Computational Neuroscience Summer School
Neural Spike Train Analysis

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An introduction to biophysical models (Part 2)
Modeling the voltage: biophysics

**Goal:** Model this,

\[ \frac{dV}{dt} = f (V, \text{current inputs}, \text{time}, ...) \]

Consider the general expression:

We need to choose \( f \) ... biophysics.
Modeling the voltage: biophysics

So far (Part 1): an equivalent circuit capturing some aspects of biophysics:

RC-circuit  Input current: I

(capacitor)  (resistor)  (battery)

(impermeable cell membrane)

(channel)

Q: What doesn’t this model do?  A: It does not spike on it’s own.

Now, add more biophysics to increase realism ... and complexity.
Modeling the voltage: biophysics

Fact: some ion channels open and close in time.

Note: gates are actually proteins that support different confirmations.

Our goal: capture the “essence” of behavior, what produces and AP.

model the gate dynamics with differential equations ...
Modeling the voltage: biophysics

Fact: some ion channels open and close in time.

Ex. low conductance gate “closed” ions flow blocked

Ex. high conductance gate “open” ions flow through

Model the dynamics of this gate ...
Fact: channels are *ion specific*.

Sodium ($\text{Na}^+$) specific ion channel: only $\text{Na}^+$ may pass.

Fact: $[\text{Na}^+]_{\text{out}} \gg [\text{Na}^+]_{\text{in}}$

So, if the gate is open ... concentration gradient pulls $\text{Na}^+$ into cell.

Q: Impact on neuron’s voltage?
Q: What could prevent Na\(^+\) flow into neuron?

A: Adjust interior voltage .... make interior voltage very positive.

Fact: positive ions flee high voltages. 

at \(V_{\text{in}} = +60 \text{ mV}\) “Nernst potential” 

balance the force of concentration gradient and voltage gradient.
Modeling the voltage: sodium

Model Na⁺ specific ion channel as an equivalent circuit:

\[ V_{in} = V \]

\[ I_{Na} \]

\[ V_{out} = 0 \text{ mV} \]

\[ V_{Na} = \text{high voltage side} \]

\[ 0 \text{ mV} = \text{low voltage side} \]

**Ohm’s law:**

\[ V = I \cdot R \]

\[ V - V_{Na} = I_{Na} \cdot R_{Na} \] or

\[ I_{Na} = g_{Na} (V - V_{Na}) \]

“conductance”

- Represents sodium channel
- Battery
- Voltage across battery = Nernst potential = + 60 mV = \( V_{Na} \)
Modeling the voltage: sodium

Implications:

\[ I_{Na} = g_{Na} (V - V_{Na}) \]

When \( V = V_{Na} \),

\[ I_{Na} = 0 \quad \text{no net current flow through the channel} \]

the cell interior is ... very positive (+60 mV, note “rest” -70 mV)

concentration gradient and voltage gradient ... balance
**Modeling the voltage: potassium**

**Fact:** channels are ion specific

Potassium (\(K^+\)) specific ion channel: only \(K^+\) may pass.

**Fact:** \([K^+]_{\text{out}} << [K^+]_{\text{in}}\)

So, if the gate is open ... concentration gradient pushes \(K^+\) out of cell.

**Q:** Impact on neuron’s voltage?
Q: What could prevent $K^+$ flow out of the neuron?

A: Make interior voltage very ... negative

Fact: positive ions approach lower voltages.

at $V_{in} = -90$ mV “Nernst potential”

balance the force of concentration gradient and voltage gradient.
Modeling the voltage: potassium

Model $K^+$ specific ion channel as an equivalent circuit:

\[ \text{Ohm's law:} \quad V = I R \]
\[ V - V_K = I_K R_K \]

\[ I_K = g_K (V - V_K) \]

$V_K =$ low voltage side

$0 \text{ mV} =$ high voltage side

$V_{\text{out}} = 0 \text{ mV}$

$V_{\text{in}} = V$

represents potassium channel

resistor $R_K$

battery

voltage across battery

$= \text{Nernst potential}$

$= -90 \text{ mV}$

$= V_K$
Modeling the voltage: leak

We’ll include one additional channel: “leak” - represents other ions - example: chlorine (Cl\(^-\))

