Computing in carbon

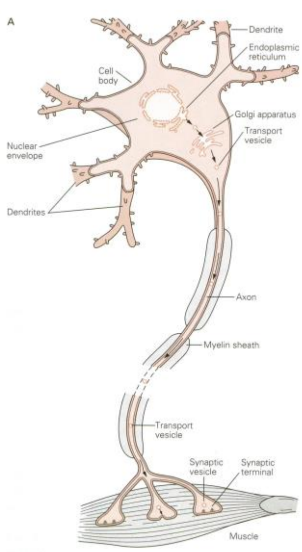
Basic elements of neuroelectronics
- -- membranes
- -- ion channels
- -- wiring

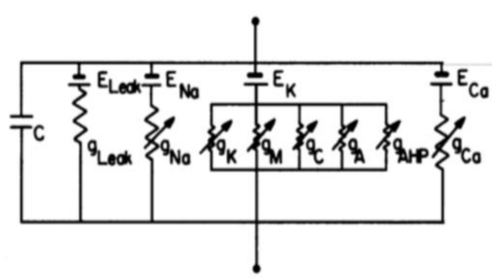
Elementary neuron models
- -- conductance based
- -- modelers' alternatives

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

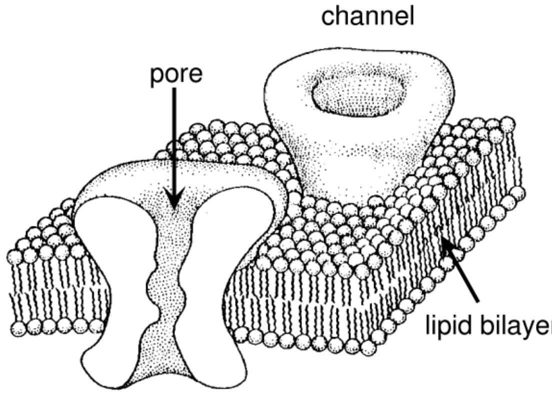
Wiring neurons together
- -- synapses
- -- long term plasticity
- -- short term plasticity

Equivalent circuit model

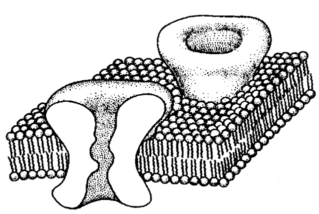


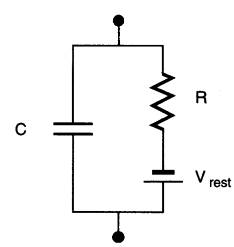


Membrane patch



The passive membrane





Ohm's law: $V = I_R R$

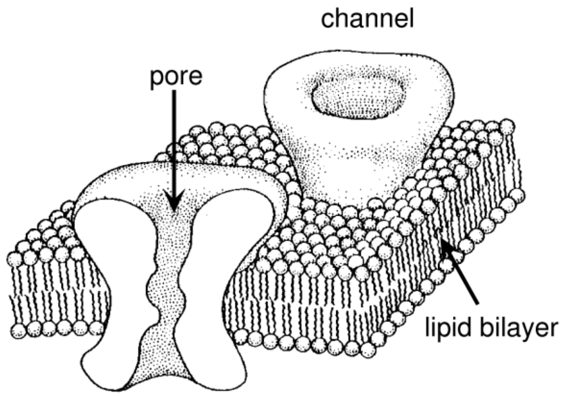
Capacitor: C = Q/V

$$I_C = C\frac{dV}{dt}$$

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

$$C\frac{dV}{dt} = -\frac{V}{R} - I_{\text{ext}}$$

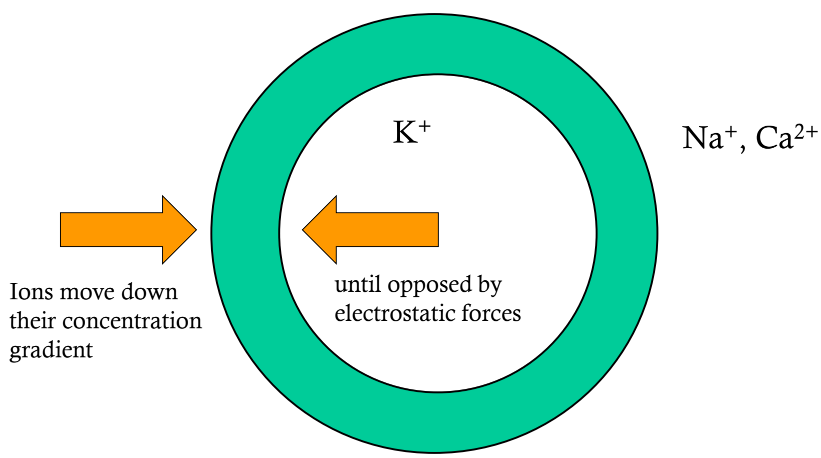
Movement of ions through ion channels



Energetics: $qV \sim k_B T$

$V \sim 25mV$

The equilibrium potential



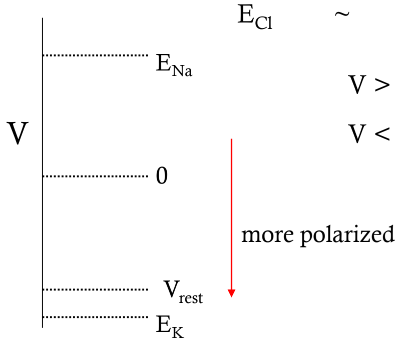
Nernst: $$E = \frac{k_B T}{zq} \ln \frac{[\text{inside}]}{[\text{outside}]}$$

