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Basic neuron models
Conductance-based models

\[- I_C(t) = c_m \frac{dV_m(t)}{dt} \]

\[ \begin{align*} I_C(t) &= g_L V_m(t) + I_{syn}(t), I_{ext} = 0 \\ I_{syn} &= g_{syn}(t)(V_m(t) - E_{syn}) \\ \tau_{syn} \frac{dg_{syn}(t)}{dt} &= -g_{syn}(t) + \delta(t - t_{pre} - t_{delay}) \end{align*} \]

A. Electric circuit of basic synapse

B. Time course of variables
MATLAB Program

%% 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:')
Hodkin and Huxley experiment NOBEL 1963

Sir Alan Lloyd Hodgkin

The Squid Giant Axon

Axial electrode

Sir Andrew Fielding Huxley

~ 0.5 mm
First direct (intracellular) recorded action-potential (spike) - 1939!!
Very nice theory

\[ I = C_m \frac{dV}{dt} + g_{Na} h m^3 (V - V_{Na}) + g_K n^4 (V - V_k) + g_L (V - V_L) \]  \hspace{1cm} (1)

\[ \frac{d}{dt} m = \alpha_m (V) (1 - m) - \beta_m (V) m \]  \hspace{1cm} (2)

\[ \frac{d}{dt} n = \alpha_n (V) (1 - n) - \beta_n (V) n \]  \hspace{1cm} (3)

\[ \frac{d}{dt} h = \alpha_h (V) (1 - h) - \beta_h (V) h \]  \hspace{1cm} (4)
Giant Nerve Cells of Squid

(A) Diagram of a squid, showing the location of its giant nerve cells. Different colors indicate the neuronal components of the escape circuitry. The first- and second-level neurons originate in the brain, while the third-level neurons are in the stellate ganglion and innervate muscle cells of the mantle. (B) Giant synapses within the stellate ganglion. The second-level neuron forms a series of fingerlike processes, each of which makes an extraordinarily large synapse with a single third-level neuron. (C) Structure of a giant axon of a third-level neuron lying within its nerve. The enormous difference in the diameters of a squid giant axon and a mammalian axon are shown below.

Squid giant axon = 800 \mu m diameter

Mammalian axon = 2 \mu m diameter
Voltage Clamp Method

1. One internal electrode measures membrane potential ($V_m$) and is connected to the voltage clamp amplifier.

2. Voltage clamp amplifier compares membrane potential to the desired (command) potential.

3. When $V_m$ is different from the command potential, the clamp amplifier injects current into the axon through a second electrode. This feedback arrangement causes the membrane potential to become the same as the command potential.

4. The current flowing back into the axon, and thus across its membrane, can be measured here.

Voltage clamp technique for studying membrane currents of a squid axon.
Membrane current in response to voltage clamp (VC)

For subthreshold depolarizing voltage clamp, the recorded membrane current is the current that flows via the leak (passive) conductance + a small capacitative current (at start and end of the VC).

For suprathreshold depolarizing voltage clamp, the recorded membrane current (after the fast capacitative current) flows first inwards (into the axon) and later outward (from inside to the outside).
Separating voltage-dependent active (excitable) currents Using pharmacological agents 2 different currents flow via the membrane during the spike.
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TEA blocks the late – slow non-inactivating current

Tetraethylammonium (TEA)

outward

inward
Changing ion concentration at bath with giant axon showed that early current is carried by Na$^+$ ions and late one by K$^+$ ions.
Ion currents (K+ and Na+) for various depolarizing voltage clamp (and extracting respective ion conductances)

\[ I_K = g_K (V_m - E_K); \quad I_{Na} = g_{Na} (V_m - E_{Na}) \]

The slow (K) current (conductance) does not inactivate during VC.

The K conductance rises slower than it decays at end of VC.

