# Computing in carbon

**Basic elements of neuroelectronics**

-- membranes
-- ion channels
-- wiring

**Elementary neuron models**

-- conductance based
-- modelers' alternatives

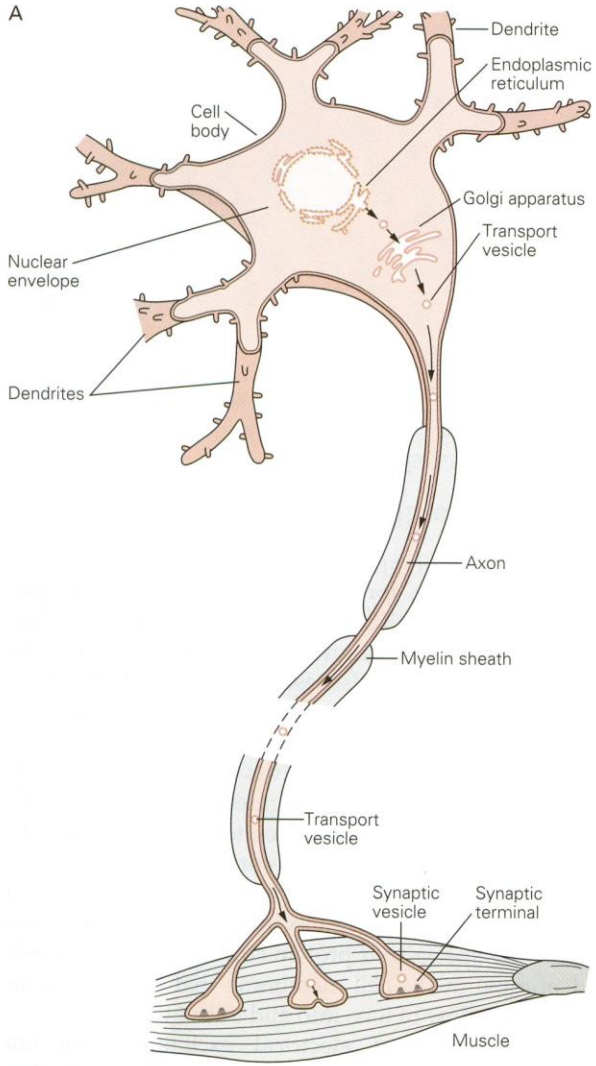
**Wires**

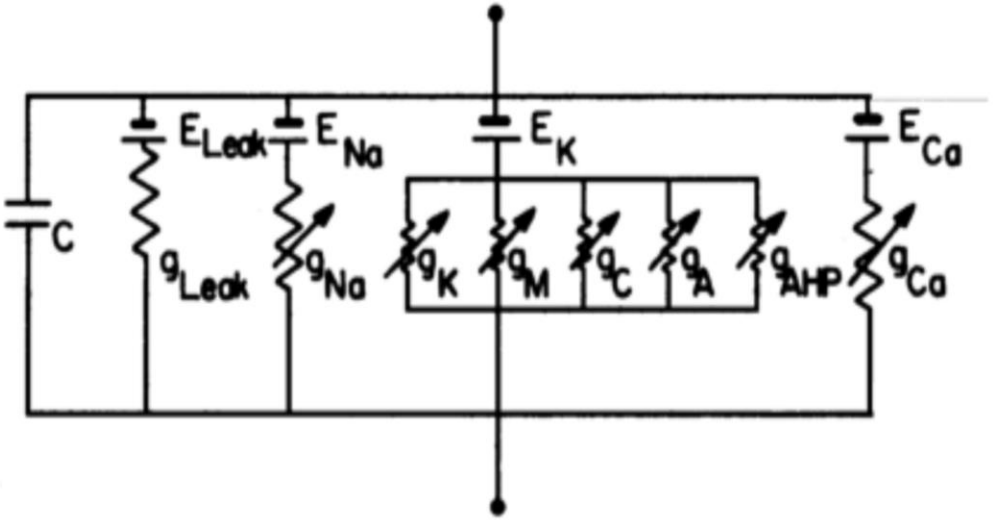
-- signal propagation
-- processing in dendrites

**Wiring neurons together**

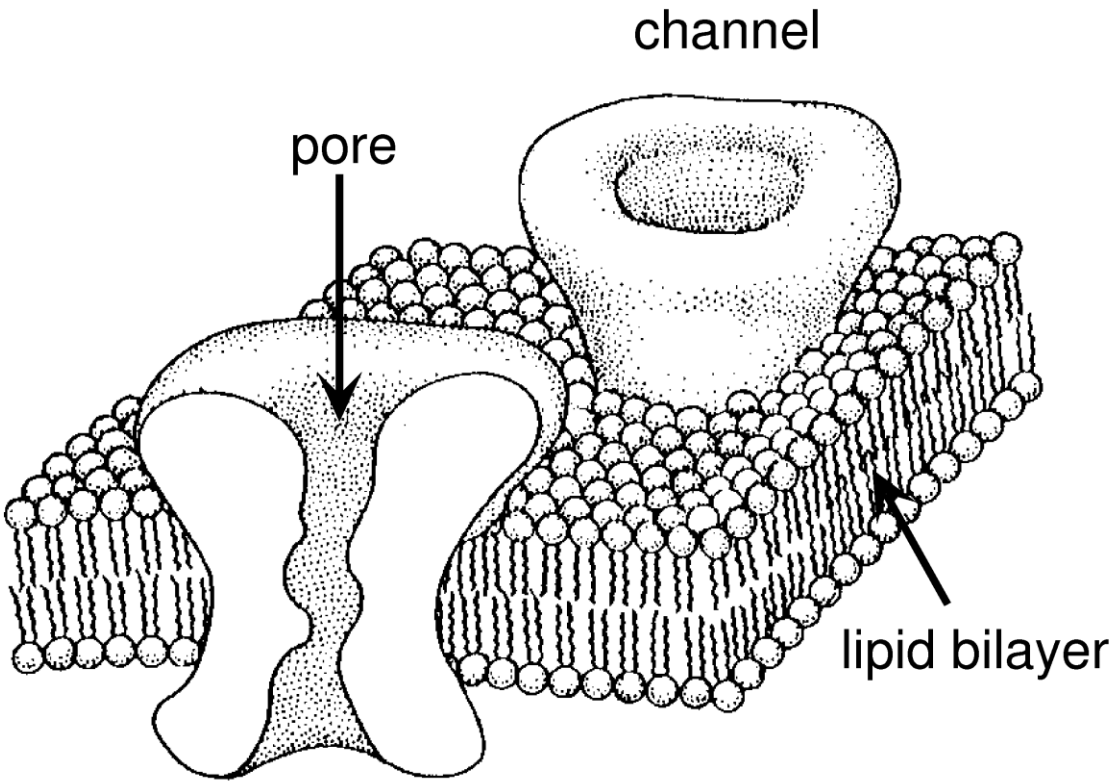
-- synapses
-- long term plasticity
-- short term plasticity