Model in the same way as Na\(^+\) and K\(^+\) :

\[ V_{\text{in}} = V \]

\[ V_{\text{out}} = 0 \text{ mV} \]

\[ I_L = g_L (V - V_L) \]

\[ V_L = \text{low voltage side} \]

\[ 0 \text{ mV} = \text{high voltage side} \]

\[ V = \text{voltage across battery} = -54 \text{ mV} = V_L \]
Modeling the voltage: currents

Our (modified) model has three currents:

- **sodium current:**
  \[ I_{Na} = g_{Na} (V - V_{Na}) \]
  \[ +60 \, \text{mV} \]

- **leak current:**
  \[ I_{L} = g_{L} (V - V_{L}) \]
  \[ -54 \, \text{mV} \]

- **potassium current:**
  \[ I_{K} = g_{K} (V - V_{K}) \]
  \[ -90 \, \text{mV} \]

To generate a spike, we need more biology ...

**Idea:** let the \( \text{Na}^+ \) and \( \text{K}^+ \) conductances vary in time.
Modeling the voltage: $K^+$ variable conductances

**Idea:** conductances change, channels open/close in time.

Update our models of the conductance

\[ I_K = g_K (V - V_K) \]

Replace with: \( g_K = \bar{g}_K \times p \) \leftarrow \text{probability channel is open}

\[ g_K = \bar{g}_K \times n^4 \]

\( n = \text{probability that each (of 4) gate is open} \)

\[ 0 \leq n \leq 1 \]

potassium “gating variable”
Modeling the voltage: $K^+$ variable conductances

Q: Why $n^4$?

A: Visualize the potassium channel as consisting of 4 gates:

Examples:

For channel to be open, we need all 4 gates open ...

channel conductance $\sim$ (probability 1st gate open) $n$
  * (probability 2nd gate open) $n$
  * (probability 3rd gate open) $n$
  * (probability 4th gate open) $n$

A: That’s what fits the data! [Hodgkin & Huxley, 1952]
Modeling the voltage: $K^+$ variable conductances

Let’s model the dynamics of the gating variable $n$.

Consider the reaction equation:

$$\alpha_n \quad \text{closed gates (1-n) } \xleftrightarrow{\beta_n} \text{ open gates (n)}$$

- $\alpha_n$ rate of transition: closed to open
- $\beta_n$ rate of transition: open to closed

Motivates the differential equation:

$$\frac{dn}{dt} = \alpha_n (1-n) - \beta_n n$$

or

$$\frac{dn}{dt} = -n - n_\infty(V) \quad \frac{1}{\tau_n(V)}$$

$n_\infty(V)$ = steady state value $\tau_n(V)$ = time constant
Modeling the voltage: $K^+$ variable conductances

Consider the differential equation,

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

looks simple, but ... there’s voltage dependence.

**Q:** What are these functions?

**A:** Note $n_\infty(V)$ and $\tau_n(V)$ are functions of $\alpha_n$ and $\beta_n$

$$\alpha_n(V) = \frac{0.1 - 0.01(V + 65)}{e^{1 - 0.1(V + 65)} - 1}$$

$$\beta_n(V) = 0.125e^{(-V - 65)/80}$$

**Q:** Why?

**A:** It’s biology.
Modeling the voltage: $K^+$ variable conductances

Visualize the potassium steady state function & time constant:

$n_\infty[V]$ is the steady state value for $K$, $\tau_n[V]$ is the time constant for $K$.

So, when neuron is depolarized ...

$$n \rightarrow n_\infty(V) \sim 1$$

potassium channels are ... open
$K^+$ flows ... out
voltage ... decreases
potassium channels ... close
Modeling the voltage: Na\(^+\) variable conductances

In the same way, create a variable sodium conductance ...

\[ I_{Na} = g_{Na} (V - V_{Na}) \]

\[ g_{Na} = g_{Na}^\text{max} \cdot m^3 h \]

m = sodium activation gating variable

h = sodium inactivation gating variable

Gate dynamics:

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

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

where the steady state and time constants are functions of V ...
**Modeling the voltage: Na\(^+\) gating variables**

**steady state values for Na**

**time constants for Na.**

So, when neuron is **depolarized** ...

m \(\sim 1\) (open) \& h \(\sim 0\) (closed)

**Q:** Can ions pass?

**activation gates**

m\(^3\)

3 gates ...