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

E_{Na}	~	50mV	depolarizing
E_{Ca}	~	150mV	depolarizing
E_K	~	-80mV	hyperpolarizing
E_{Cl}	~	-60mV	shunting

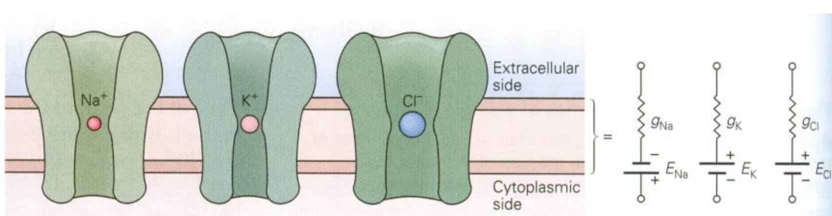


V > E → positive current will flow outward

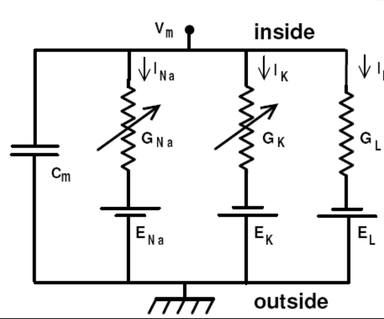
V < E → positive current will flow inward

Parallel paths for ions to cross membrane

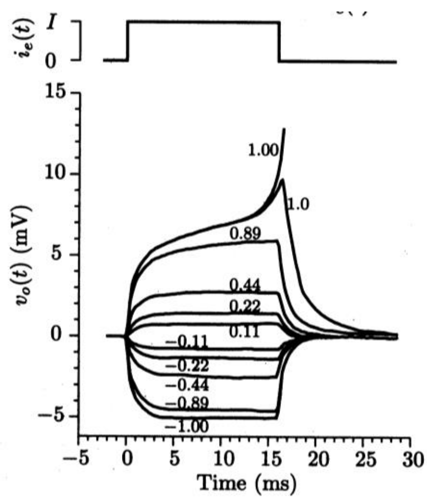
Several *I-V* curves in parallel:



New equivalent circuit:

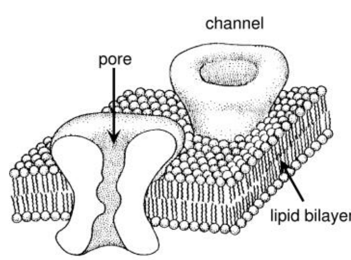


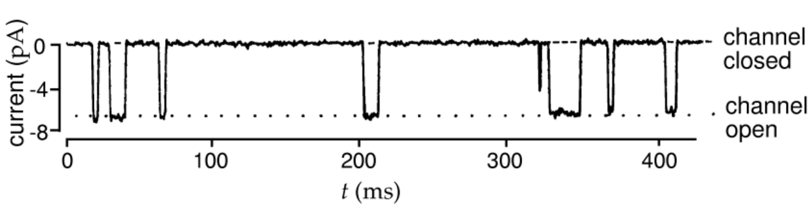
Neurons are excitable



Excitability arises from ion channel nonlinearity

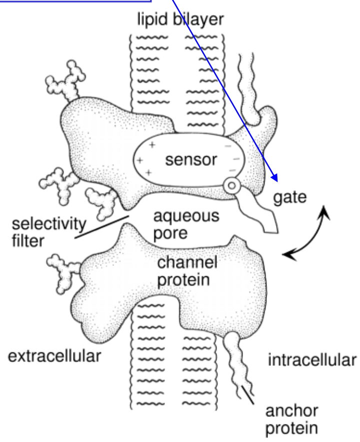
- Voltage dependent
- transmitter dependent (synaptic)
- Ca dependent





The ion channel is a cool molecular machine

K channel: open probability increases when depolarized



$P_K \sim n^4$

Persistent conductance

n describes a subunit

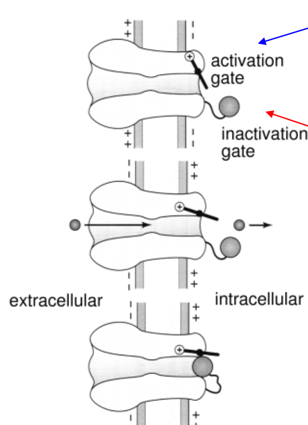
n is open probability
$1 - n$ is closed probability

