§III  Hodgkin-Huxley model (HH) - 1952

- study squid giant axon
- realistic treatment of ionic currents
- we focus on ‘big ideas’ of HH, don’t dwell on their numbers
  (voltage convention in their paper is confusing)

§III(a)  motivation

A cartoon picture of a HH neuron:

New details to include in the model
- multiple ion types
- variable conductance

What is the new equivalent electrical circuit?

Some numbers to keep in mind
- neuron size
  - ion concentration
- membrane capacitance
  - membrane resistance
  - membrane potential
§III(b) multiple ion channels
dealing with concentration gradients

- ion pumps
  - establish and maintain gradients
  - can move ions from low to high concentration
  - use energy (ATP)
  - Example:

- diffusion
  - pushes ions through channels, from high to low concentration
  - strength of push measured by Nernst potential

\[
V_{ion} = \frac{R}{z} \ln \left( \frac{[ions]^+}{[ions]^-} \right)
\]

\[
R = 8.314 \text{ J/mol} \cdot \text{K}
\]

\[
F = 96485 \text{ C/mol}
\]

\[
T = ^{\circ} \text{K}
\]

\[
z = \text{valence}
\]

the HH model includes 3 channels:
potassium channel

\[ [K^+]_{\text{inside}} \sim \quad [K^+]_{\text{outside}} \sim \quad V_K \sim \]

(HH chose \(V_K = -75\, \text{mV}\))

circuit analysis:

- 
- 

behavior of this circuit (i.e., channel):

- if \(V = V_K\) then no current flows

- if \(V > V_K\) then \(I_K > 0\)

- if \(V < V_K\) then \(I_K < 0\)
sodium channel

\[ [\text{Na}^+]_{\text{inside}} \sim \quad [\text{Na}^+]_{\text{outside}} \sim \quad V_{\text{Na}} \sim \]

(HH chose \( V_{\text{Na}} = +55 \text{ mV} \))

circuit analysis:

behavior of this circuit (i.e., channel):

- if \( V = V_{\text{Na}} \) then no current flows

- if \( V > V_{\text{Na}} \) then \( I_{\text{Na}} > 0 \)

- if \( V < V_{\text{Na}} \) then \( I_{\text{Na}} < 0 \)

leak channel

could try numbers for chlorine:

\[ [\text{Cl}^-]_{\text{inside}} \sim 4 \text{ mM}, \quad [\text{Cl}^-]_{\text{outside}} \sim 110 \text{ mM} \rightarrow \quad V_{\text{Cl}} \sim -90 \text{ mV} \]

or pick numbers to fit the data:

(HH chose \( V_{\text{L}} = -55 \text{ mV} \))

but still model this like Na and K channels:

\[ I_{\text{L}} = \]

even with all this extra detail, the model is still 1st order, so no AP!
§III(c) variable conductance

- each ‘channel’ is $\sim 10^6$ holes in membrane
  define $\bar{g}_i =$

- each hole fluctuates randomly between open and closed
  statistically, this averages out
  define $p =$

- the actual conductance is

- **voltage-gated** variable conductance:
  the differential equation for $p(t)$ depends on the membrane potential $V$

- on a circuit diagram:

---

*How do we model this?* It’s a little different for each channel.

- **L** leak current
  - passive conductance: no time evolution, so $p = 1$
  - HH chose $g_L = \bar{g}_L \approx 0.3 \mu S$
‘delayed rectifier’ potassium current

- includes four activating gates
- cartoon picture:

\[ g_K = \tilde{g}_K p \]

- \[ p = \text{ where } n = \]

\[ = \text{ probability of each gate being open } (0 \leq n \leq 1) \]

What is the differential equation that determines \( n(t) \)?

- rate equation: closed gates \((1 - n) = \) open gates \((n)\)

- the rates \( \alpha_n \) and \( \beta_n \) depend on \( V \) (hence ‘voltage-gated’)

  for example, \( \alpha_n(V) = \frac{0.01(55 - V)}{e^{(-V-55)/10} - 1}, \quad \beta_n(V) = 0.125e^{(-V-65)/80} \)

- rewrite in a more familiar format:

\[ -100 \text{ mV} \quad 0 \text{ mV} \quad +40 \text{ mV} \]

\[ +1 \quad 0.5 \quad 0 \]

\[ n_\infty(V) \]

\[ 10 \text{ ms} \]

\[ -100 \text{ mV} \quad 0 \text{ mV} \quad +40 \text{ mV} \]

\[ +1 \quad 0 \quad -1 \]

\[ \tau_n(V) \]

comments:

- don’t dwell on the complicated equations - think of it as data fitting

- qualitatively, \( n_\infty(V) \) is sigmoidal and \( \tau_n(V) \) is bell-shaped

- ‘activating’ gate because
'fast transient' sodium current

- includes three activating gates, one inactivating gate

- cartoon picture:

- $g_{Na} = \bar{g}_{Na} p$

- $p = \frac{m}{1 - m}$

  where $m$ = activating gating variable

  $h$ = inactivating gating variable

- differential equations for $m(t)$ and $h(t)$ are decay-type:

  \[
  m(t) = m(V) - \tau_m(V) m(V)
  \]

  \[
  h(t) = h(V) - \tau_h(V) h(V)
  \]

  where

  \[\begin{align*}
  m(V) &= \frac{\alpha_m(V)}{\alpha_m(V) + \beta_m(V)}, \\
  \alpha_m(V) &= \frac{0.1 e^{-V - 40}}{e^{-V - 40}/10 + 1}, \\
  \beta_m(V) &= 4 e^{-(V - 65)/18} \\
  h(V) &= \frac{\alpha_h(V)}{\alpha_h(V) + \beta_h(V)}, \\
  \alpha_h(V) &= 0.07 e^{-(V - 65)/20}, \\
  \beta_h(V) &= e^{-(V - 85)/10 + 1}
  \end{align*}\]

comments:

- $m$ is activating because $m_\infty \to 0$ at small $V$
  
  $m_\infty \to 1$ at large $V$

- $h$ is inactivating because $h_\infty \to 1$ at small $V$
  
  $h_\infty \to 0$ at large $V$

- again, much of the details is just data fitting
§III(d)  The HH model

The equivalent circuit:

Analysis:

- define $V$ = membrane potential
- (junction) $I_{\text{input}} =$
- (capacitor)

- channels $I_K =$
  
  $I_{Na} =$
  
  $I_L =$

combine:

\[
\begin{align*}
C \frac{dV}{dt} &= I_{\text{input}}(t) - \bar{g}_K n^4 (V - V_K) - \bar{g}_{Na} m^3 h (V - V_{Na}) - \bar{g}_L (V - V_L) \\
\frac{dn}{dt} &= -\frac{n - n_\infty(V)}{\tau_n(V)} \\
\frac{dm}{dt} &= -\frac{m - m_\infty(V)}{\tau_m(V)} \\
\frac{dh}{dt} &= -\frac{h - h_\infty(V)}{\tau_h(V)}
\end{align*}
\]

looks intimidating, but each piece now makes sense...
§III(e)  analysis of the HH model

- HH model is 4\textsuperscript{th} order - i.e., 4 differential equations for 4 dependent variables

- mathematical aside:
  - and \(N\)\textsuperscript{th} order system consists of \(N\) 1\textsuperscript{st} order equations
  - Example (\(N = 2\)) \[
  \frac{du}{dt} = v \\
  \frac{dv}{dt} = -ku
  \]

- HH model has a four-dimensional phase space

- fixed points
  - intuitively, we expect a fixed point (why?)
  - to locate it . . .
§III(f) dynamics of an AP in the HH model

Simulation of HH system provides insight into behavior of currents during an AP.

Four stages of an AP:

1. $I_{\text{input}}$ partially depolarizes the neuron
   - $n$ is slow to increase
   - $h$ is slow to decrease
   - $m$ is fast to increase

2. Positive feedback - the Na current depolarizes neuron, further increasing $g_{Na}$

3. $n$ eventually catches up
   $h$ eventually catches up

4. $n$ is slow to decrease in response to lower $V$
§III(g) good and bad of HH model

good:
- physiologically motivated
- realistic treatment of ion channels (Nernst potentials, variable conductance, etc.)
- matches experiments (NOTE: ‘Experiments’ from §I(b) were simulations of HH model)
- insight into dynamics of AP
- broadly applicable beyond squid giant axons (lots of parameters, easily extended, etc.)

bad:
- mathematically complex
- potentially slow to simulate large networks
- can’t do much analytically (resting potential, threshold, etc.)

What next?

