Mathematical Neuroscience
Training workshop

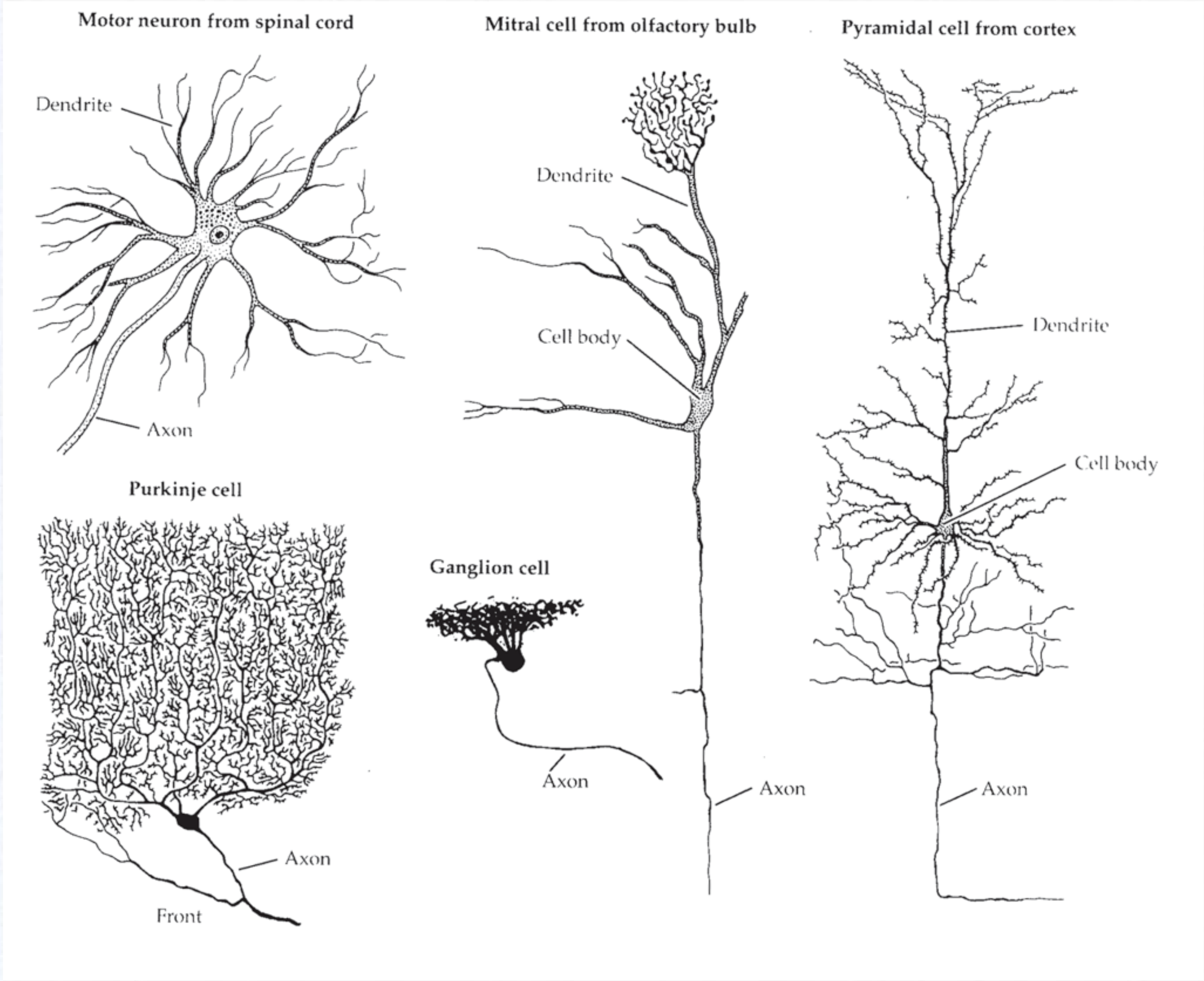
Single neuron models

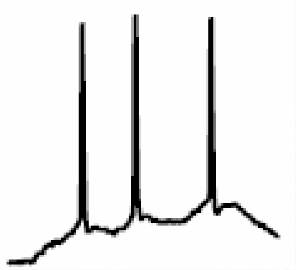
Yulia Timofeeva (Warwick)

Overview

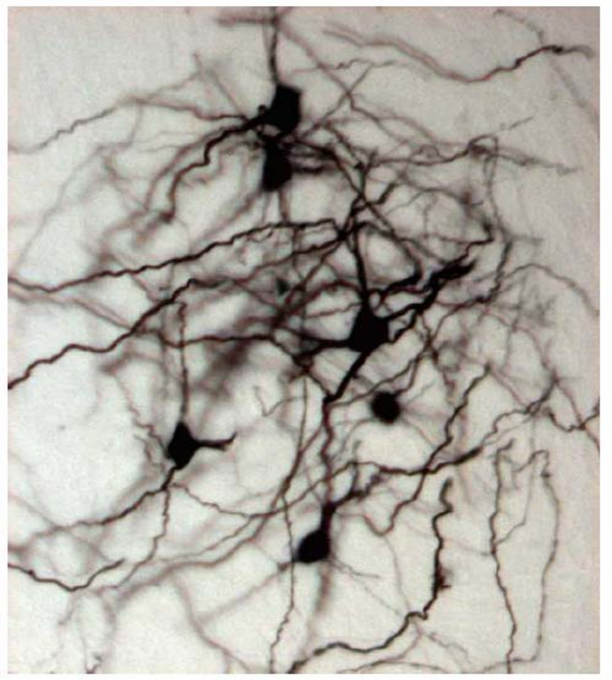
- Biological background
- The conductance-based membrane model
- Spatially extended models