Transitions between states occur at voltage dependent rates

$\alpha_n(V)$ C → O
$\beta_n(V)$ O → C

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

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

$$\frac{dn}{dt} = \alpha_n(V)(1-n) - \beta_n(V)n$$
$$\frac{dm}{dt} = \alpha_m(V)(1-m) - \beta_m(V)m$$
$$\frac{dh}{dt} = \alpha_h(V)(1-h) - \beta_h(V)h$$

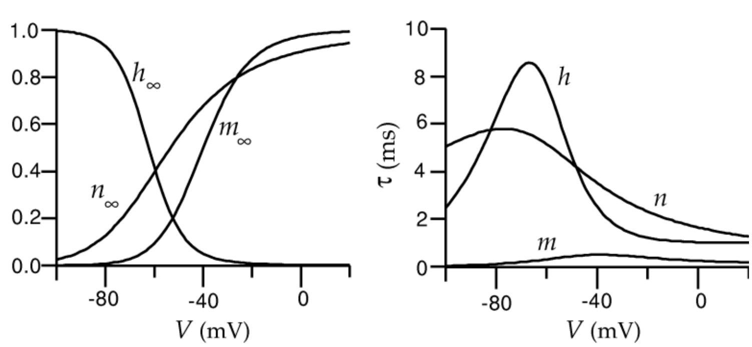
We can rewrite:

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

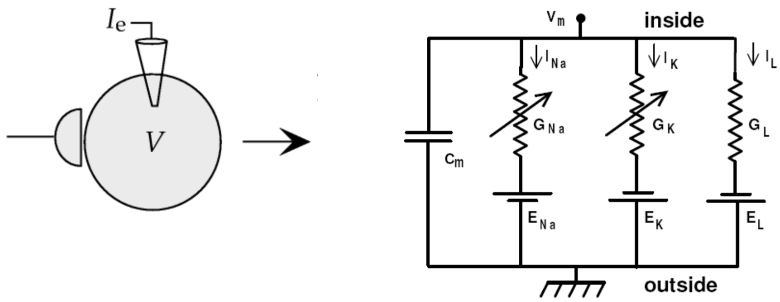
where

$$\tau_n(V) = \frac{1}{\alpha_n(V) + \beta_n(V)}$$
$$n_\infty(V) = \frac{\alpha_n(V)}{\alpha_n(V) + \beta_n(V)}$$

Dynamics of activation and inactivation



Putting it together



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

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

Capacitative current

Ionic currents

Externally applied current

The Hodgkin-Huxley equation

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

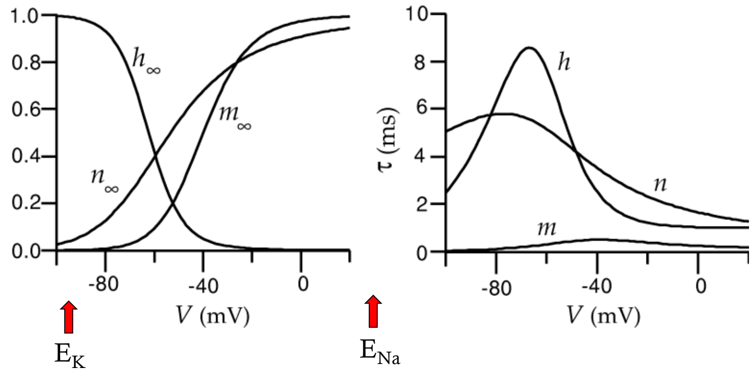
$$-C_m \frac{dV}{dt} = g_L (V - E_L) + \bar{g}_{\mathrm{K}} n^4 (V - E_{\mathrm{K}}) + \bar{g}_{\mathrm{Na}} m^3 h (V - E_{\mathrm{Na}})$$

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

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

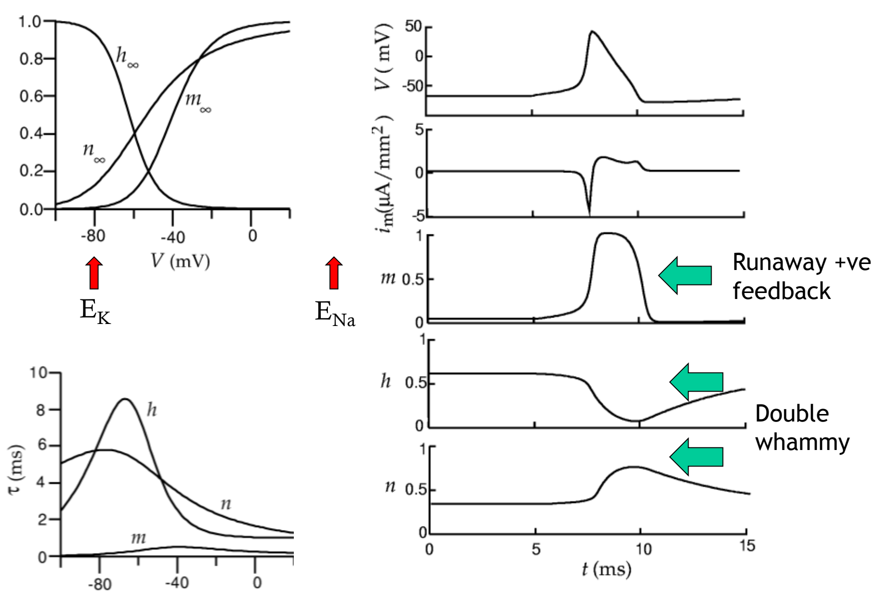
$$\frac{dh}{dt} = \alpha_h(V)(1-h) - \beta_h(V)h$$