- figure out how to measure the parameters in the model
- increase complexity - more channels, more gating options, etc.
- decrease complexity
1-page summary of the HH model:

The Hodgkin-Huxley model of a neuron consists of a system of four coupled first-order differential equations. The four dependent variables are \( V, n, m, h \); these are, in order, the membrane potential, a gating variable for the potassium channel, and two gating variables for the sodium channel. Set \( V = 0 \) outside the cell (though Hodgkin and Huxley adopted a different voltage convention) and the differential equations take the form:

\[
C \frac{dV}{dt} = I_{\text{input}}(t) - \bar{g}_n n^4 (V - V_K) - \bar{g}_m n^3 m(V - V_{Na}) - \bar{g}_L (V - V_L) \tag{1}
\]

\[
\frac{dn}{dt} = -\frac{n - n_\infty(V)}{\tau_n(V)} \tag{2}
\]

\[
\frac{dm}{dt} = -\frac{m - m_\infty(V)}{\tau_m(V)} \tag{3}
\]

\[
\frac{dh}{dt} = -\frac{h - h_\infty(V)}{\tau_h(V)}, \tag{4}
\]

where the externally applied current \( I_{\text{input}}(t) \) is a prescribed function. Typical values of the parameters are:

- **Nernst potentials:** \( V_K = -77 \text{ mV}, \ V_{Na} = +50 \text{ mV}, \ V_L = -54.4 \text{ mV} \)
- **maximum conductances:** \( \bar{g}_K = 36 \mu \text{mho}, \ \bar{g}_{Na} = 120 \mu \text{mho}, \ \bar{g}_L = 0.3 \mu \text{mho}, \)

and \( C = 1 \text{nF} \) (based on a neuron with 0.1 \text{mm}^2 area). The nonlinear functions \( \mu_\infty(V), \tau_\mu(V) \) — where \( \mu = n, m, h \) — are plotted in Figure 1, and are based on experimental measurements. Often, the differential equations (2)–(4) for the gating variables are written instead in the form:

\[
\frac{d\mu}{dt} = \alpha_\mu(V)(1 - \mu) - \beta_\mu(V)\mu \quad \text{where} \quad \mu = n, m, h.
\]

The \( V \)-dependent functions are related by:

\[
\mu_\infty(V) = \frac{\alpha_\mu(V)}{\alpha_\mu(V) + \beta_\mu(V)}; \quad \tau_\mu(V) = \frac{1}{\alpha_\mu(V) + \beta_\mu(V)} \quad \text{for} \quad \mu = n, m, h.
\]

A typical choice of the \( \alpha_\mu(V) \) and \( \beta_\mu(V) \) functions, again based on fitting data, is:

\[
\alpha_n(V) = \frac{0.01(-V - 55)}{e^{(-V - 55)/10} - 1} \quad \alpha_m(V) = \frac{0.1(-V - 40)}{e^{(-V - 40)/10} - 1} \quad \alpha_h(V) = 0.07e^{(-V - 65)/20}
\]

\[
\beta_n(V) = 0.125e^{(-V - 65)/80} \quad \beta_m(V) = 4e^{(-V - 65)/18} \quad \beta_h(V) = \frac{1}{e^{(-V - 35)/10} + 1}
\]

where \( \alpha_\mu \) and \( \beta_\mu \) are measured in \text{ms}^{-1}, and \( V \) in \text{mV}. Note that one must always be careful to use \( \alpha_\mu(V) \) and \( \beta_\mu(V) \) functions that are consistent with the voltage convention.

![Figure 1: Plots of the functions \( \mu_\infty(V) \) and \( \tau_\mu \), where \( \mu = n, m, h \).](image-url)
Example of a modern HH-style model - excerpts from:

In Eq. 1, $C_p$ is the capacitance of compartment $i$ and $V_i$ the transmembrane voltage. The sum is taken over all compartments $m$ that are connected to compartment $i$: $\tau_mC_p$ is the conductance (internal) between the respective compartments (with the assumption that the extracellular space is isopotential): $I_{\text{ion}}$ is the transmembrane ionic current for compartment $i$: one must be careful about the sign of this term, as inward currents (which depolarize the membrane) are, by convention, negative. For the membrane potential to increase during an inward current, we need the minus sign before $I_{\text{ion}}$

$$\tau_mC_p \frac{dV_i}{dt} = -\sum_{m} \tau_mC_p (V_m - V_i) - I_{\text{ion}}$$

(1)

In Eq. 2, $\delta x_{\text{syn}}$ is the (time-dependent) $\alpha$-amino-3-hydroxy-5-methyl-4-isoxazolopyridine (AMPA) receptor conductance, which has a reversal potential of 0 mV and $g_{\text{Ca, K-dependent}}$ is the (time-dependent) $\gamma$-aminobutyric acid-A (GABA)$A$ receptor conductance, with −81 mV reversal potential. Other types of synaptic conductance were not simulated.

$$I_{\text{ion}}(V + 70) = (g_{\text{Ca, K-dependent}} + g_{\text{Ca, V-dependent}})(V - 90) + \frac{g_{\text{Ca, K-dependent}} - g_{\text{Ca, V-dependent}}}{A} (V - 95) + \frac{(g_{\text{Ca, K-dependent}} + g_{\text{Ca, V-dependent}})(V - 125) + g_{\text{Ca, K-dependent}}(V + 35)}{(V + 81)}$$

(2)

The evolution of the $m$ and $A$ variables follows the Hodgkin-Huxley first-order differential equations

$$\frac{d\alpha}{dt} = a_1(1 - \alpha)(\beta_1 - \beta_2) \frac{V}{40}$$

(4)

Here, $a_1$, $a_2$, $a_3$, and $a_4$ are predefined functions of membrane potential, or—in the case of the AHP conductance—of $4 - [\text{Ca}]$.

