The Hodgkin-Huxley model

CO6 – Introduction to Computational Neuroscience

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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

$E_{Na} \approx 60$ mV

Rest: Na+ channels are closed

Channels open: Na+ enters

Depolarization ($V_m \uparrow$)

Repolarization ($V_m \downarrow$)

Channels inactivate: no current

$V_m$
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 $\rightarrow$ open

transition requires energy proportional to $V$

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

(id. open $\rightarrow$ 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

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

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

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

\[ m_\infty(V) = \frac{1}{1 + \exp\left(\frac{V - V_{1/2}}{k}\right)} \quad \text{sigmoidal} \]
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 \( m = m_\infty (V) \)

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

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

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

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

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

Product = independence hypothesis
Repolarization: potassium channel

Neurones also have potassium channels that open when $V$ is high.

$$C \frac{dV}{dt} = g_l (E_l - V) + g_{m} n m (E_{Na} - V) + g_{K} n (E_K - V)$$

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

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

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

$E_K \approx -90$ mV
The Hodgkin-Huxley model

The Hodgkin-Huxley model is a mathematical model of the squid giant axon, which was developed by Alan Hodgkin and Andrew Huxley. It describes the ionic currents that underlie the action potential in the giant axon of Loligo pealei, a type of squid. The model is based on the following equations:

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

The sodium channel has 3 independent «gates» and there are 4 gates in total.

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

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

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

The model won the Nobel Prize in Physiology or Medicine in 1963.
The Hodgkin-Huxley model
Generation of an action potential

resting potential
Generation of an action potential

brief current injection at $t=0$

resting potential
Generation of an action potential

Voltage increases briefly following a current injection at $t=0$.
Generation of an action potential

Voltage increases briefly at \( t=0 \)

- Voltage increases
- brief current injection at \( t=0 \)
- Voltage increases

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

\[ h(V), m(V), n(V) \]

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

Voltage increases very fast: Na channels activate

Voltage increases

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

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

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

Graphs show the time course of various gating variables and time constants as a function of voltage.
Generation of an action potential

Voltage keeps increasing very fast: Na channels activate

Voltage keeps increasing
Almost all Na channels activated
Voltage keeps increasing

Generation of an action potential

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

$\tau_h(V)$
$\tau_m(V)$
$\tau_n(V)$
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

Voltage starts decreasing

Generation of an action potential

steady-state value

Voltage V (mV)

time constant $\tau$ (msec)

Voltage V (mV)
Generation of an action potential

- Voltage keeps decreasing
- In addition, K channels really kick in
- But!! Many Na channels become inactivated
- Voltage keeps decreasing

**Graphs:**
- $h_\infty(V)$, $m_\infty(V)$, $n_\infty(V)$
- $\tau_h(V)$, $\tau_m(V)$, $\tau_n(V)$
Voltage keeps decreasing.

In addition, K channels really kick in.

Na channels completely inactivated.

Voltage keeps decreasing.

Generation of an action potential.
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**
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

- **K gating var n**
- **Na gating var m**
- **Na gating var h**
- **Voltage (mV)**

![Graphs showing time courses of K, Na, and voltage](image)

- **steady-state value**
- **time constant τ**

![Graphs of steady-state values and time constants](image)
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.

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

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

- Max conductance
- Proportion of open channels
- Time constant
- Equilibrium value

Na⁺ (sodium)
K⁺ (potassium) – many different types
Ca²⁺ (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:

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

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

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

- Ionic channel conductance
- Synaptic reversal potential

\[ g_s(t) \]

- Presynaptic spike

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

"Conductance-based integrate-and-fire model"
The synaptic reversal potential

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

  ![Graph showing depolarization with a threshold]

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

  ![Graph showing hyperpolarization]
The post-synaptic current

Stochastic transitions in a single channel

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

opening rate

closing rate

current (pA)

channel closed

channel open

t (ms)
The post-synaptic current

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

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

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

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

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

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

fraction of closed channels

fraction of open channels
Opening rate depends on transmitter concentration

- Stochastic transitions between open and closed
  \[
  \begin{align*}
  \text{C} & \xrightleftharpoons[\beta]{\alpha[L]} \text{O} \\
  \end{align*}
  \]
  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
\[g_s(t) = P(t) \times g_{\text{max}}\]

Assuming neurotransmitters are present for a very short duration:

\[
\tau_s \frac{dg_s}{dt} = -g_s
\]
\[g_s \to g_s + \gamma\]
\[\tau_s = 1/\beta\]
The post-synaptic potential

- Post-synaptic effect:

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

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

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

\[ I_i(x) = \frac{V(x) - V(x + dx)}{R_a \, dx} = -\frac{1}{R_a} \frac{\partial V}{\partial x} \]
**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: \[ R_a \cdot dx = \frac{4 R_i \cdot dx}{\pi d^2} \]
The cable equation

Kirchhoff’s law at position \( x \):

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

\( \tau = R_m C_m \)  
membrane time constant

\( \lambda = \sqrt{dR_m \over 4 R_i} \)  
space constant or « electrotonic constant »
Myelin

myelin = insulator

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

« Saltatory » conduction, faster for thicker axons

We can show that \( v \propto d \)