# Equivalent circuit model

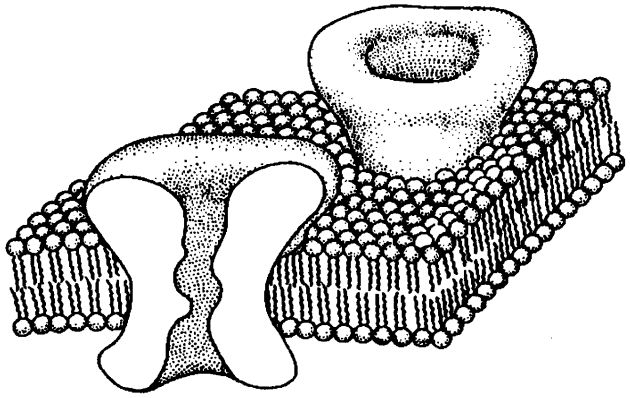


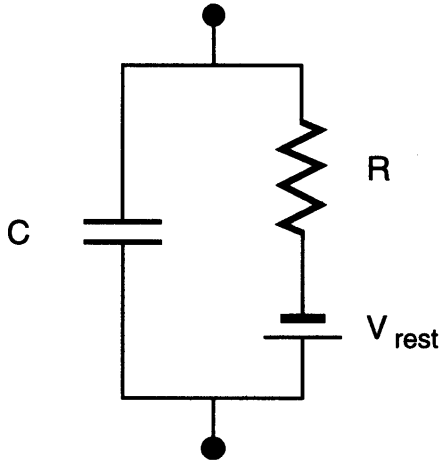



# Membrane patch



# The passive membrane






Ohm's law: $V = I_R R$

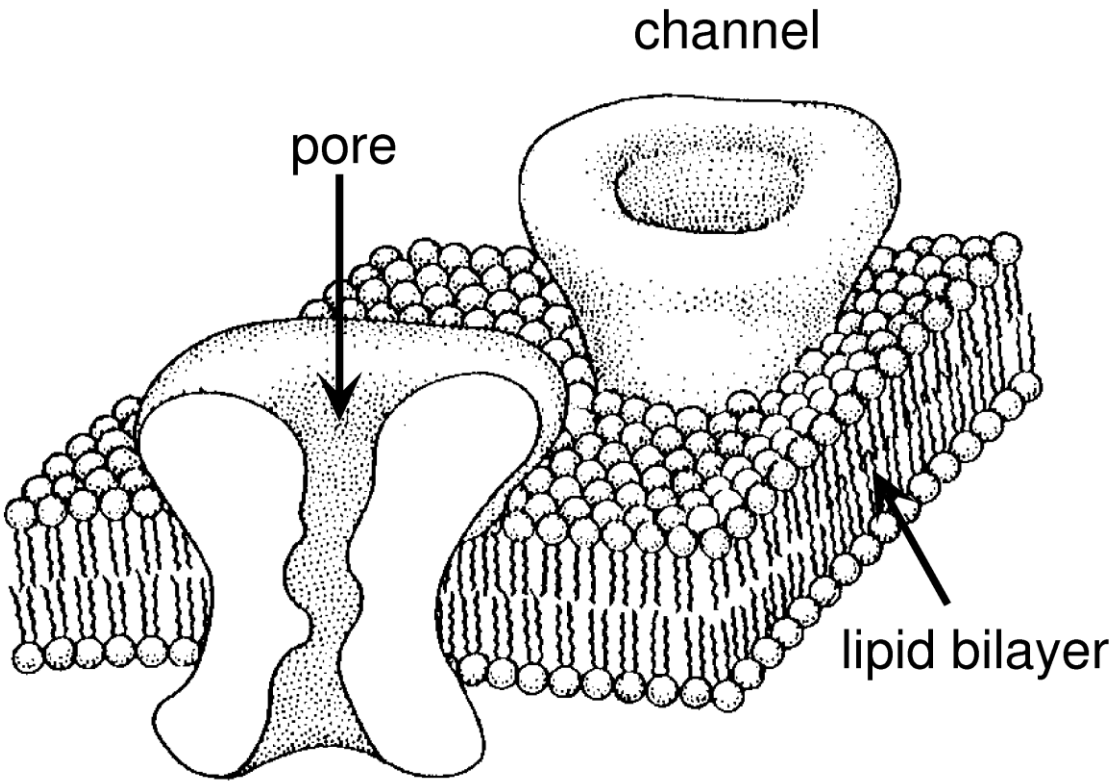
Capacitor: C = Q/V

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

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

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

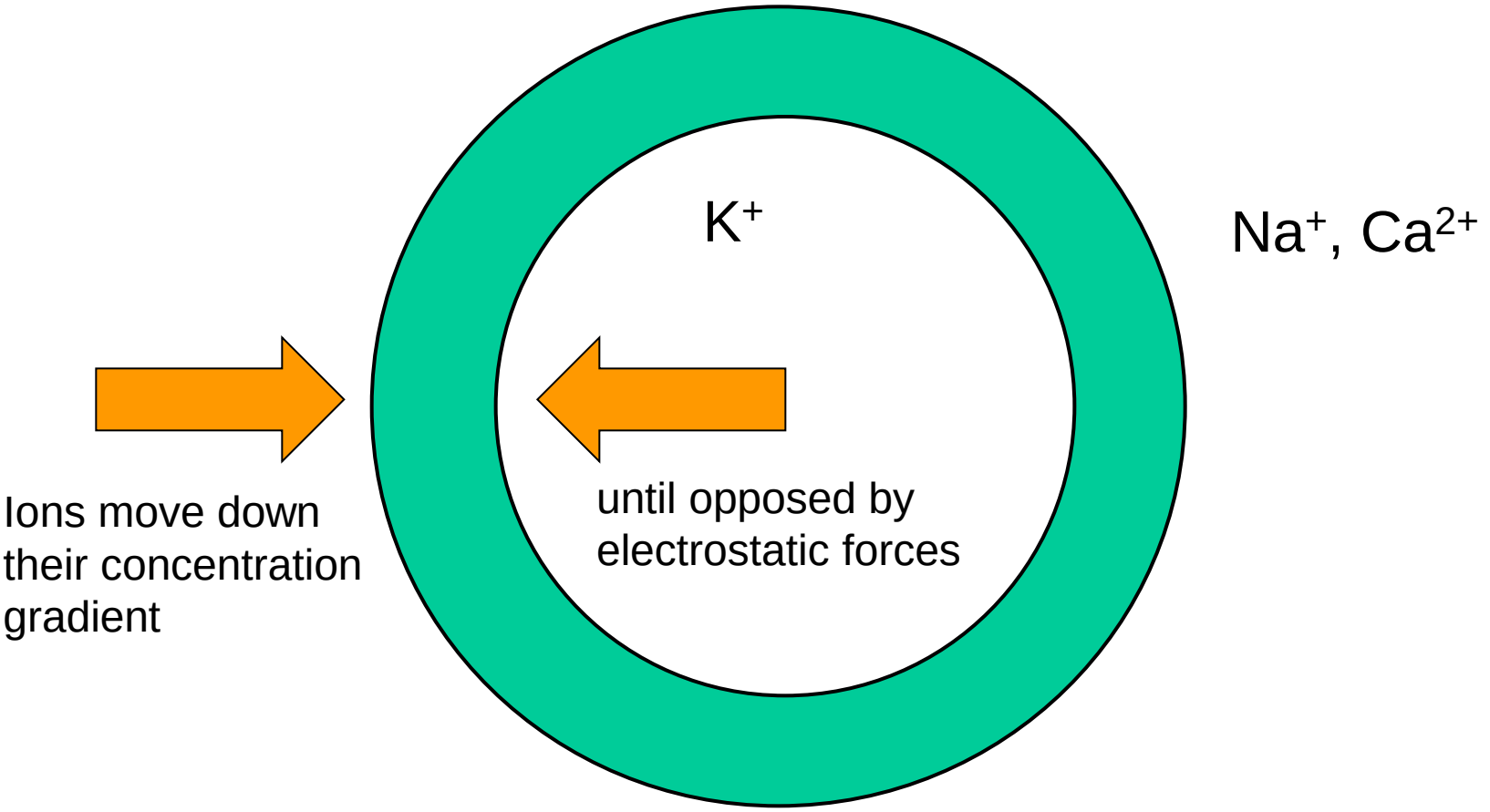
# Movement of ions through ion channels




Energetics: $qV \sim k_B T$

$V \sim 25mV$

# The equilibrium potential



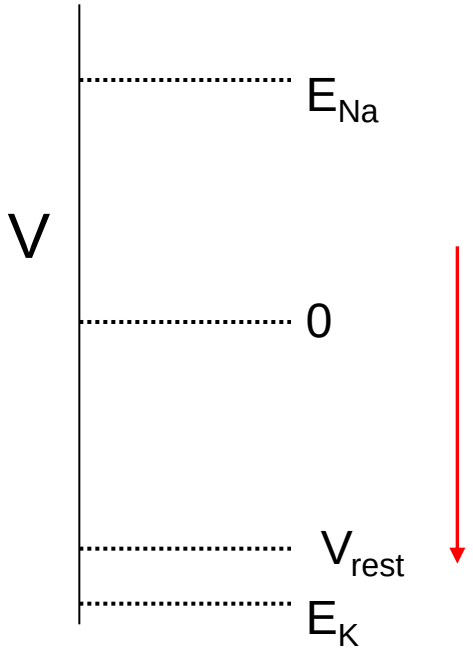

Nernst: $$E = \frac{k_B T}{zq} \ln \frac{[\text{inside}]}{[\text{outside}]}$$

# 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 |

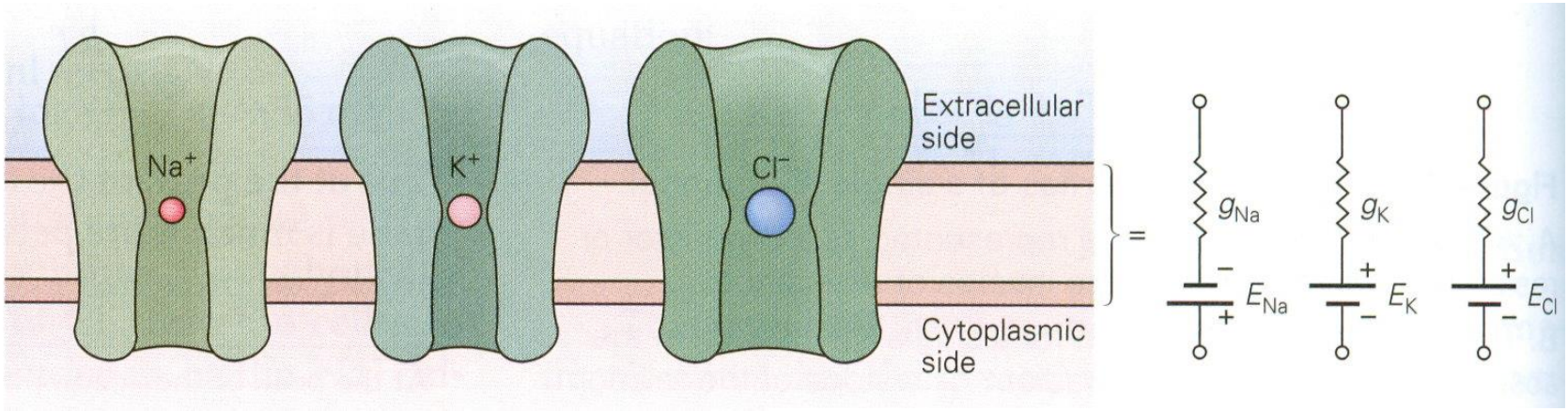



$V > E$ → positive current will flow outward

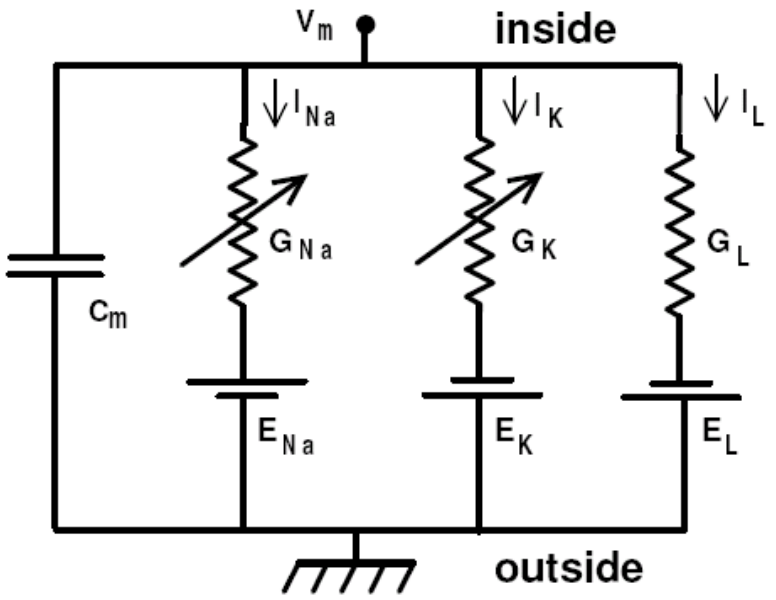
$V < E$ → positive current will flow inward

# Parallel paths for ions to cross membrane

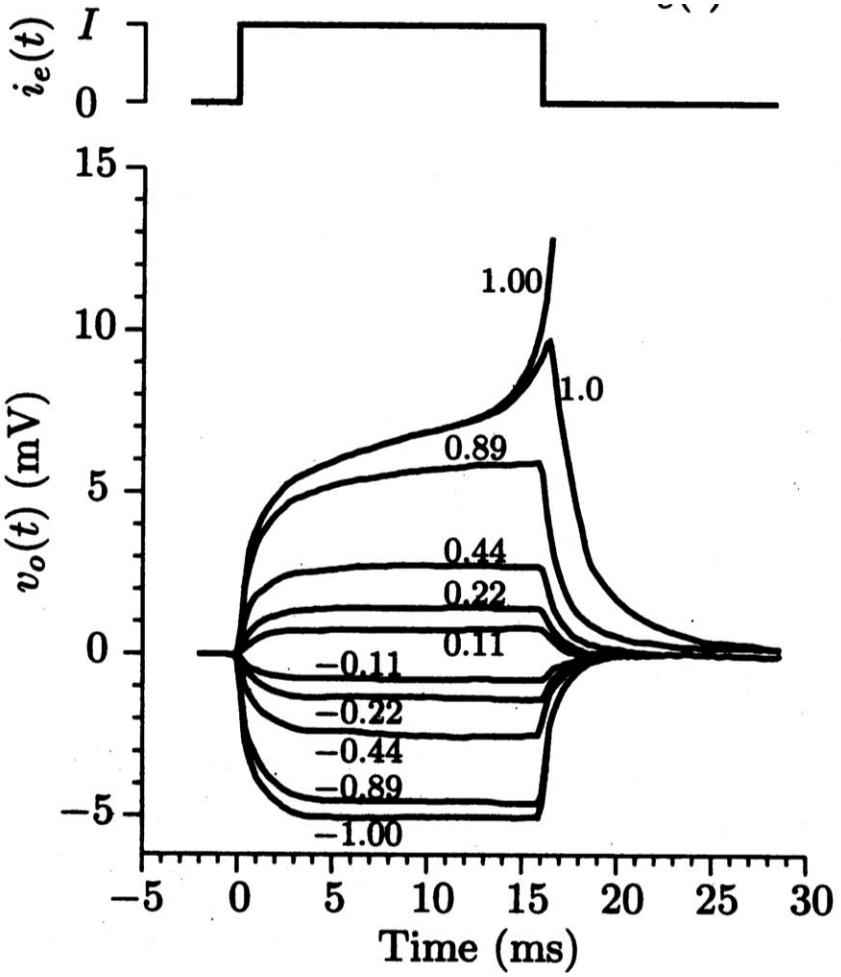
Several *I-V* curves in parallel:




New equivalent circuit:

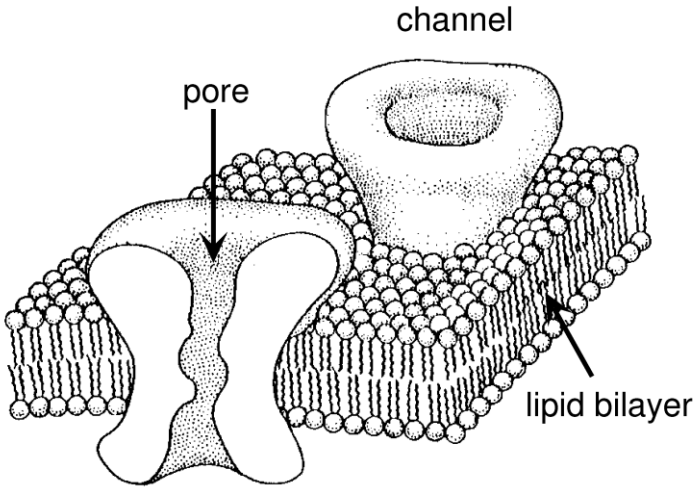


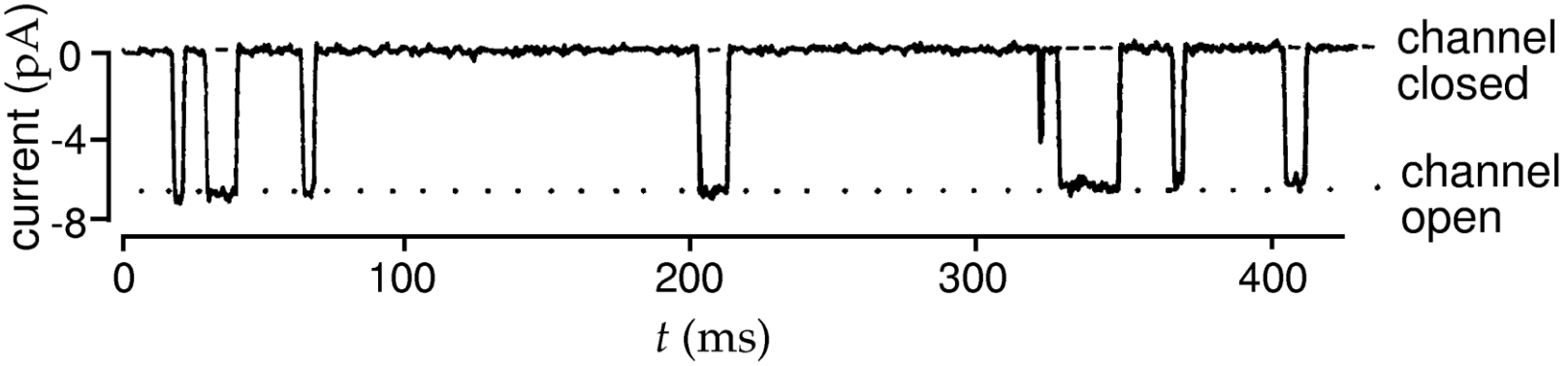
# Neurons are excitable



# Excitability arises from ion channel nonlinearity

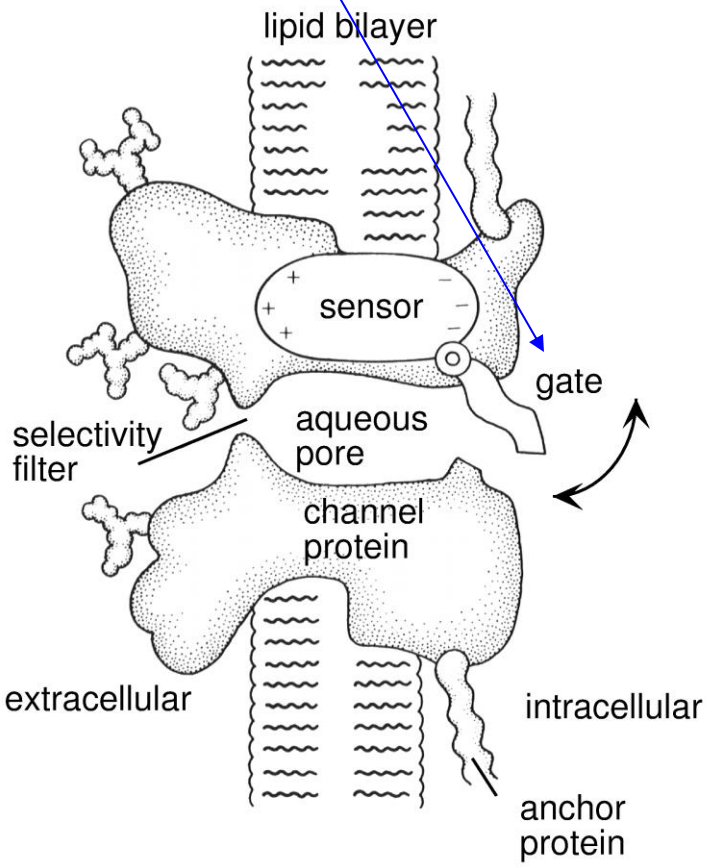
- Voltage dependent
- transmitter dependent (synaptic)
- Ca dependent



# The ion channel is a cool molecular machine

K channel: open probability increases when depolarized




$P_K \sim n^4$

*n* describes a subunit

| | |
|---|---|
| *n* | is open probability |
| 1 – *n* | is closed probability |

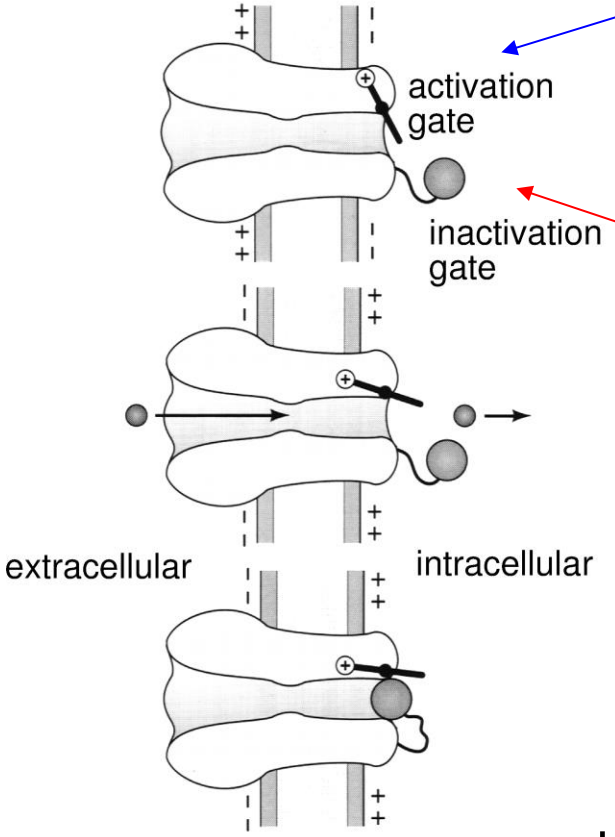
Transitions between states occur at voltage dependent rates

