Computing in carbon

**Basic elements of neuroelectronics**
- membranes
- ion channels
- wiring

**Elementary neuron models**
- conductance based
- modelers’ alternatives

**Wires**
- signal propagation
- processing in dendrites

**Wiring neurons together**
- synapses
- long term plasticity
- short term plasticity
Equivalent circuit model
Membrane patch

- pore
- channel
- lipid bilayer
The passive membrane

Ohm’s law: \[ V = I_R R \]

Capacitor: \[ C = \frac{Q}{V} \]

Kirchhoff: \[ I_R + I_C + I_{\text{ext}} = 0 \]

\[ C \frac{dV}{dt} = -\frac{V}{R} - I_{\text{ext}} \]
Movement of ions through ion channels

Energetics: \( qV \sim k_B T \)

\( V \sim 25\text{mV} \)
The equilibrium potential

Ions move down their concentration gradient until opposed by electrostatic forces

Nernst: \[
E = \frac{k_B T}{zq} \ln \left( \frac{[\text{inside}]}{[\text{outside}]} \right)
\]
Different ion channels have associated *conductances*. A given conductance tends to move the membrane potential toward the equilibrium potential for that ion.

\[
\begin{array}{lll}
E_{\text{Na}} & \sim & 50 \text{mV} \quad \text{depolarizing} \\
E_{\text{Ca}} & \sim & 150 \text{mV} \quad \text{depolarizing} \\
E_{\text{K}} & \sim & -80 \text{mV} \quad \text{hyperpolarizing} \\
E_{\text{Cl}} & \sim & -60 \text{mV} \quad \text{shunting}
\end{array}
\]

\[
V > E \rightarrow \text{positive current will flow outward}
\]

\[
V < E \rightarrow \text{positive current will flow inward}
\]

Each ion type travels through independently.
Parallel paths for ions to cross membrane

Several $I$-$V$ curves in parallel:

New equivalent circuit:
Neurons are excitable
Excitability arises from ion channel nonlinearity

- Voltage dependent
- Transmitter dependent (synaptic)
- Ca dependent
The ion channel is a cool molecular machine

\[ P_K \sim n^4 \]

**Persistent conductance**

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

\[ n \text{ describes a subunit} \]

\[ n \text{ is open probability} \]

\[ 1 - n \text{ is closed probability} \]

Transitions between states occur at voltage dependent rates

\[ \alpha_n(V) \quad \text{C} \rightarrow \text{O} \]

\[ \beta_n(V) \quad \text{O} \rightarrow \text{C} \]
Gate acts as in previous case

Additional gate can block channel when open

$P_{Na} \sim m^3h$

$m$ is activation variable
$h$ is inactivation variable

$m$ and $h$ have opposite voltage dependences:
- Depolarization increases $m$, activation
- Hyperpolarization increases $h$, deinactivation
Dynamics of activation and inactivation

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

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

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

We can rewrite:

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

where

\[ \tau_n(V) = \frac{1}{\alpha_n(V) + \beta_n(V)} \]

\[ n_\infty(V) = \frac{\alpha_n(V)}{\alpha_n(V) + \beta_n(V)} \]
Dynamics of activation and inactivation

Graphs showing the dynamics of activation and inactivation with variables $h$, $m$, and $n$ plotted against $V$ (mV) and $\tau$ (ms).
Putting it together

Ohm’s law: \[ V = IR \] and Kirchhoff’s law

\[-C_m \frac{dV}{dt} = \sum \sum \left[ g_i(V - E_i) \right] + I_e\]

- Capacitative current
- Ionic currents
- Externally applied current
The Hodgkin-Huxley equation

\[ C_m \frac{dV}{dt} = - \sum_i g_i (V - E_i) - I_e \]

\[ -C_m \frac{dV}{dt} = g_L (V - E_L) + \tilde{g}_K n^4 (V - E_K) + \tilde{g}_{Na} m^3 h (V - E_{Na}) \]

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

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

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

- $E_K$ for potassium (K) channels
- $E_{Na}$ for sodium (Na) channels

- $h_\infty$ for potassium channels
- $m_\infty$ for sodium channels
- $n_\infty$ for sodium channels

- $V$ (mV) for voltage

- $Na \sim m^3h$ for sodium channels
- $K \sim m^3h$ for potassium channels
Anatomy of a spike

- Runaway positive feedback
- Double whammy

- $h_\infty$, $m_\infty$, $n_\infty$
- $E_K$, $E_{Na}$
Where to from here?

Hodgkin-Huxley

Biophysical realism
Molecular considerations
Geometry

Simplified models
Analytical tractability
Ion channel stochasticity
Microscopic models for ion channel fluctuations

approach to macroscopic description
Different from the continuous model:
interdependence between inactivation and activation transitions to inactivation state 5 can occur only from 2, 3 and 4
$k_1$, $k_2$, $k_3$ are constant, not voltage dependent.
The integrate-and-fire neuron

Like a passive membrane:

$$C_m \frac{dV}{dt} = -g_L (V - E_i) - I_e$$

but with the additional rule that
when \( V \rightarrow V_T \), a spike is fired
and \( V \rightarrow V_{\text{reset}} \).

\( E_L \) is the resting potential of the “cell”.

