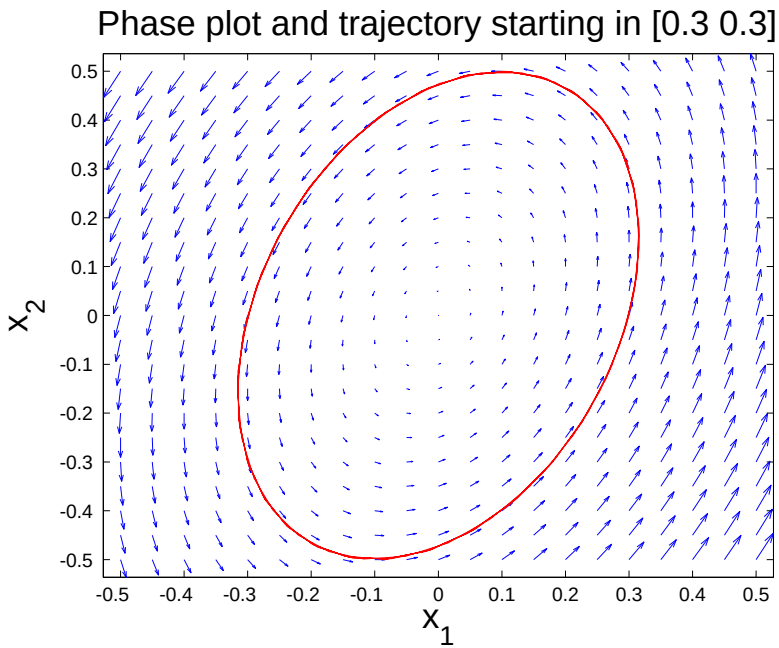
$$\begin{pmatrix} \dot{x}_1 \\ \dot{x}_2 \end{pmatrix} = \begin{pmatrix} 1 & -2 \\ 5 & -1 \end{pmatrix} \begin{pmatrix} x_1 \\ x_2 \end{pmatrix}$$

Poles of the system: $3i$, $-3i$

```
% Differential Equation
dxdt = @(t,x) [1 -2; 5 -1]*x;

% Solution
init_value = [0.3 0.3];
[t X] = ode45(dxdt,[0 10],init_value);
```

2D LTI: Center





Stability possibilities for center: Stable/Neutrally stable.

Linearization and non-linear behavior

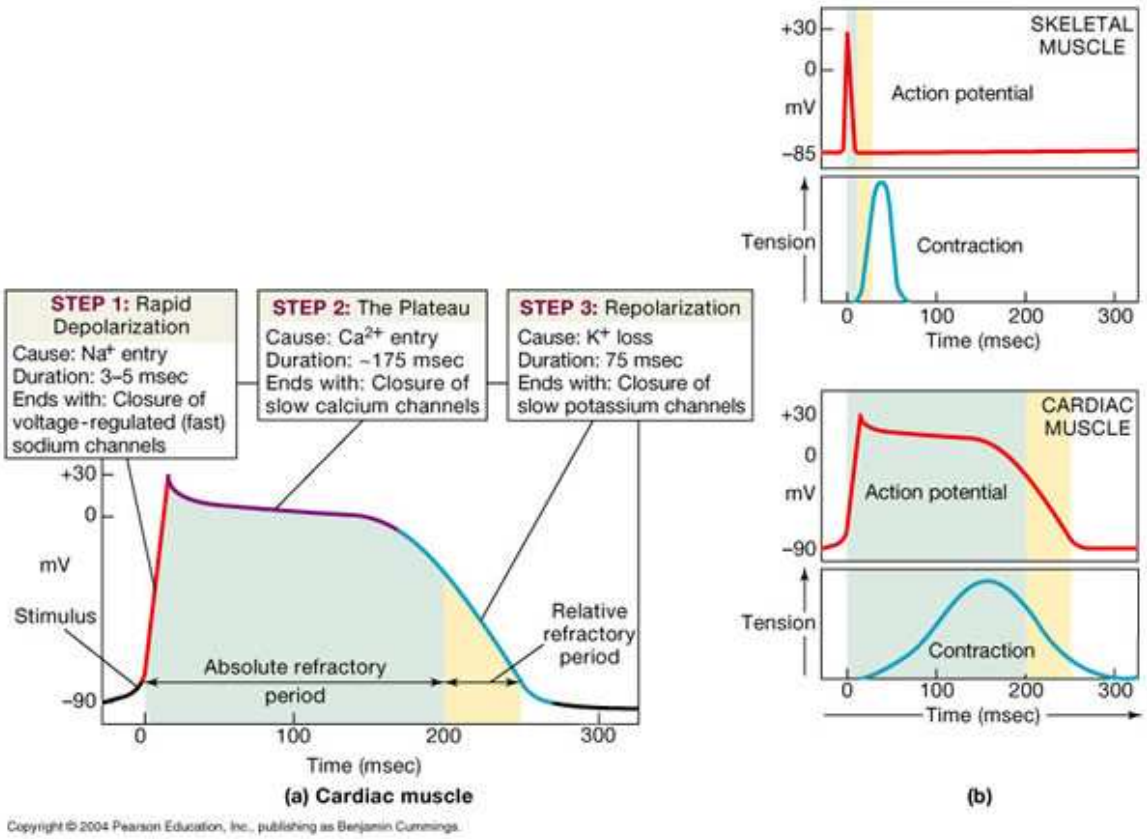
- Approximate non-linear system around an equilibrium point by Taylor series expansion
- Good tool when analyzing behavior around equilibrium points
- Does not captivate nonlinear behavior as limit cycles [think back to HW1!].

Now to some examples of nonlinear systems in electrophysiology!

Electrophysiology of the Heart
The Heartbeat

- Two types of cardiac cells: **contractile cells** (99%) and specialized non-contractile muscle cells, **pacemaker cells**.
- Pacemaker cells controls and coordinates the activities of the contractile cells, without neural stimulation; **automaticity**.
- Cellular connections enables rapid passage of action potentials from cell to cell.
- Pacemaker cells sets the pace at which the heart beats.
- Contraction as in skeletal muscle cells described before.
- Contraction of individual cardiac cells (first in atria then in the ventricles).

Refractory period



Ref: Martini and Bartholomew, Essentials of Anatomy and Physiology p.414, 2004.