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

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

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:

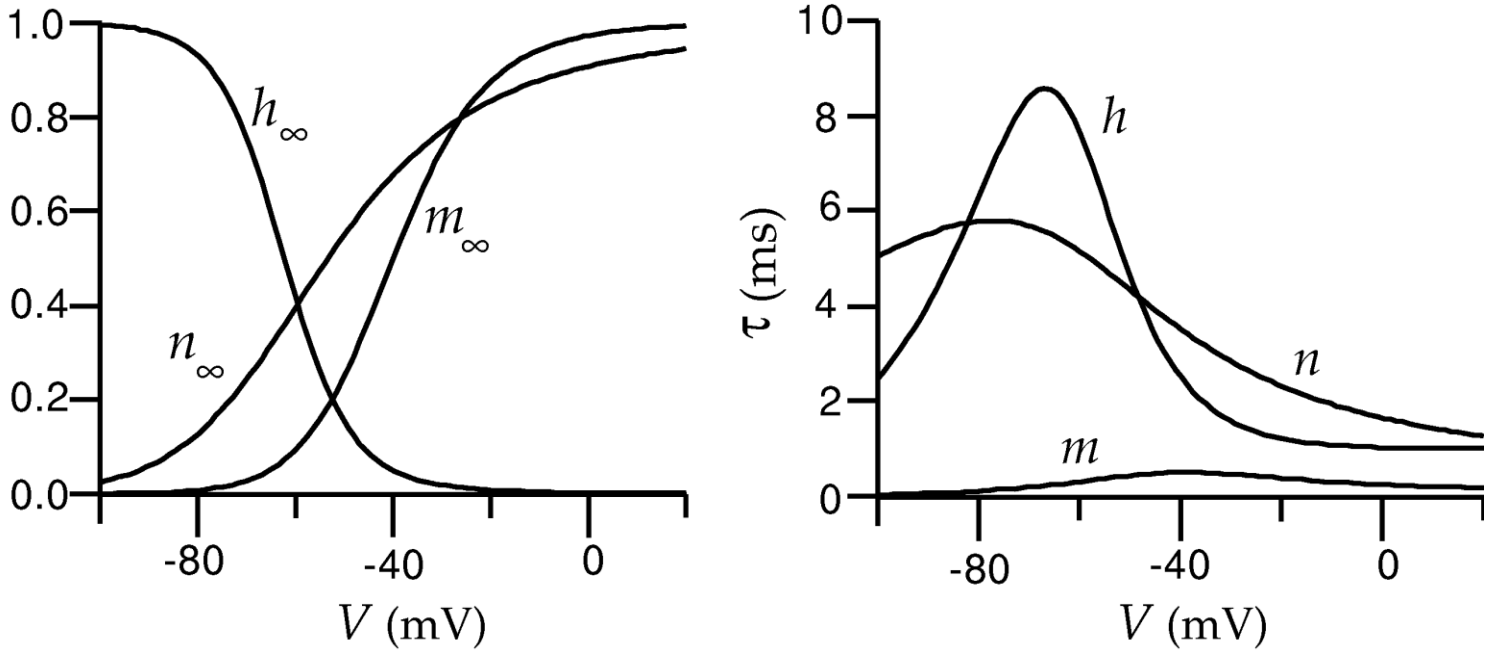
$$\tau_n(V)\frac{dn}{dt} = n_\infty(V) - n$$

where

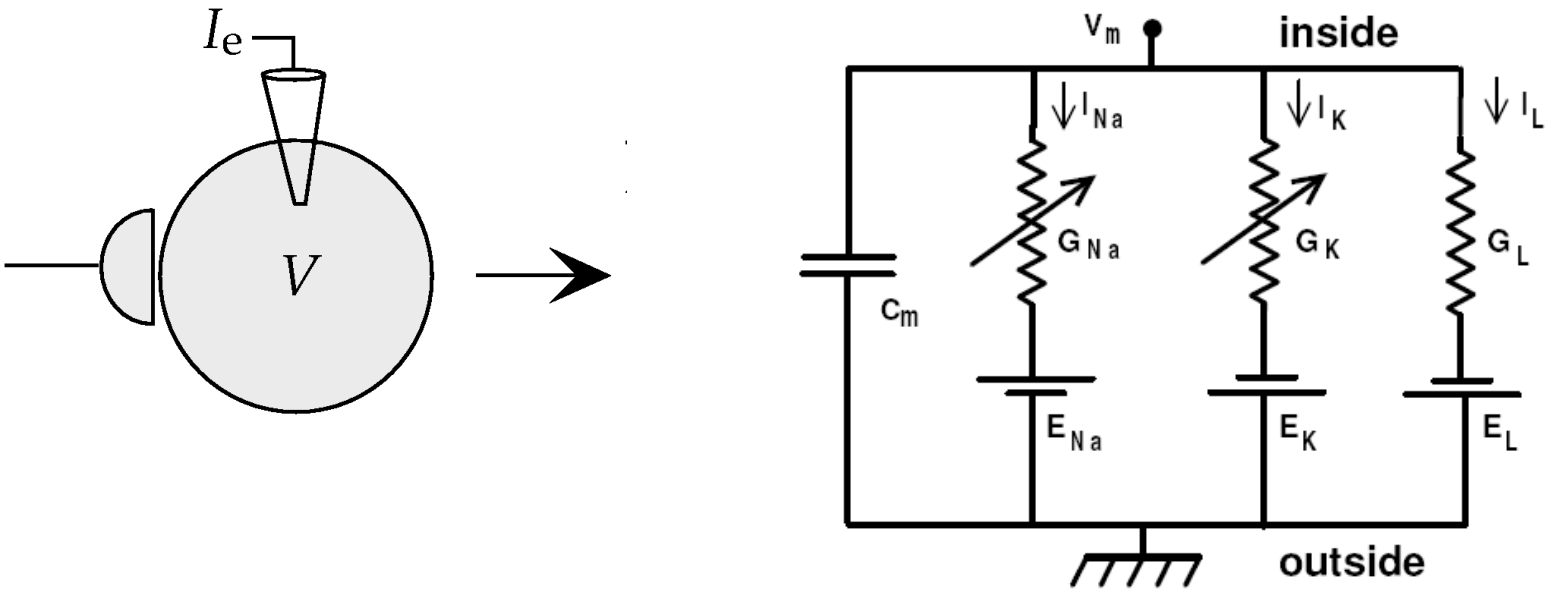
$$\tau_n(V) = \frac{1}{\alpha_n(V) + \beta_n(V)}$$

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

# 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

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

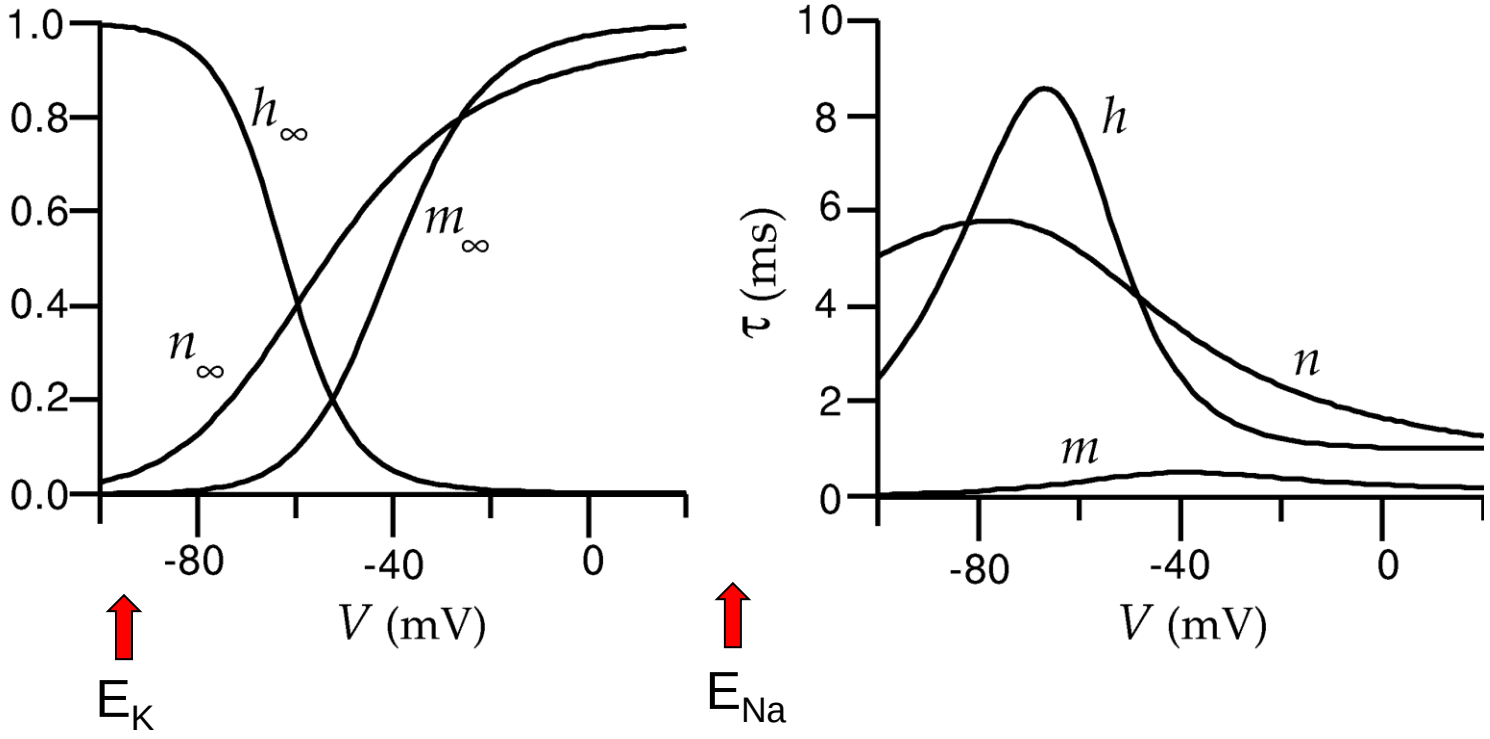
$$-C_m \frac{dV}{dt} = g_L(V - E_L) + \bar{g}_{\mathrm{K}} n^4 (V - E_{\mathrm{K}}) + \bar{g}_{\mathrm{Na}} m^3 h (V - E_{\mathrm{Na}})$$

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

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

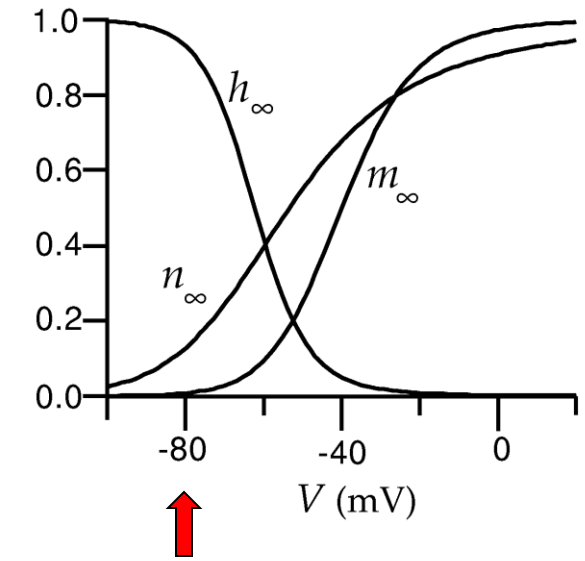
$$\frac{dh}{dt} = \alpha_h(V)(1 - h) - \beta_h(V) h$$