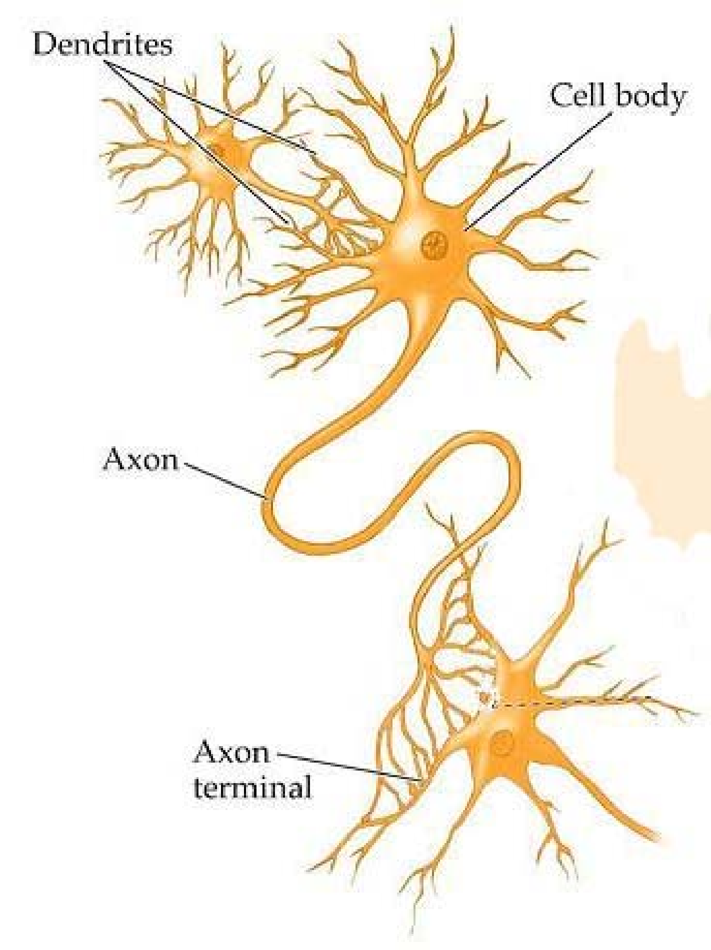
The neuron

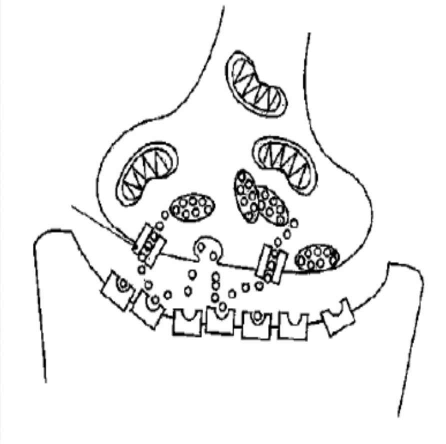




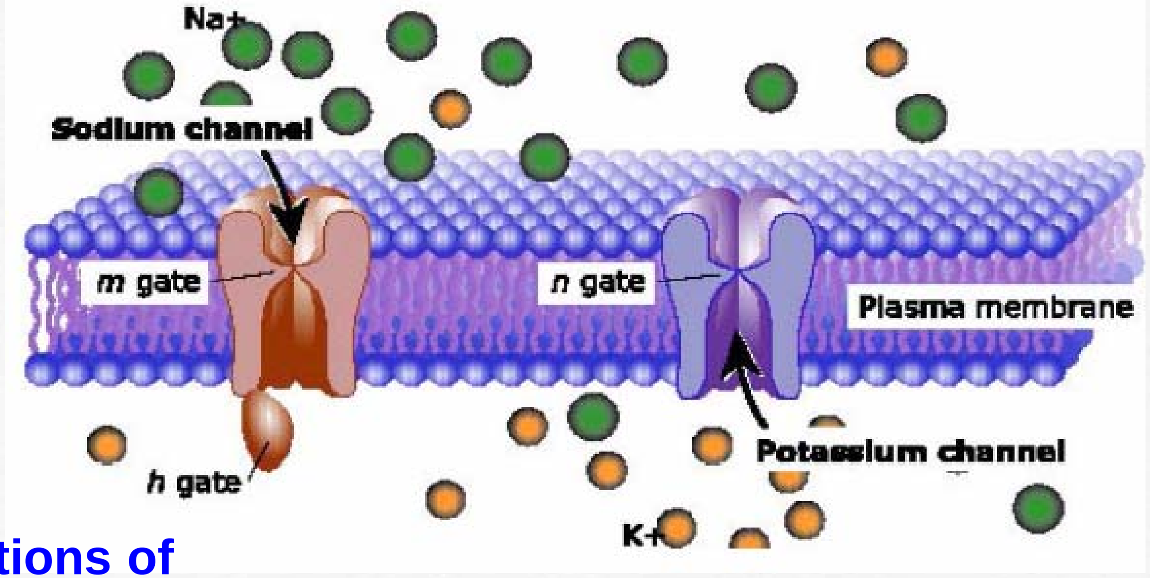
Action potentials
(short electrical spikes)







The contacts of the axon to target neurons are either located on the dendritic tree or directly on the soma, and are known as synapses

