Mathematical Model of Neuron

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Review -- One Basic Circuit

By Kirchhoff’s Current Law

\[ 0 = I_C + I_R + I_L - I_{\text{ext}} \]

By Kirchhoff’s Voltage Law and device IV-characteristics

\[ I_C = C \frac{dV}{dt} \]
\[ I_R = \frac{1}{R} (V - E_2) = g (V - E_2) \]
\[ \frac{dI_L}{dt} = L (V - E_1) \]

where \( C \) is the capacitance, \( R \) is the resistance (\( g \) is the conductance), and \( L \) is the inductance.
Change of a variable $P$ is proportional to itself and the change of another variable $t$:

\[ \Delta P \sim P \Delta t \]

i.e.

\[ \frac{dP}{dt} = r P \]

\[ \rightarrow P(t) = P_0 e^{rt} \]

where $r$ is the growth or decay parameter, $P_0$ is the initial amount.

Applications

--- Population dynamics
--- Radioactive decay
--- Ion channel activation
Neuron -- Overview

Schematic of biological neuron:

- Axon hillock
- Soma
- Axon
- Dendrite
- Nucleus
- Terminal buttons

**Figure 2.17**
Ion channels. When they are open, ions can pass through them, entering or leaving the cell.
Kenneth Cole (1936-1941) determined that the bilipid membrane has a consistent capacitance around $C = 1\mu F$ so that it can be modeled as a capacitor: $I_C = C \frac{dV}{dt}$

- Two ion currents: sodium ion ($\text{Na}^+$) current $I_{\text{Na}}$, and potassium ion ($\text{K}^+$) current $I_{\text{K}}$
- Each ion species has an electrical potential created by a biochemical pump $E_{\text{Na}} \sim 70 \text{ mV}$ and $E_{\text{K}} \sim -60 \text{ mV}$
- The early attempted conceptual model is

\[I_{\text{Na}} = g_{\text{Na}} (V - E_{\text{Na}}) \quad \text{and} \quad I_{\text{K}} = g_{\text{K}} (V - E_{\text{K}}),\]

where $g_{\text{Na}}$, $g_{\text{K}}$ are the conductances
Differential equation (device IV-characteristics) for individual ion pump current

\[
\frac{dI}{dt} = \lambda IV
\]

Namely, the rate of change of pump current is proportional to the power across the pump.
The differential equations for the circuit loop are

\[ CV' = I, \quad I' = -\lambda I(V + \gamma I) \]

Solve the system explicitly, and express the solution in term so the asymptotic steady-state potential as

\[ V(t) = V_\infty \frac{1 - \exp(-\lambda V_\infty t)}{1 + \exp(-\lambda V_\infty t)} \sim V_\infty [1 - 2 \exp(-\lambda V_\infty t)] \]
Resting Potentials -- Battery Equivalence of Ion Pump

Ion Pump

\[ CV' = I, \quad I' = -\lambda I(V + \gamma I) \]

Solution with initial \( V(0) = 0 \)

\[ V(t) = V_\infty \frac{1 - \exp(-\lambda V_\infty t)}{1 + \exp(-\lambda V_\infty t)} \sim V_\infty [1 - 2 \exp(-\lambda V_\infty t)] \]

Battery Circuit

\[ CV' = I = -(V + E)/r \]

Solution with initial \( V(0) = 0 \)

\[ V(t) = -E[1 - \exp(-t/(rC))] = V_\infty [1 - \exp(-t/(rC))] \]

With

\[ 1/r = \lambda CV_\infty \]

These two circuits are exponentially equivalent to each other
As the potassium pump is capable of establishing any asymptotical potential $E = -V_\infty$, the question is what is the actual resting potential $E_K$ under the action of across-membrane diffusion and electrical neutrality?

The equation for this setting is the Goldman equation (1943):

$$0 = I_d + I_p = D \left( -\frac{dn}{dx} \right) + \mu n \left( -\frac{E_K}{a} \right)$$

Solving this linear equation for the concentration $n(x)$ with the boundary conditions $n(0) = [K]_o$, $n(a) = [K]_i$ leads to the Nernst potential

$$E_K = \frac{RT}{F} \ln \frac{[K]_i}{[K]_o}$$
Resting Potentials -- Membrane Resting Potential $E_m$ with Ion Pump and Electrical Neutrality

Equation for the steady state

$$0 = \sum z_k D_k \left( -\frac{dn_k}{dx} \right) + \mu_k n_k \left( -\frac{E_m}{a} \right)$$

with $z_k = +1$ we have

$$0 = \sum D_k \left( -\frac{dn_k}{dx} \right) + \mu_k n_k \left( -\frac{E_m}{a} \right)$$

and

$$\frac{E_m}{a} \frac{d}{dx} = -\frac{RT}{F} \frac{d}{dx} \left( \sum \mu_k n_k \right)$$

$$E_m = \frac{RT}{F} \ln \frac{\mu_K [K]_o + \mu_{Na} [Na]_o}{\mu_K [K]_i + \mu_{Na} [Na]_i} \sim -55 \text{ mV}$$
Back to the conceptual circuit model, Cole and others soon realized that a neuronal circuit model could not be a linear circuit.

\[
C \frac{dV}{dt} = -[I_{Na} + I_K - I_{ext}] = -[g_{Na} (V - E_{Na}) + g_{K} (V - E_{K}) - I_{ext}]
\]

with \( g_{Na}, g_{K} \) being constants. One reason is that \( g_{Na} \) must be near zero despite the potential difference \( E_{m} - E_{Na} \) \( \sim -125 \) mV at rest, and large during action potential depolarization.