The Heartbeat Model

Van der Pol model (1929), mathematical model of the heartbeat:

$$\frac{d^2x}{dt^2} - \nu(1 - x^2)\frac{dx}{dt} + x = 0$$

- ν is a positive constant
- describes nonlinear damping

Analysis of diff. eq:

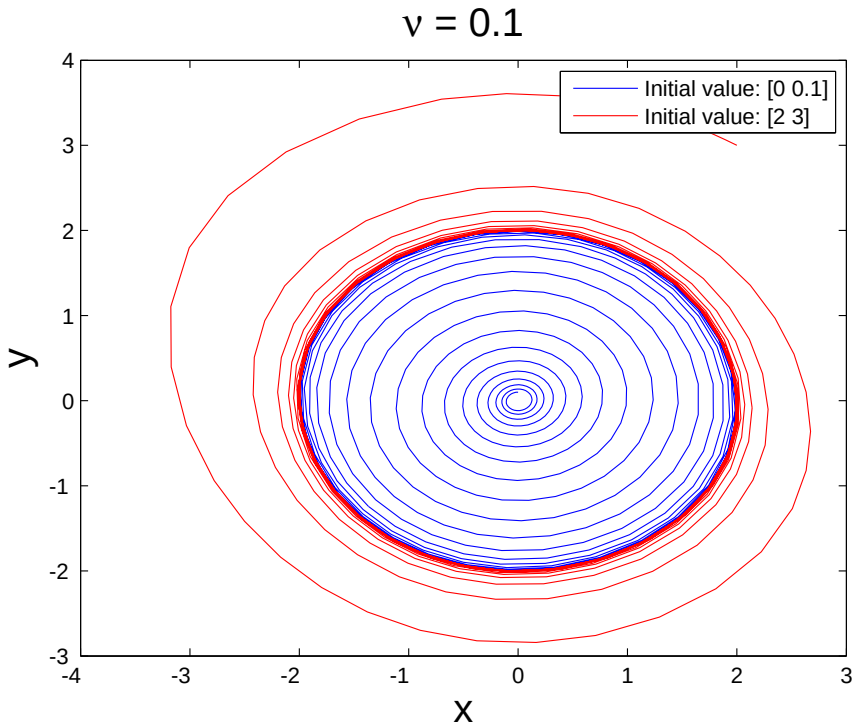
- Negative damping when $|x|$ is small
- Positive damping when $|x|$ is large

Analysis of the heartbeat model

Use $y = \nu \cdot \left(x - x^3/3\right) - \dot{x}$ to rewrite the system as follows:

$$\dot{x} = \nu \left(x - \frac{x^3}{3} \right) - y$$

$$\dot{y} = x$$

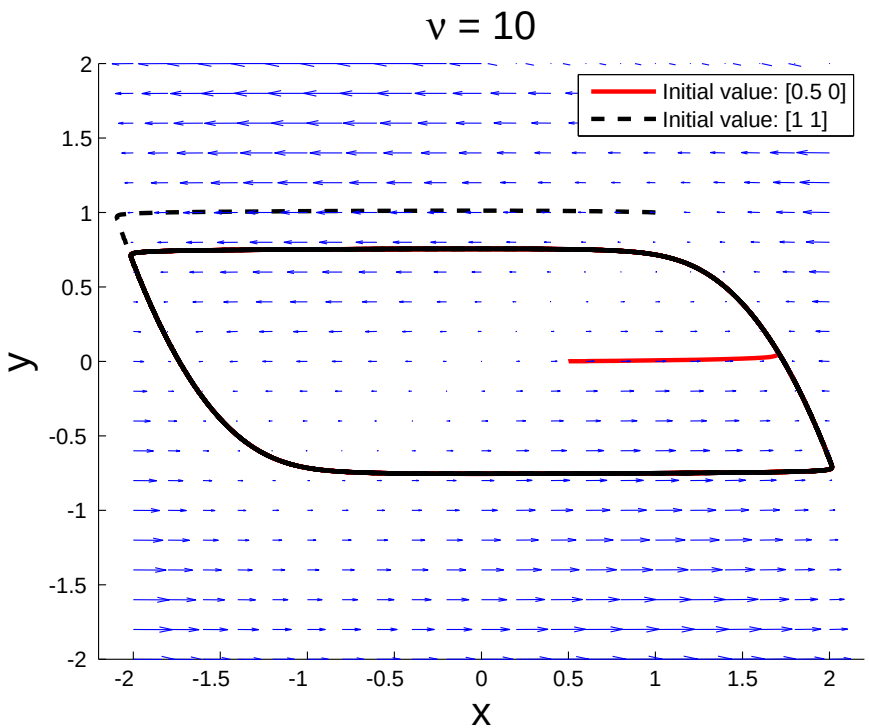


Analysis of the heartbeat model

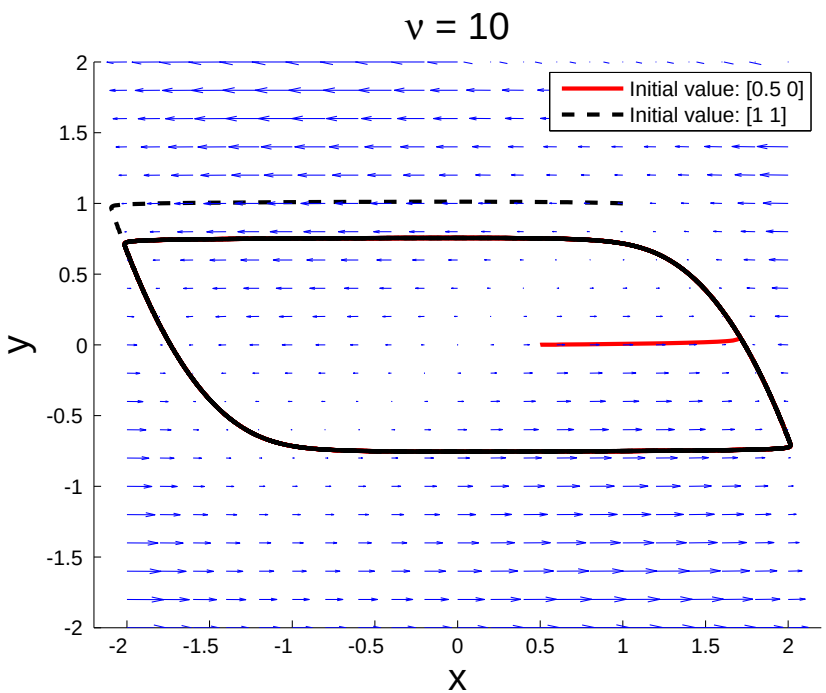
When ν is large use $y = x - x^3/3 - \dot{x}/\nu$ to rewrite the system as follows:

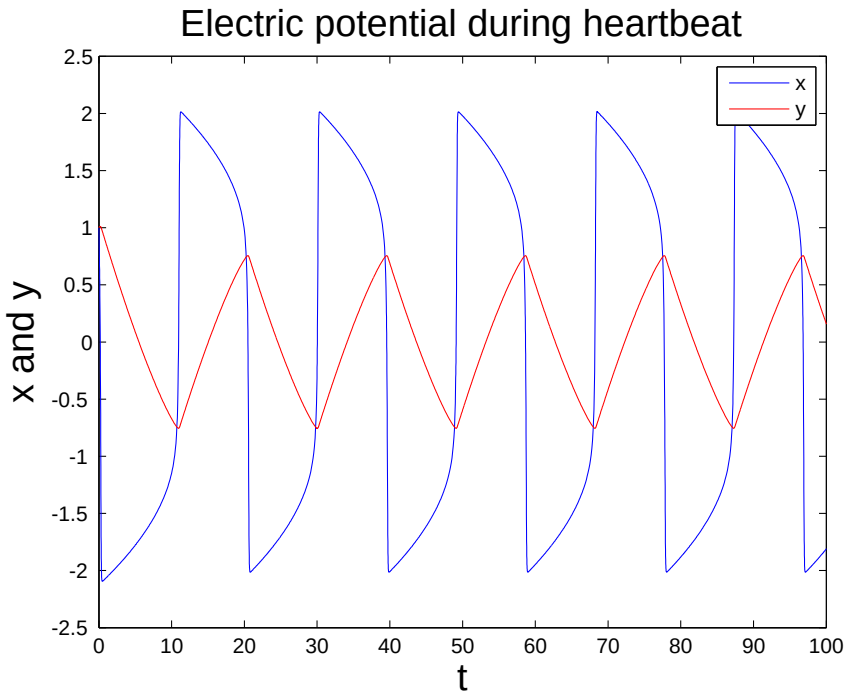
$$\dot{x} = \nu \left(x - \frac{x^3}{3} - y \right)$$

$$\dot{y} = \frac{x}{\nu}$$



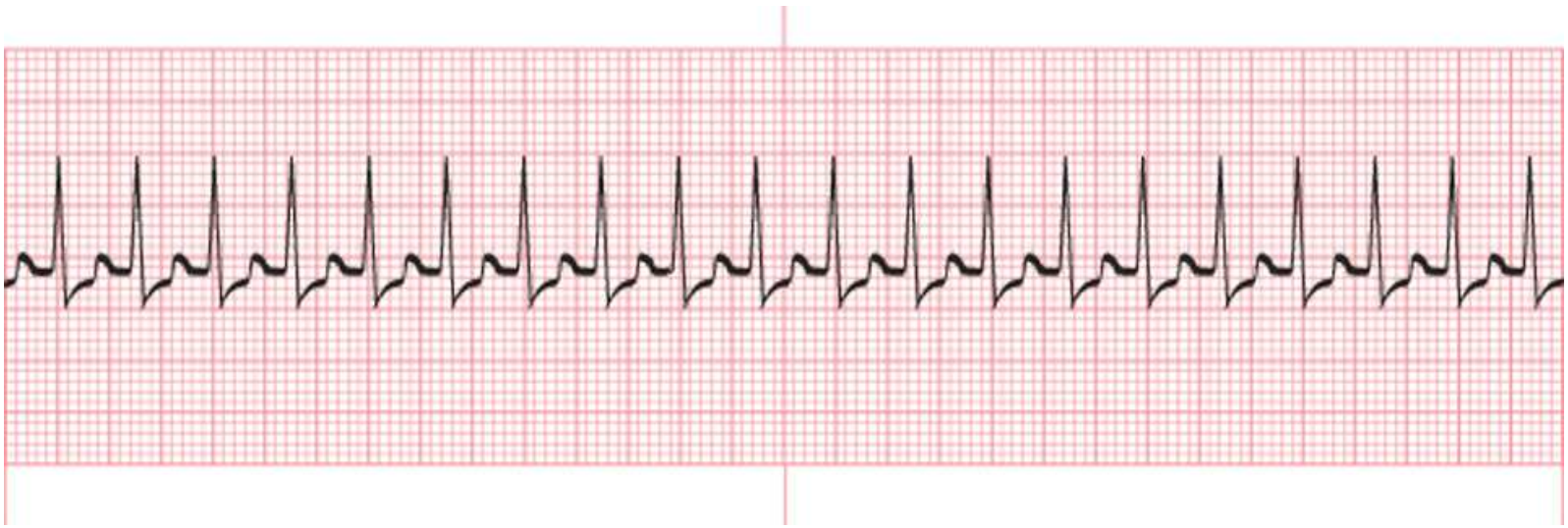
Analysis of the heartbeat model





EKG - Electrocardiography

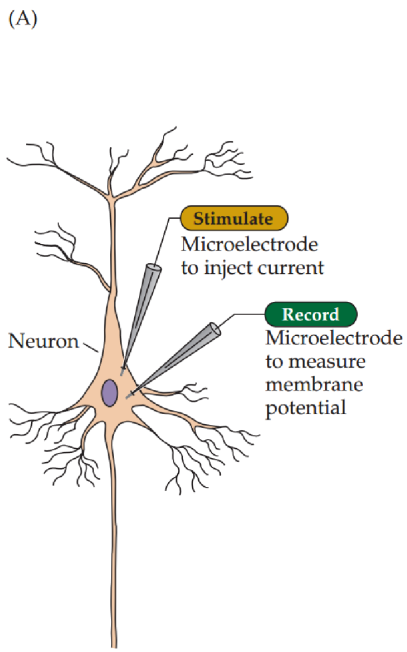
- EKG (or ECG) used to record the electrical activity of the heart
- More detailed model