Anatomy of a spike



Na ~ m^3h K ~ m^3h

Anatomy of a spike



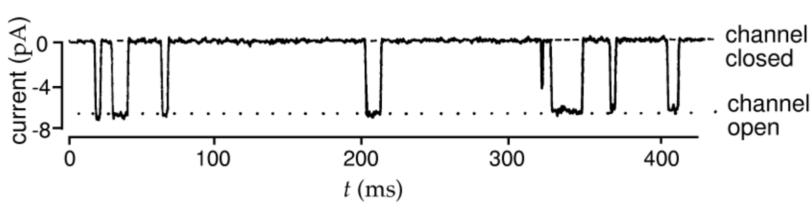
Where to from here?

Hodgkin-Huxley

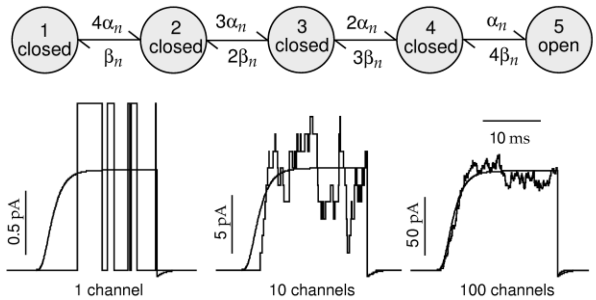
Biophysical realism
Molecular considerations
Geometry

Simplified models
Analytical tractability

Ion channel stochasticity

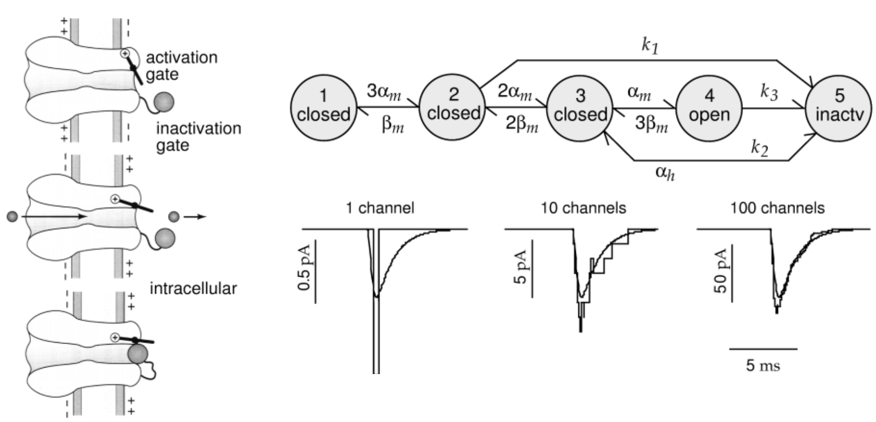


Microscopic models for ion channel fluctuations



approach to macroscopic description

Transient conductances



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

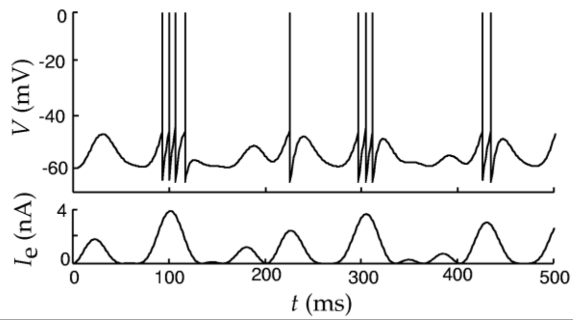
The integrate-and-fire neuron

Like a passive membrane:

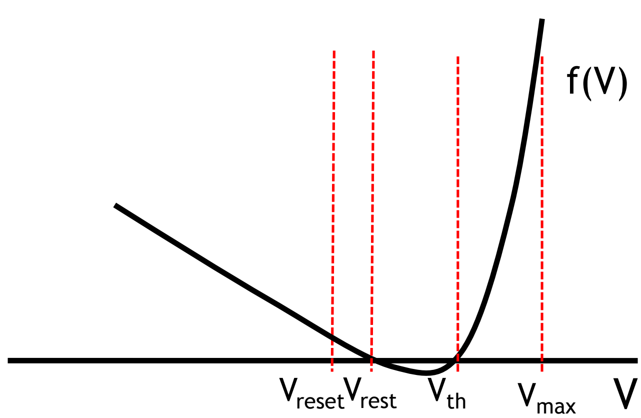
$$C_m \frac{dV}{dt} = -g_L(V - E_i) - I_e$$

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

E_L is the resting potential of the "cell".