![Graph showing the integrate-and-fire neuron behavior](image)
Exponential integrate-and-fire neuron

\[ f(V) = -V + \exp\left(\frac{V - V_{th}}{\Delta}\right) \]
The theta neuron

\[ \frac{d\theta}{dt} = 1 - \cos \theta + (1+ \cos \theta) I(t) \]

Ermentrout and Kopell
The spike response model

Kernel $f$ for subthreshold response $\leftarrow$ replaces leaky integrator
Kernel for spikes $\leftarrow$ replaces “line”

- determine $f$ from the linearized HH equations
- fit a threshold
- paste in the spike shape and AHP
Two-dimensional models

Simple™ model:

\[ V' = -aV + bV^2 - cW \]

\[ W' = -dW + eV \]
The generalized linear model

- general definitions for $k$ and $h$
- robust maximum likelihood fitting procedure

Truccolo and Brown, Paninski, Pillow, Simoncelli
Dendritic computation

Dendrites as computational elements:

Passive contributions to computation

Active contributions to computation

Examples
Geometry matters

Injecting current $I_0$

$V_m = I_m R_m$

Current flows uniformly out through the cell: $I_m = I_0 / 4\pi r^2$

Input resistance is defined as $R_N = V_m(t \rightarrow \infty) / I_0$

$= R_m / 4\pi r^2$
$r_m$ and $r_i$ are the membrane and axial resistances, i.e. the resistances of a thin slice of the cylinder.
Axial and membrane resistance

For a length $L$ of membrane cable:

- $r_i \rightarrow r_i L$
- $r_m \rightarrow r_m / L$
- $c_m \rightarrow c_m L$
The cable equation

(1) \[ \frac{\partial V_m}{\partial x} = -r_i i_i \]

(2) \[ \frac{\partial i_i(x)}{\partial x} = -i_m \]
The cable equation

(1) \[ \frac{\partial V_m}{\partial x} = -r_i i_i \]

(2) \[ \frac{\partial i_i(x)}{\partial x} = -i_m \]

\[ \frac{\partial}{\partial x} (1) \rightarrow \frac{\partial^2 V_m}{\partial x^2} = -r_i \frac{\partial i_i}{\partial x} = r_i i_m. \]

\[ i_m = i_C + i_{ionic} = c_m \frac{\partial V_m}{\partial t} + \frac{V_m}{r_m} \]

\[ \frac{1}{r_i} \frac{\partial^2 V_m(x,t)}{\partial x^2} = c_m \frac{\partial V}{\partial t} + \frac{V_m}{r_m}. \]

\[ \lambda^2 \frac{\partial^2 V_m}{\partial x^2} = \tau_m \frac{\partial V_m}{\partial t} + V_m \]

or

where \[ \tau_m = r_m c_m \]

\[ \lambda = \sqrt{\frac{r_m}{r_i}} \]

Time constant

Space constant
General solution: filter and impulse response

\[ V(x, t) \propto \sqrt{\frac{\tau}{4\pi \lambda^2 t}} e^{-\frac{t}{\tau}} - \frac{\tau x^2}{4\lambda^2 t} \]

Diffusive spread

Exponential decay
Voltage decays exponentially away from source

Current injection at $x=0$, $T \to \infty$

$$V_m(x, \infty) = \frac{r_i I_0 \lambda}{2} e^{-x/\lambda}$$
Properties of passive cables

\[ \lambda = \sqrt{\frac{r_m}{r_i}} \]

\( \rightarrow \) Electrotonic length
Electrotonic length

\[ V_{max} = V(\infty, 0) \]

\[ V_m(\infty, x) = V_m(\infty, 0)e^{-x/\lambda} \]
Properties of passive cables

→ Electrotonic length  \( \lambda = \sqrt{\frac{r_m}{r_i}} \)

→ Current can escape through additional pathways: speeds up decay
Voltage rise time

- Current can escape through additional pathways: speeds up decay
Properties of passive cables

- Electrotonic length \( \lambda = \sqrt{\frac{r_m}{r_i}} \)

- Current can escape through additional pathways: speeds up decay

- Cable diameter affects input resistance \( R_N = \frac{\sqrt{R_m R_i}}{2\pi a^{3/2}} \)

![Amplitude and Time course graphs showing differences between Dendrite and Soma](image-url)
Properties of passive cables

→ Electrotonic length

\[ \lambda = \sqrt{\frac{r_m}{r_i}} \]

→ Current can escape through additional pathways: speeds up decay

→ Cable diameter affects input resistance

\[ R_N = \frac{\sqrt{R_m R_i / 2}}{2\pi a^{3/2}} \]

→ Cable diameter affects transmission velocity
Step response: pulse travels

Conduction velocity

\[ \theta = \frac{2\lambda}{\tau_m} = \sqrt{\frac{2a}{R_m R_i C_m^2}} \]
Conduction velocity

- **Myelinated fibres**

- **Unmyelinated fibres**

Conduction Velocity (m/s) vs. Fibre diameter (μm)
Other factors

Finite cables

Active channels
Impedance matching:

If $a^{3/2} = d_1^{3/2} + d_2^{3/2}$

can collapse to an equivalent cylinder with length given by electrotonic length

$$R_N = \frac{\sqrt{R_m R_i / 2}}{2\pi a^{3/2}}$$
New cable equation for each dendritic compartment
Who’ll be my Rall model, now that my Rall model is gone
Passive computations

London and Hausser, 2005
Enthusiastically recommended references

• **Johnson and Wu, *Foundations of Cellular Physiology, Chap 4***
The classic textbook of biophysics and neurophysiology: lots of problems to work through. Good for HH, ion channels, cable theory.

• **Koch, *Biophysics of Computation***
Insightful compendium of ion channel contributions to neuronal computation

• **Izhikevich, *Dynamical Systems in Neuroscience***
An excellent primer on dynamical systems theory, applied to neuronal models

• **Magee, *Dendritic integration of excitatory synaptic input***,
Nature Reviews Neuroscience, 2000
Review of interesting issues in dendritic integration

• **London and Hausser, *Dendritic Computation***,
Annual Reviews in Neuroscience, 2005
Review of the possible computational space of dendritic processing