Mathematical Modeling of Biological Neurons

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Outline:

- **Introduction**
  1. cerebral cortex and neuron
  2. synapse and neuronal network

- **Hodgkin-Huxley model**
  1. experimental setup
  2. mathematical modeling

- **Theoretical and numerical results**
  1. phase plane analysis
  2. numerical simulation of dynamics
  3. your project
Neuron and neuronal network
Cerebral Cortex

- $10^{11}$ neurons and $10^{15}$ connections in human brain
- $10^4$ cells and 1 km wiring per mm$^2$ in the cortex
- different shape, size and function

Area: ~2200cm$^2$
Thickness: 2~3mm
Neuron

**Dendrite** (树突)  “input device”

**Soma** (胞体)  “central processing unit”

**Axon** (轴突)  “output device”

**Action Potentials** (电脉冲)

Information encoding and decoding

- Encoding
  - $u(t)$ → $t_0, t_1, t_2, \ldots$

- Decoding
  - $t_0, t_1, t_2, \ldots$ → $u(t)$
Synapses

The connection between two neurons

• Axons of Presynaptic neuron (sending signal)

• Synapse

• Dendrites of Postsynaptic neuron (receiving signal)

• A neuron may be connected to $10^2-10^4$ other postsynaptic neurons
• Some axons reach several cm’s away!
• Chemical synapses: most common in vertebrate brain
• Electrical synapses (gap junctions): direct electrical coupling (may be involved in ‘synchronization’ of neurons)
What happens at a Synapse?

1. **Calcium channels** open leading to calcium influx
2. **Synaptic vesicles** fuse with cell membrane
3. **Neurotransmitters** released into synaptic cleft
4. Neurotransmitters diffuse across synaptic cleft and **binds to receptors** on postsynaptic dendrite
5. **Ion channels** open
6. Inward or outward **flux of ions** changes membrane potential of postsynaptic neuron
RC circuit (warm up)
Cell Membrane

Membrane: 3 to 4 nm thick, essentially impermeable

Ionic Channels: Selectively permeable
The Membrane: Capacitance

\[ C = \frac{Q}{V} \quad (Q = CV) \]

1 Farad = 1 Coulomb/ 1 Volt

\[ \frac{dQ}{dt} = I \]

\[ I = C \frac{dV}{dt} \]
The Membrane: Resistance

$$R = \frac{V}{I}$$

1 Ohm = 1 Volt/1 Ampere

$$I = \frac{V}{R}$$
The Membrane: Capacitance and Resistance

\[ I = C \frac{dV}{dt} + \frac{V}{R} \]

\[ (C*R) \frac{dV}{dt} = -V + IR \]

Outside

Inside

Current I

Voltage V

Current I

Voltage V
The Membrane Potential

Two types of ions (sodium $\text{Na}^+$ and potassium $\text{K}^+$)

Reversal Potential: when opposing currents balance each other out.

Nernst Equation: $E \propto \log \frac{[\text{extra}]}{[\text{intra}]}$

$\text{Na}^+: +50 \text{ mV}, \quad \text{K}^+: -77 \text{ mV}$

Equilibrium Potential: averaged by different ions (-70 mV).
Mathematical modeling
Hodgkin-Huxley model

Alan L. Hodgkin 1914-1998
Andrew F. Huxley 1917-

1963 Nobel Prize

Squid giant axon

J. Physiol. (1952) 117, 500–544

A QUANTITATIVE DESCRIPTION OF MEMBRANE CURRENT AND ITS APPLICATION TO CONDUCTION AND EXCITATION IN NERVE

By A. L. HODGKIN AND A. F. HUXLEY
From the Physiological Laboratory, University of Cambridge
(Received 10 March 1952)

This article concludes a series of papers concerned with the flow of electric current through the surface membrane of a giant nerve fibre (Hodgkin, Huxley & Katz, 1952; Hodgkin & Huxley, 1952a–c). Its general object is to discuss the results of the preceding papers (Part I), to put them into mathematical form (Part II) and to show that they will account for conduction and excitation in quantitative terms (Part III).
Hodgkin-Huxley Equations

\[ V(x,t) \quad I(x,t) \]