Ref: `http://hmphysiology.blogspot.se/p/blog-page_25.html`

The Neuron

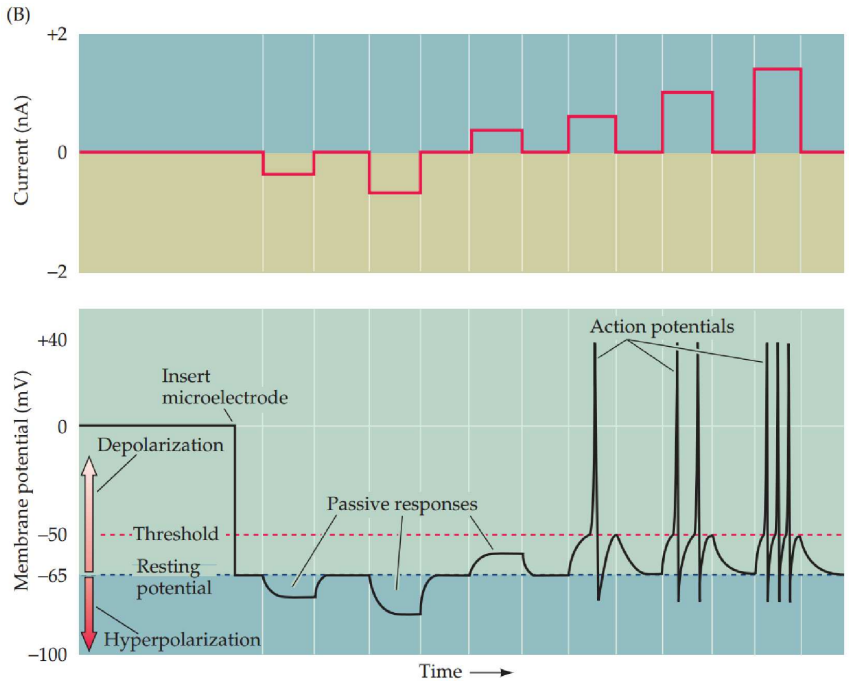
- Soma, dendrites, axon, synapse.
- Electrophysical recording intracellularly with microelectrode $\rightarrow$ detect action potential
- Microelectrode: instrument to measure electric potential (by oscilloscope)
- Single cell recording - receptive field of a neuron



Ref: Purves et al, Neuroscience p.33, 2004

The Neuron

- Input: stimuli (heat, light), synaptic contact.
- Every nerve cell gets 1-1000 synapses from other nerve cells - integrate information.
- Inhibitory or excitatory neurons
- Action potential is an all or none phenomenon



Ref: Purves et al, Neuroscience p.33, 2004

The nervous system is **highly complex** and **highly nonlinear**.

Example: Threshold for producing spikes; weak stimulation has no effect yet several weak stimuli together produce a dramatic spike response.

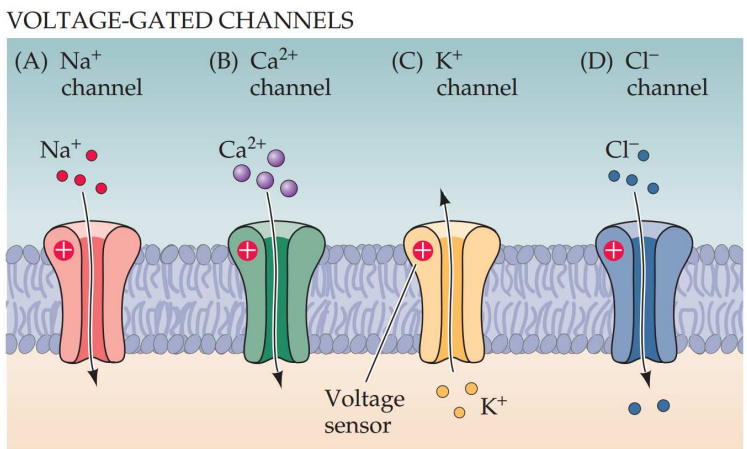
How to model a neuron

Some examples of neuronal models are:

- Device which is either on (1) or off (0).
- Spike rate: varies continuously between 0 (postsynaptic potential is below threshold) and some maximum saturated level (1000 Hz) due to the refractory period.
- **Hodgkin and Huxley (1952) described the generation and shape of an individual action potential as a function of the underlying ionic currents. Nobel Prize 1963!**
- Even more detailed models that incorporate the geometry and spatial distribution of the neurons.

Ionic movement produce electric potential

- **Active transporters**: moves ions against their concentration gradient
- **Selective permeability** (ion channels) allows only certain ions to cross the membrane.
- Working against each other, creating the **resting potential**.

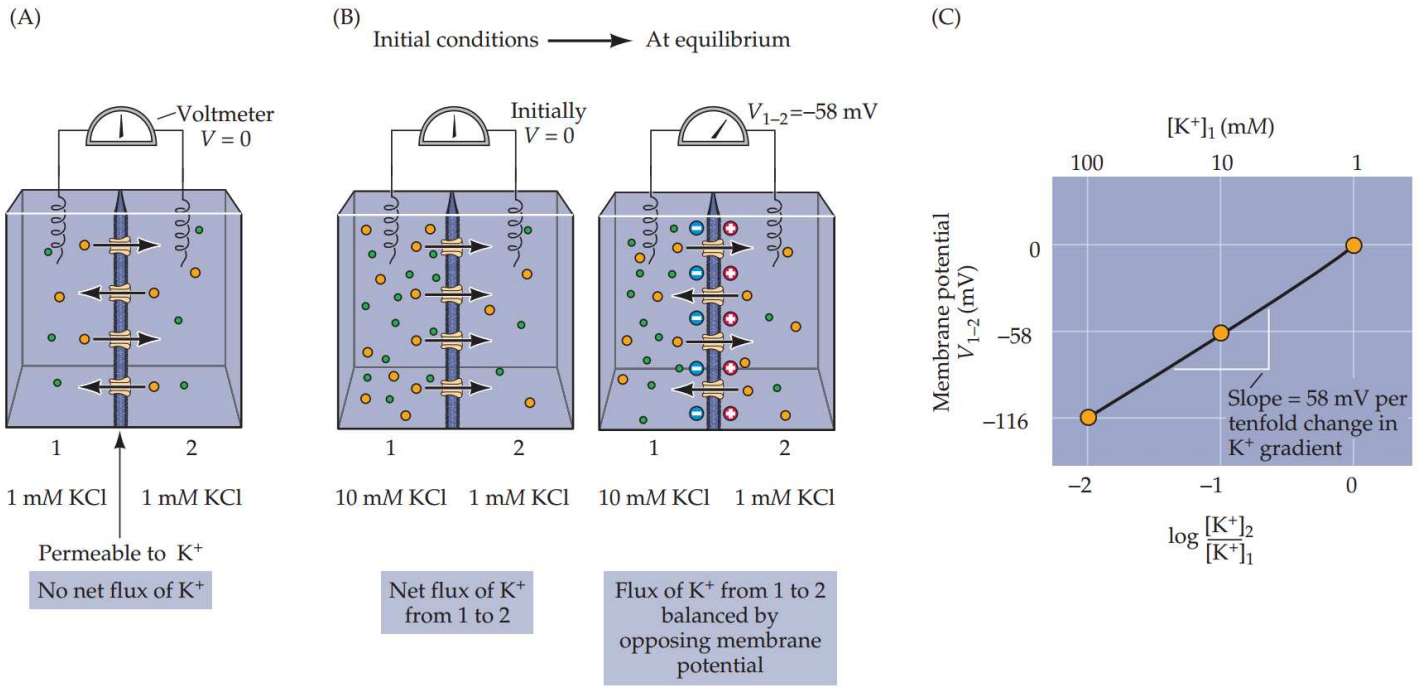


Ref: Purves et al., Neuroscience p. 76, 2004

Ionic movement produce elctrical signals

Electrochemical equilibrium:

1. Concentration gradient that causes K^+ to move to compartment 2.
2. Opposing electrical gradient impedes further flow of K^+.