# Anatomy of a spike



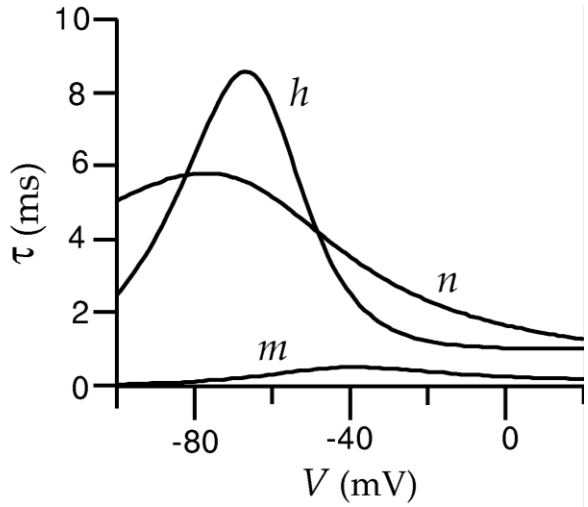

Na ~ $m^3h$ K ~ $m^3h$

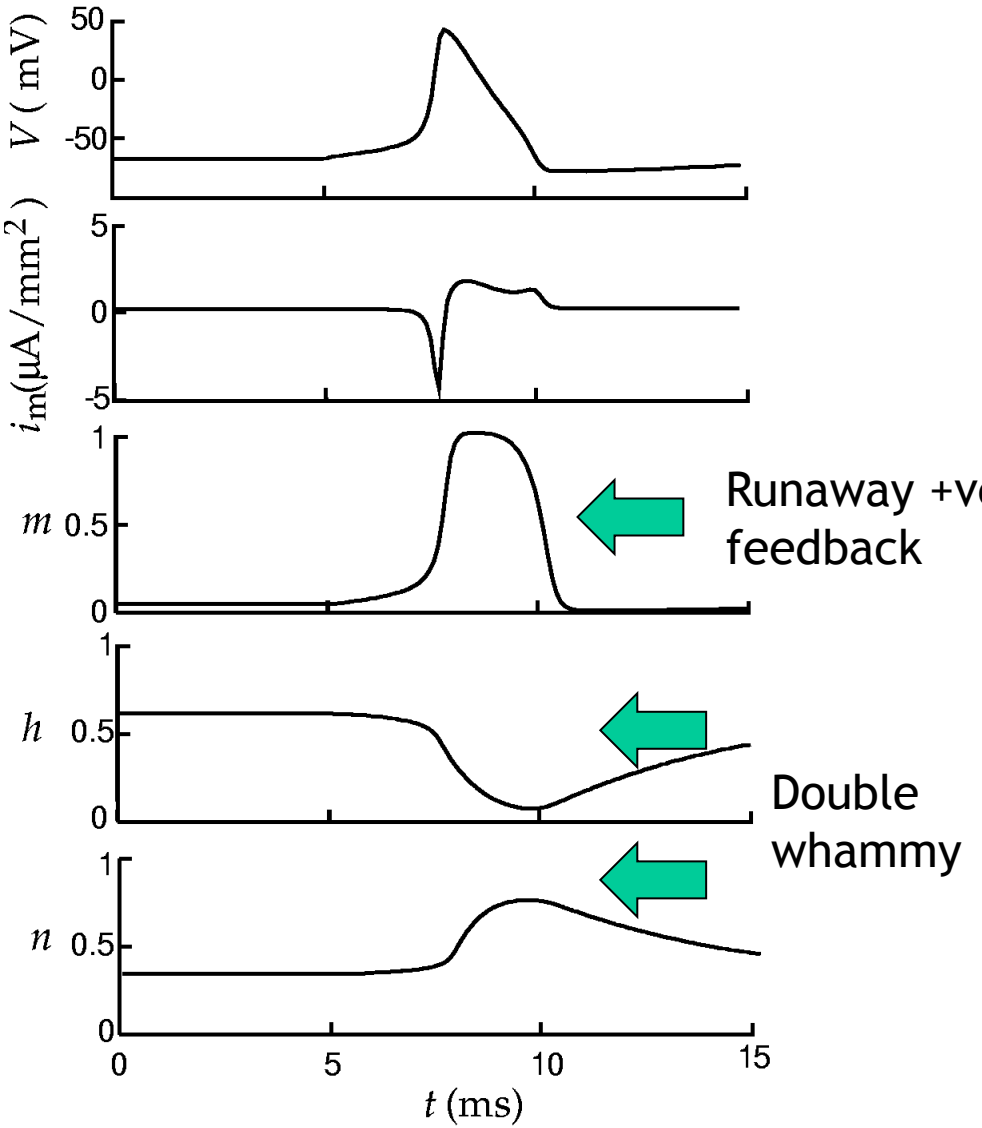
# Anatomy of a spike




$E_K$

$E_{Na}$

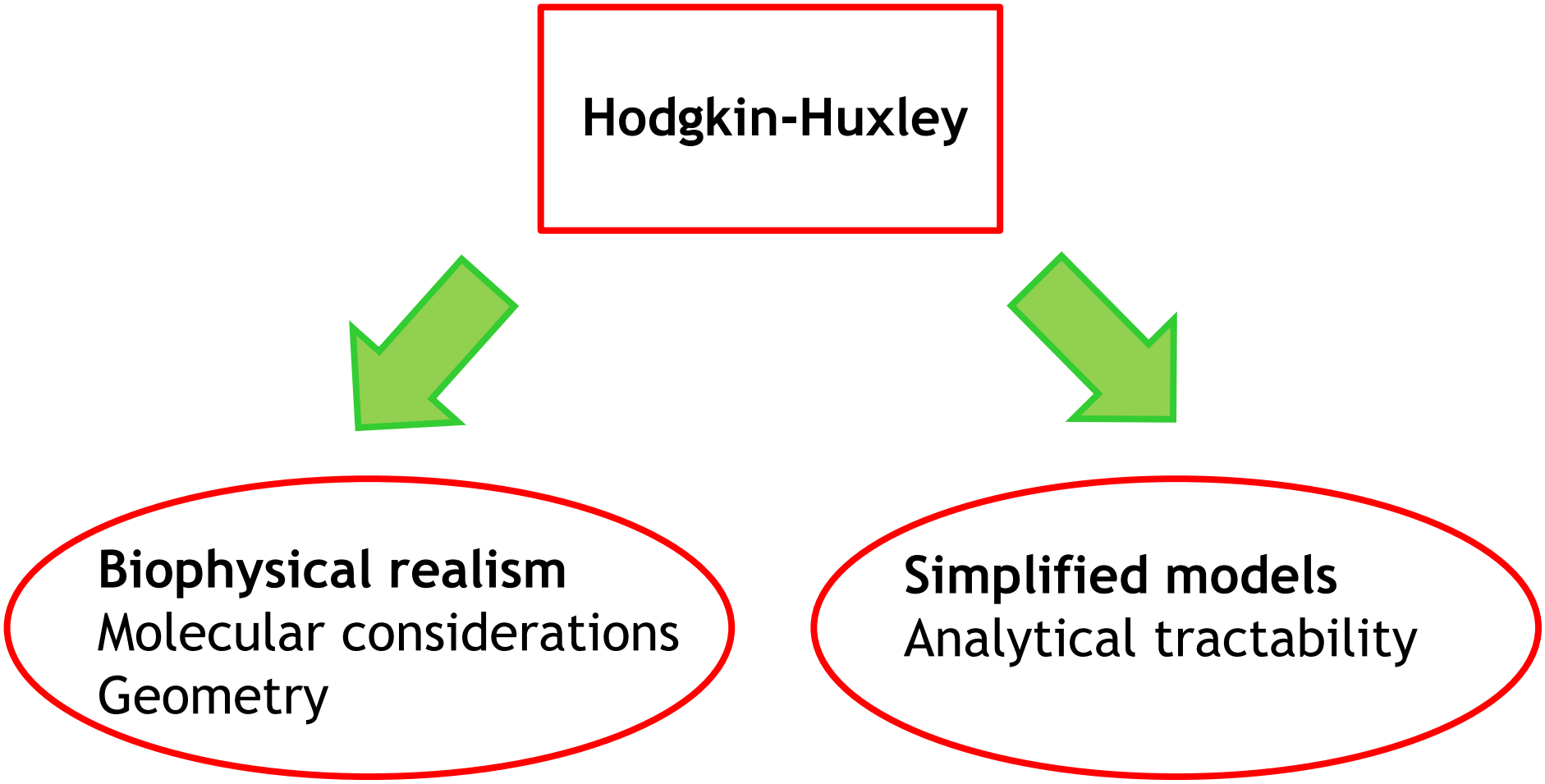


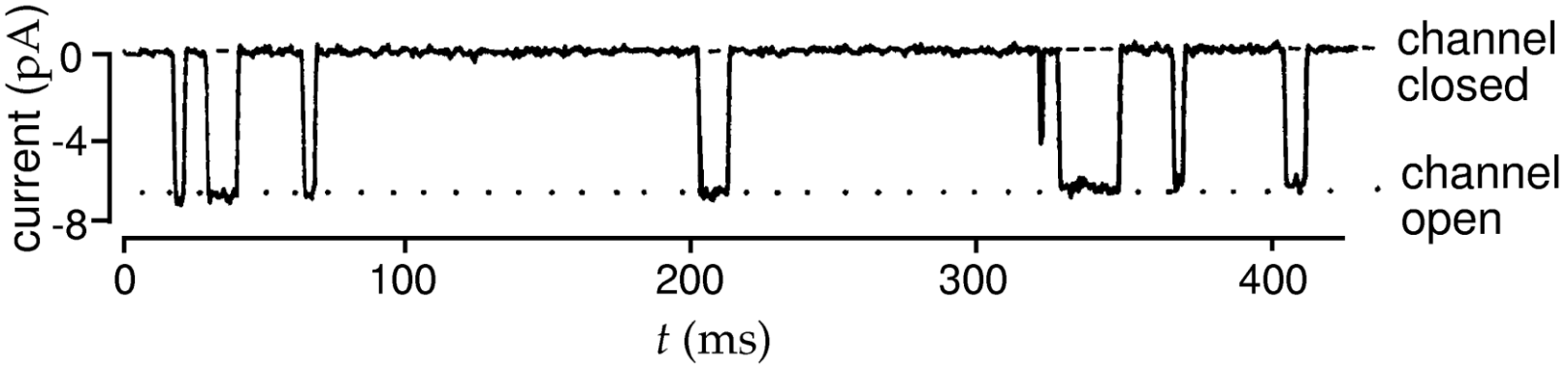

Runaway +ve feedback

Double whammy

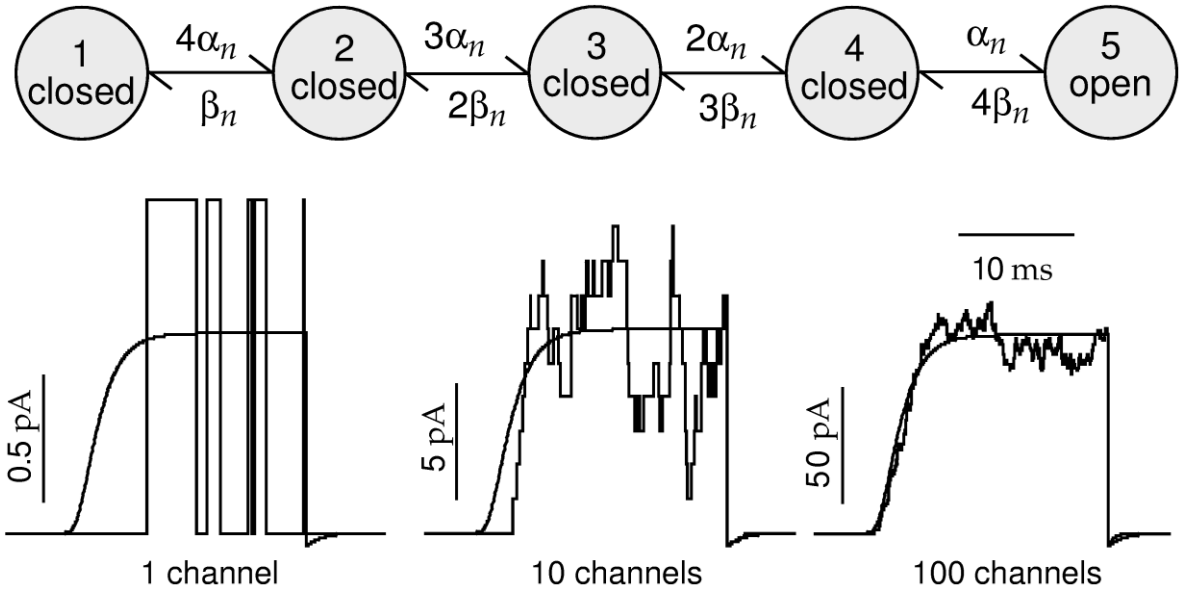
# Where to from here?



# Ion channel stochasticity

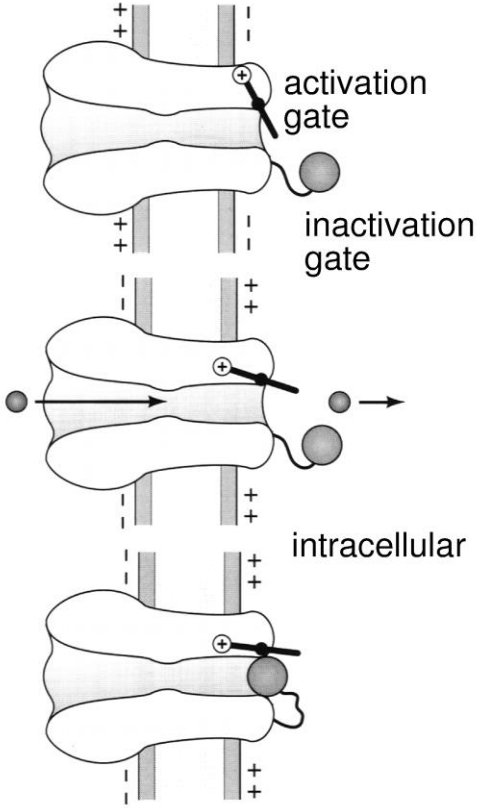


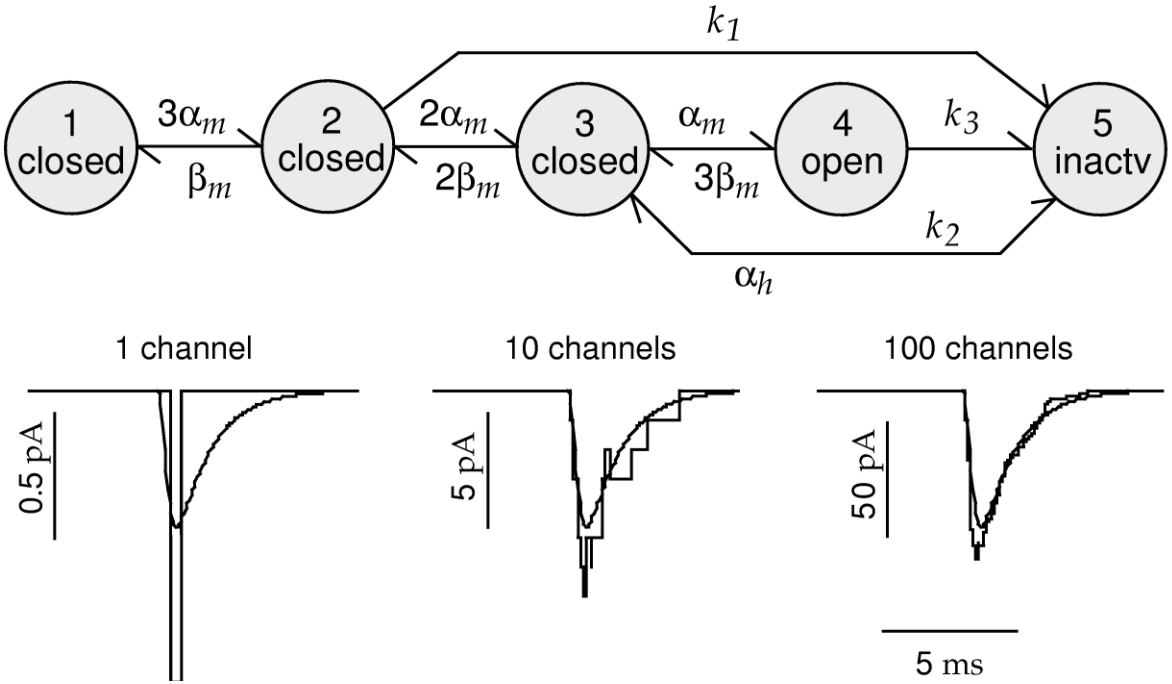
# Microscopic models for ion channel fluctuations




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:

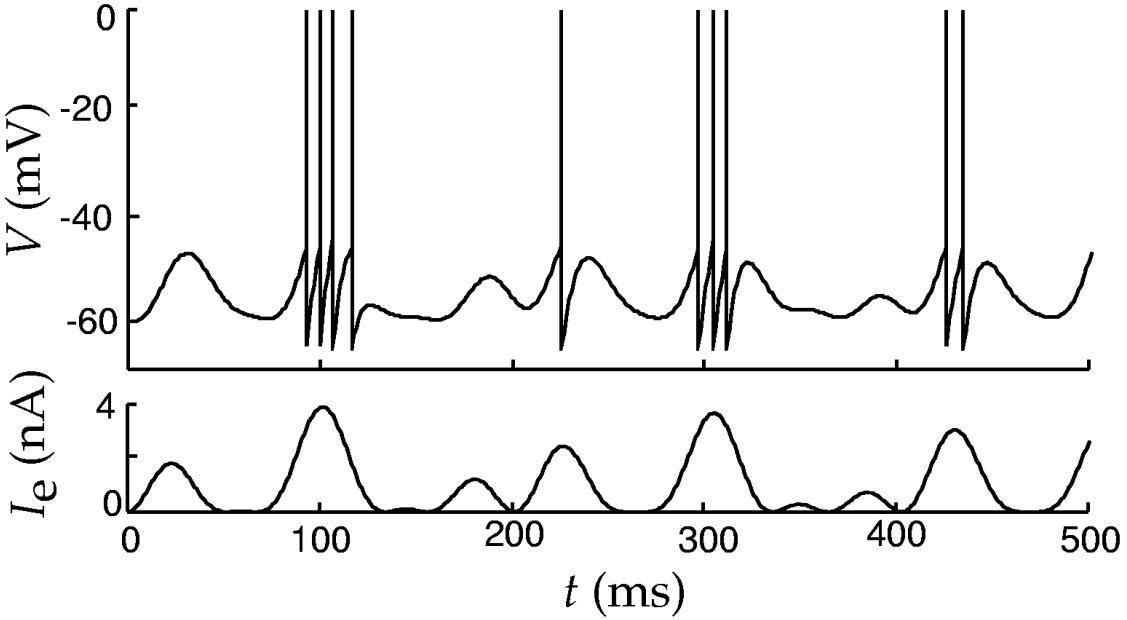
$$C_m \frac{dV}{dt} = -g_L(V - E_i) - I_e$$

but with the additional rule that

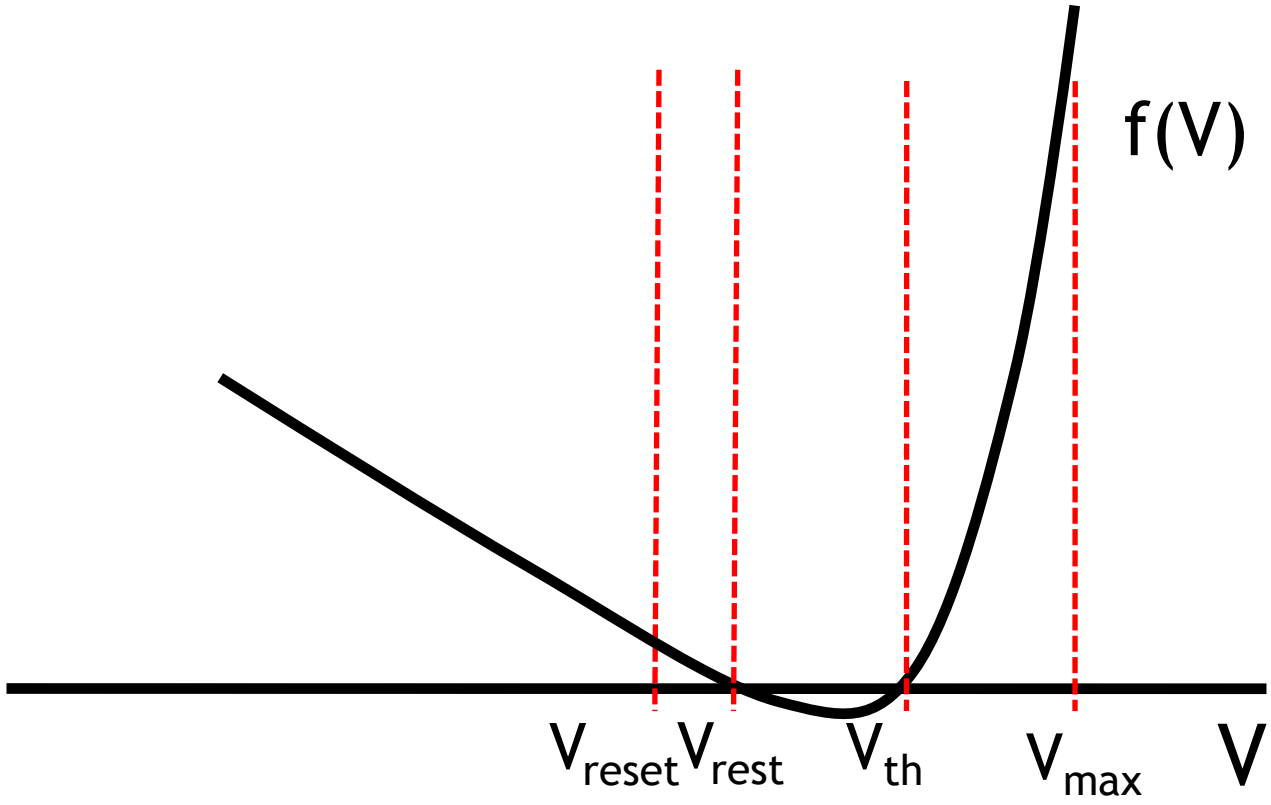
when $V \rightarrow V_T$, a spike is fired

and $V \rightarrow V_{reset}$.

$E_L$ is the resting potential of the "cell".

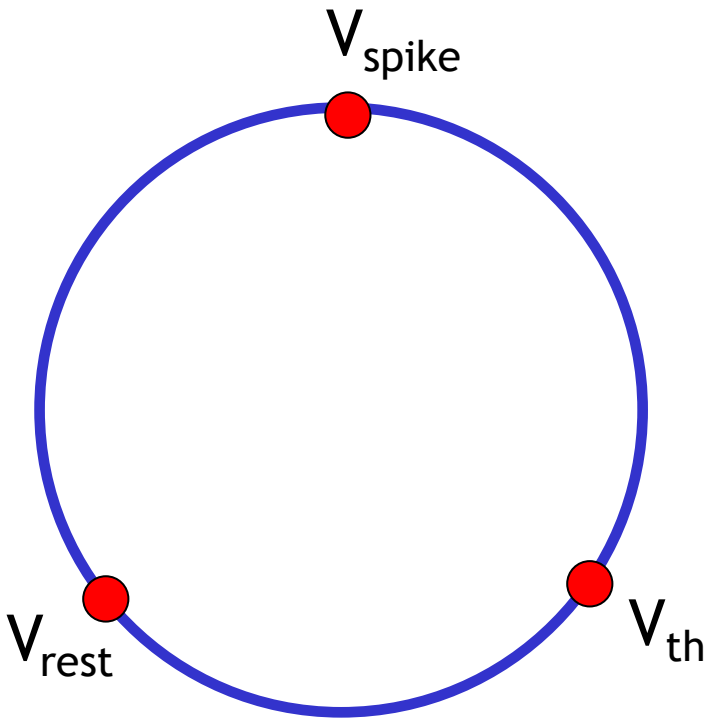


# Exponential integrate-and-fire neuron




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

# The theta neuron




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

Ermentrout and Kopell

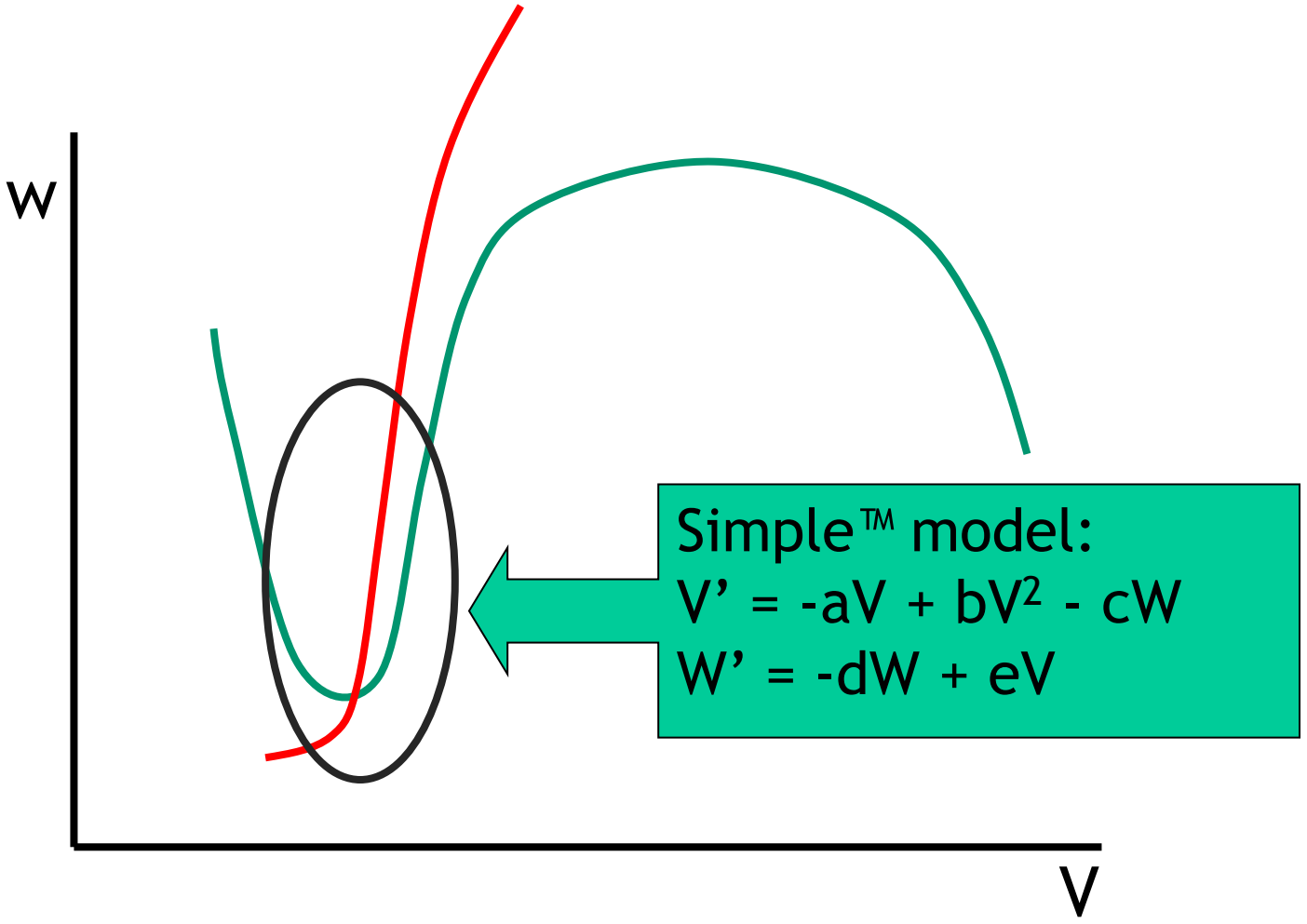
# The spike response model

Kernel *f* for subthreshold response ← replaces leaky integrator
Kernel for spikes ← replaces “line”

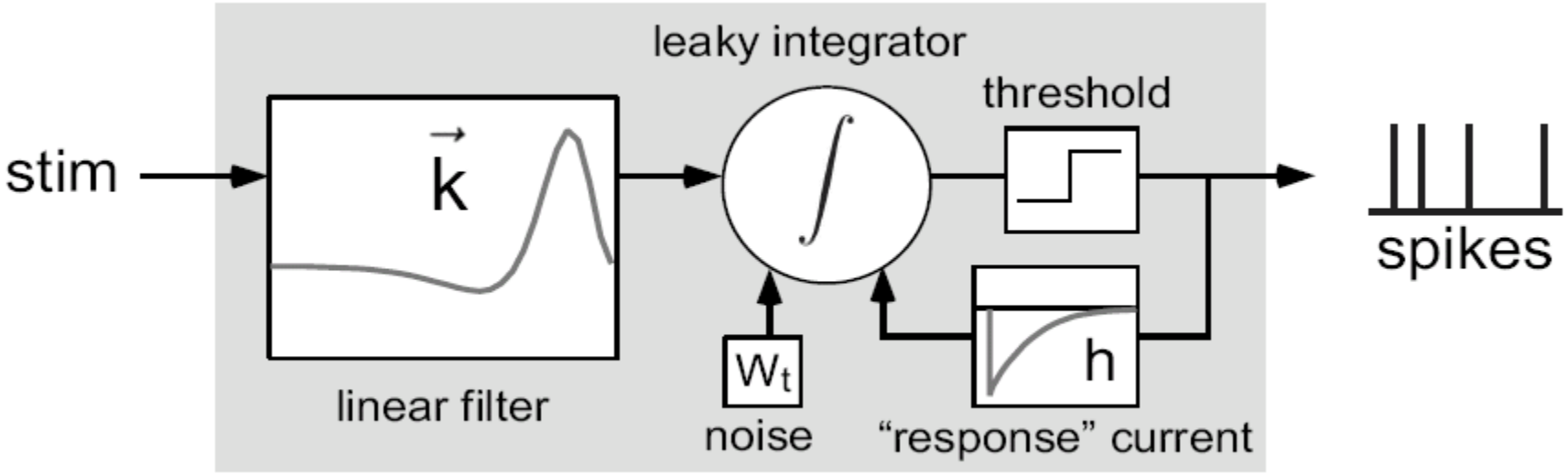
- determine *f* from the linearized HH equations
- fit a threshold
- paste in the spike shape and AHP