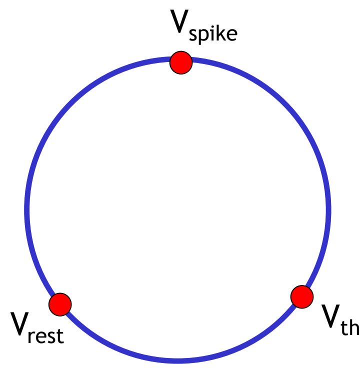


Exponential integrate-and-fire neuron



$$f(V) = -V + \exp([V-V_{th}]/\Delta)$$

The theta neuron



$$d\theta/dt = 1 - \cos\theta + (1 + \cos\theta)\, I(t)$$

Ermentrout and Kopell

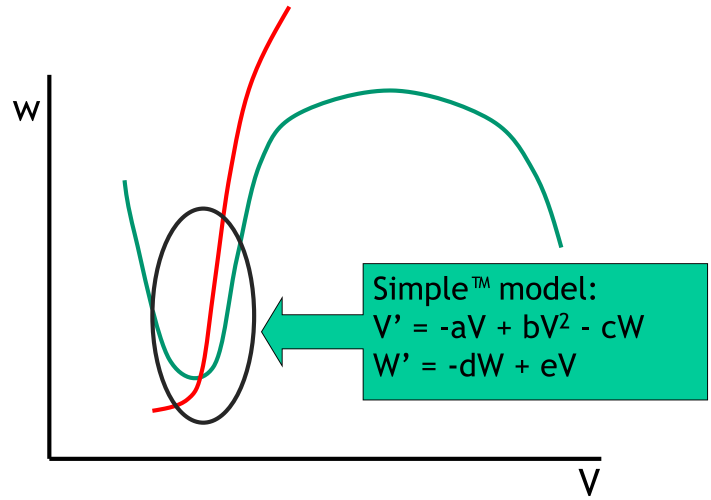
The spike response model

Kernel f for subthreshold response ← replaces leaky integrator
Kernel for spikes ← replaces "line"

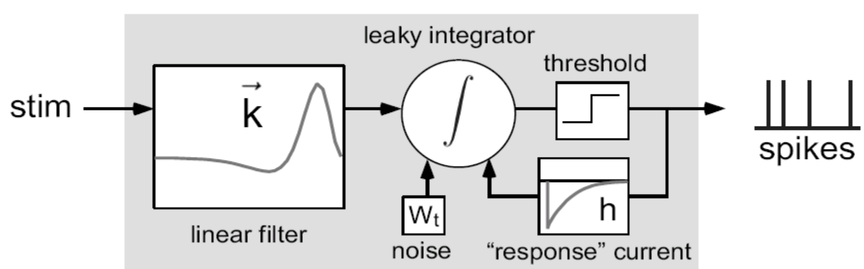
- determine f from the linearized HH equations
- fit a threshold
- paste in the spike shape and AHP

