3.2 The Hodgkin-Huxley model
The integrate-and-fire model

« Integrate-and-fire »:

\[ \tau \frac{dV_m}{dt} = E_L - V_m + RI \]

If \( V = V_t \) (threshold)

then: neuron spikes and \( V \rightarrow V_r \) (reset)

Phenomenological description of action potentials: how are they generated?
Action potentials

The Hodgkin-Huxley model
Biophysics of spike initiation

Rest: Na+ channels are closed

$E_{Na} \approx 60 \text{ mV}$

channels inactivate: no current

channels open: Na+ enters

depolarization ($V_m \uparrow$)

repolarization ($V_m \downarrow$)
State transitions

Macroscopic equation (many channels):

\[
\frac{dm}{dt} = \alpha(V)(1 - m) - \beta(V)m
\]

\(m = \text{proportion of open channels}\)
Kinetic equation

\[ \frac{dm}{dt} = \alpha(V)(1 - m) - \beta(V)m \]

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

\[ \tau_m(V) = \frac{1}{\alpha(V) + \beta(V)} \] time constant

\[ m_\infty(V) = \frac{\alpha(V)}{\alpha(V) + \beta(V)} \] equilibrium value

\[ m_\infty(V) = \frac{1}{1 + \exp\left(\frac{V - V^{1/2}}{k}\right)} \] sigmoidal
The sodium current

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

\[ I = g_m(E_{Na} - V) \]

max. conductance (= all channels open)

reversal potential (= 50 mV)

\[ C \frac{dV}{dt} = g_l(E_l - V) + g_m(E_{Na} - V) \]

\[ \tau_m(V) \frac{dm}{dt} = m_\infty(V) - m \]
Triggering of an action potential

\[ C \frac{dV}{dt} = g_l (E_l - V) + g_m (E_{Na} - V) \]

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

The time constant of the sodium channel is very short (fraction of ms): we approximate \( m = m_\infty (V) \)

\[ C \frac{dV}{dt} = g_l (E_l - V) + g m_\infty (V) (E_{Na} - V) = f (V) \]
Triggering of an action potential

\[
C \frac{dV}{dt} = g_l(E_l - V) + g_{m\infty}(V)(E_{Na} - V) = f(V)
\]

What happens when the neuron receives a presynaptic spike?

\( V \rightarrow V + w \)

Below \( V_2 \), we go back to rest, above \( V_2 \), the potential grows (to \( V_3 \approx E_{Na} \))

\( V_2 \) is the threshold
Repolarization

- **Problem:** the potential does not go back to rest!
- **Solution:** inactivation of the channel

The channel inactivates when the potential is high.
Repolarization: inactivation

\[ C \frac{dV}{dt} = g_i(E_i - V) + \frac{ghm}{\tau_h} E_{Na} - V \]

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

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

\( h = \) proportion of non-inactivated channels

Product = independence hypothesis
Repolarization: potassium channel

Neurones also have potassium channels that open when \(V\) is high.

\[
C \frac{dV}{dt} = g_l (E_l - V) + \bar{g} m h (E_Na - V) + \bar{g}_K n (E_K - V)
\]

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

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

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

\(E_K \approx -90 \text{ mV}\)
The Hodgkin-Huxley model

Model of the squid giant axon

\[ C \frac{dV}{dt} = g_l (E_l - V) + g_m n^3 h (E_{Na} - V) + g_K n^4 (E_K - V) \]

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

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

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

the sodium channel has 3 independent « gates »

4 gates
The Hodgkin-Huxley model
Generation of an action potential

- Resting potential
- Generation of an action potential

Graphs showing the change in voltage over time.
Generation of an action potential

- Resting potential
- Brief current injection at $t=0$
- Resting potential
Generation of an action potential

brief current injection at t=0

Voltage increases
Voltage increases
brief current injection at t=0
Generation of an action potential