| Na\(^+\) |

**inactivation gate**

h \(1\) gate ...
Modeling the voltage: Na\(^+\) gating variables

steady state values for Na

\[ m_\infty(V) \]

\[ h_\infty(V) \]

\begin{align*}
\alpha_m & = 2.5 - 0.1(V + 65) \\
\beta_m & = 4e^{\frac{-(V + 65)}{18}} \\
\alpha_h & = 0.07 e^{\frac{-(V + 65)}{20}} \\
\beta_h & = 1e^{\frac{3 - 0.1(V + 65)}{18}} + 1
\end{align*}

time constants for Na.

\[ \tau_m(V) \]

\[ \tau_h(V) \]

So, when neuron is hyperpolarized ... \( m \sim 0 \) (closed) \& \( h \sim 1 \) (open)

Q: Can ions pass?
Modeling the voltage: Na\(^+\) variable conductances

**Q:** How do Na\(^+\) ions get through channel?

**A:** Timescales matter.

\[ \begin{align*}
\tau_m(V) & = \frac{1}{\alpha_m} - \beta_m V + \frac{\beta_m}{18} \\
\tau_h(V) & = \frac{1}{\alpha_h} - \beta_h V + \frac{\beta_h}{20}
\end{align*} \]

*Note:* Compared to the inactivation gate (h), the activation gate (m) is much faster.

We’ll examine implications in simulation ...
Summary

Put it all together:

Input current: \( I = I_K + I_{Na} + I_L + I_{cap} \)

Voltage equations:

- Potassium current:
  \[ I_K = g_K \cdot n^4 (V - V_K) \]

- Sodium current:
  \[ I_{Na} = g_{Na} \cdot m^3 h (V - V_{Na}) \]

- Leak current:
  \[ I_L = g_L (V - V_L) \]

Solve for \( \frac{dV}{dt} \) ...
Model 3: Hodgkin-Huxley equations

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

\[
\begin{align*}
\frac{dn}{dt} &= - \frac{n - n_\infty(V)}{\tau_n(V)} \\
\frac{dm}{dt} &= - \frac{m - m_\infty(V)}{\tau_m(V)} \\
\frac{dh}{dt} &= - \frac{h - h_\infty(V)}{\tau_h(V)},
\end{align*}
\]

voltage dynamics

gate dynamics

steady state functions & time constants

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

where

\[
\begin{align*}
\alpha_n(V) &= \frac{0.1 - 0.01(V + 65)}{e^{1 - 0.1(V+65)} - 1} \\
\beta_n(V) &= 0.125 e^{(-V-65)/80} \\
\alpha_m(V) &= \frac{2.5 - 0.1(V + 65)}{e^{2.5 - 0.1(V+65)} - 1} \\
\beta_m(V) &= 4 e^{(-V-65)/18} \\
\alpha_h(V) &= 0.07 e^{(-V-65)/20} \\
\beta_h(V) &= \frac{1}{e^{3 - 0.1(V+65)} + 1}
\end{align*}
\]
Model 3: Hodgkin-Huxley equations

Arguably, the most important computational model in neuroscience.
— Nobel prize, 1963

The basis for more complex models...

\[
C_k \frac{dV_k}{dt} = \sum_m \gamma_{m,k} (V_m - V_k) - I_{ionic,k}
\]

\[
\hat{g}_L(V + 70) + \left[ \hat{g}_{Na(F)} m_{Na(F)}^3 h_{Na(F)} + \hat{g}_{Na(P)} m_{Na(P)} \right] (V - 50)
\]

\[
+ \left[ \hat{g}_{K(DR)} m_{K(DR)}^4 + \hat{g}_{K(A)} m_{K(A)}^4 h_{K(A)} + \hat{g}_{K2} m_{K2} h_{K2} + \hat{g}_{K(M)} m_{K(M)} \right]
\]

\[
+ \hat{g}_{K(C)} m_{K(C)} \Gamma(\chi) + \hat{g}_{K(AHP)} m_{K(AHP)} \right] (V + 95)
\]

\[
+ \left[ \hat{g}_{Ca(T)} m_{Ca(T)}^2 h_{Ca(T)} + \hat{g}_{Ca(H)} m_{Ca(H)}^2 \right] (V - 125) + \hat{g}_{AR} m_{AR} (V + 35)
\]

[Traub et al, J Neurophysiol, 2003]
Model 3: Hodgkin-Huxley equations

Challenges:
– It’s complicated:
  • 4-dimensional
  • Many parameters impacting dynamics

The price for biological realism ...

Examples in MATLAB of Model 3 (Hodgkin-Huxley)

If you’d like, please start MATLAB and download the file:

http://math.bu.edu/people/mak/samsi/Modeling_Session_2.m