Neuroinformatics

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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**
  - Dendrite
  - Axon
  - Soma

- **Bipolar cell**
  - Dendrite
  - Soma
  - Axon

(Invertebrate N.)

- **Retinal bipolar cell**

Different Types of Multi-polar Cells

- **Spinal motoneuron**
- **Hippocampal pyramidal cell**
- **Purkinje cell of the cerebellum**
(Chemical) Synapse

Motor Endplate
(Frog muscle)

Post-synaptic potential (PSP)
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

\[ \Delta V \]

Time course of response (alpha-function)

\[ \Delta V_{m}^{\text{non-NMDA}} \propto t e^{-t/t_{\text{peak}}} \]
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-concentrations across the membrane a potential difference arises:

\[ V_m \]

In addition, the membrane acts like a capacitor:

\[ Q = CV_m \]

\[ I_C = \frac{dQ}{dt} = C \frac{dV_m}{dt} \]
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 (Ca²⁺)
- 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

[Diagram of ion channel with labeled parts: Ions, Protein subunits of ion channel, Pore of ion channel, Lipid molecules in membrane, Open ion channel, Closed ion channel, Outside of Cell, Inside of Cell]
Ion channels consist of big (protein) molecules which are inserted into the membrane and connect intra- and extracellular space.

Channels act as a resistance 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: $K^+$, $Na^+$, $Ca^{2+}$, $Cl^-$

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

A. Leakage channel

B. Voltage-gated ion channel

C. Ion pump

D. Ionotropic

E. Metabotropic (second messenger)
In order to describe the electrical properties of a membrane you need the membrane capacitance $C$, the conductivity $g = 1/R$ and the resting potential $V_{\text{rest}}$.

Current across the membrane is given by:

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

or:

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

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

1  % Synaptic conductance model to simulate an EPSP
2  clear; clf; hold on;
3
4  % Setting some constants and initial values
5  c_m=1; g_L=1; tau_syn=1; E_syn=10; delta_t=0.01;
6  g_syn(1)=0; I_syn(1)=0; v_m(1)=0; t(1)=0;
7
8  % Numerical integration using Euler scheme
9  for step=2:10/delta_t
10     t(step)=t(step-1)+delta_t;
11     if abs(t(step)-1)<0.001; g_syn(step-1)=1; end
12     g_syn(step)= (1-delta_t/tau_syn) * g_syn(step-1);
13     I_syn(step)= g_syn(step) * (v_m(step-1)-E_syn);
14     v_m(step) = (1-delta_t/c_m*g_L) * v_m(step-1) ...
15       - delta_t/c_m * I_syn(step);
16  end
17
18  % Plotting results
19  plot(t,v_m); plot(t,g_syn*5,'r--'); plot(t,I_syn/5,'k:')
1939: Laboratory of the Marine Biological Association at Plymouth

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

1. Sodium channel opens, sodium ions enter.
2. K+ channels open, K+ begins to leave cell.
3. Na+ channels become refractory, no more Na+ enters cell.
4. K+ continues to leave cell, causes membrane potential to return to resting level.
5. K+ channels close, Na+ channels reset.

Graph:
- Membrane potential (mV) on the y-axis.
- Time (ms) on the x-axis.
- Depolarization, Repolarization, Hyperpolarization, Resting Membrane Potential indicated.

Legend:
- Na+ (sodium)
- K+ (potassium)
Nernst equation (equilibrium potential; not considering active ionically selective channels):

\[ V_x = \frac{RT}{zF} \ln \left( \frac{[X]_o}{[X]_i} \right) \]

For T=25°C:

\[ V_x = -\frac{60}{z} \log \left( \frac{[X]_i}{[X]_o} \right) \text{[mV]} \]
Goldman-Hodgkin-Katz equation (equilibrium potential):

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

For T=37°C:

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

P: permeability for that Ion

Applies only when \( V_m \) is not changing!
The minimal mechanism
Hodgkin Huxley Model:

\[ C_m \frac{dV_m(t)}{dt} = \text{Na-Current} + \text{K-Current} + \text{Leakage Current} + \text{injec. Current} \]
Hodgkin Huxley Model:

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

plus Equations for \( m \) and \( h \)
Hodgkin Huxley Model:

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

plus Equ. for \( m, h \) and \( n \)
Hodgkin-Huxley equations and simulation

\[
C \frac{dV}{dt} = -g_K n^4 (V - E_K) - g_{Na} m^3 h (V - E_{Na}) - g_L (V - E_L) + I(t)
\]

\[
\tau_n(V) \frac{dn}{dt} = -[n - n_0(V)]
\]

\[
\tau_m(V) \frac{dm}{dt} = -[m - m_0(V)]
\]

\[
\tau_h(V) \frac{dh}{dt} = -[h - h_0(V)]
\]
\[ C \frac{dV_m}{dt} = -\bar{g}_{Na} m^3 h (V_m - V_{Na}) - \bar{g}_K n^4 (V_m - V_K) - \bar{g}_L (V_m - V_L) + I_{inj} \]

\[ \dot{x} = -\frac{1}{\tau_x(u)} [x - x_0(u)] \]

**Figure 2.3:** Equilibrium function (A) and time constant (B) for the three variables \( m, n, h \) in the Hodgkin-Huxley model. The resting potential is at \( u = 0 \).

- If \( u \) increases, \( m \) increases -> Na+ ions flow into the cell
- at high \( u \), Na+ conductance shuts off because of \( h \)
- \( h \) reacts slower than \( m \) to the voltage increase
- K+ conductance, determined by \( n \), slowly increases with increased \( u \)
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?
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 potential 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

- Nernst / Goldman Simulator:  
  http://www.nernstgoldman.physiology.arizona.edu/
- Hodgkin Huxley Simulator:  
  http://www.cs.cmu.edu/~dst/HHsim/
- Neuron  
  http://www.neuron.yale.edu/neuron/
- Genesis  
  http://genesis-sim.org/
Further readings


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


Questions


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