Gerstner and Kistler

# Two-dimensional models

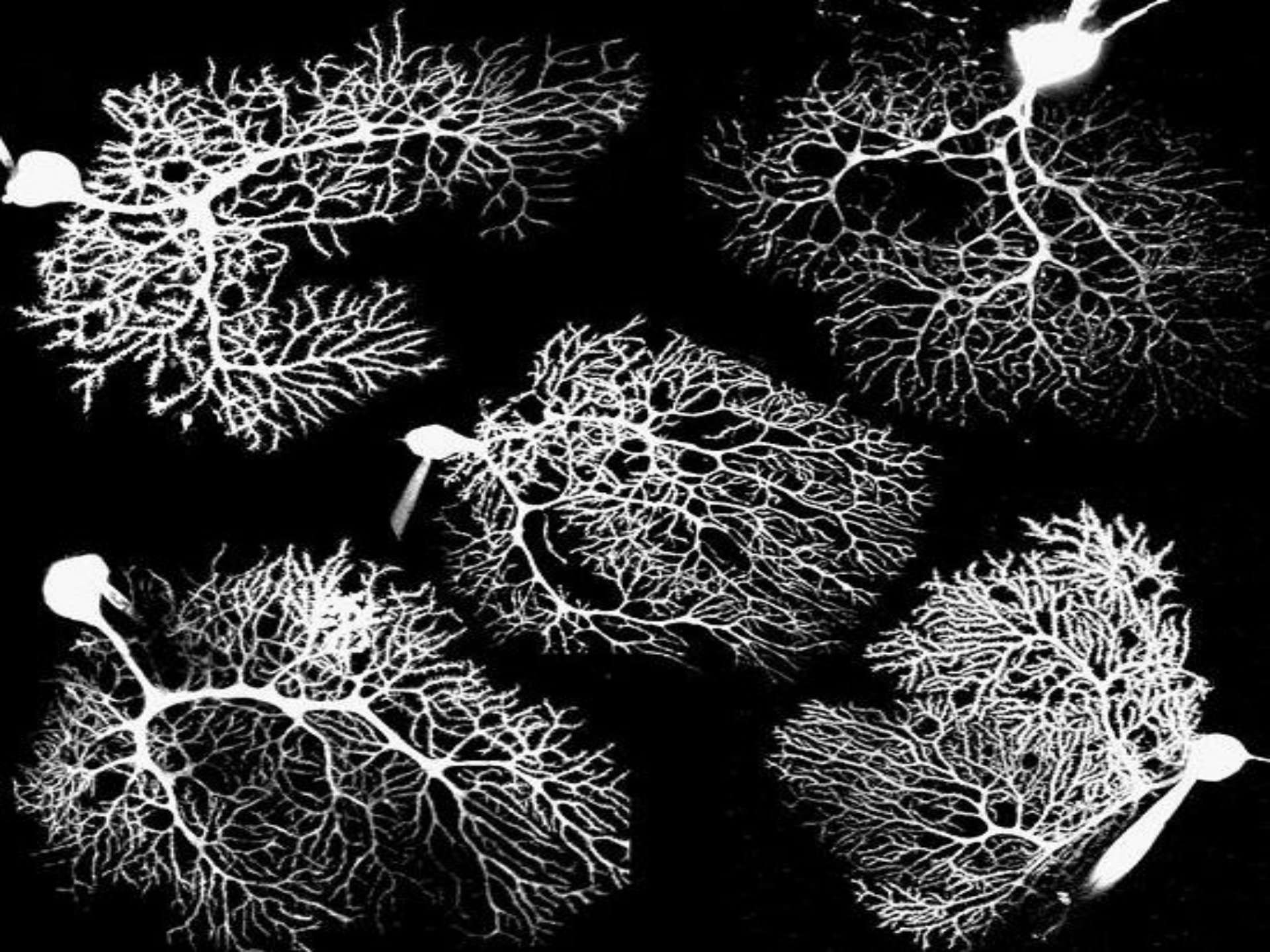


# The generalized linear model




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

Truccolo and Brown, Paninski, Pillow, Simoncelli



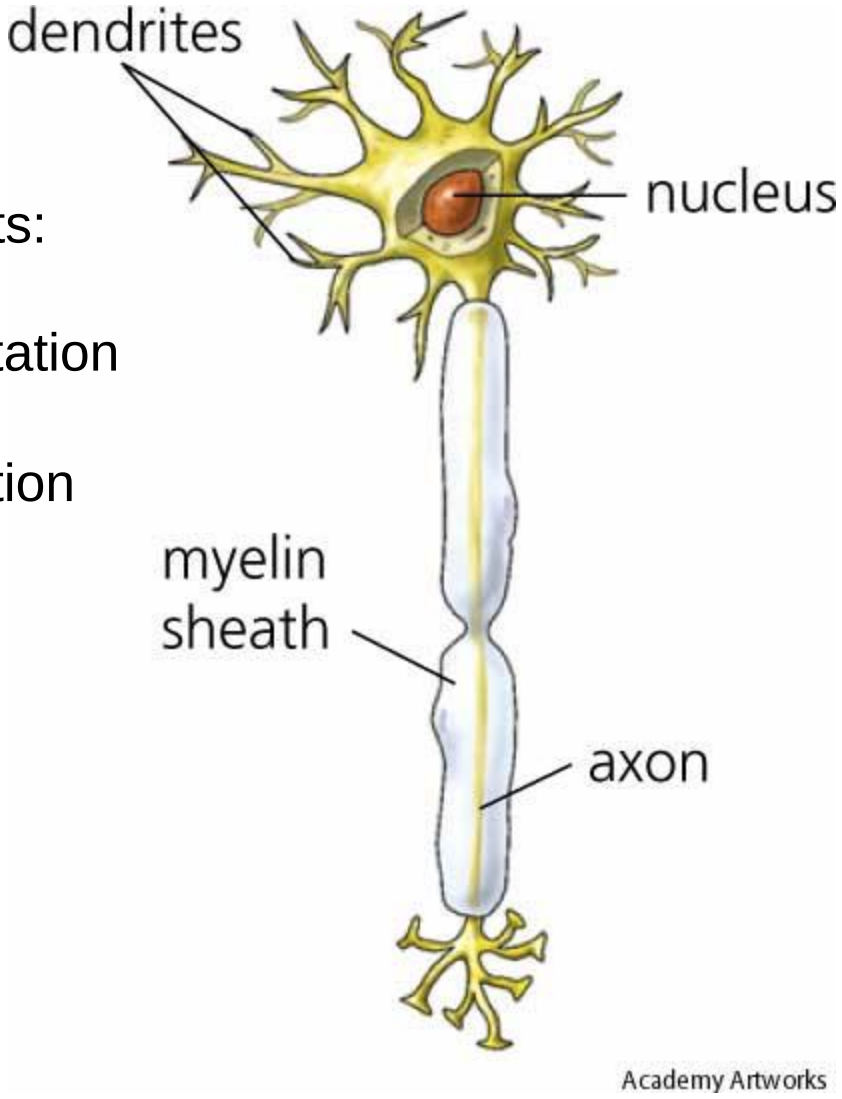
# Dendritic computation

Dendrites as computational elements:

Passive contributions to computation

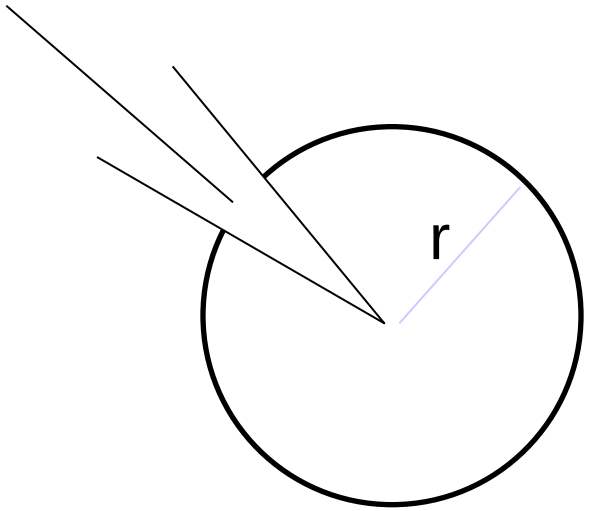
Active contributions to computation

Examples



# Geometry matters

Injecting current $I_0$



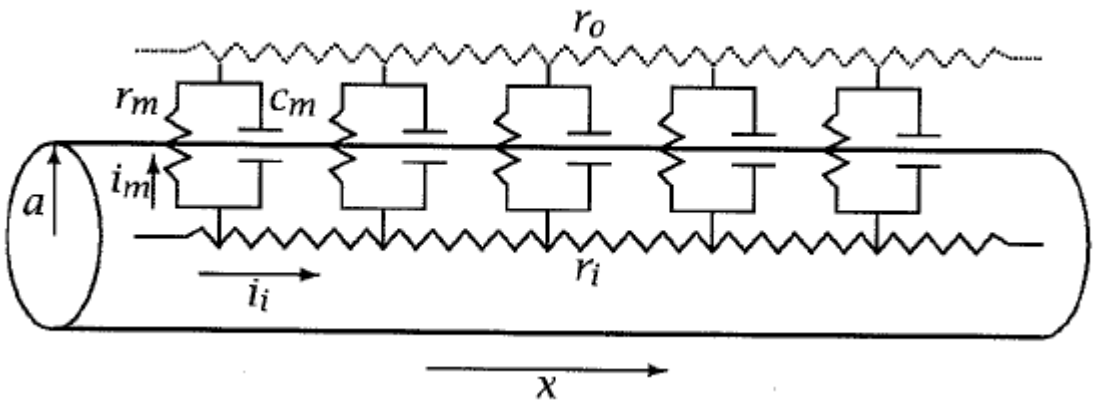

$$V_m = I_m R_m$$

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

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

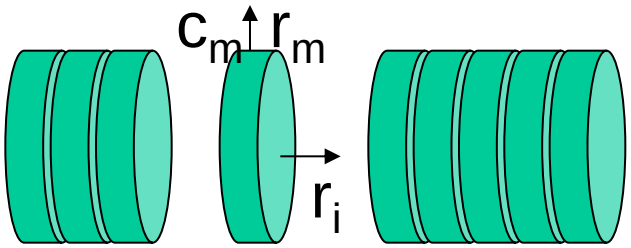
$$= R_m/4\pi r^2$$

# 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:

$r_i \rightarrow r_i L$

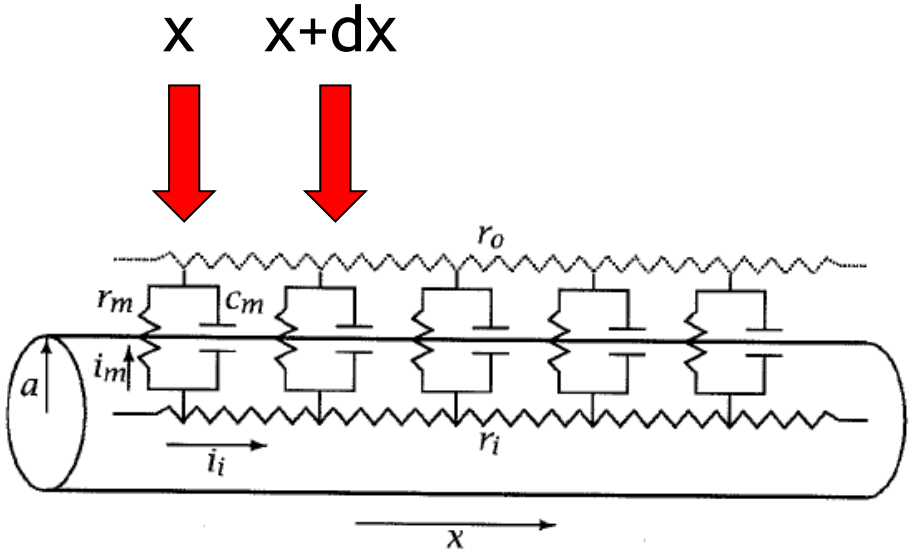
$r_m \rightarrow r_m / L$

$c_m \rightarrow c_m L$

# 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

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

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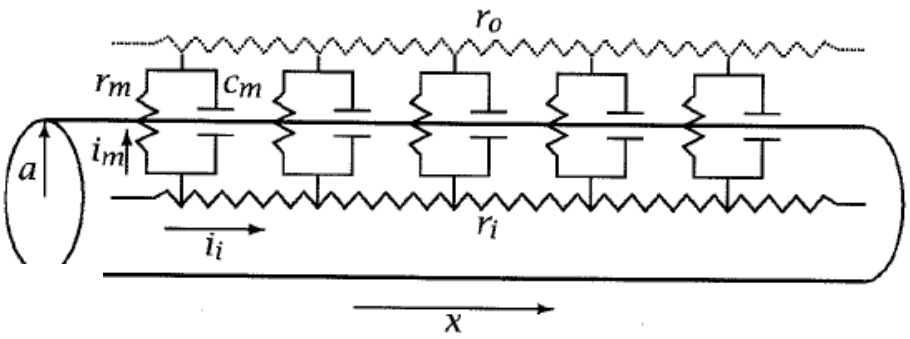



$\frac{\partial}{\partial x}$ (1) → $$\frac{\partial^2 V_m}{\partial x^2} = -r_i \frac{\partial i_i}{\partial x} = r_i i_m.$$

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

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

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

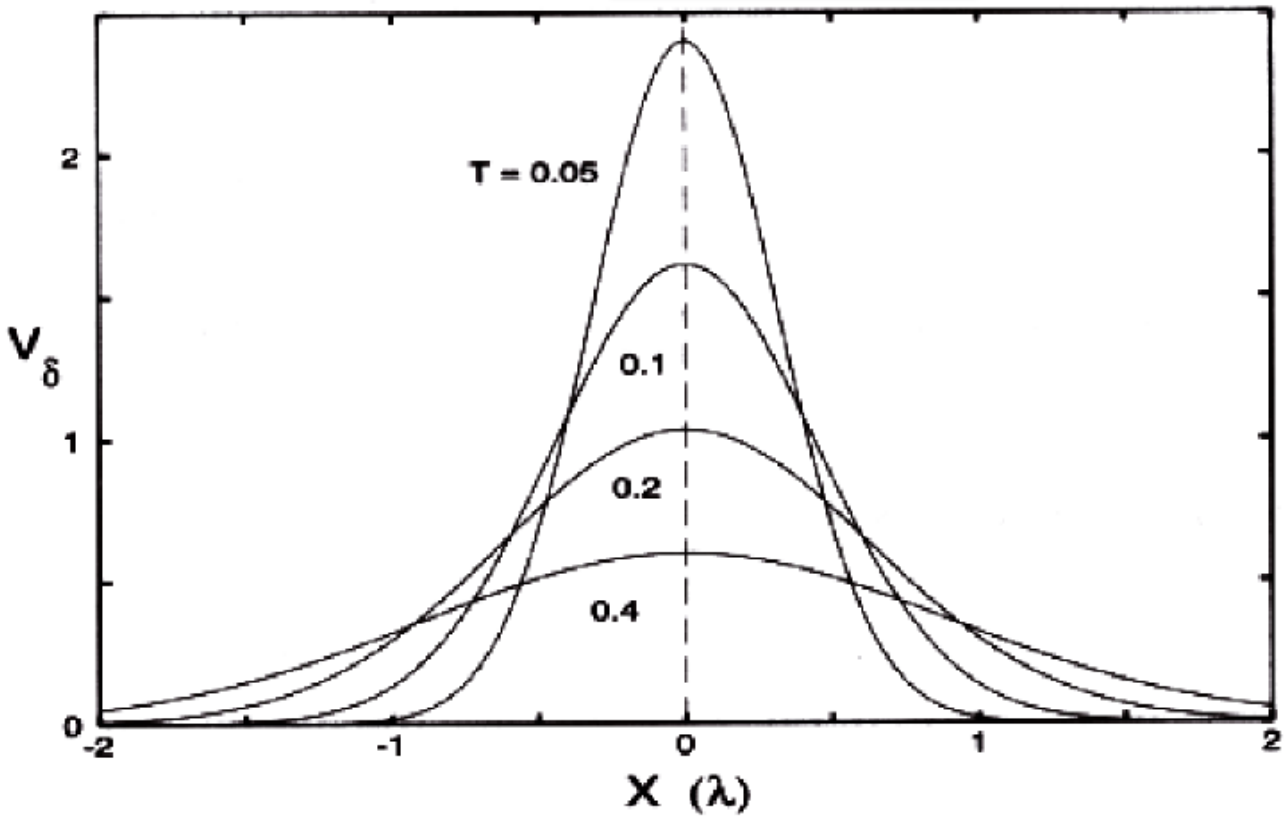
$\lambda = \sqrt{\frac{r_m}{r_i}}$ Space constant

