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

The passive membrane

Ohm’s law: \( V = I_R R \)

Capacitor: \( C = \frac{Q}{V} \)

Kirchhoff: \( I_R + I_C + I_{ext} = 0 \)

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

Energetics: \( qV \sim k_B T \)
\( V \sim 25 \text{mV} \)

The equilibrium potential

Nernst: \( E = \frac{k_B T}{zq} \ln \left( \frac{[\text{inside}]}{[\text{outside}]} \right) \)
Each ion type travels through independently

Different ion channels have associated conductances.

A given conductance tends to move the membrane potential toward the equilibrium potential for that ion

\[ V > E \Rightarrow \text{positive current will flow outward} \]
\[ V < E \Rightarrow \text{positive current will flow inward} \]

- \( E_{Na} \sim 50\text{mV} \) depolarizing
- \( E_{Ca} \sim 150\text{mV} \) depolarizing
- \( E_{K} \sim -80\text{mV} \) hyperpolarizing
- \( E_{Cl} \sim -60\text{mV} \) shunting

Parallel paths for ions to cross membrane

Several I-V curves in parallel:

New equivalent circuit:
Neurons are excitable

• Voltage dependent
• Transmitter dependent (synaptic)
• Ca dependent

Excitability arises from ion channel nonlinearity

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

K channel: open probability increases when depolarized

\[ P_K \sim n^4 \]

\( n \) describes a subunit

\[ n \] is open probability

\[ 1 - n \] is closed probability

Transitions between states occur at voltage dependent rates

\[ \alpha_n(V) \quad C \rightarrow O \]

\[ \beta_n(V) \quad O \rightarrow C \]

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

Persistent conductance

Transient conductances

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

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

\[
n_\infty(V) = \frac{\alpha_n(V)}{\alpha_n(V) + \beta_n(V)}
\]
Putting it together

Ohm’s law: $V = IR$ and Kirchhoff’s law

$$-C_m \frac{dV}{dt} = \sum g_i(V - E_i) + I_c$$

- Capacitative current
- Ionic currents
- Externally applied current

The Hodgkin-Huxley equation

$$C_m \frac{dV}{dt} = -\sum g_i(V - E_i) - I_c$$

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

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

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

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

$E_{K}$

$E_{Na}$

$Na \sim m^3h$

$K \sim m^3h$
Where to from here?

- Hodgkin-Huxley
- Biophysical realism
  - Molecular considerations
  - Geometry
- Simplified models
  - Analytical tractability

Ion channel stochasticity

![Ionic Current Graph](image-url)
Microscopic models for ion channel fluctuations

Different from the continuous model:
interdependence between inactivation and activation
transitions to inactivation state 5 can occur only from 2, 3 and 4
k₁, k₂, k₃ are constant, not voltage dependent

Transient conductances
The integrate-and-fire neuron

Like a passive membrane:

\[ C_m \frac{dV}{dt} = -g_L(V - E_i) - I_c \]

but with the additional rule that

when \( V \rightarrow V_T \), a spike is fired
and \( V \rightarrow V_{\text{reset}} \).

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

Exponential integrate-and-fire neuron

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

Gerstner and Kistler
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 $R_N = V_m(t \to \infty) / I_0$

$$= R_m / 4\pi r^2$$

Linear cables

$r_m$ 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

\begin{align*}
(1) \quad \frac{\partial V_m}{\partial x} &= -r_i i_i \\
(2) \quad \frac{\partial i_i(x)}{\partial x} &= -i_m \\
\frac{\partial}{\partial x} (1) \rightarrow \quad \frac{\partial^2 V_m}{\partial x^2} &= -r_i \frac{\partial i_i}{\partial x} = r_i i_m.
\end{align*}

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

or

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

where \( \tau_m = r_m c_m \) Time constant

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

General solution: filter and impulse response

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

Exponential decay

Diffusive spread
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

→ Electrotonic length

\[
\lambda = \sqrt{\frac{r_m}{r_i}}
\]
**Electrotonic length**

*Properties of passive cables*

- Electrotonic length  

\[ \lambda = \sqrt{\frac{\tau_m}{r_s}} \]

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

Current can escape through additional pathways:
- speeds up decay

![Graph showing voltage rise time](image)

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: \( R_N = \frac{\sqrt{R_m R_i / 2}}{2\pi a^{3/2}} \)

![Graph showing amplitude and time course](image)
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 $R_N = \sqrt{\frac{R_m R_i}{2\pi R^3}}$

→ Cable diameter affects transmission velocity

Step response: pulse travels

Conduction velocity $\theta = \frac{2\lambda}{r_m} = \sqrt{\frac{2\alpha}{R_m R_i C^2_m}}$
Conduction velocity

![Graph showing conduction velocity vs. fibre diameter](www.physiol.usyd.edu.au/~daved/teaching/cv.html)

Other factors

- Finite cables
- Active channels
Rall model

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

$$R_N = \frac{\sqrt{R_m R_i}}{2 \pi \alpha^{3/2}}$$

Active cables

New cable equation for each dendritic compartment
Who’ll be my Rall model, now that my Rall model is gone

A. Characterized Neuron

B. Cable Model

C. Compartmental Model

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