The units are m$^2$. The dynamics defined this mean that, if voltage is fixed, the $m$ and $A$ variables relax toward steady-state values, $m_\infty$ and $A_\infty$, with respective time constants $\tau_m$ and $\tau_A$. The rate functions and the steady-state values/time constants are interchangeable through the easily derived relations $m = m_\infty + (m_\infty - m_\infty) \exp(-t/\tau_m)$ and similar relations holding for the $A$ variables. Thus specification of the rate functions, or of the steady-values and time constants, are equivalent. This information is provided in the appendix. Axonal and somata/dendritic conductances were assumed to possess the same kinetics.

**APPENDIX**

**Further model parameters**

<table>
<thead>
<tr>
<th>Table A1. Ionic conductance densities (mS/cm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conductance Type</td>
</tr>
<tr>
<td>------------------</td>
</tr>
<tr>
<td>$g_{\text{Na, transient}}$</td>
</tr>
<tr>
<td>$g_{\text{Na, persistent}}$</td>
</tr>
<tr>
<td>$g_{\text{K transient}}$</td>
</tr>
<tr>
<td>$g_{\text{K delayed rectifier}}$</td>
</tr>
<tr>
<td>$g_{\text{K transient (KA)}}$</td>
</tr>
<tr>
<td>$g_{\text{K low threshold}}$</td>
</tr>
<tr>
<td>$g_{\text{Na-AHP}}$</td>
</tr>
<tr>
<td>$g_{\text{K transient (KA)}}$</td>
</tr>
</tbody>
</table>

---

**Table A2. Ionic conductance kinetic parameters**

<table>
<thead>
<tr>
<th>Conductance Type</th>
<th>Steady-State Activation/Inactivation</th>
<th>Time Constant (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$g_{\text{Na, transient}}$</td>
<td>1/(1 + exp[(-V - 34.9)/10])</td>
<td>0.025 + 0.14 exp[10 - 26.9]/10</td>
</tr>
<tr>
<td>$g_{\text{Na, transient}}$</td>
<td>1/(1 + exp[(-V - 59.6)/10])</td>
<td>0.15 + 1.13 exp[10 - 33.8]/15</td>
</tr>
<tr>
<td>$g_{\text{Na, delayed rectifier}}$</td>
<td>1/(1 + exp[(-V - 20.9)/10])</td>
<td>0.02 + 0.14 exp[10 - 40.1]/10</td>
</tr>
<tr>
<td>$g_{\text{K transient (KA)}}$</td>
<td>1/(1 + exp[(-V - 40.8)/1])</td>
<td>0.25 + 4.35 exp[10 - 10]/1</td>
</tr>
<tr>
<td>$g_{\text{K low threshold}}$</td>
<td>1/(1 + exp[(-V - 78))/1])</td>
<td>0.185 + 0.85 exp[10 - 33.8]/15</td>
</tr>
<tr>
<td>$g_{\text{K transient (KA)}}$</td>
<td>1/(1 + exp[(-V - 80.7)/1])</td>
<td>0.19 + 0.26 exp[10 - 80.7]/1</td>
</tr>
<tr>
<td>$g_{\text{K transient (KA)}}$</td>
<td>1/(1 + exp[(-V - 50.9)/1])</td>
<td>0.25 + 4.35 exp[10 - 10]/1</td>
</tr>
<tr>
<td>$g_{\text{K low threshold}}$</td>
<td>1/(1 + exp[(-V - 78))/1])</td>
<td>0.15 + 0.3 exp[10 - 33.8]/15</td>
</tr>
<tr>
<td>$g_{\text{Na-AHP}}$</td>
<td>1/(1 + exp[(-V - 91.3)/1])</td>
<td>0.02 + 0.14 exp[10 - 26.9]/10</td>
</tr>
</tbody>
</table>

---

**Kinetie data for activation, unless specified otherwise: Membrane potential, V, in mV. [Ca]-dependence of “C” and AHP conductances are described in method, as is description of [Ca] dynamics. “y” designates [Ca], units arbitrary.**