\( x : \) distance along axon

\( a : \) radius of the axon  \quad \rho : \) resistivity of axon

t: time,  \( i(x,t) : \) axial current,  \( V(x,t) : \) internal voltage
\( I(x,t) : \) trans-membrane current per unit area
C: membrane capacitance per unit area
\( g_L : \) leakage conductance per unit area
\( g_{Na}, g_K : \) conductance per unit area of \( Na^+, K^+ \)
\( E_L : \) equilibrium potential for leakage ccurrent
\( E_{Na}, E_K : \) equilibrium potential for \( Na^+, K^+ \)
Hodgkin-Huxley Equations

Charge conservation:

\[ i(x_2, t) - i(x_1, t) = - \int_{x_1}^{x_2} 2\pi a \cdot I(x, t) \, dx \]

\[ \Rightarrow \int_{x_1}^{x_2} \left( \frac{\partial i}{\partial x} + 2\pi a I \right) \, dx = 0 \]

Since \( x_1 \) and \( x_2 \) are arbitrary, we have:

\[ \frac{\partial i}{\partial x} + 2\pi a I = 0 \]
Hodgkin-Huxley Equations

Ohm’s law for axial current:

\[ i(x,t) = -\frac{\pi a^2}{\rho} \frac{\partial V}{\partial x} \]

Membrane current is the sum of capacitance and ionic current

\[ I = C \frac{\partial V}{\partial t} + g_L (V - E_L) + G_{Na} (V - E_{Na}) + G_K (V - E_K) \]
Hodgkin-Huxley Equations

Sodium ion channels (Na⁺)
Let the sodium channel consist of 4 independent subunits, but 3 of them are one type (S¹) and 1 is another type (S²). Let each type of subunits have two states with voltage dependent transitions

\[ S^1 \overset{\alpha_m(V)}{\leftrightarrow} \beta_m(V) \rightarrow (S^1)^* \quad S^2 \overset{\alpha_h(V)}{\leftrightarrow} \beta_h(V) \rightarrow (S^2)^* \]

The channel is open if and only if all 4 subunits are in the state \(S^*\). Now consider a large population of channels, and let \(m\) be the fraction of subunits in the state \((S^1)^*\) and \(h\) be the fraction of subunits in the state \((S^2)^*\). Then the conductance due to sodium channel is given by

\[ G_{Na} = g_{Na} m^3 h \]

And \(m\) and \(h\) satisfy the kinetic differential equation as:

\[ \frac{\partial m}{\partial t} = \alpha_m(V)(1-m) - \beta_m(V)m, \quad \frac{\partial h}{\partial t} = \alpha_h(V)(1-h) - \beta_h(V)h \]
Hodgkin-Huxley Equations

Potassium ion channels (K⁺)

Let the potassium channel consist of 4 identical and independent subunits, each of which has two possible states (S and S*) with voltage dependent transitions

\[ S \overset{\alpha_n(V)}{\underset{\beta_n(V)}{\leftrightarrow}} S^* \]

The channel is open if and only if all 4 subunits are in the state S*. Now consider a large population of channels, and let n be the fraction of subunits in the state S*. Then the conductance due to potassium channel is given by

\[ G_K = g_K n^4 \]

And n satisfies the kinetic differential equation as:

\[ \frac{\partial n}{\partial t} = \alpha_n(V)(1-n) - \beta_n(V)n \]
Hodgkin-Huxley Equations

\[
\begin{align*}
C \frac{\partial V}{\partial t} + g_L (V - E_L) + g_{Na} m^3 h (V - E_{Na}) + g_K n^4 (V - E_K) &= \frac{a}{2 \rho} \frac{\partial^2 V}{\partial x^2} \\
\frac{\partial m}{\partial t} &= \alpha_m (V) (1 - m) - \beta_m (V) m \\
\frac{\partial h}{\partial t} &= \alpha_h (V) (1 - h) - \beta_h (V) h \\
\frac{\partial n}{\partial t} &= \alpha_n (V) (1 - n) - \beta_n (V) n
\end{align*}
\]