**Anatomy of action potential pulse:**
- membrane voltage arises as sodium ions rush inside
- membrane voltage falls as potassium ions rush outside
- membrane voltage returns to its resting potential as both ion currents fall to near zero.

(Cole and Curtis (1939))
Researchers concluded that the conductances must be functions of the voltage 
\[ g_{Na} = g_{Na}(V) \quad \text{and} \quad g_K = g_K(V) \]

Hodgkin and Huxley (1952) proposed the following model:

Membrane as a Capacitor
\[
\begin{align*}
C_m \frac{dV}{dt} &= I(t) \\
I(t) &= I_{Na}^- + I_{K}^+ - I_L \\
I_{Na}^- &= g_{Na}m^3h(V - V_{Na}) \\
I_{K}^+ &= g_{K}h^4(V - V_K) \\
I_L &= g_L(V - V_L)
\end{align*}
\]

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

Voltage-dependence of Channel Kinetics (Hodgkin & Huxley, 1952)
\[
\begin{align*}
\alpha_n &= \frac{10 - V}{100(e^{0.1V}-1)} \quad \beta_n = 0.125e^{-V/80} \\
\alpha_m &= \frac{25 - V}{10(e^{0.1(25-V)}-1)} \quad \beta_m = 4e^{-V/18} \\
\alpha_h &= 0.07e^{-V/20} \quad \beta_h = \frac{1}{e^{0.1(30-V)}-1}
\end{align*}
\]

Constants in the Hodgkin-Huxley Model
\[
\begin{align*}
\bar{g}_{Na} &= 120\text{mS/cm}^2 \quad V_{Na} = 115\text{mV} \\
\bar{g}_{K} &= 36\text{mS/cm}^2 \quad V_K = -12\text{mV} \\
\bar{g}_L &= 0.3\text{mS/cm}^2 \quad V_L = 10.6\text{mV}
\end{align*}
\]
Hodgkin-Huxley model fits experiments very well

- It has been the benchmark of excitable membranes in electrophysiology since 1952
- One fundamental drawback is the lack of a mechanistic basis for the voltage activated conductances
- It also fails to include the voltage gating current discovered later in the 1970s
For the steady state IV-characteristics of the sodium current, \( I_{Na} = g_{Na} (V - E_{Na}) \), we assume the conductance change is proportional to the conductance and the voltage change:

\[ \Delta g_{Na} \sim g_{Na} \Delta V \]

i.e.

\[ \frac{dg_{Na}}{dV} = \frac{g_{Na}}{b_{Na}} \]

\[ \rightarrow g_{Na} (V) = \bar{g}_{Na} e^{(V - E_{Na})/b_{Na}} \]

where \( b_{Na} \) is the sodium activation range parameter and \( \bar{g}_{Na} \) is the intrinsic conductance \( \bar{g}_{Na} = g_{Na} (E_{Na}) \)

Similarly, we have the voltage activated potassium steady state conductance

\[ g_{K} (V) = \bar{g}_{K} e^{(V - E_{K})/b_{K}} \]

where \( b_{K} \) is the potassium activation range parameter and \( \bar{g}_{K} \) is the intrinsic conductance
Voltage gating is the phenomenon that when the membrane potential $V$ is perturbed away from and above its resting potential $E_m$, the sodium channel undergoes some conformal changes which in turn release some positively charged particles to the outside for the effect of cancelling out the perturbation (depolarization).

This so-called gating current is modeled similarly but with a conductance which is exponentially deactivated by the voltage:

$$I_G = g_G (V - E_G)$$

$$\Delta g_G \sim -g_G \Delta V$$

i.e.

$$\frac{d g_G}{dV} = \frac{-g_G}{b_G}$$

$$\Rightarrow g_G (V) = \bar{g}_G e^{-(V - E_G)/b_G}$$

where $b_G$ is the voltage-gating range parameter and $\bar{g}_G$ is the intrinsic gating conductance.
Assume there is a time delay (adaptation) of the electrical dynamics to the activation and gating conductances, the full model for the membrane is

\[
CV' = -\left[ \bar{g}_K n(V - E_K) + \bar{g}_{Na} m(V - E_{Na}) + \bar{g}_G h(V - E_G) - I_{ext} \right]
\]

where \( \tau_i \) are the time adaptation parameters.
Find parameter values so that the error between the predicted and the observed is minimal. (This is done by Newton’s line search method in Matlab)

\[
\mathcal{E} = \frac{1}{N} \sum_{j=1}^{N} \left[ \frac{|V(t_j) - \bar{V}|}{\bar{V}} \right]^2
\]

It has a better best-fit than the HH model does, and with 13 fewer parameters
Action Potentials -- Nerve Impulse Propagation Along Axon

[Diagram of a neuron showing dendrite, cell body, axon, node of Ranvier, and Schwann cell.]

[Graphs showing voltage (V) over time and node, illustrating action potential propagation.]
Action Potentials -- Bursting Spikes on Cell Body
Neuron model can be constructed mechanistically

- Ion channel activation follows an exponential growth law, voltage gating follows an exponential decay law
- We can now teach undergraduate students the model with little arbitrariness
- It is hugely important to have a more accurate and simpler model when a large number of individual neuron models are connected in networks
Abstract: All information processed by animal brain is done by electrical pulses of neurons. Modeling neurons as electrical circuits is extremely important for the field of electrophysiology. In this talk we will talk about the benchmark neuron model which have been around for over sixty years and our recent effort to improve it. Only basic theory of circuit and elementary differential equation knowledge will be assumed.