Ref: Purves et al., Neuroscience p. 35, 2004

The Nernst Equation

The Equilibrium potential for some ion is given by:

$$E = \frac{\mathrm{RT}}{\mathrm{zF}} \ln\left(\frac{C_{out}}{C_{in}}\right)$$

z - valence charge

C_{out} - the ion concentration outside (2) the cell

C_{in} - the ion concentration inside (1) the cell

R - thermodynamic gas constant, $8.31447\ [\mathrm{J/mol \cdot K}]$

F - Faraday constant, $9.648534 \cdot 10^4\ [\mathrm{C/mol}]$

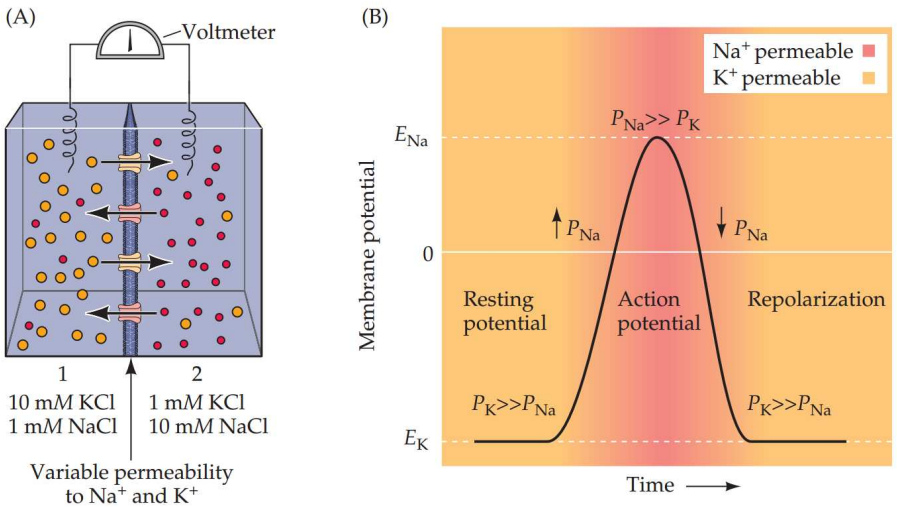
T - temperature in Kelvin.

The Goldman Equation

The membrane potential when more than one permeant ion exist:

$$V = \frac{\mathrm{RT}}{\mathrm{F}} \ln \left(\frac{P_K[K]_2 + P_{Na}[Na]_2 + P_{Cl}[Cl]_1}{P_K[K]_1 + P_{Na}[Na]_1 + P_{Cl}[Cl]_2} \right)$$

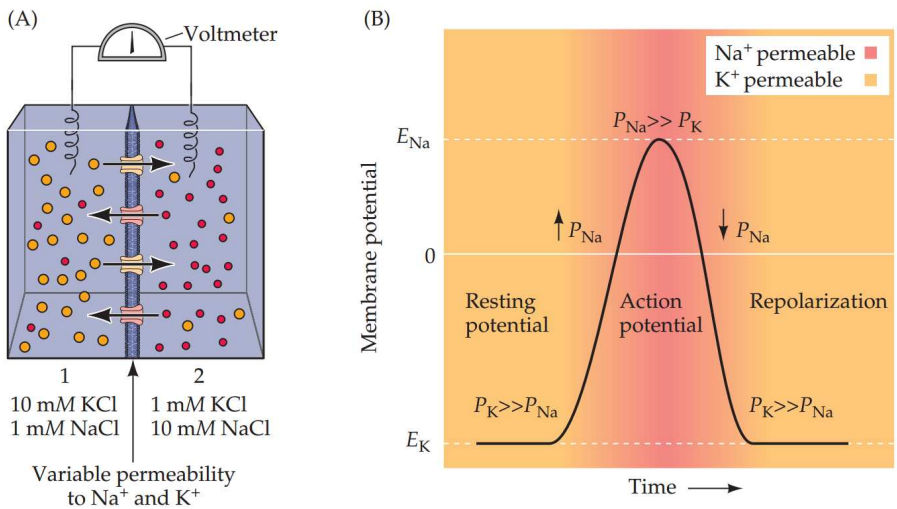
P_i - permeability for ion [i], is time and voltage dependent.



Ref: Purves et al., Neuroscience p. 39, 2004

Permeabilities

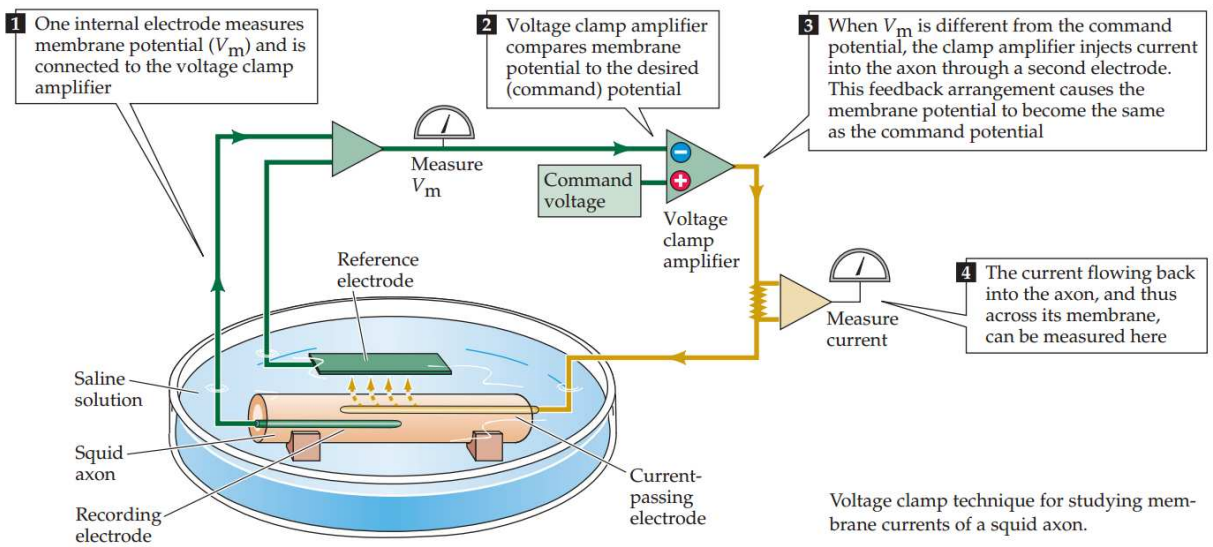
- Experiments on squid axon (large) $\rightarrow$ initial insights on membrane electrochemical behavior
- Resting membrane more permeable to K^+
- Action potential: Increased permeability to Na^+, then K^+ permeability increases (more than at rest), creates hyperpolarization.