The fast (early) Na conductance inactivates during VC.
Fitting an equation for the K current (K-conductance) during/following VC

K-current in response to a step voltage clamp of 25 mV (upstroke) – slow rise following the VC and faster decay at the end of the VC

Mathematically – the rising phase of K-current can be described as a power of 4 (namely as $(1 - \exp(-t))^4$ and the decay as $\exp(-4t)$

\[ g_K = \bar{g}_K n^4 \]

$n$ represents the proportion of K-ion channels in the open state

“These equations may be given a physical basis if we assume that potassium ions can only cross the membrane when four similar particles occupy a certain region of the membrane…” Hodgkin AL, Huxley AF. 1952 J Physiol (Lond) 117:500–544
Graphical interpretation of H&H model for the K channel

Closed K channel (by 4 n gates)

n gate
n gate
n gate
n gate

4 n gates open with depolarization

K⁺ INSIDE

Open K channel (by 4 n gates)

K⁺ INSIDE
The activation function, \( n \), and the rate functions \( \alpha_n \) and \( \beta_n \)

\[
g_K = \bar{g}_K n^4, \\
\frac{dn}{dt} = \alpha_n (1 - n) - \beta_n n,
\]

where \( \bar{g}_K \) is a constant with the dimensions of conductance/cm\(^2\), \( \alpha_n \) and \( \beta_n \) are rate constants which vary with voltage but not with time and have dimensions of [time]\(^{-1}\), \( n \) is a dimensionless variable which can vary between 0 and 1.
Similar procedure is used to extract the activation (m) and inactivation (h) parameters for the Na current.

\[ g_{Na} = m^3 h \tilde{g}_{Na}, \]
\[ \frac{dm}{dt} = \alpha_m (1 - m) - \beta_m m, \]
\[ \frac{dh}{dt} = \alpha_h (1 - h) - \beta_h h, \]
Fitting Na current for different VC depolarizing values
Graphical interpretation of H&H model for the Na channel

Na channel (by 3 activated m gates and 1 inactivated h gate)

3 (fast) m (activated) gates open with depolarization

1 (slow) h (inactivated) gate closes with depolarization

Open Na channel
Na outside
Overlay of the action potential (voltage) and underlying Na and K conductances.

Fig. 17. Numerical solution of eqn. (31) showing components of membrane conductance ($g$) during propagated action potential ($-V$). Details of the analysis are as in Fig. 15.
Hodgkin–Huxley model

Figure: Typical form of an action potential; redrawn from an oscilloscope picture from Hodgkin and Huxley (1939).
The minimal mechanisms

Resting potential

+Na +Na
+Na +Na +Na
+K
+K
+K
+K
+K
+K
+K +K
+K
+Na

Depolarization

Hyperpolarization

+Na
+Na +Na
+Na
+Na +Na
+Na
+Na
+Na
+Na
+Na
+Na
+Na
+Na
\( l_{ion} = g_{ion}(V - E_{ion}) \)

- voltage and time dependent variables \( n(V, t), m(V, t), h(V, t) \)

\[
\hat{g}_K(V, t) = g_K n^4 \\
g_{Na}(V, t) = g_{Na} m^3 h
\]

HH structure

- \( l_{ext} \)
- Capacitor \( C \)
- Resistor of ion channels \( R_{Na}, R_{K} \)
- Reversal potentials \( E_{L}, E_{Na}, E_{K} \)
Hodgkin–Huxley equations and simulation

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

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

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

\[ \tau_h(V) \frac{dh}{dt} = -[h - h_0(V)] \]

\[ \frac{dx}{dt} = - \frac{1}{\tau_x(V)} [x - x_0(V)] \rightarrow x(t + \Delta t) = (1 - \frac{\Delta t}{\tau_x}) x(t) + \frac{\Delta t}{\tau_x} x_0 \]
Ion channels resistance

\[ x(0) = \frac{\alpha}{\alpha + \beta}, \quad t_x = \alpha \beta, \quad x \in \{n, m, h\} \]

\[ \alpha_n = \frac{10 - V}{100(e^{10 - V} - 1)}, \quad \beta_n = 0.125e^{-\frac{V}{80}} \]

\[ \alpha_m = \frac{25 - V}{10(e^{25 - V} - 1)}, \quad \beta_m = 4e^{-\frac{V}{18}} \]

\[ \alpha_h = 0.07e^{\frac{V}{20}}, \quad \beta_h = \frac{1}{e^{\frac{30 - V}{10}} + 1} \]
%% Integration of Hodgkin-Huxley equations with Euler method
clear; figure;%clf;

%% Setting parameters
% Maximal conductances (in units of mS/cm^2); 1=K, 2=Na, 3=R
% g(1)=36; g(2)=120; g(3)=0.3;
% Battery voltage (in mV); 1=n, 2=m, 3=h
% E(1)=-12; E(2)=115; E(3)=10.613;
% Initialization of some variables
I_ext=0; V=-10; x=zeros(1,3); x(3)=1; t_rec=0;
% Time step for integration
dt=0.01;

