The Hodgkin-Huxley Model: A Quick Historical Overview

Rob Kass

Department of Statistics
and
The Center for the Neural Basis of Cognition
Carnegie Mellon University
Action Potential and Spike Trains

The conception that information is conveyed by sequences of action potentials (spike trains) has resulted from more than 100 years of neurophysiological investigation.

It involves both the relation of action potentials to behavior, and an explicit, detailed understanding of how action potentials work. The latter is the triumph of the Hodgkin-Huxley model. I have broken the basic argument into 6 historical steps, of which the Hodgkin-Huxley model is the last.

Neuronal representation of information: Timeline relative to Statistics.

- Pearson
- Fisher
- Wald
- Savage
- Box–Cox
- Cooley–Tukey
- 1900
- Bernstein
- Cajal
- Sherrington

- Adrian

- Wiener
- Shannon
- McCulloch–Pitts
- 1970

- Hodgkin–Huxley
- Katz
- Hubel and Wiesel
- Evarts
Minimum Background on Circuits

Q=Charge
C=Capacitance
V=Voltage=E
I=Current
g=Conductance=1/Resistance=1/R

\[ Q(t) = CV(t) \]
\[ I(t) = \frac{dQ}{dt} \]
\[ C \frac{dV}{dt} = I(t) \]
\[ I = \frac{V}{R} \]
\[ I(t) = g(t)V(t) \]
1. Signals are transmitted electrically (Galvani, 1791).
1. Signals are transmitted electrically.

Volterra disputed Galvani’s interpretation and, in trying to prove him wrong, invented the battery (the “Voltaic pile”).

In the mid-1800s Matteucci, and then Du Bois-Reymond, reported an increase in current in a pile of frog thighs in proportion to the number of thighs in the pile.

In the mid-1800s von Helmholtz, then Bernstein measured the speed of propagation of the nervous impulse. Bernstein also carefully matched the speed of the impulse with the speed of the electrical field and showed the duration of the field at any location to be roughly 1 millisecond.

But a puzzle emerged: why was the propagation of “animal electricity” many orders of magnitude slower than that of other electrical fields?
2. Nerves are made up of individual neurons (the “neuron doctrine”; Cajal, 1886).
3. Signals are transmitted from one neuron to another across synapses (Sherrington, 1897).

4. Action potentials are not graded in intensity; they are “all or nothing” (Adrian, 1926).

5. Substantial information is contained in the neuronal firing rate (Adrian, 1926; Hubel and Wiesel, 1962; Evarts, 1966).

Textbook depiction: A neuron responds to a relevant stimulus, or contributes to the production of an action, by increasing its firing rate. (next slide)
6. Action potentials result from the flow of ions across excitable membranes.

- Membranes can be electrically excitable (Bernstein, 1902; based on Nernst, 1888).
- Ion channels gate the flow of ions across membranes (Cole and Curtis, 1939).
- Sodium ions (in addition to potassium ions) are involved in action potential generation (Hodgkin and Katz, 1949).
- Hodgkin and Huxley (1952): Action potential generation may be described quantitatively using
  - voltage-current-capacitance relationships, and
  - voltage-dependent conductances of distinct ions.
6A. The “membrane hypothesis.”

Nernst Equation:

\[ \Delta V = \frac{RT}{ZF} \log \left( \frac{[ion]_o}{[ion]_i} \right) \]
First jiffy

\[ E = 0 \]

\[ K^+ \rightarrow K^+ \]

\[ A^- \rightarrow A^- \]

Equilibrium

\[ E = E_K \]

\[ K^+ \leftrightarrow K^+ \]

\[ A^- \leftrightarrow A^- \]
\[ \phi(x) = \text{Concentration} \]

Consider current flowing from \( x \) to \( x + dx \)

current due to concentration gradient \( \propto d\phi = \frac{d\phi}{dx} dx \)

current due to electrical potential gradient \( \propto \phi(x)dV = \phi(x) \frac{dV}{dx} dx \)

Equating these, dividing by \( \phi(x) \), and integrating gives

\[ V(x_2) - V(x_1) \propto \log \frac{\phi(x_2)}{\phi(x_1)} \]
(A) EQUIVALENT CIRCUIT