Ref: Purves et al., Neuroscience p. 39, 2004

The Voltage Clamp method

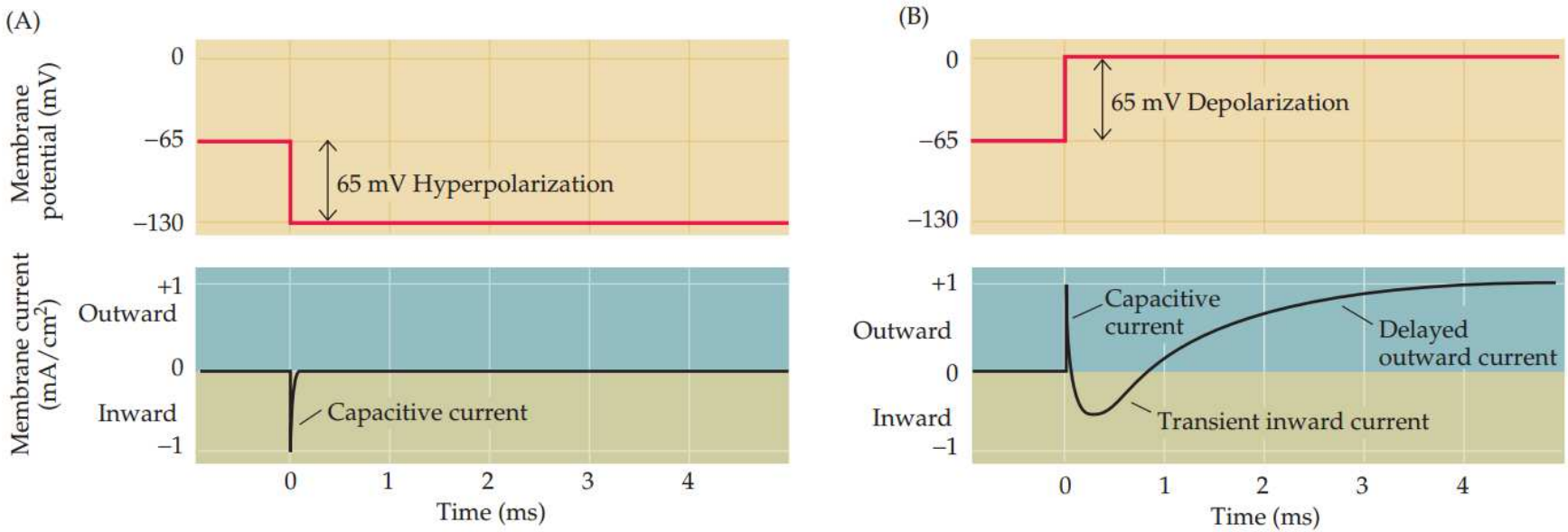
Hodgkin and Huxley used the voltage clamp technique, invented by Kenneth Cole in the 1940s, to understand how the permeabilities depend on the membrane potential and time.



Ref: Purves et al, Neuroscience p.48, 2004.

The measured current is the flow of ions across the membrane.

The Voltage Clamp method



Ref: Purves et al, Neuroscience p.49, 2004.

Mathematical model of Ion Channels

Ion channels are governed by Ohm's law which states that

$$I = \frac{U}{R}$$

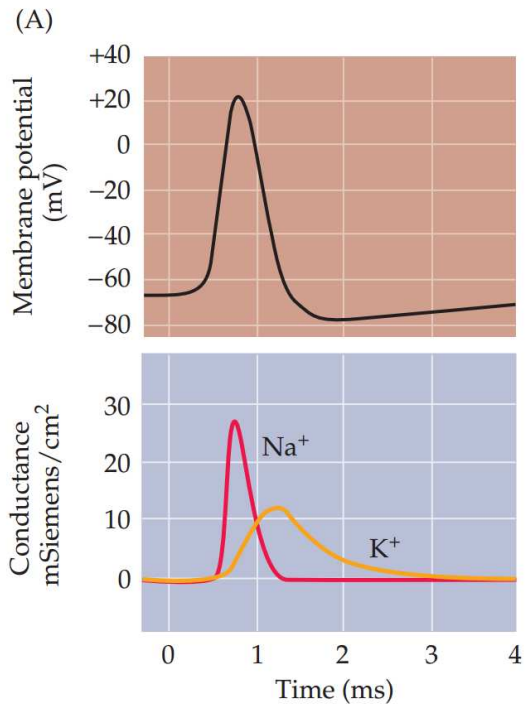
Or with the conductance $\tilde{g} = 1/R$ [nS] and the equilibrium potential E [mV]:

$$I = \tilde{g} \cdot (V - E)$$

where V [mV] is the membrane potential. I is the ionic current over the nerve cell membrane for a specific ion with equilibrium potential E.

Determine the conductance

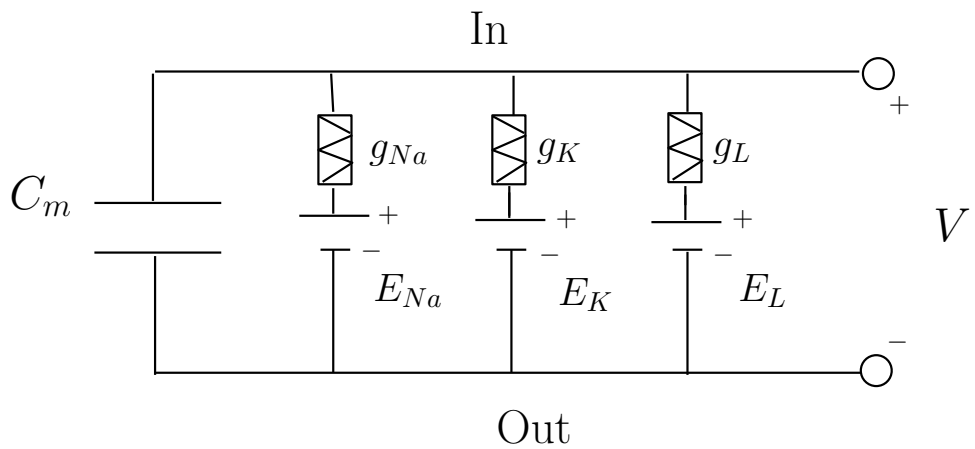
- E determined through Nernst eq.
- Voltage clamp experiment to get I at different V (separate ions)



Ref: Purves et al, Neuroscience p.55, 2004.