%% Integration with Euler method
for t=-30:dt:500
    if t==10; I_ext=6; end % turns external current on at t=10
    if t==400; I_ext=0; end % turns external current off at t=40
    % alpha functions used by Hodgkin-and Huxley
    Alpha(1)=(10-V)/(100*(exp((10-V)/10)-1));
    Alpha(2)=(25-V)/(10*(exp((25-V)/10)-1));
    Alpha(3)=0.07*exp(-V/20);
    % beta functions used by Hodgkin-and Huxley
    Beta(1)=0.125*exp(-V/80);
    Beta(2)=4*exp(-V/18);
    Beta(3)=1/(exp((30-V)/10)+1);
    % tau_x and x_0 (x=1,2,3) are defined with alpha and beta
    tau=1./(Alpha+Beta);
    x_0=Alpha.*tau;
    % leaky integration with Euler method
    x=(1-dt./tau).*x+dt./tau.*x_0; % x is m,n,h
    % calculate actual conductances g with given n, m, h
    gmnh(1)=g(1)*x(1)^4;
    gmnh(2)=g(2)*x(2)^3*x(3);
    gmnh(3)=g(3);
    % Ohm's law
    I=gmnh.*(V-E);
    % update voltage of membrane
    V=V+dt*(I_ext-sum(I));
    % record some variables for plotting after equilibration
    if t>=0;
        t_rec=t_rec+1;
        x_plot(t_rec)=t;
        y_plot(t_rec)=V;
    end
end
Refractory period

- waiting for inactivation of sodium channels about 1 ms
- absolute refractory period limiting firing rate to 1000Hz
- hyperpolarizing activity further limits the neuron’s rate
- relative refractory period
- brainstem neurons 600 Hz, cortical neurons 3 Hz
Propagation of action potentials

- action potentials = spikes travel about 10 m/s.
- non-loss signal transfer - SLOW
- myelin = FAST lossy signal transfer in axon
- Ranvier nodes = AP regeneration
- myelination happens after second year of age
- Alzheimer deceased - DESmyelination!
NON-LOSS transfer

1. Na⁺ channels locally open in response to stimulus, generating an action potential here.

2. Some depolarizing current passively flows down axon.

3. Local depolarization causes neighboring Na⁺ channels to open and generates an action potential here.

4. Upstream Na⁺ channels inactivate, while K⁺ channels open. Membrane potential repolarizes and axon is refractory here.

5. The process is repeated, propagating the action potential along the axon.
LOSSY transfer

(A) Myelinated axon

(B) Action potential propagation

$t=1$

$t=1.5$

$t=2$
Stimulation of neuron

(A) Neuron

(B) Graph showing current (mA) and membrane potential (mV) over time. The graph displays depolarization, resting potential, hyperpolarization, passive responses, and action potentials. The y-axis represents membrane potential in mV, ranging from -100 to +40, and the x-axis represents time.
HH - simplification: Hugh Wilson model for neocortical neurons

- \( h = 1 - n \)
- \( \tau_m \approx m_0(V) \)
- \( h = 1 \) no inactivation of the fast Na\(^+\) channel combining leakage and Na channel, only for cortical neurons
- \( R \) describes recovery of membrane potential
- 2 differential equations

\[
\begin{align*}
C \frac{dV}{dt} &= -g_K R(V - E_K) - g_{Na}(V)(V - E_{Na}) + I_{ext}(t) \\
\tau_R \frac{dR}{dt} &= -[R - R_0(V)]
\end{align*}
\]
Wilson model

- more realistic mammalian neocortical neurons
- two more channels types → more diverse firing
- cation $C_{a}^{2+}$ described by gating variable $T$
- slow hyperpolarizing current $Ca^{2+}$-mediated $K^+$ described by gating variable $H$

\[
C \frac{dV}{dt} = -g_{Na}(V - E_{Na}) - g_{K}R(V - E_{K}) - g_{T}(V - E_{T}) - g_{H}H(V - E_{H}) - I(t)
\]

\[
\tau_{R} \frac{dR}{dt} = -[R - R_{0}(V)]
\]

\[
\tau_{T} \frac{dT}{dt} = -[T - T_{0}(V)]
\]

\[
\tau_{H} \frac{dH}{dt} = -[H - 3T(V)]
\]

\[
g_{Na}(V) = 17.8 + 0.476V + 33.8V^2
\]