Gerstner and Kistler

Two-dimensional models

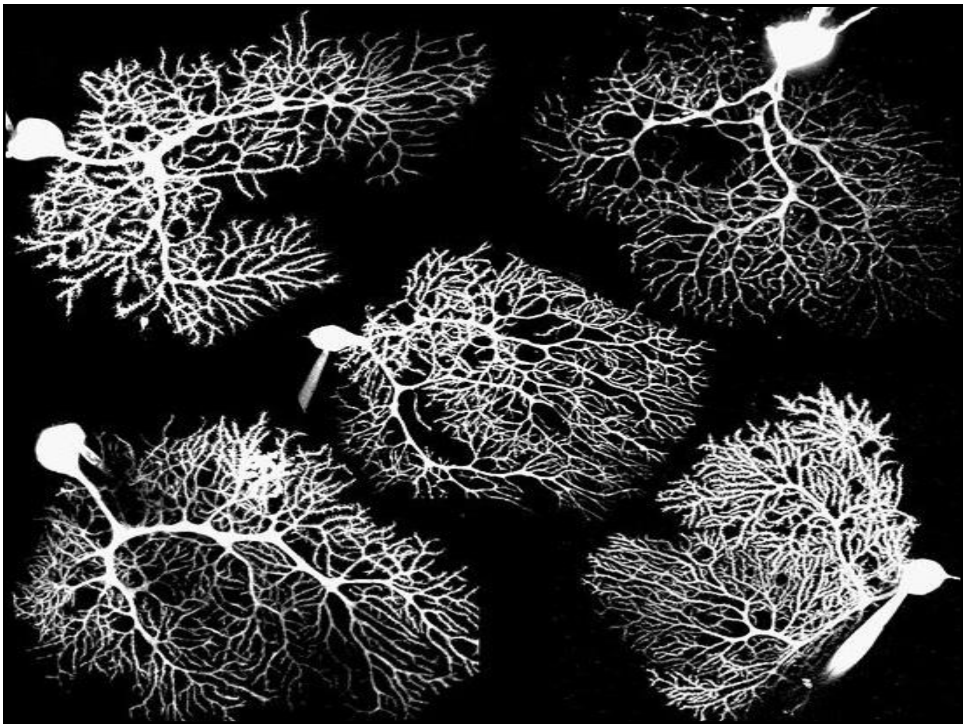


The generalized linear model



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

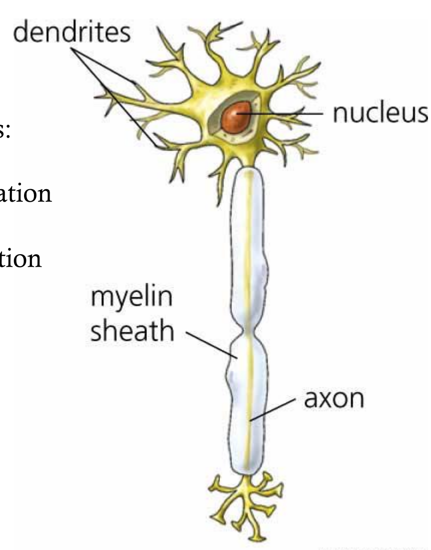
Truccolo and Brown, Paninski, Pillow, Simoncelli



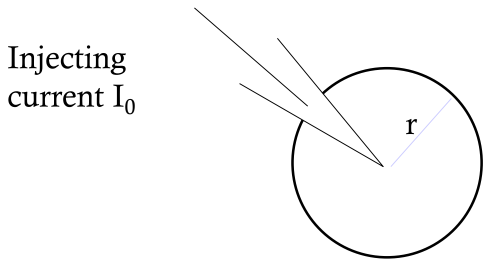
Dendritic computation

Dendrites as computational elements:

- Passive contributions to computation
- Active contributions to computation
- Examples



Geometry matters



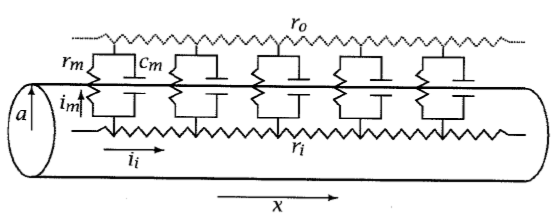
$V_m = I_m R_m$

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

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

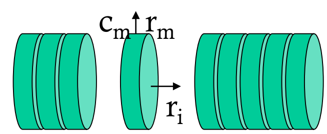
$= R_m/4\pi r^2$

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



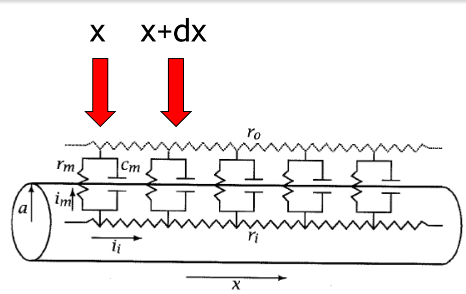
For a length L of membrane cable:

$r_i \rightarrow r_i L$
$r_m \rightarrow r_m / L$
$c_m \rightarrow c_m L$

The cable equation

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

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



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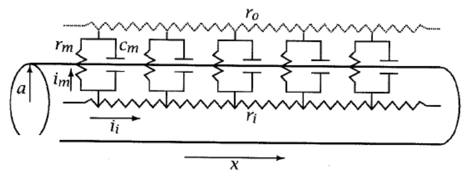


$\frac{\partial}{\partial x}$ (1) → $$\frac{\partial^2 V_m}{\partial x^2} = -r_i \frac{\partial i_i}{\partial x} = r_i i_m.$$

$$i_m = i_C + i_{\text{ionic}} = c_m \frac{\partial V_m}{\partial t} + \frac{V_m}{r_m}$$

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

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

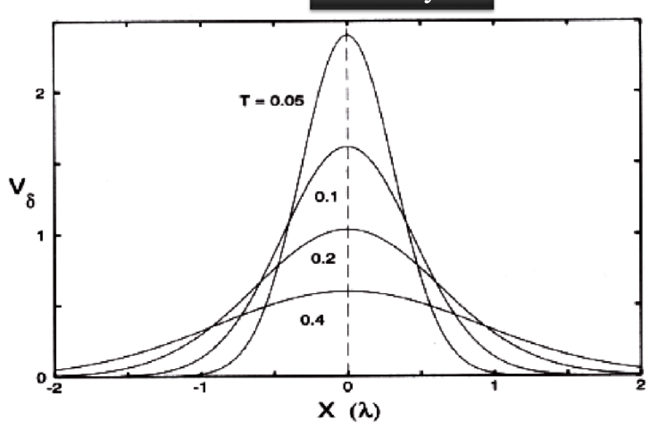
$\lambda = \sqrt{\frac{r_m}{r_i}}$ Space constant