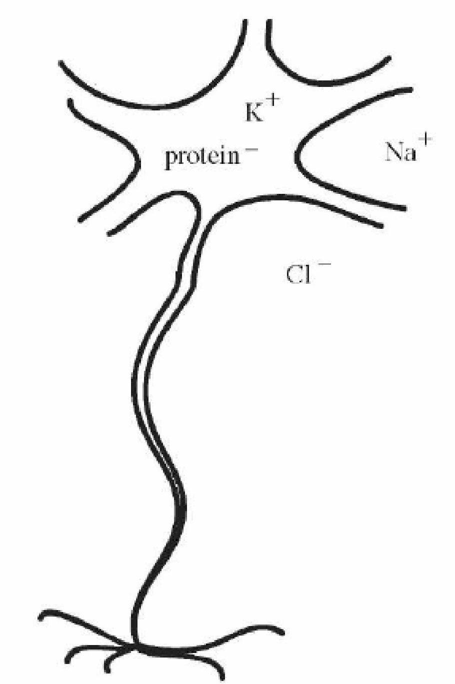


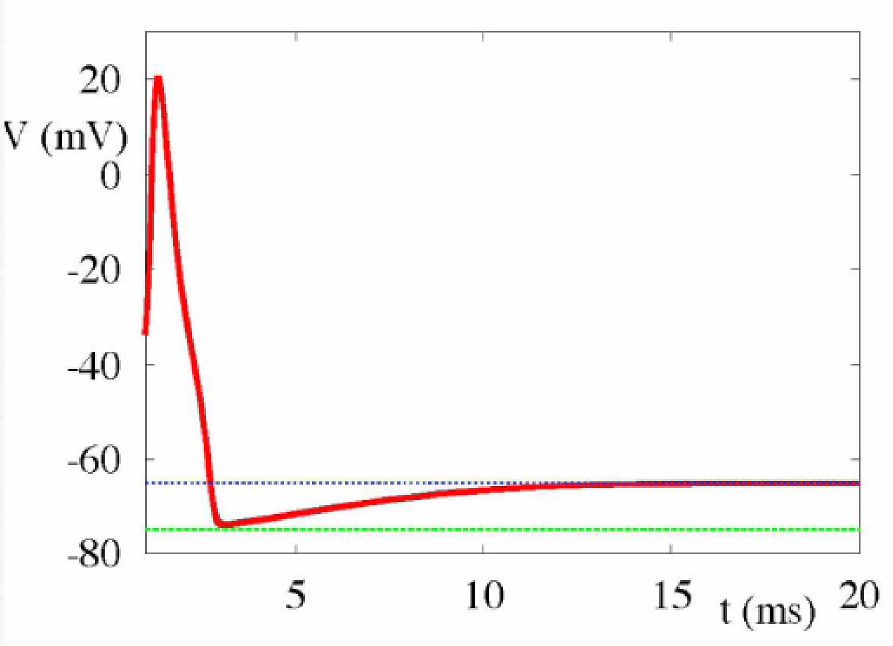
Differences in the ionic concentrations of the intra/extracellular fluids create a potential difference across the cell

Ionic gates are embedded in the cell membrane and control the passage of ions

Neuron.mov

Action potential



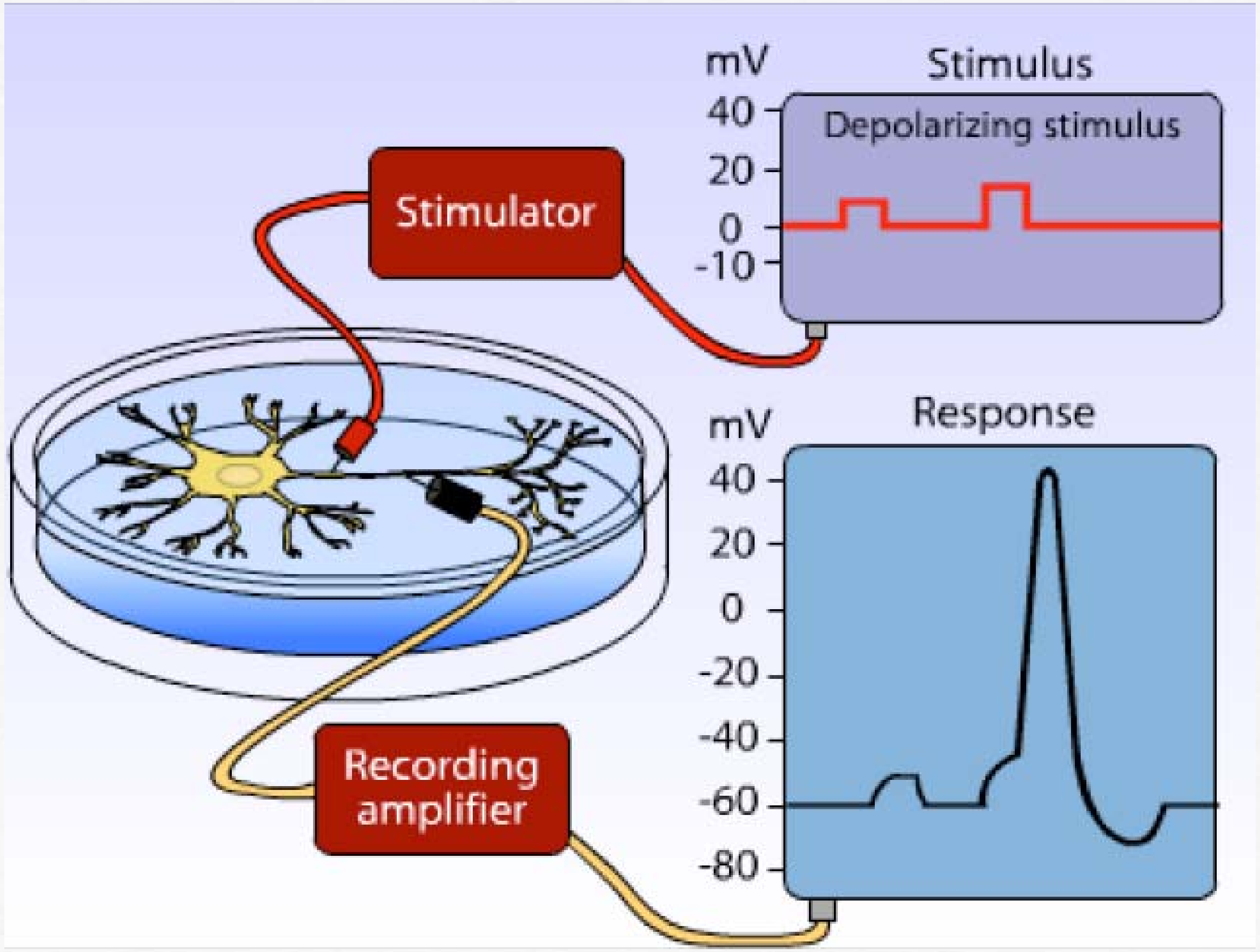


- In the absence of a signal, there is a resting potential of ~ -65mV.

- During an action potential, the membrane potential increase rapidly to ~ 20mV, returns slowly to ~ -75mV and then slowly relaxes to the resting potential.