# General solution: filter and impulse response

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

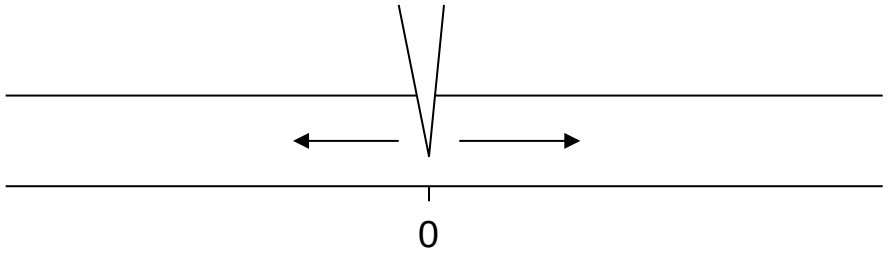
Exponential decay

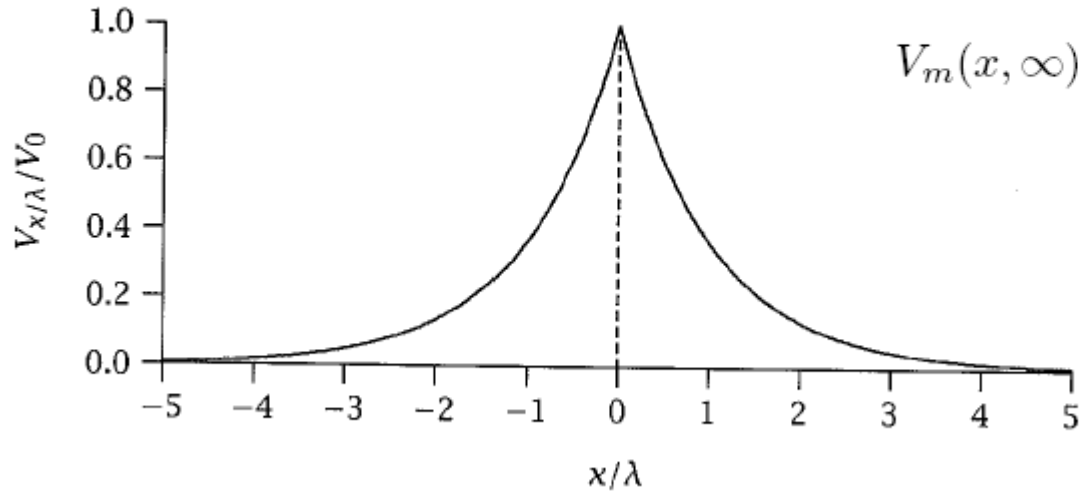
Diffusive spread



# Voltage decays exponentially away from source

Current injection at x=0, T → ∞



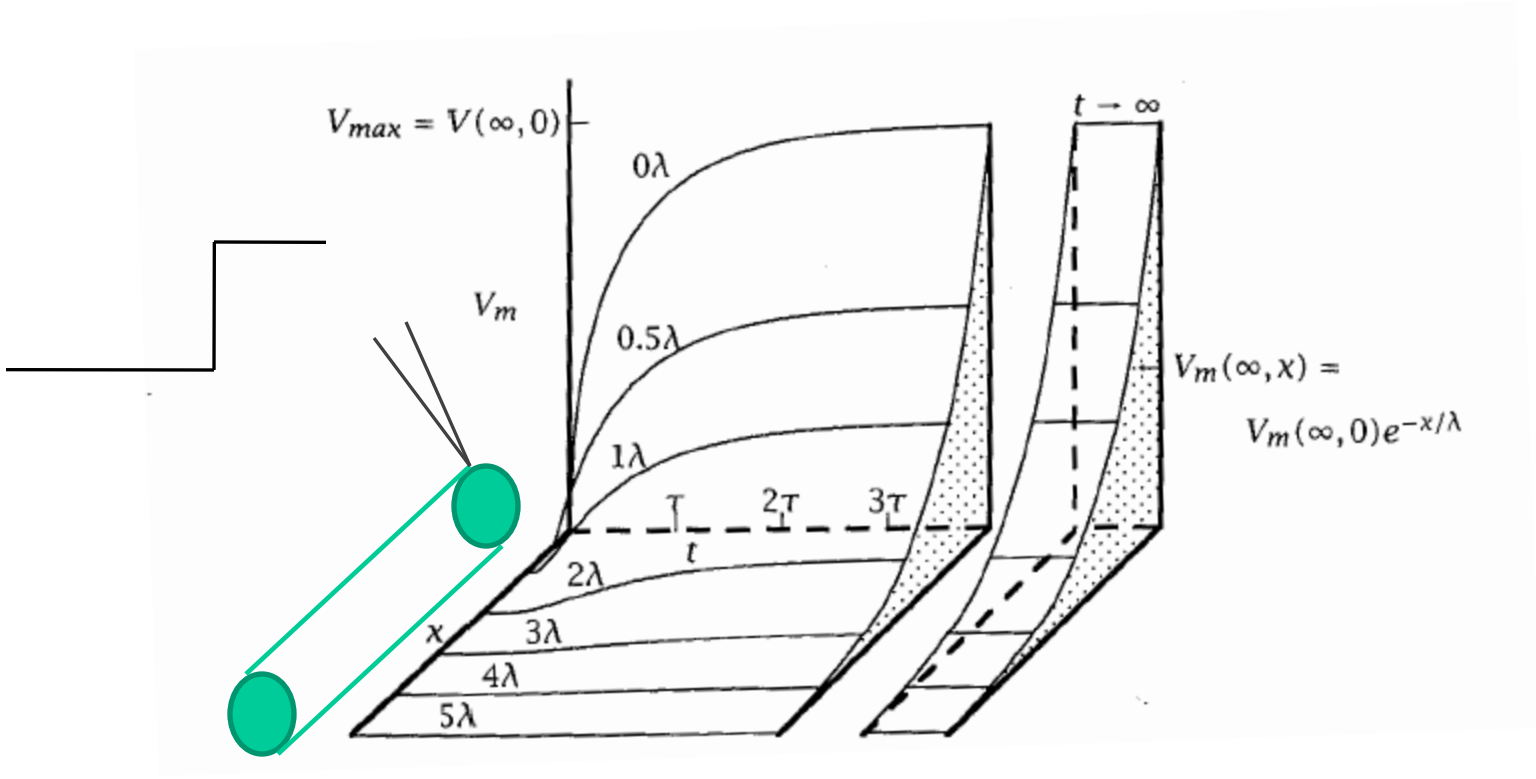




$$V_m(x,\infty) = \frac{r_i I_0 \lambda}{2} e^{-x/\lambda}$$

# Properties of passive cables

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

# Electrotonic length




Johnson and Wu

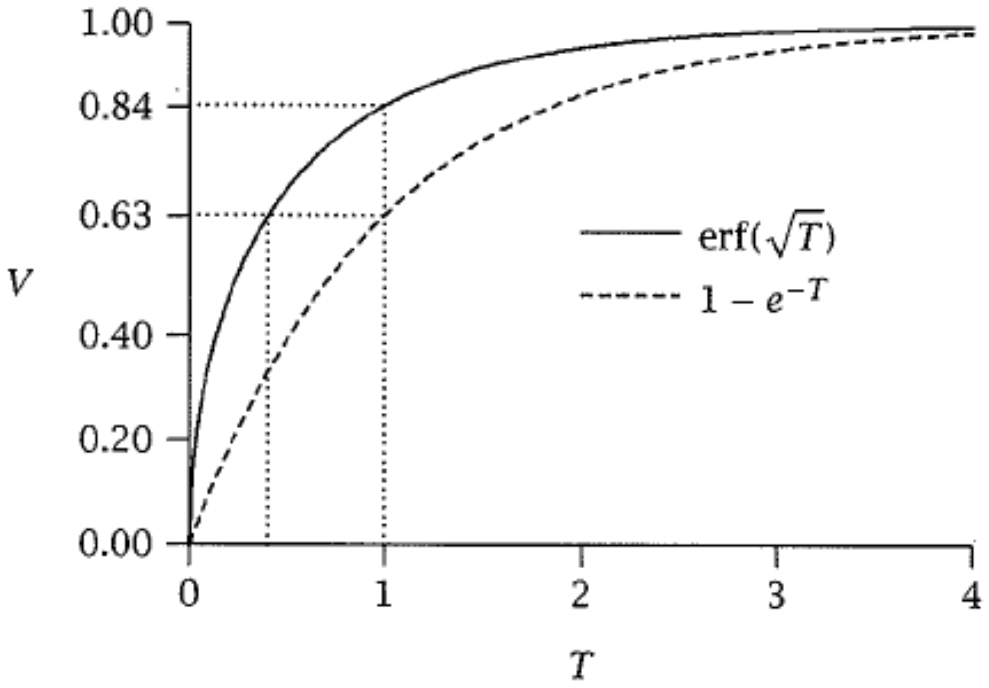
# Properties of passive cables

→ 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 $\lambda = \sqrt{\frac{r_m}{r_i}}$

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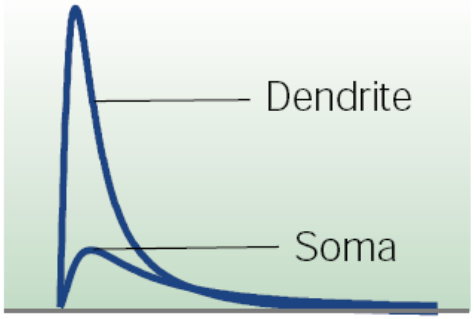
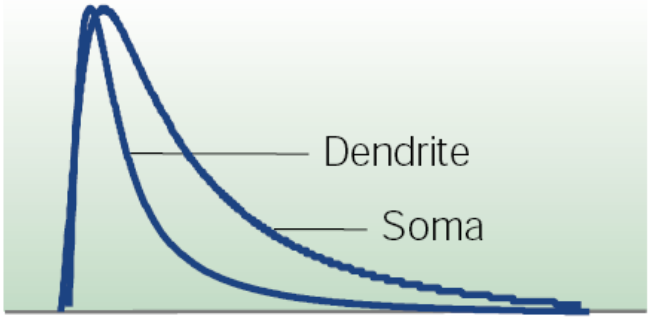
→ Cable diameter affects input resistance $R_N = \frac{\sqrt{R_m R_i / 2}}{2\pi a^{3/2}}$