$K_{gating\ var~n}$

$Na_{gating\ var~m}$

brief current injection at t=0

Voltage increases

$h_\infty(V)$

$m_\infty(V)$

$n_\infty(V)$

steady-state value

Voltage V (mV)

0 0.2 0.4 0.6 0.8 1

$-100 -75 -50 -25 0 25$

$\tau_h(V)$

$\tau_m(V)$

$\tau_n(V)$

time constant $\tau$ (msec)

$-100 -75 -50 -25 0 25$

time (msec)
Generation of an action potential

Voltage increases very fast: Na channels activate

Voltage increases

\( h_\infty(V) \)
\( m_\infty(V) \)
\( n_\infty(V) \)

\( \tau_h(V) \)
\( \tau_m(V) \)
\( \tau_n(V) \)
Generation of an action potential

- Slower: Na channels inactivate
- Slower: K channels activate

Graphs showing time evolution of Na and K gating variables with voltage (mV) and time (msec) axes.
Generation of an action potential

Voltage keeps increasing very fast:

- Na channels activate

Voltage keeps increasing
Generation of an action potential

Almost all Na channels activated

Voltage keeps increasing
Generation of an action potential

Voltage keeps increasing

Almost all Na channels activated

But!! Many Na channels become inactivated

Voltage keeps increasing
Voltage starts decreasing

Almost all Na channels activated

But!! Many Na channels become inactivated

Generation of an action potential
Voltage keeps decreasing

In addition, K channels really kick in

But!! Many Na channels become inactivated

Voltage keeps decreasing
Generation of an action potential

- Voltage keeps decreasing.
- In addition, K channels really kick in.
- Na channels completely inactivated.
- Generation of an action potential.

Graphs showing the change in voltage over time, with corresponding changes in gating variables and time constants for Na, K, and h channels.
Voltage keeps decreasing

In addition, K channels really kick in

Na channels start deactivating

Generation of an action potential
Generation of an action potential

K channels still activated

Na channels deactivated

Na channels inactivated

Voltage hyperpolarized!
Generation of an action potential

- K channels still activated
- Na channels deactivated
- Na channels slowly de-inactivate
- Refractory period

Graphs showing the kinetics of sodium and potassium channels.
Generation of an action potential

Recovery of resting potential

- K channels slowly deactivate
- Na channels deactivated
- Na channels slowly de-inactivate
- Recovery of resting potential
Generation of an action potential

- $h_\infty(V)$
- $m_\infty(V)$
- $n_\infty(V)$
- $\tau_h(V)$
- $\tau_m(V)$
- $\tau_n(V)$
The refractory period

- Just after a spike, it is harder to trigger another one.
- Two causes:
  - Inactivation of sodium channels (fast): absolute refractory period (impossible to spike)
  - Opening of potassium channels (slower): relative refractory period (harder to spike)

the membrane resistance decreases

the threshold increases (possibly to infinity)
Other voltage-dependent channels

- Other channels open depending on potential.

\[ I = g_m (E - V_m) \]

\[ \tau_m(V_m) \frac{dm}{dt} = m_\infty(V_m) - m \]

- \( I \): Current
- \( g_m \): Max conductance
- \( m \): Proportion of open channels
- \( \tau_m \): Time constant
- \( m_\infty \): Equilibrium value

- \( V_m \): Voltage

\( \text{Na}^+ \) (sodium)

\( \text{K}^+ \) (potassium) – many different types

\( \text{Ca}^{2+} \) (calcium)

many other types of channels
Synaptic currents
Synaptic currents

\[ \tau \frac{dV_m}{dt} = E_L - V_m + R I_s \]
Idealized synapse

- Total charge \( Q = \int I_s \)
- Opens for a short duration
- \( I_s(t) = Q \delta(t) \)

\[
\tau \frac{dV_m}{dt} = E_L - V_m + RQ \delta(t)
\]