Where \( E_L = -54.387 \text{mV} \), \( E_{Na} = +50 \text{mV} \), \( E_K = -77 \text{mV} \)

\[
C = 1 \mu F / \text{cm}^2, \quad a = 0.0238 \text{cm}, \quad \rho = 35.4 \Omega \text{cm} = 0.0354 \left( \frac{\text{mV}}{\mu A} \right) \text{cm}
\]

\[
g_L = 0.3 \left( \frac{\mu A}{\text{mV}} \right) / \text{cm}^2, \quad g_{Na} = 120 \left( \frac{\mu A}{\text{mV}} \right) / \text{cm}^2, \quad g_K = 36 \left( \frac{\mu A}{\text{mV}} \right) / \text{cm}^2
\]
Hodgkin Huxley Equations

\[ \alpha_m, \alpha_h, \alpha_n : \text{opening rate. } \beta_m, \beta_h, \beta_n : \text{closing rate} \]

\[ \alpha_m = \frac{0.1(V + 40)}{1 - \exp\left(-\frac{V + 40}{10}\right)} \]

\[ \beta_m = 4 \exp\left(-\frac{V + 65}{18}\right) \]

\[ \alpha_h = 0.07 \exp\left(-\frac{V + 65}{20}\right) \]

\[ \beta_h = \frac{1}{1 + \exp\left(-\frac{V + 35}{10}\right)} \]

\[ \alpha_n = \frac{0.01(V + 55)}{1 - \exp\left(-\frac{V + 55}{10}\right)} \]

\[ \beta_n = 0.125 \exp\left(-\frac{V + 65}{80}\right) \]

1. System contains both time and space (PDE)
2. The dimension is four (e.g. phase plane analysis)
3. Functional forms comes from data fitting (complicated)
4. Boundary conditions (geometrical structure)
Hodgkin Huxley Equations

Quantitative behavior of the Hodgkin-Huxley equations:
1. Hodgkin and Huxley worked with the squid giant axon, an axon which is so large that it is possible to insert a silver wire along its length.
2. The silver is an excellent conductor, this forces \( V(x,t) \) to be independent of \( x \). Then \( m, h \) and \( n \) rapidly fall into like \( V \) and become \( x \)-independent also.

- The system becomes ordinary differential equations.
- We can apply current to the membrane through the silver wire

\[
C \frac{\partial V}{\partial t} + g_L (V - E_L) + g_{Na} m^3 h (V - E_{Na}) + g_K n^4 (V - E_K) = \frac{\alpha_m \partial^2 V}{2 \beta m} \\
C \frac{\partial V}{\partial t} + g_L (V - E_L) + g_{Na} m^3 h (V - E_{Na}) + g_K n^4 (V - E_K) = I_0(t)
\]
Hodgkin-Huxley (HH) model

\[
C \frac{dV}{dt} = -G_L (V - E_L) - G_{Na} m^3 h (V - E_{Na}) - G_K n^4 (V - E_K) + I_{\text{external}}(t)
\]

\[
\begin{align*}
\frac{dm}{dt} &= \alpha_m (1 - m) - \beta_m m \\
\frac{dh}{dt} &= \alpha_h (1 - h) - \beta_h h \\
\frac{dn}{dt} &= \alpha_n (1 - n) - \beta_n n
\end{align*}
\]

- \(E_{Na}\) \(\sim 40\) mv
- \(E_{L}\) \(\sim -70\) mv
- \(E_{K}\) \(\sim -80\) mv
- \(V_T\) \(\sim -50\) mv
- \(E_{Na}\) \(0\) mv

Gating variables: \(m, h, n\)
Phase plane analysis
Hodgkin Huxley Equations

\begin{equation}
\begin{aligned}
C \frac{\partial V}{\partial t} + g_L (V - E_L) + g_{Na} m^3 h (V - E_{Na}) + g_K n^4 (V - E_K) &= I_0 (t) \\
\frac{\partial m}{\partial t} &= \alpha_m (V) (1 - m) - \beta_m (V) m = \frac{1}{\tau_m (V)} \left( m_\infty (V) - m \right) \\
\frac{\partial h}{\partial t} &= \alpha_h (V) (1 - h) - \beta_h (V) h = \frac{1}{\tau_h (V)} \left( h_\infty (V) - h \right) \\
\frac{\partial n}{\partial t} &= \alpha_n (V) (1 - n) - \beta_n (V) n = \frac{1}{\tau_n (V)} \left( n_\infty (V) - n \right)
\end{aligned}
\end{equation}