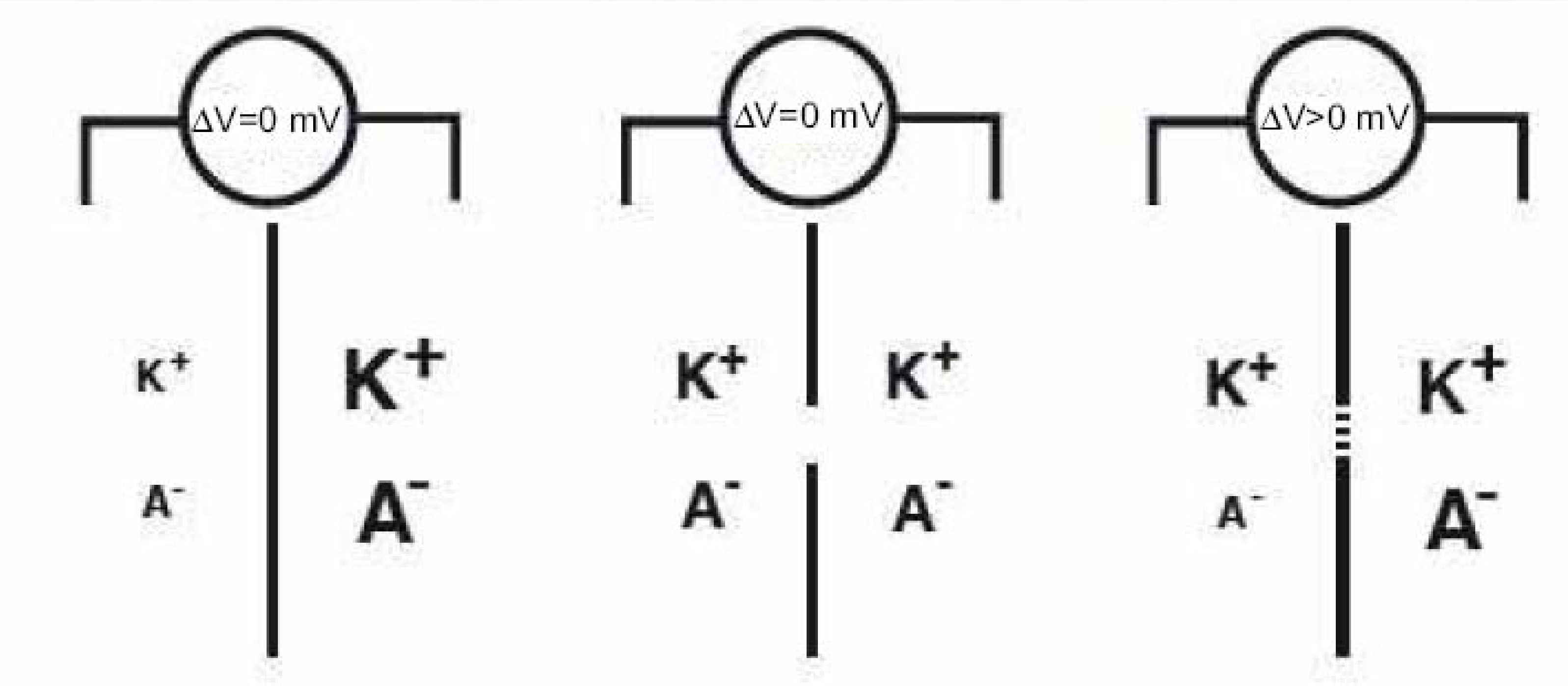
- The rapid membrane depolarisation corresponds to an influx of Na$^+$ across the membrane. The return to -75mV corresponds to the transfer of K$^+$ out of the cell. The final recovery stage back to the resting potential is associated with the passage of Cl$^-$ out of the cell.

