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
Several types of active ion channels

+ light-gated (in the retina)
Biophysics of spike initiation

Na⁺ Cl⁻

K⁺

Rest: Na⁺ channels are closed

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

depolarization ($V_m \uparrow$)

channels open: Na⁺ enters

repolarization ($V_m \downarrow$)

channels inactivate: no current

$E_{Na} \approx 60 \text{ mV}$
The sodium channels

heterogeneous distribution of charges -> protein conformation can change with potential

Two stable conformations: open and closed

Sodium enters when the «gate» is open
State transitions

closed → open

transition requires energy proportional to $V$

$$\text{transition rate prop. to } e^{-\frac{aV}{T}}$$

(id. open → closed)

transition rate prop. to $e^{-\frac{bV}{T}}$ and $ab<0$
State transitions

Macroscopic equation (many channels):

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

\( m = \) proportion of open channels
Kinetic equation

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

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

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

equilibrium value

generates sigmoidal behavior

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

time constant

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

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

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

reversal potential (= 50 mV)

max. conductance (= all channels open)

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

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

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

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

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

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

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

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

\[ h = \text{proportion of non-inactivated channels} \]

Product = independence hypothesis

\( h_\infty(V) \) and \( m_\infty(V) \)
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

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

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

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

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

the sodium channel has 3 independent « gates »

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

K gating var n

Na gating var m

Na gating var h

resting potential
Generation of an action potential

brief current injection at $t=0$

resting potential
Generation of an action potential

brief current injection at \( t=0 \)

Voltage increases
Generation of an action potential

Voltage increases

brief current injection at t=0

Voltage increases
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
Voltage remains increasing very fast. Na channels activate.

Generation of an action potential.

- Voltage keeps increasing.
- Na channels activate.
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

Generation of an action potential
Generation of an action potential

- Voltage starts decreasing
- Almost all Na channels activated
- But!! Many Na channels become inactivated
- Voltage starts decreasing
Voltage keeps decreasing

In addition, K channels really kick in

But!! Many Na channels become inactivated

Voltage keeps decreasing
Voltage keeps decreasing. In addition, K channels really kick in. Na channels completely inactivated. Voltage keeps decreasing.

Generation of an action potential.
Generation of an action potential

In addition, K channels really kick in

Na channels start deactivating

Voltage keeps decreasing
Generation of an action potential

- Voltage hyperpolarized!
- 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**
Generation of an action potential

- **K channels** slowly deactivate
- **Na channels** deactivated
- **Na channels** slowly de-inactivate
- Recovery of resting potential

\[ h_\infty(V) \quad m_\infty(V) \quad n_\infty(V) \]

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

- **Graph 1**: Time evolution of the gating variables for potassium (K) and sodium (Na) channels. The blue line represents the potassium channel, and the red line represents the sodium channel.

- **Graph 2**: Steady-state values of the gating variables as a function of voltage. The red line represents $n_\infty(V)$, the green line represents $m_\infty(V)$, and the blue line represents $h_\infty(V)$.

- **Graph 3**: Time constants $\tau_h(V)$, $\tau_m(V)$, and $\tau_n(V)$ as a function of voltage.
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.

\[ I = \bar{g}m(E - V_m) \]

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

- \( \bar{g} \): Max conductance
- \( m \): Proportion of open channels
- \( \tau_m \): Time constant
- \( m_\infty \): Equilibrium value

- Na\(^+\) (sodium)
- K\(^+\) (potassium) – many different types
- Ca\(^{2+}\) (calcium)
- Many other types of channels
Synaptic currents
Synaptic currents

\[ \tau \frac{dV_m}{dt} = E_L - V_m + RI_s \]
**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:

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

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

Spike-based notation:

\[
V_m(t) \rightarrow V_m + \frac{RQ}{\tau}
\]

\( \text{en } t=0 \)
A more realistic synapse model

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

  - Ionic channel conductance
  - Synaptic reversal potential

- Conductance-based integrate-and-fire model

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

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

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

Stochastic transitions in a single channel

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

Opening rate

Closing rate

Channel closed

Channel open
The post-synaptic current

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

Opening rate

Closing rate

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

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

\[ N_{closed} \overset{\beta}{\underset{\alpha}{\rightleftharpoons}} N_{open} \]

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

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

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

fraction of closed channels

fraction of open channels
Opening rate depends on transmitter concentration

- Stochastic transitions between open and closed
  - Opening rate, proportional to concentration: \( \alpha[L] \)
  - Constant closing rate: \( \beta \)

**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:

\[
\tau_s \frac{dg_s}{dt} = -g_s \quad \quad g_s \rightarrow g_s + \gamma
\]

- \( \tau_s = 1/\beta \)
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 in the axon

Propagation is unidirectional because of the refractory period

We can show that \( v \propto \sqrt{d} \)
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 $V(x) = V_{\text{intra}}(x) - V_{\text{extra}}$
Electrical model of an axon

\[ I_i(x) = \frac{V(x) - V(x + dx)}{R \cdot dx} = - \frac{1}{R} \frac{\partial V}{\partial x} \]
Electrical model of an axon

Capacitance: \[ C \cdot dx = C_m \pi d \cdot dx \]

Membrane resistance: \[ \frac{R}{dx} = \frac{R_m}{\pi d \cdot dx} \]

Axial resistance: \[ R_a dx = \frac{4 R_i dx}{\pi d^2} \]
The cable equation

Kirchhoff’s law at position $x$:

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

$$\tau = R_mC_m$$  \hspace{1cm} \text{membrane time constant}

$$\lambda = \sqrt{\frac{dR_m}{4R_i}}$$  \hspace{1cm} \text{space constant or «electrotonic constant»}
Myelin

\[ \text{myelin = insulator} \]

sodium channels at « Ranvier nodes »
(= non-myelinized points)

« Saltatory » conduction, faster for thicker axons

We can show that \[ v \propto d \]