Spike-based notation:

\[
\tau \frac{dV_m}{dt} = E_L - V_m
\]

\[
V_m(t) = E_L + \frac{RQ}{\tau} e^{-\frac{t}{\tau}}
\]

\[
V_m \rightarrow V_m + \frac{RQ}{\tau} \text{ en } t=0
\]
A more realistic synapse model

Electrodiffusion: \[ I_s = g_s (E_s - V_m) \]

- ionic channel conductance
- synaptic reversal potential

\[ \tau \frac{dV_m}{dt} = E_L - V_m + R g_s (t) (E_s - V_m) \]
The synaptic reversal potential

- $E_s > V_t$: excitation
  - Threshold
  - Depolarization:
    - excitatory post-synaptic potential
    - excitatory synapse

- $E_s < V_t$: inhibition
  - Hyperpolarization:
    - inhibitory post-synaptic potential
    - inhibitory synapse
The post-synaptic current

Stochastic transitions in a single channel

\[ \begin{align*}
N_{\text{closed}} & \xrightarrow{\alpha} N_{\text{open}} \\
N_{\text{open}} & \xrightarrow{\beta} N_{\text{closed}}
\end{align*} \]

channel closed

channel open
The post-synaptic current

\[ N_{\text{closed}} \xrightarrow{\alpha} N_{\text{open}} \xrightarrow{\beta} N_{\text{closed}} \]

\[ N_{\text{total}} = N_{\text{open}} + N_{\text{closed}} \]

\[ P = \frac{N_{\text{open}}}{N_{\text{total}}} \]
First-order kinetics

\[ N_{\text{total}} = N_{\text{open}} + N_{\text{closed}} \]

\[ P = \frac{N_{\text{open}}}{N_{\text{total}}} \]

\[ \frac{dP}{dt} = \alpha (1 - P) - \beta P \]

fraction of closed channels

fraction of open channels
Opening rate depends on transmitter concentration

- Stochastic transitions between open and closed
  
  \[
  \begin{align*}
  C & \xrightarrow{\alpha[L]} O \\
  \beta & \xleftarrow{} C
  \end{align*}
  \]
  
  opening rate, proportional to concentration
  
  constant closing rate

Macroscopic equation (many channels):

\[
\frac{dP}{dt} = \alpha[L](1 - P) - \beta P
\]

proportion of open channels

\[
g_s(t) = P(t) \cdot g_{\text{max}}
\]

Assuming neurotransmitters are present for a very short duration:

\[
\tau_s \frac{dg_s}{dt} = -g_s \\
\]

\[
g_s \rightarrow g_s + \gamma
\]

\[
\tau_s = 1/\beta
\]
The post-synaptic potential

Post-synaptic effect:

\[ C \frac{dV_m}{dt} = g_L (E_L - V_m) + g_s (E_s - V_m) \]

\[ \tau_s \frac{dg_s}{dt} = -g_s \]

Presynaptic spike:

\[ g_s \rightarrow g_s + \gamma \]

\[ \tau_s = 1/\beta \]
Propagation of action potentials
Propagation is unidirectional because of the refractory period
Fig. 4. Highly integrated NW-neuron devices. (A) Optical image of aligned axon crossing an array of 50 NW devices with a 10-μm interdevice spacing. (B) Electrical data from the 50-device array shown above. The yield of functional devices is 86%. The peak latency from NW1 (top arrow) to NW49 (bottom arrow) was 1060 μs.
Electrical model of an axon

Assumptions:
• Extracellular milieu is conductor (= isopotential)
• Intracellular potential varies mostly along the dendrite (not across)

Let $V(x) = V_{\text{intra}}(x) - V_{\text{extra}}$
The cable equation

Kirchhoff’s law at position \( x \):

\[
\lambda^2 \frac{\partial^2 V}{\partial x^2} = \tau \frac{\partial V}{\partial t} + V - E_L
\]

\[\tau = R_mC_m\] membrane time constant

\[\lambda = \sqrt{\frac{dR_m}{4R_i}}\] space constant or «electrotonic constant»