(B) INTERPRETATION
\[
\frac{dV}{dt} = -\frac{V}{CR}
\]
6B. Ion channels

Open

Closed
6B. Ion channel gating

**Open-Shut Gating of an Ionic Channel**

Ionic current flowing across a tiny patch of excitable membrane showing eight brief openings (downward current deflections) of single ionic channels. The membrane patch has been excised from a cultured rat myotube and is bathed on both sides by Na salt solutions. Approximately 300 nM of the neurotransmitter, acetylcholine, applied to the extracellular membrane face is causing channels to open occasionally. At the −140 mV applied membrane potential, one open channel passes −6.6 pA, corresponding to a prodigious flow of $4.1 \times 10^7$ ions per second through a single pore. $T = 23^\circ C$. [From Sánchez et al., 1986.]
6C. Sodium ions are involved in action potential generation.
6. Action potentials result from the flow of ions across excitable membranes.

- Membranes can be electrically excitable (Bernstein, 1902; based on Nernst, 1888).
- Ion channels gate the flow of ions across membranes (Cole and Curtis, 1939).
- Sodium ions (in addition to potassium ions) are involved in action potential generation (Hodgkin and Katz, 1949).
- Hodgkin and Huxley (1952): Action potential generation may be described quantitatively using voltage-current-capacitance relationships, and voltage-dependent conductances of distinct ions.
6D. Hodgkin-Huxley Model (1)

[Diagram of the Hodgkin-Huxley model showing the states of sodium channels and the changes in membrane potential.]

1. Sodium channel in closed state.
2. sodium channels open, Na+ begins to enter cell.
3. Na+ channels become refractory, no more Na+ enters cell.
4. K+ continues to leave cell, causes membrane potential to return to resting level.
5. K+ channels close, Na+ channels reset.

Membrane potential (mV)

Threshold of excitation: -70 mV

Sodium ions enter

Refactory

Reset

Open

Closed
6D. Hodgkin-Huxley Model (2)

Hodgkin-Huxley model

\[ \text{inside} \]

\[ \text{outside} \]

\[ I_K \]

\[ g_K \]

\[ E_K \]

\[ I_Na \]

\[ g_{Na} \]

\[ E_{Na} \]

\[ I_L \]

\[ g_L \]

\[ E_L \]

\[ I_C \]

\[ C_m \]
Hodgkin-Huxley equations

\[
C_m \frac{dV}{dt} = -g_L(V - V_L) - g_{Na} m^3 h (V - V_{Na}) - g_K n^4 (V - V_K)
\]

\[
\frac{dm}{dt} = \alpha_m(V)(1 - m) - \beta_m(V) m
\]

\[
\frac{dh}{dt} = \alpha_h(V)(1 - h) - \beta_h(V) h
\]

\[
\frac{dn}{dt} = \alpha_n(V)(1 - n) - \beta_n(V) n
\]
Potassium Channel Kinetics

For each “gate,” consider transition from time $t$ to time $t + dt$

$P(\text{open at time } t) = n(t)$
$P(\text{transition open } \rightarrow \text{ closed}) = \beta dt$
$P(\text{transition closed } \rightarrow \text{ open}) = \alpha dt$

These imply

$$dn = (1 - n(t))\alpha dt - n(t)\beta dt$$

And if 4 gates operate independently,

$P(\text{all gates open at time } t) = n(t)^4$
6D. Hodgkin-Huxley conductance measurements

(A) Na CONDUCTANCE

(B) K CONDUCTANCE

Conductance (mS/cm²)

Time after start of test pulse (ms)

- 44 mV
- 23 mV
- -2 mV
- -27 mV
- -39 mV
6E. Successes of Hodgkin-Huxley Model

150-year-old problem of “animal electricity” solved; correct predictions of
- conductances (shown above);
- form of action potential (obtained by laborious solution of equations; 8 hours per 5 milliseconds), including “undershoot”;
- change in action potentials with varying concentrations of sodium;
- number of sodium ions involved in inward flux;
- speed of action potential propagation;
- voltage curves for sodium and potassium separately.