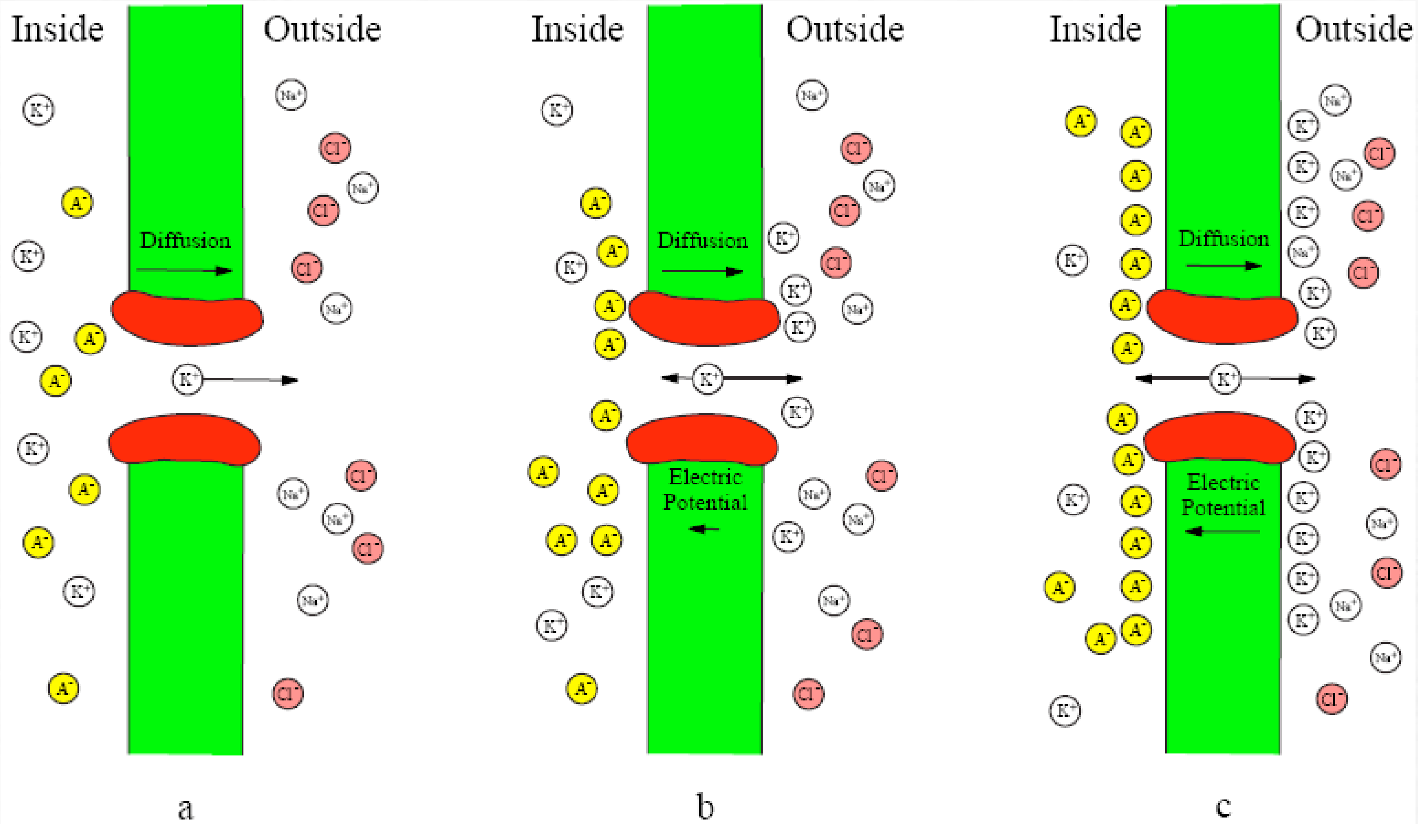
Experimental setup *in vitro*



Single-compartment models

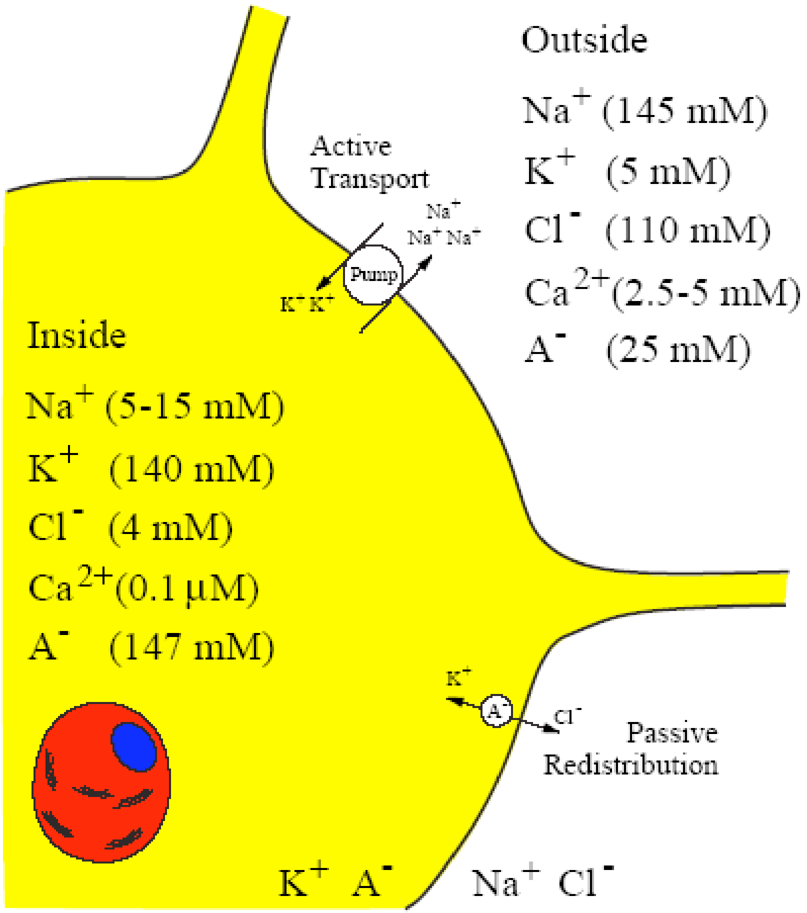
The Nernst potential





Diffusion of K^+ ions down the concentration gradient through the membrane (a) creates an electric potential force directed at the opposite direction (b) until the diffusion and electrical forces counter each other (c) resulting in the Nernst equilibrium potential for K^+

$$\Delta V \propto \log \frac{[\text{ion}]_{\text{out}}}{[\text{ion}]_{\text{in}}}$$



Outside

Na^+ (145 mM)
K^+ (5 mM)
Cl^- (110 mM)
Ca^{2+} (2.5-5 mM)
A^- (25 mM)

Inside

Na^+ (5-15 mM)
K^+ (140 mM)
Cl^- (4 mM)
Ca^{2+} (0.1 µM)
A^- (147 mM)

Reversal potentials

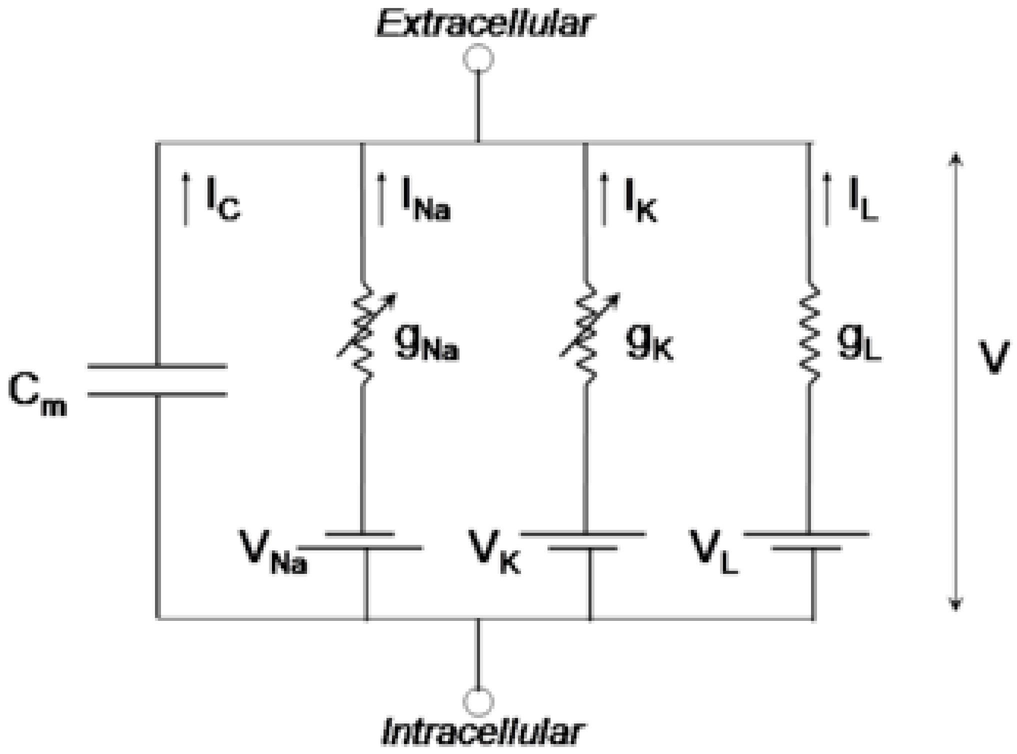
↓

Equilibrium Potentials

$$
\begin{array}{lrcl}
\mathrm{Na}^+ & 62\log\frac{145}{5} & = & 90\ \mathrm{mV} \\
 & 62\log\frac{145}{15} & = & 61\ \mathrm{mV} \\
\mathrm{K}^+ & 62\log\frac{5}{140} & = & -90\ \mathrm{mV} \\
\mathrm{Cl}^- & -62\log\frac{110}{4} & = & -89\ \mathrm{mV} \\
\mathrm{Ca}^{2+} & 31\log\frac{2.5}{10^{-4}} & = & 136\ \mathrm{mV} \\
 & 31\log\frac{5}{10^{-4}} & = & 146\ \mathrm{mV}
\end{array}
$$