Where

\begin{align*}
m_\infty (V) &= \frac{\alpha_m (V)}{\alpha_m (V) + \beta_m (V)}, \quad h_\infty (V) = \frac{\alpha_h (V)}{\alpha_h (V) + \beta_h (V)}, \quad n_\infty (V) = \frac{\alpha_n (V)}{\alpha_n (V) + \beta_n (V)} \\
\tau_\infty (V) &= \frac{1}{\alpha_m (V) + \beta_m (V)}, \quad \tau_\infty (V) = \frac{1}{\alpha_h (V) + \beta_h (V)}, \quad \tau_\infty (V) = \frac{1}{\alpha_n (V) + \beta_n (V)}
\end{align*}
Hodgkin Huxley Equations

\[ m_\infty, h_\infty, n_\infty, \tau_m, \tau_h, \tau_n \] as functions of \( V \)

1. As \( V \uparrow \), \( \alpha_m, \alpha_n, \beta_h \uparrow \), \( \alpha_h, \beta_m, \beta_n \downarrow \) \( \Rightarrow \) \( m, n \uparrow \) and \( h \downarrow \)

2. fast variable: \( m \),  slow variables: \( h, n \) (time scale separation)
Phase plane analysis

If we consider fast time scale (~1ms) dynamics and \( I_0(t) = 0 \)

- h and n can be regarded as constants
- we need only consider the dynamics of V and m
- plot the curves along which V and m reaches steady states

\[
\frac{\partial m}{\partial t} = 0 \quad \Rightarrow \quad m = m_\infty(V)
\]

\[
\frac{\partial V}{\partial t} = 0 \quad \Rightarrow \quad V = \frac{g_{Na} m^3 h E_{Na} + g_K n^4 E_K + g_L E_L}{g_{Na} m^3 h + g_K n^4 + g_L}
\]

Notice that: \( E_K < E_L < 0 < E_{Na} \)
Depending on parameters and the values of $h$ and $n$ (here $h$ and $n$ are treated as parameters in the fast time scale analysis), the curves $\frac{\partial V}{\partial t} = 0$ and $\frac{\partial m}{\partial t} = 0$ may have one or three intersections.

R: rest state (stable),  T: threshold (unstable),  E: excited state (stable)

**Bistable!**
Phase plane analysis

Fast time scale dynamics: \((m, V)\) plane

At \(T\), there are two special trajectories (indicated by thick black lines) that end up at \(T\), all others turn away from \(T\) and end up at \(R\) or \(E\). The special trajectories form a separatrix which divide the phase plane into two parts. Any initial condition to the left of the separatrix will end at state \(R\); any initial condition to the right will end at state \(E\)
Phase plane analysis

Sub-threshold and supra-threshold excitation:

Let the system be in state R prior to $t=0$, and let $I_0(t) = Q_0 \delta(t)$ so that $Q_0$ is the total charge per unit area delivered to the membrane by a current shock applied at $t=0$. This produces a jump in voltage $Q_0/C$. Since $m$ cannot change instantaneously, the move in the phase plane is a horizontal shift $\Delta V$. If this takes the system past the separatrix (case in brown), the result is excitation, otherwise, the system returns to rest (case in magenta).
Phase plane analysis

Sub-threshold and supra-threshold excitation:

Let the system be in state R prior to \( t=0 \), and let \( I_0(t) = Q_0\delta(t) \) so that \( Q_0 \) is the total charge per unit area delivered to the membrane by a current shock applied at \( t=0 \). This produces a jump in voltage \( Q_0/C \). Since \( m \) cannot change instantaneously, the move in the phase plane is a horizontal shift \( \Delta V \). If this takes the system past the separatrix (case in brown), the result is excitation, otherwise, the system returns to rest (case in magenta).
Phase plane analysis

Recovery following excitation (effects of slow time scale process)

If $h$ and $n$ were really constants, the excited state would persist indefinitely (unless a negative stimulus were applied of sufficient magnitude to cross the separatrix again and return the system to rest). In fact, however, $h$ and $n$ change slowly, and the whole phase portrait evolves in such a way that the state $E$ and $T$ collide and mutually annihilate leaving only the state $R$, to which the system then returns.
Phase plane analysis

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Phase plane analysis

Slow time scale dynamics: (n,V) plane

As a preliminary step, we simply the situation by setting: \( h = 1 - n \)

In order to be consistent with HH equations, we also need:

\[
\begin{align*}
    h_\infty (V) + n_\infty (V) &= 1 \quad \text{and} \quad \tau_h (V) = \tau_h (V)
\end{align*}
\]