General solution: filter and impulse response

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

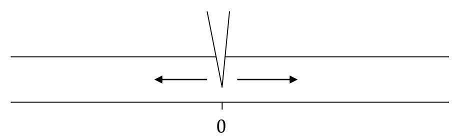
Exponential decay

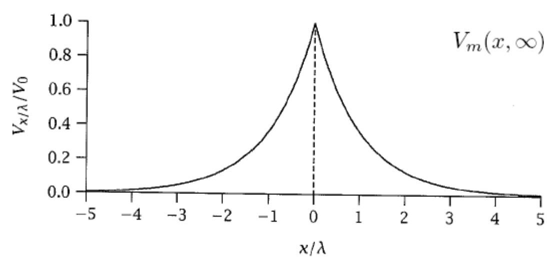
Diffusive spread



Voltage decays exponentially away from source

Current injection at x=0, T → ∞



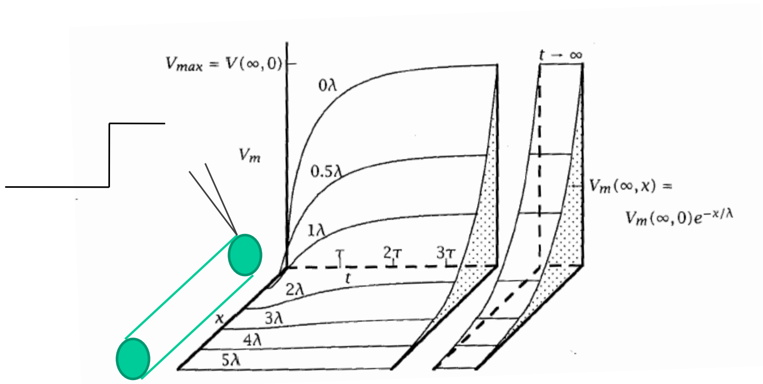


$$V_m(x,\infty) = \frac{r_i I_0 \lambda}{2} e^{-x/\lambda}$$

Properties of passive cables

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

Electrotonic length



Johnson and Wu

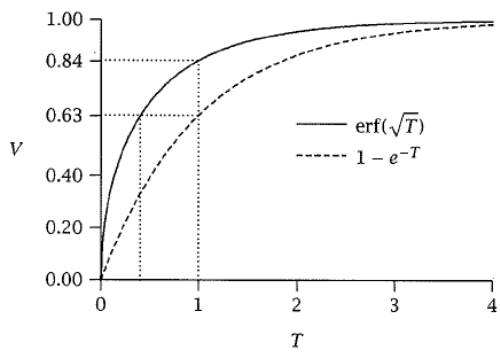
Properties of passive cables

→ 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



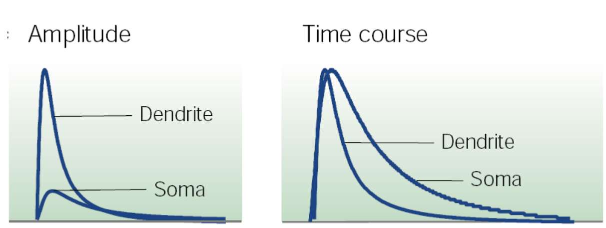
Johnson and Wu

Properties of passive cables

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

→ Current can escape through additional pathways: speeds up decay

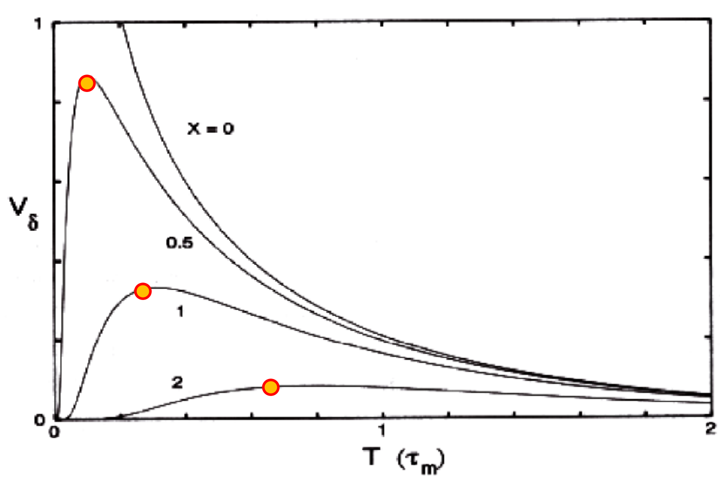
→ Cable diameter affects input resistance $R_N = \frac{\sqrt{R_m R_i / 2}}{2\pi a^{3/2}}$