Passive redistribution and active transport support the concentration asymmetry

The membrane model



Ohm's law: $$I = \frac{V}{R} = gV$$

g - conductance

1. the phospholipid bilayer, which is analogous to a capacitor in that it accumulates ionic charge
2. the ionic permeabilities of the membrane, which are analogous to resistors
3. the electrochemical driving forces, which are analogous to batteries driving the ionic currents

the current flow through a single K^+ channel

$$\boxed{I_K = g_K(V - V_K)}$$

$g_K \ (mS/cm^2)$ **- the conductance of the K^+ channel**

$(V - V_K)$ **- the K^+ driving force across the membrane**

$$\boxed{I_{ion} = \sum I_i = \sum g_i(V - V_i) = g_K(V - V_K) + g_{Na}(V - V_{Na}) + \ldots}$$

the capacitive current across the membrane

$$\boxed{I_{cap} = C\frac{dV}{dt}}$$

$$\boxed{I_{app} = C\frac{dV}{dt} + I_{ion}}$$

The ODE of the membrane model

$$C\frac{dV}{dt} = -\sum_i g_i(V - V_i) + I_{app}$$

The Hodgkin-Huxley model

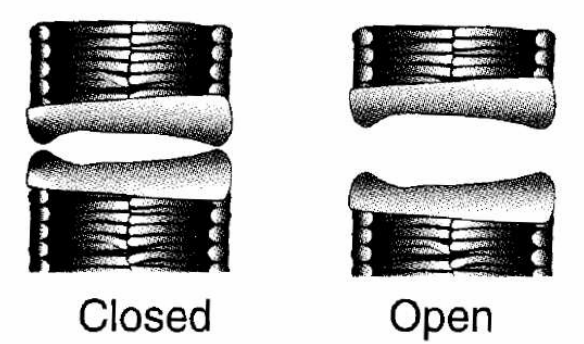
1949, Plymouth

$$-g_K(V - V_K) - g_{Na}(V - V_{Na}) - g_L(V - V_L)$$

They established experimentally the voltage dependence of ion conductances in the electrically excitable membrane of the squid giant axon

A gated ionic channel

$$C \underset{k^-}{\overset{k^+}{\rightleftharpoons}} O$$



the transition from state O to state C $J_- = k^-[O]$ $J_- = k^- f_O$

the transition from state C to state O $J_+ = k^+[C]$ $J_+ = k^+(1 - f_O)$

f_O is the fraction of open channels

$$f_O = N_O/N$$

$$f_C = N_C/N$$

rate of change = inflow rate - outflow rate

$$\begin{aligned}\frac{df_O}{dt} &= J_+ - J_- \\ &= k^+(1-f_O) - k^- f_O \\ &= -(k^- + k^+)\left(f_O - \frac{k^+}{k^- + k^+}\right)\end{aligned}$$

$$\frac{df_O}{dt} = \frac{-(f_O - f_\infty)}{\tau}$$

$$\tau = 1/(k^- + k^+)$$

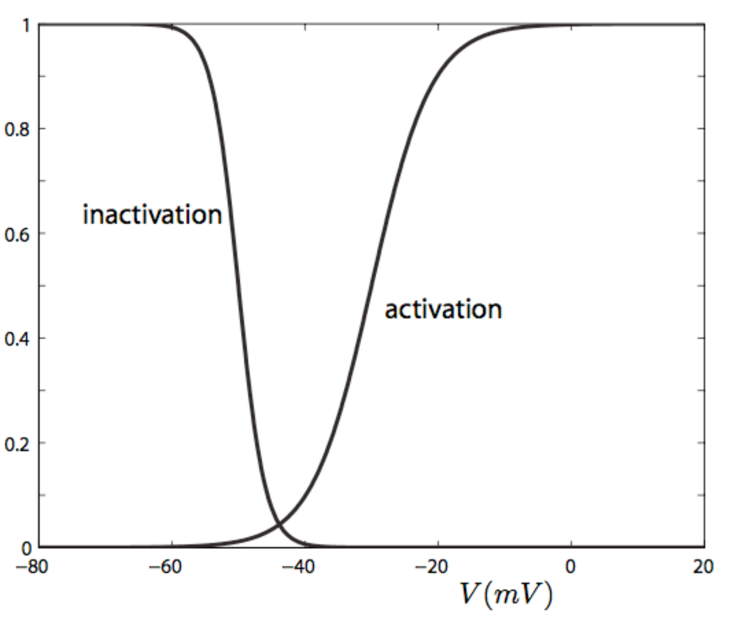
$$f_\infty = k^+/(k^- + k^+)$$

Voltage-gated channel

$$k^+ = k_0^+ e^{-\alpha V}, \qquad k^- = k_0^- e^{-\beta V}$$

$$\frac{1}{1 + e^{-(V-V_0)/S_0}}$$

$$V_0 = \frac{1}{\beta - \alpha} \ln(k_0^-/k_0^+), \qquad S_0 = \frac{1}{\beta - \alpha}$$



$$g_K = g_K(V) \text{ and } g_{Na} = g_{Na}(V)$$

The great insight of Hodgkin and Huxley was to realise that g_K depend upon four activation gates:

$$\boxed{g_K = \overline{g}_K n^4}$$

g_{Na} depends upon three activation gates and one inactivation gate:

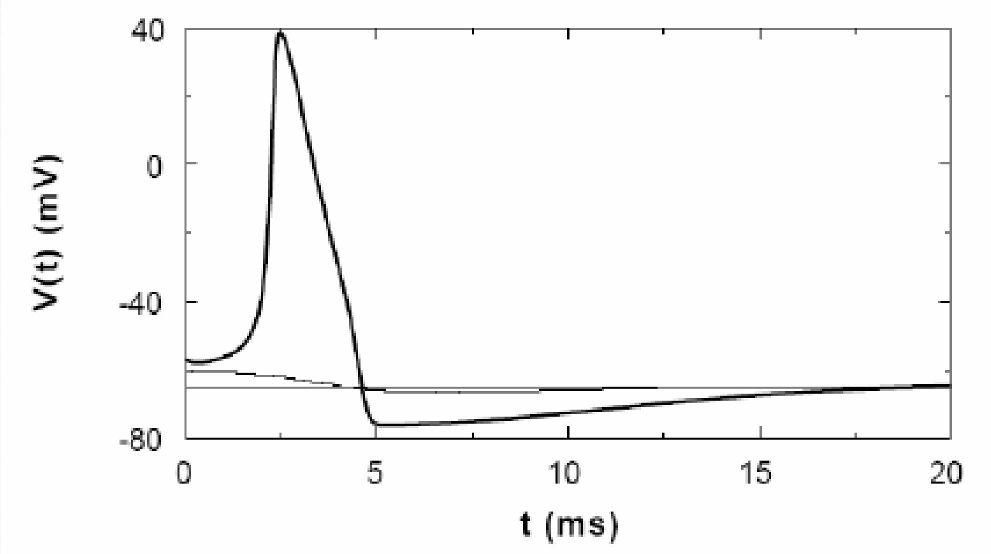
$$\boxed{g_{Na} = \overline{g}_{Na} m^3 h}$$