Amplitude




Time course



# Properties of passive cables

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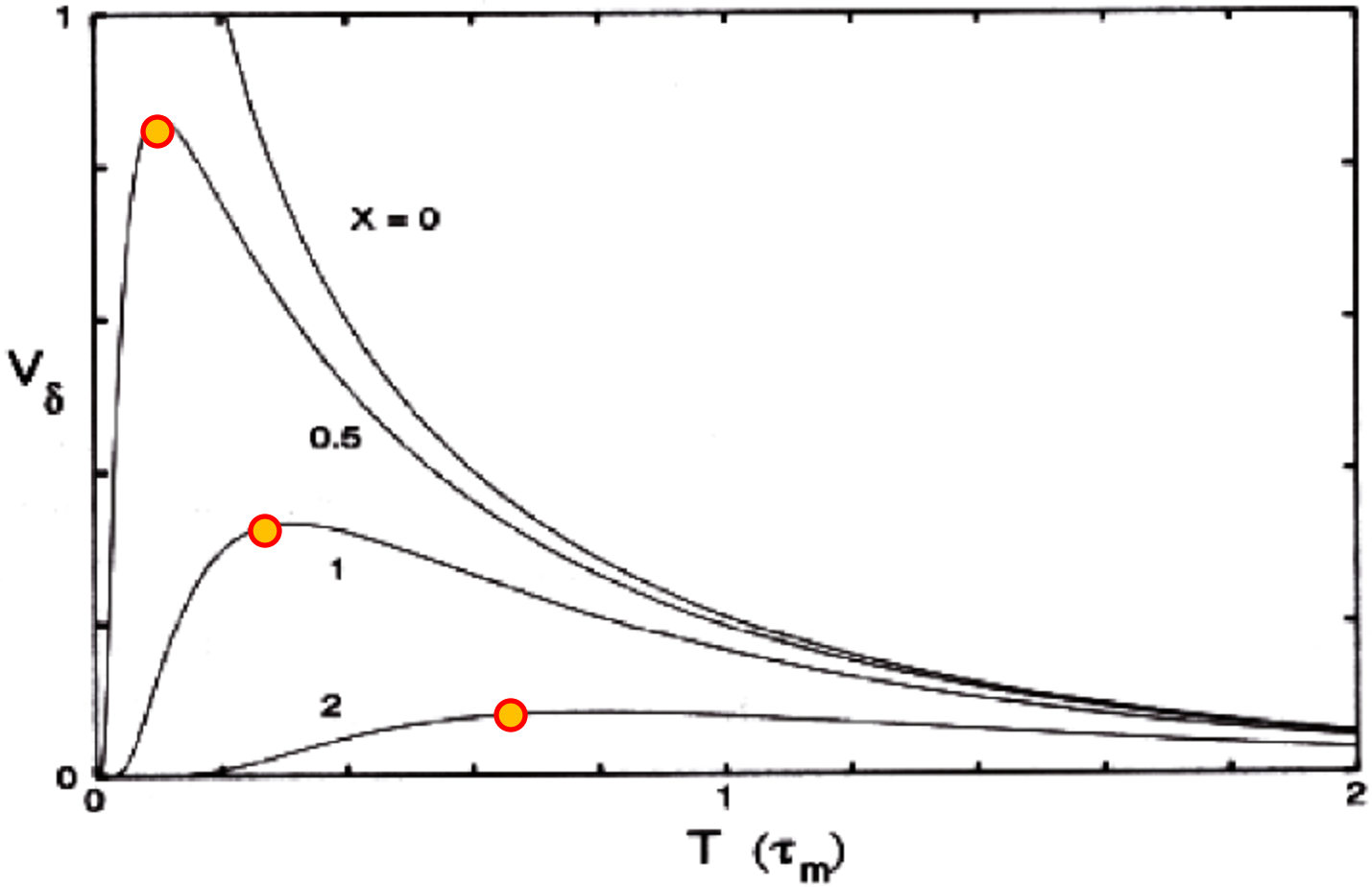
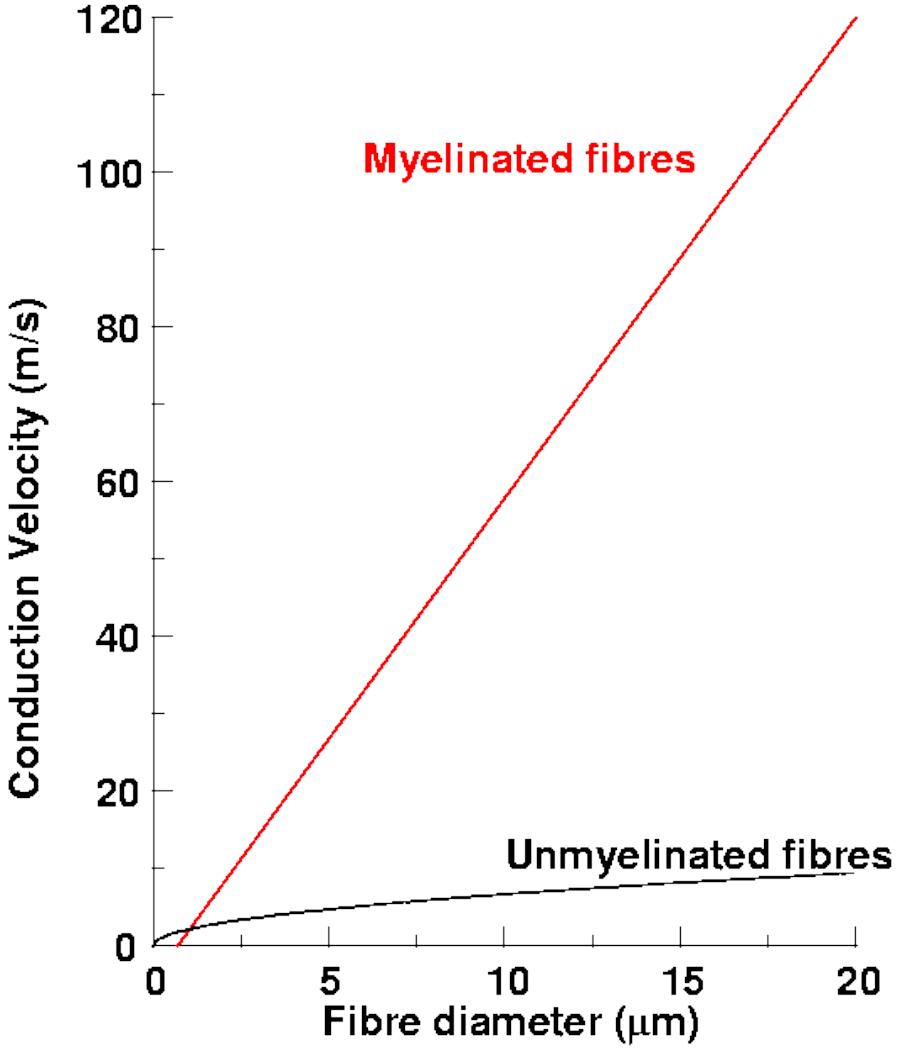
→ Cable diameter affects transmission velocity

# Step response: pulse travels




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

# Conduction velocity



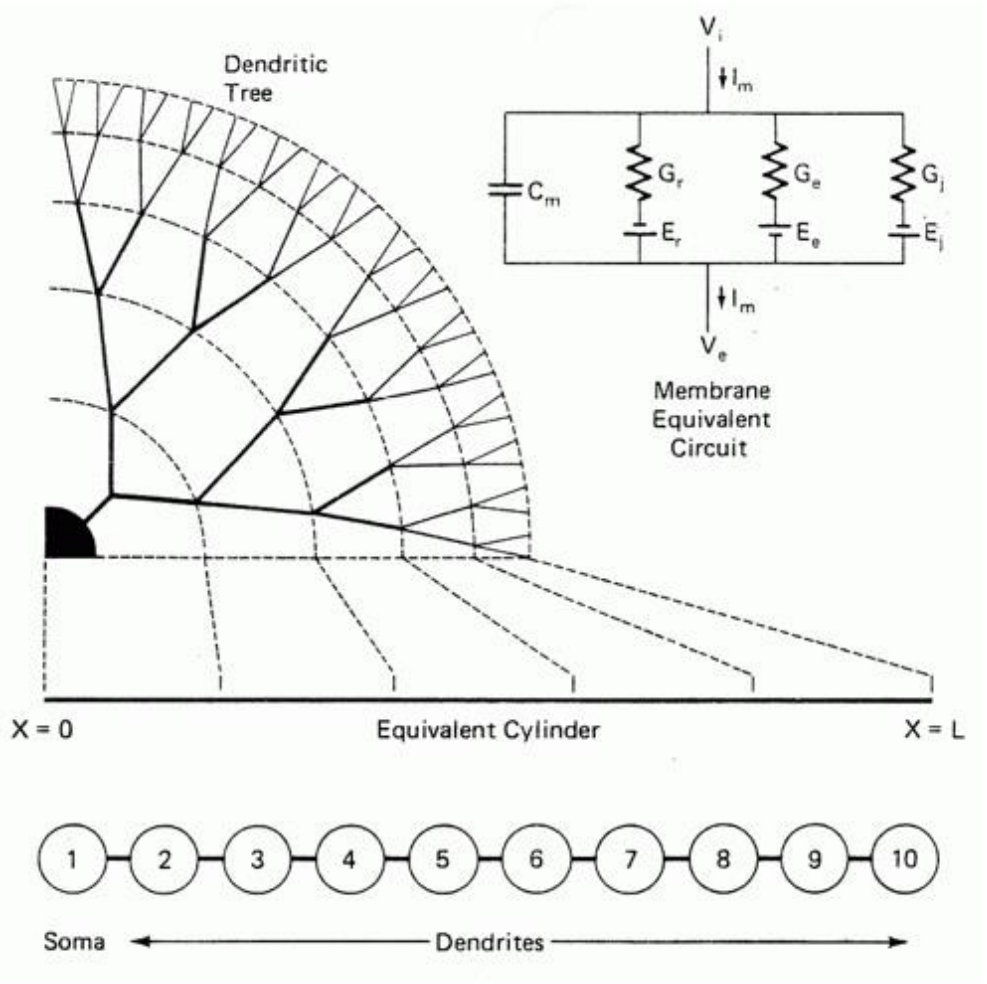

www.physiol.usyd.edu/au/~daved/teaching/cv.html

# Other factors

Finite cables

Active channels

# Rall model




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

Impedance matching:

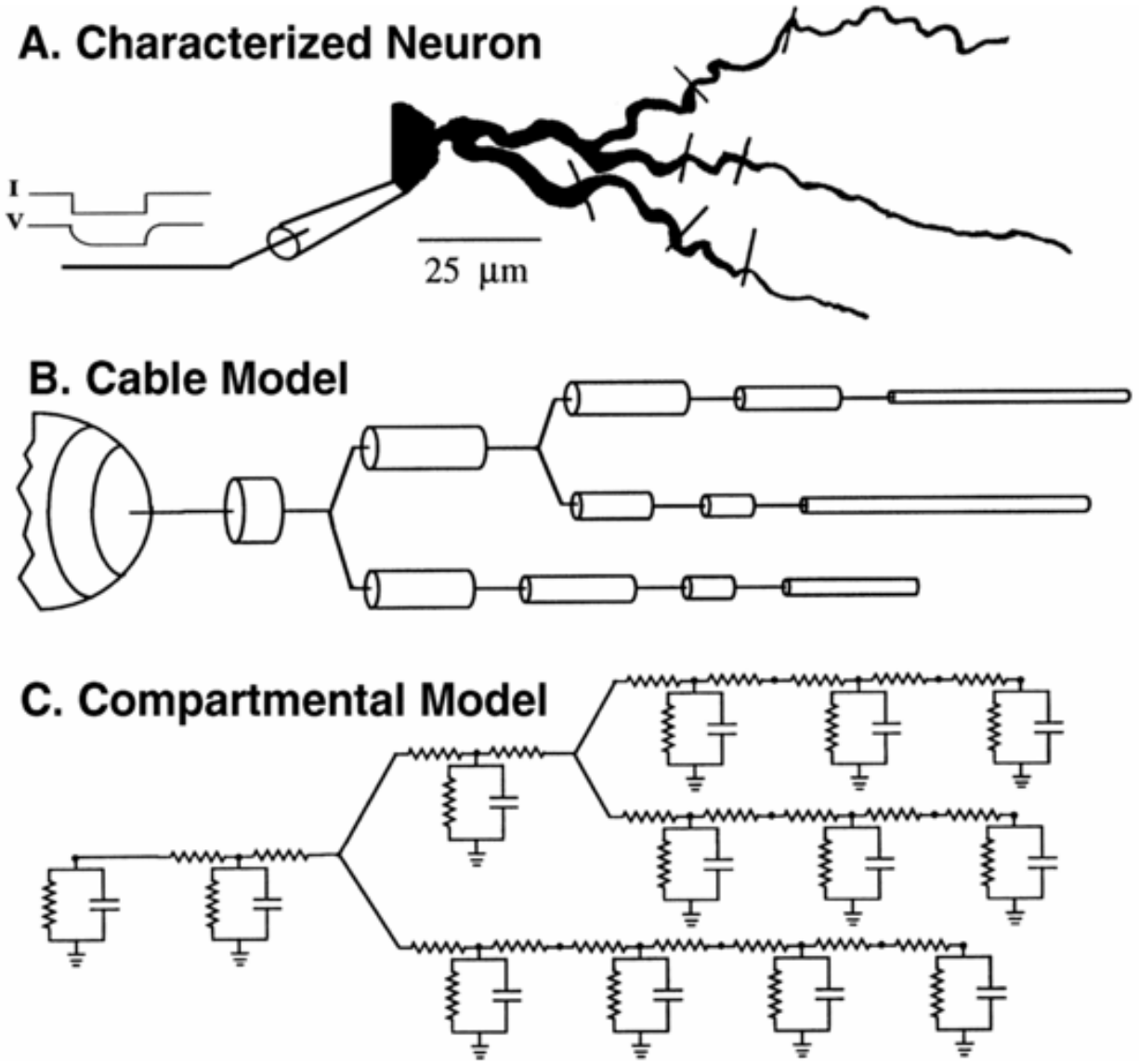
If $a^{3/2} = d_1^{3/2} + d_2^{3/2}$

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

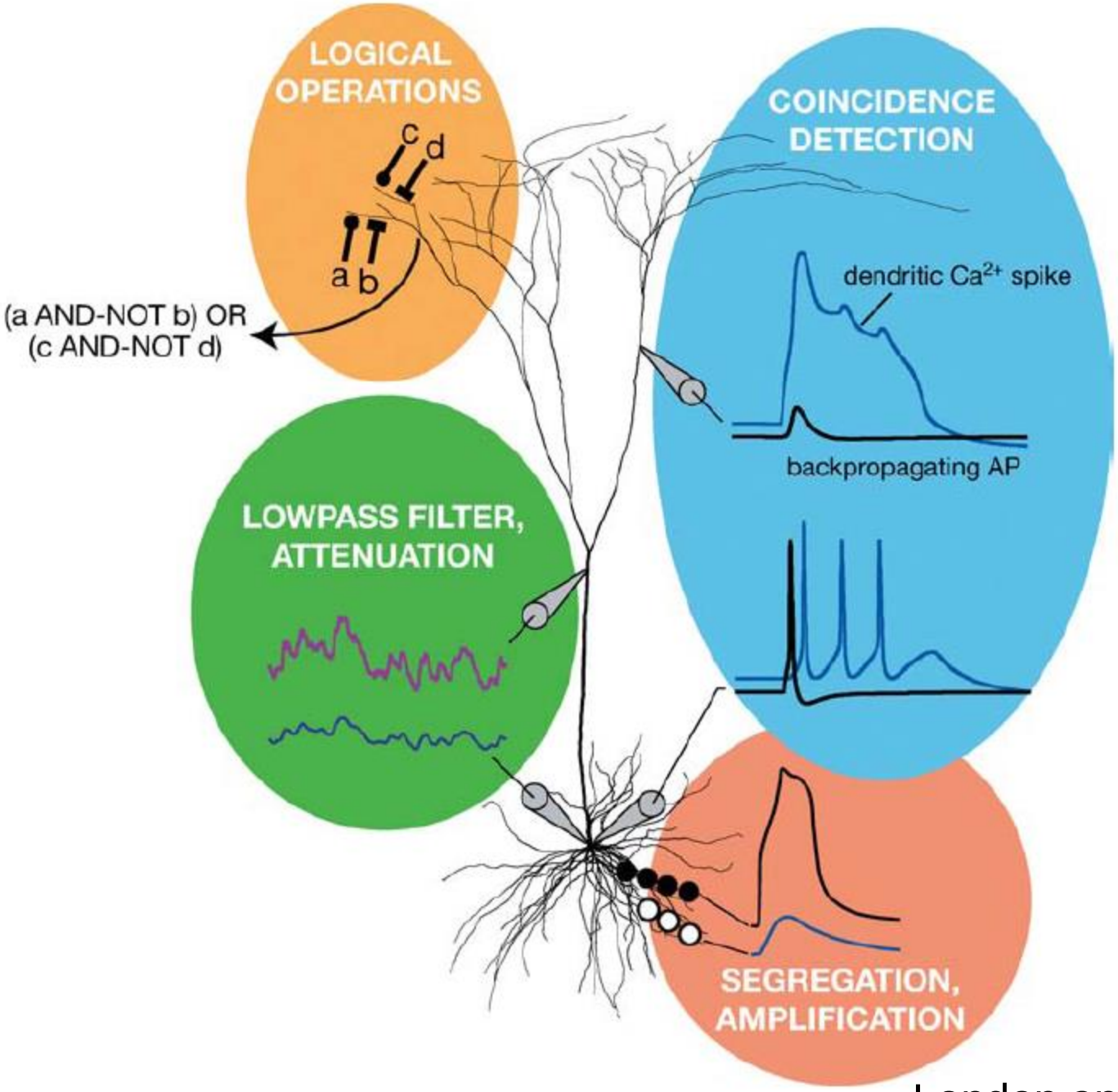
# Active cables

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