Properties of passive cables

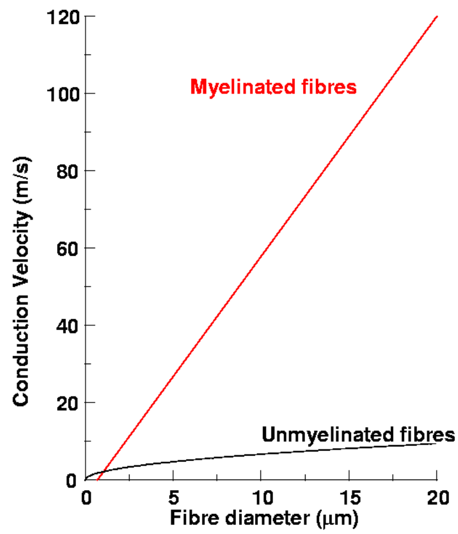
- → Electrotonic length $\lambda = \sqrt{\frac{r_m}{r_i}}$
- → Current can escape through additional pathways: speeds up decay
- → Cable diameter affects input resistance $R_N = \frac{\sqrt{R_m R_i / 2}}{2\pi a^{3/2}}$
- → Cable diameter affects transmission velocity

Step response: pulse travels



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

Conduction velocity



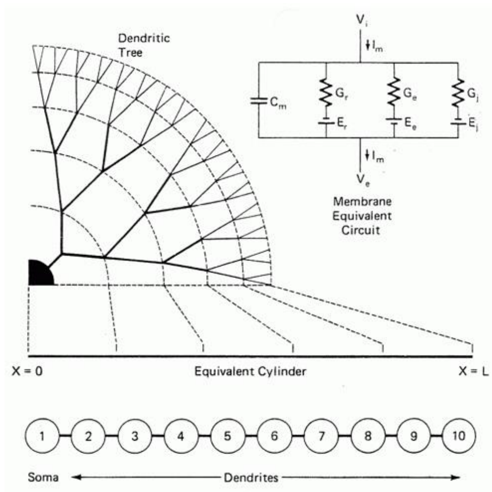
www.physiol.usyd.edu/au/~daved/teaching/cv.html

Other factors

Finite cables

Active channels

Rall model



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

Impedance matching:

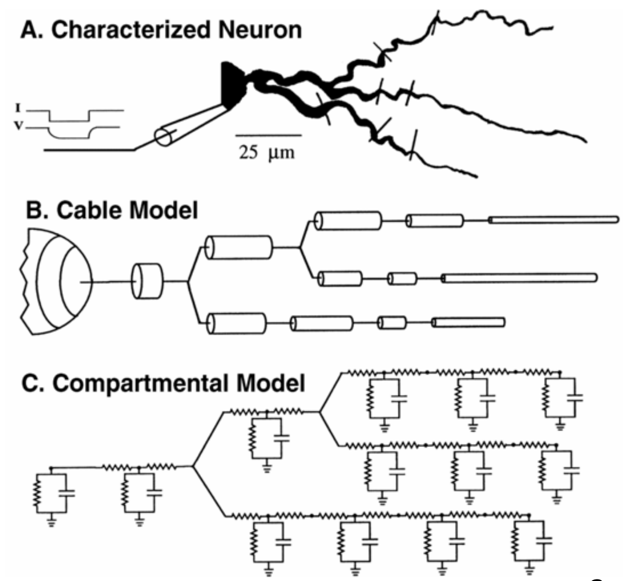
If $a^{3/2} = d_1^{3/2} + d_2^{3/2}$

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

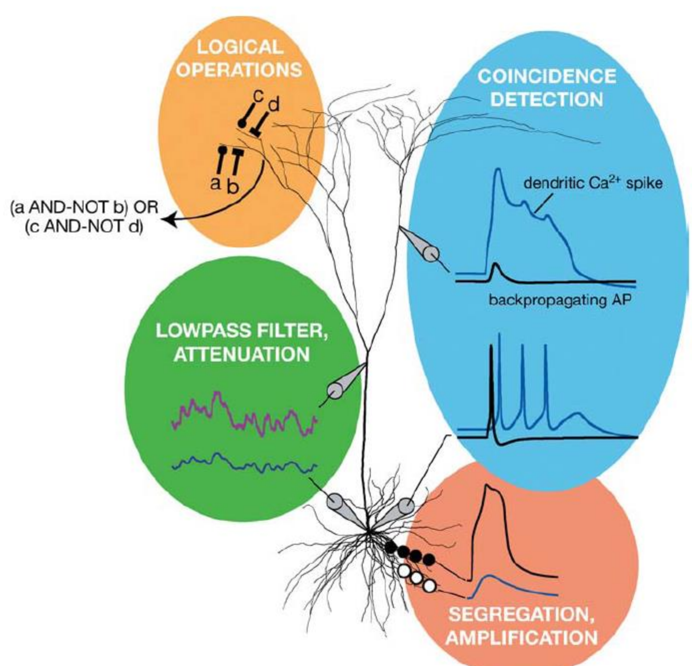
Active cables

New cable equation for each dendritic compartment

Who'll be my Rall model, now that my Rall model is gone



Genesis, NEURON



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