\[
R_{0}(V) = 1.24 + 3.7V + 3.2V^2
\]

\[
T_{0}(V) = 4.205 + 11.6V + 8V^2
\]
Wilson model: results

- RS: regular spiking neuron
- FS: fast spiking neuron
- CS: continuously spiking neuron
- IB: bursting neuron
Matlab implementation

```matlab
%% Integration of Wilson model with the Euler method
clear; clf;

%% Parameters of the model: 1=K, 2=Ca, 3=KCa, 4=Na
    g(1)=26; g(2)=2.25; g(3)=9.5; g(4)=1;
    E(1)=-0.95; E(2)=1.20; E(3)=E(1); E(4)=-0.50;

%% Initial values
    dt=0.01; I_ext=0; V=-1; x=zeros(1,4);
    tau(1)=dt./4.2; tau(2)=dt./14; tau(3)=dt./45; tau(4)=1;

%% Integration
    t_rec=0;

for t=-100:dt:200
    switch t;
        case 0; I_ext=1;
    end

    x0(1)=1.24 + 3.7*V + 3.2*V^2;
    x0(2)=4.205 + 11.6*V + 8*V^2;
    x0(3)=3*x(2);
    x0(4)=17.8 + 47.6*V + 33.8*V^2;

    x=x-tau.*(x-x0); %rem x(4)=x0(4) because tau(4)=1
    I=g.*x.*(V-E);
    V=V+dt*(I_ext-sum(I));

    if t==0;
        t_rec=t_rec+1;
        x_plot(t_rec)=t;
        y_plot(t_rec)=V;
    end
end % time loop

%% Plotting results
plot(x_plot,100*y_plot); xlabel('Time'); ylabel('Membrane potential');```
Physiology versus Neuron Models

Rall (1964)
Histological Vs. Schmertic Neurons

Histological Neurons

Schmertic Neurons
Understand experimental synaptic potentials recorded at the soma

1. Most of the input current flows into the dendrites (not directly to soma)
2. Dendrites are non-isopotential electrical devices
   (i) voltage attenuates from synapse to soma;
   (ii) it takes time (delay) for the PSP to reach the soma;
   (iii) somatic EPSP/IPSP shape is expected to change with synaptic location
Rall Cable Theory for Dendrites

Understanding (mathematically) the impact of (remote) dendritic synapses (the input) on the soma/axon (output) region

Wilfrid Rall
Cylindric model

A. Physiologically & morphologically characterized neuron

B. Cable model
Voltage attenuation

Synaptic potentials attenuate from the synapse origin towards other regions of the dendrites.
Axial and membrane current

Axial current (originated from the synapse)

Membrane current (lost via membrane resistance)

synapse
Passive cable equations

\[ \frac{r_m}{r_i} \left( \frac{2V(x,t)}{x^2} \right) - \frac{V(x,t)}{t} \left( r_m c_m \right) = 0 \]

\[ \frac{2V}{X^2} = \frac{V}{T} + V(X,T) \]

\[ X = \frac{x}{\lambda}, \quad T = \frac{t}{\tau_m} \]
Compartmental models

A. Chain of compartments

\[ j-1 \rightarrow j \rightarrow j+1 \]

B. Branching compartments

\[ j \rightarrow j+1 \rightarrow j+2 \]

C. Compartmental reconstruction
Cable theory

- discretization - compartments like branching $j, j + 1, j + 1$

\[
\lambda^2 \frac{\partial V_m(x, t)}{\partial x^2} - \tau_m \frac{\partial V_m(x, t)}{\partial t} - V_m(x, t) + V_0 = R_m l_{inj}(x, t)
\]

\[
\lambda = \sqrt{\frac{dR_m}{2R_i}}
\]

\[
\tau_m = R_m C_m
\]

\[
V_m = V_0 e^{-\frac{x}{\lambda}}
\]

\[
\frac{\partial V_m(x, t)}{\partial x^2} \leftarrow \frac{V_{j+1} - 2V_j(t) + V_{j-1}(t)}{(x_{j-1} - x_j)^2}
\]
Steady state condition

\[ \frac{d^2 V}{dX^2} = \frac{V}{T} + V(X,T) \]

("Sealed-end" boundary) \( dV/dX = 0; \ x=L \)
Simulating voltage attenuation

Rall and Rinzel, 1973
Simulators
Further Readings


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