The Hodgkin and Huxley Model

A.L. Hodgkin and A.F. Huxley,
A Quantitative Description of Membrane Current and its Application to Conduction and Excitation in Nerve in Journal of Physiology, 1952.
Nobel Prize in Physiology or Medicine in 1963.



The Hodgkin and Huxley Model

The total membrane current can be written as

$$\frac{a}{2R_2\theta^2}\frac{\mathrm{d}^2V}{\mathrm{d}t^2} = C_m\frac{\mathrm{d}V}{\mathrm{d}t} + I_{Na} + I_K + I_L$$

where a is the radius of the fibre and R_2 the specific resistance of the axoplasm. The left hand side can be written as; $\frac{a}{2R_2\theta^2}\frac{\mathrm{d}^2V}{\mathrm{d}t^2} = I_{ext}$, some external current input.

The Hodgkin and Huxley Model

Remember $I = \tilde{g}(V - E)$. In Hodgkin and Huxley

$$I_{Na} = \tilde{g}_{Na}\,(V - E_{Na})$$
$$I_K = \tilde{g}_K\,(V - E_K)$$
$$I_L = \tilde{g}_L\,(V - E_L)$$

where the $\tilde{g}$ are functions of the membrane voltage V and the time t. The ion [L] stands for the leakage, covering the behavior of all other ions except [Na] and [K].

The Hodgkin and Huxley Model

The $\tilde{g}$-functions are defined as

$$\tilde{g}_{Na} = g_{Na} m^3 h$$
$$\tilde{g}_K = g_K n^4$$
$$\tilde{g}_L = g_L$$

where m, h and n are functions of the membrane voltage V and the time t while g_{Na}, g_K and g_L are constants.

The Hodgkin and Huxley Model

The dynamics of the gating variables are:

$$\frac{\mathrm{d}m}{\mathrm{d}t} = \alpha_m(V)(1-m) - \beta_m(V)m$$
$$\frac{\mathrm{d}h}{\mathrm{d}t} = \alpha_h(V)(1-h) - \beta_h(V)h$$
$$\frac{\mathrm{d}n}{\mathrm{d}t} = \alpha_n(V)(1-n) - \beta_n(V)n$$

where the rate functions are, unit [1/ms]:

$$\alpha_m(V) = 0.1(V+45)/(1-\exp(-(V+45)/10))$$
$$\beta_m(V) = 4\exp(-(V+70)/18)$$
$$\alpha_h(V) = 0.07\exp(-(V+70)/20)$$
$$\beta_h(V) = 1/(1+\exp(-(V+40)/10))$$
$$\alpha_n(V) = 0.01(V+60)/(1-\exp(-(V+60)/10))$$
$$\beta_n(V) = 0.125\exp(-(V+70)/80)$$

The Hodgkin and Huxley Model

The total membrane current can then be written as

$$\frac{a}{2R_2\theta^2}\frac{\mathrm{d}^2V}{\mathrm{d}t^2} = C_m\frac{\mathrm{d}V}{\mathrm{d}t} + g_{Na}m^3h\left(V - E_{Na}\right) + g_K n^4\left(V - E_K\right) + g_L\left(V - E_L\right)$$

where the dynamics of the gating variables are

$$\begin{aligned}\frac{\mathrm{d}m}{\mathrm{d}t} &= \alpha_m\left(V\right)\left(1-m\right) - \beta_m\left(V\right)m\\ \frac{\mathrm{d}h}{\mathrm{d}t} &= \alpha_h\left(V\right)\left(1-h\right) - \beta_h\left(V\right)h\\ \frac{\mathrm{d}n}{\mathrm{d}t} &= \alpha_n\left(V\right)\left(1-n\right) - \beta_n\left(V\right)n\end{aligned}$$

Simulation of the HH-model

Parameter values:

$$C_m = 1[\mu\mathrm{F/cm}^2]$$

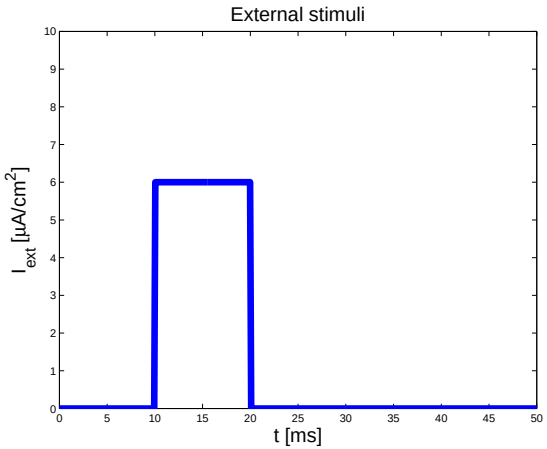
$$E_{Na} = 45[\mathrm{mV}] \qquad g_{Na} = 120[\mathrm{mS/cm}^2]$$

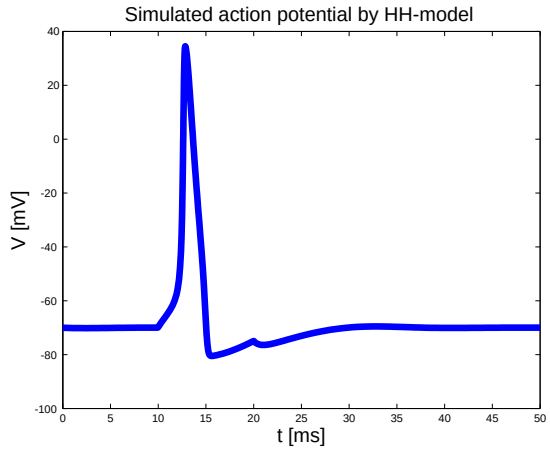
$$E_K = -82[\mathrm{mV}] \qquad g_K = 36[\mathrm{mS/cm}^2]$$