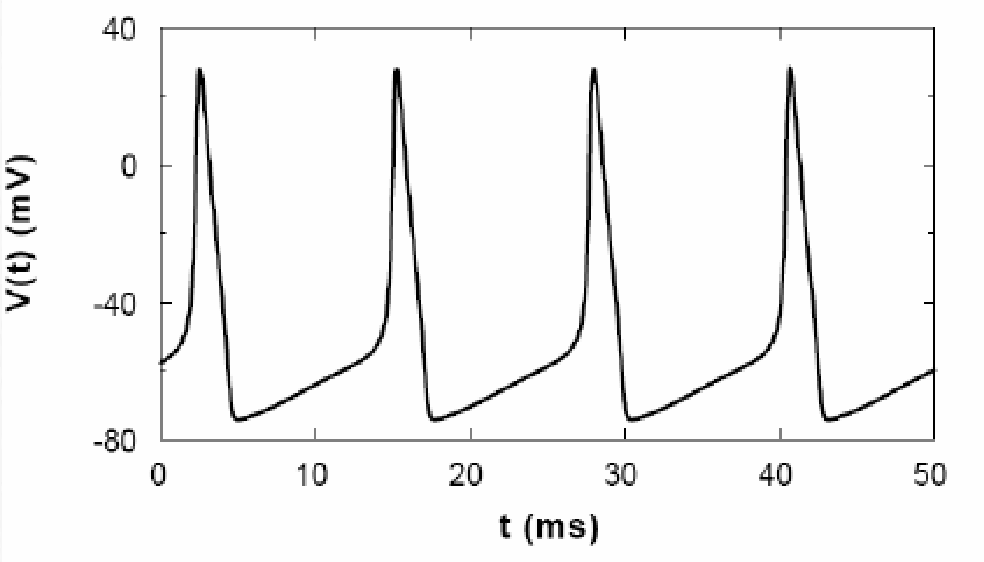
$$\frac{dm}{dt} = \frac{m_\infty(V) - m}{\tau_m(V)} \qquad \frac{dn}{dt} = \frac{n_\infty(V) - n}{\tau_n(V)} \qquad \frac{dh}{dt} = \frac{h_\infty(V) - h}{\tau_h(V)}$$

The Hodgkin-Huxley model

$$C\frac{dV}{dt} = -\overline{g}_{Na}m^3h(V - V_{Na}) - \overline{g}_K n^4(V - V_K) - \overline{g}_L(V - V_L) + I_{app}$$

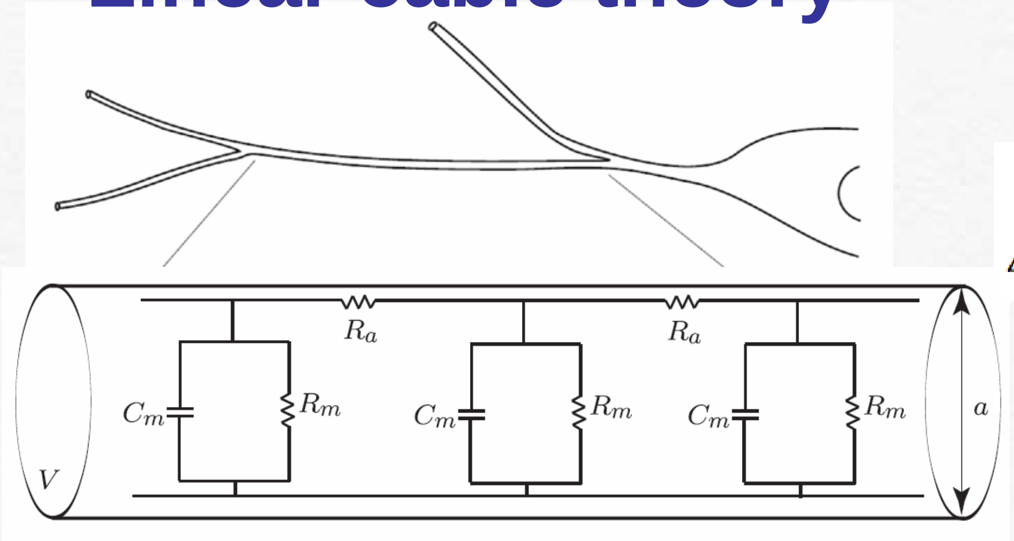
$$\frac{dm}{dt} = \frac{m_\infty - m}{\tau_m}, \qquad \frac{dh}{dt} = \frac{h_\infty - h}{\tau_h}, \qquad \frac{dn}{dt} = \frac{n_\infty - n}{\tau_n}$$





Spatially extended models

Linear cable theory



$$V_i(x) - V_i(x + \Delta x) = I_a(x) r_a \Delta x.$$

$$\lim_{\Delta x \to 0} \frac{V_i(x + \Delta x) - V_i(x)}{\Delta x} = \frac{\partial V_i}{\partial x} = -r_a I_a(x)$$

$$\frac{\partial I_a}{\partial x} = -I_m$$

$$\frac{\partial^2 V}{\partial x^2} = -r_a \frac{\partial I_a}{\partial x} \longrightarrow \frac{1}{r_a} \frac{\partial^2 V}{\partial x^2} = I_m$$