Now we consider the slow time scale analysis, which is to assume that the fast scale \( m \) are always “at equilibrium” as \( n \) (and hence \( h \)) evolves, namely, \( m = m_\infty (V) \)

\[
\frac{\partial V}{\partial t} = 0 \implies g_L (V - E_L) + g_{Na} m_\infty^3 (V) (1 - n) (V - E_{Na}) + g_K n^4 (V - E_K) = 0
\]

Record

\[
f (n, V) = g_L (V - E_L) + g_{Na} m_\infty^3 (V) (1 - n) (V - E_{Na}) + g_K n^4 (V - E_K)
\]
Phase plane analysis

Slow time scale dynamics: \((n,V)\) plane

This is called the **slow manifold**. Note that there is an interval of \(n\) between \(n_1\) and \(n_2\), where there are **three values of \(V\)** corresponding to each value of \(n\). These correspond to the three constant states \(R, T, E\) of the fast \((m,V)\) phase plane. Whenever the system is not on the slow manifold, it moves rapidly by means of changes in the fast variables. On the slow time scale, these rapid changes look like jumps. Since \(n\) can’t change fast, they appear as horizontal shift in the \((n,V)\) phase plane. Combining with the fast time scale analysis, we know that all trajectories that start off the slow manifold jump horizontally to the branch of \(R\) or \(E\).
Phase plane analysis

Slow time scale dynamics: (n,V) plane

Once the system reaches the slow manifold, the system evolves according to

\[
\frac{\partial n}{\partial t} = \frac{n_\infty (V) - n}{\tau_n (V)}
\]

Where \( V = V_R(n(t)) \) or \( V = V_E(n(t)) \) depending on whether the system happens to be on the rest (R) branch or on the excited (E) branch of the slow manifold. \( V_R(n(t)) \) and \( V_E(n(t)) \) are the two stable solutions of \( f(n,V) = 0 \) and \( V_R \) is defined for \( n_1 \leq n \leq 1 \) and \( V_E \) is defined for \( 0 \leq n \leq n_2 \), since \( n_1 < n_2 \), the domains overlap.
Phase plane analysis

Slow time scale dynamics: \((n,V)\) plane

The evolution along the slow manifold carries \(n\) towards \(n_\infty(V)\). The curve \(n = n_\infty(V)\) intersects the R branch of the slow manifold, but not the E branch. Hence, on the R branch, the \(n\) dynamics carries the system towards a stable resting state, but on the E branch, the \(n\) dynamics drives the system towards and then past the value \(n = n_2\), where the E branch terminates. The only possibility at that point is to jump to the R branch.
Phase plane analysis

Action potential in slow time scale dynamics

The rest state of the neuron is the intersection of the curve: $f(n,V) = 0$ (the slow manifold) with the curve $n = n_\infty(V)$. Let a neuron be at rest and then we apply a current pulse which is sufficient large to step the voltage across the T branch of the slow manifold. Then the neuron jumps to the E manifold, where it evolves to the top, jumps back to the R manifold, and then recoveries to its starting point.
Phase plane analysis

Action potential in slow time scale dynamics

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Phase plane analysis

Relative refractory period in dynamics

Following an action potential, a second stimulus is given during the recovery phase (between point 4 and the returning point 0 in the diagram). Discuss the following issues:

- the threshold voltage that must be reached to achieve an action potential.
- the size of the voltage step required to reach threshold
- the peak voltage achieved during the action potential
- the duration of the action potential

![Phase plane diagram](image-url)
Phase plane analysis

Spontaneous oscillations

Suppose the slow manifold is shifted so that it intersects the curve $n = n_\infty(V)$ somewhere on the unstable T branch of the Slow manifold. Then the $(n,V)$ phase plane looks like the following case, what is going to happen?
Phase plane analysis

Anode-break excitation

From \( t = -\infty \) until \( t = 0 \), the trans-membrane potential is clamped at some value \( V^* \) which is sufficiently negative that

\[ n_\infty (V^*) < n_1 \]

(notice that \( n_1 \) is the smallest value of \( n \) reached by the R branch of the slow manifold). At \( t = 0 \) the voltage clamp is removed. What is going to happen? Would the result be the same if a membrane at rest were suddenly stepped to the voltage \( V^* \)? Explain the difference between these two situations.
References


Thank You!