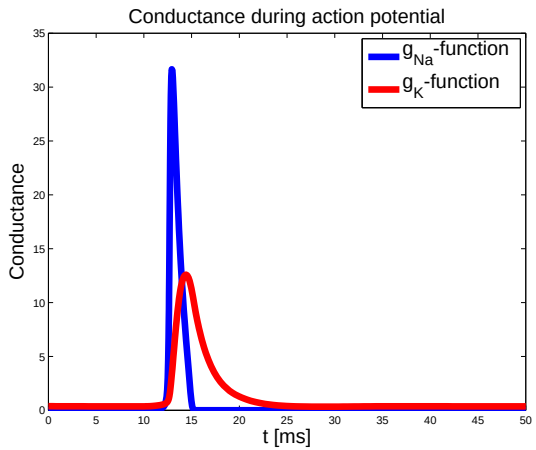
$$E_L = -59.387[\mathrm{mV}] \qquad g_L = 0.3[\mathrm{mS/cm}^2]$$

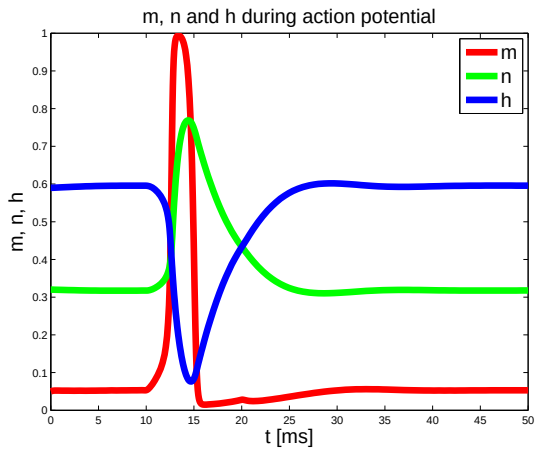
The Hodgkin and Huxley Model

$m(t)$ - Na^+ activation $h(t)$ - Na^+ de-activation $n(t)$ - K^+ activation

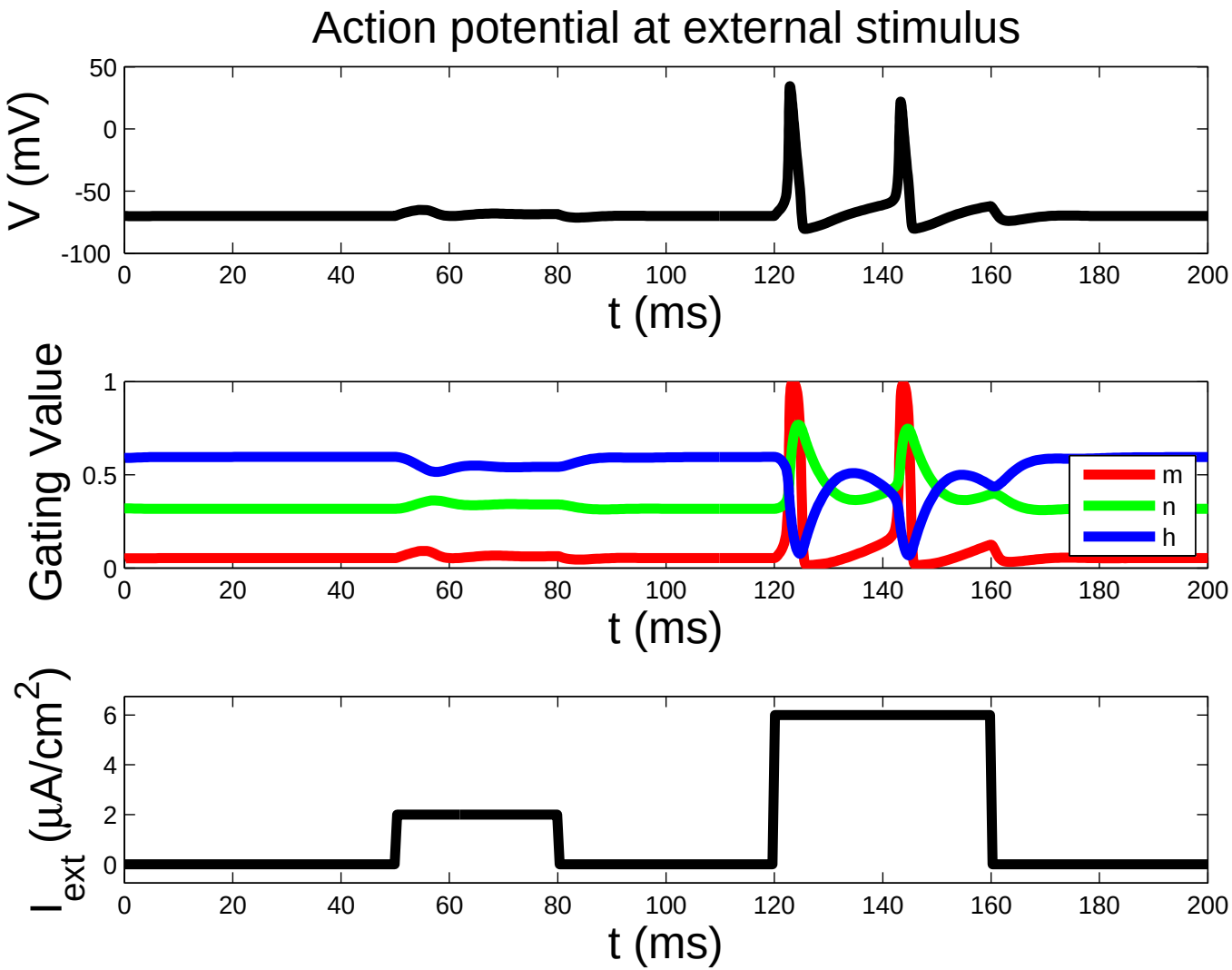








The Hodgkin and Huxley Model

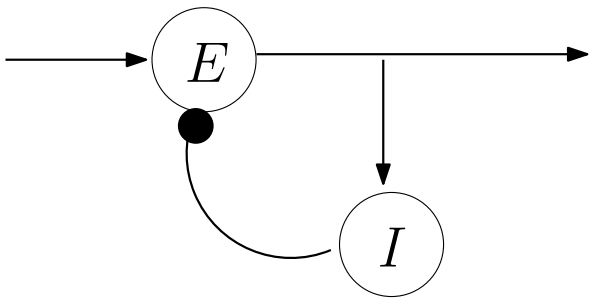


The Hodgkin and Huxley Model

- Pro: Detailed model of the action potential [HW4!]
- Con: Computationally demanding to model several neurons (network of neurons).

Networks of Neurons

Feedback loop in 2-neuron network



Summary

- LTI vs non-linear systems
- Important to keep non-linear behavior in analysis
- HH-model for action potential

Current research:

- Electrophysiological studies of interneurons
- Diseases such as epilepsy and Parkinson's
- Human Brain Project

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