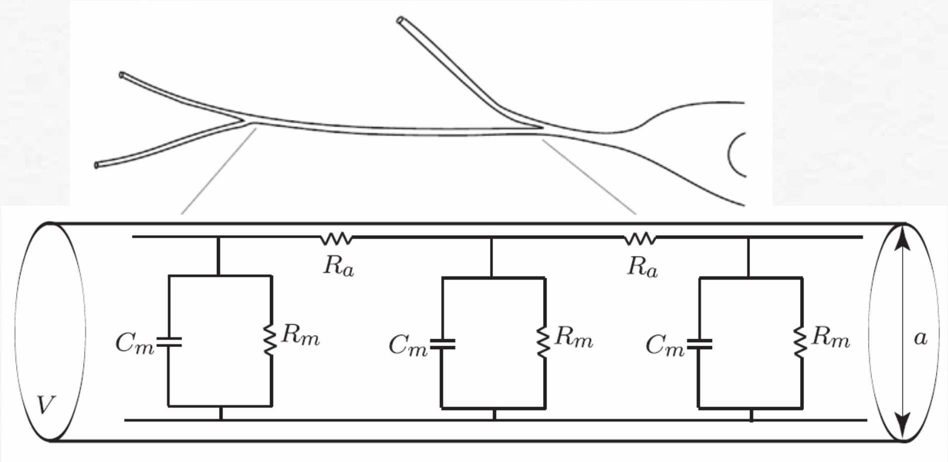
$$I_m = c_m \frac{\partial V}{\partial t} + \frac{V}{r_m}$$

from current balance

$$\boxed{\frac{1}{r_a} \frac{\partial^2 V}{\partial x^2} = c_m \frac{\partial V}{\partial t} + \frac{V}{r_m}}$$

$$r_a = \frac{4R_a}{\pi a^2} \qquad r_m = \frac{R_m}{\pi a}$$

$$c_m = \pi a C_m$$



$$\boxed{\frac{1}{r_a}\frac{\partial^2 V}{\partial x^2} = c_m\frac{\partial V}{\partial t} + \frac{V}{r_m}}$$

$$\boxed{\tau\frac{\partial V}{\partial t} = \lambda^2\frac{\partial^2 V}{\partial x^2} - V}$$

space constant $\lambda = \sqrt{r_m/r_a}$

membrane time constant $\tau = r_m c_m$

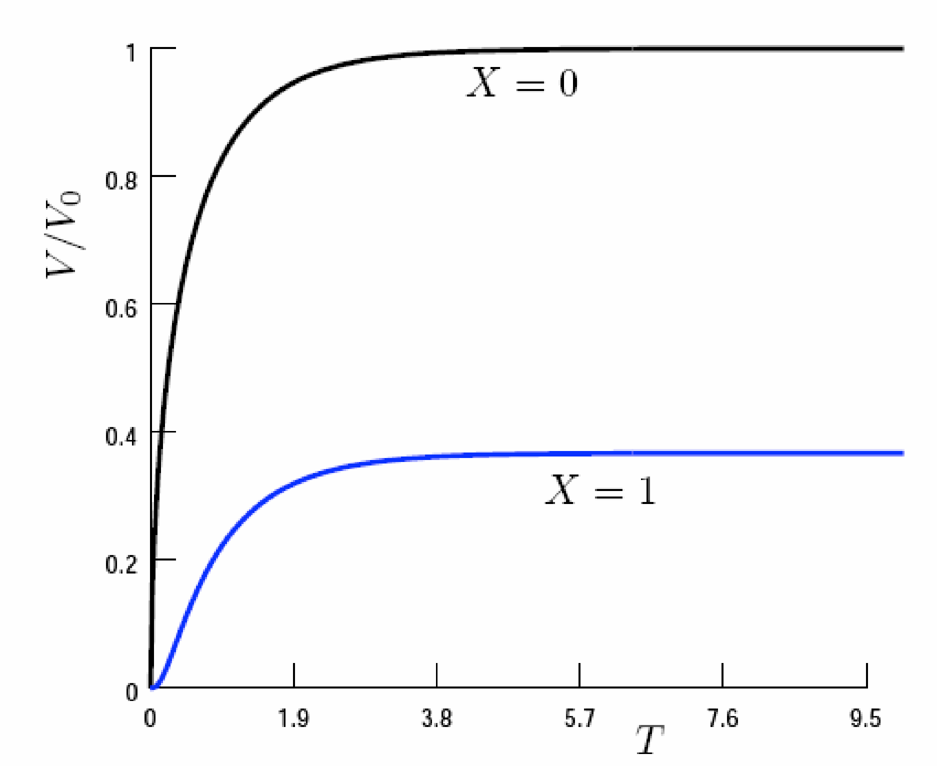
$$X = x/\lambda$$

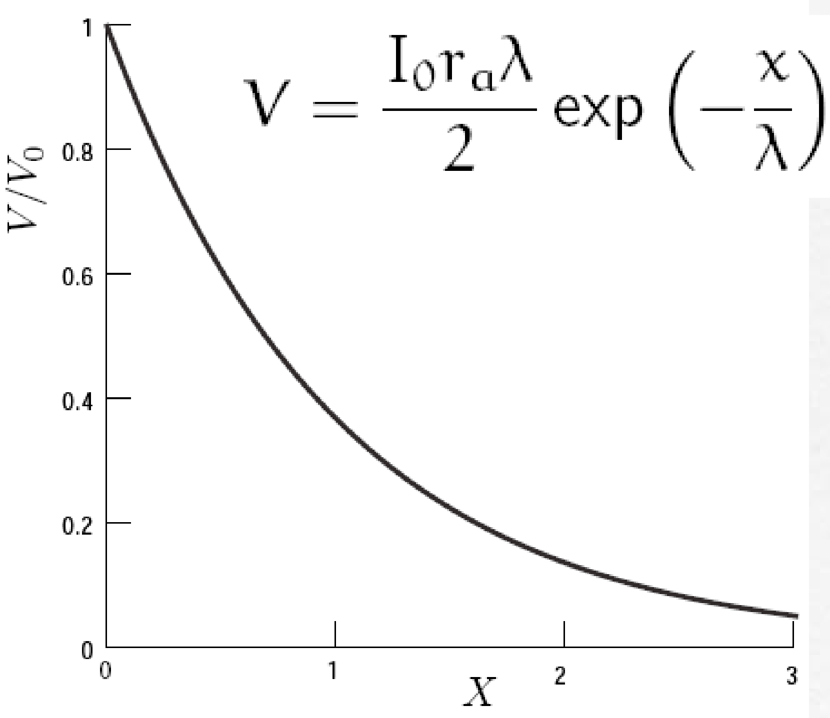
$$T = t/\tau$$

$$\frac{\partial V}{\partial T} = \frac{\partial^2 V}{\partial X^2} - V$$

Infinite cable and constant current I_o at X=0

$$V(X,T) = \frac{I_0 r_a \lambda}{4}\left[\exp(-X)\operatorname{erfc}\left(\frac{X}{2\sqrt{T}} - \sqrt{T}\right) - \exp(X)\operatorname{erfc}\left(\frac{X}{2\sqrt{T}} + \sqrt{T}\right)\right]$$





$$V = \frac{I_0 r_a \lambda}{2}\exp\left(-\frac{x}{\lambda}\right)$$

Input resistance

$$R_{in} = V(x=0, t=\infty)/I_0 = \frac{r_a \lambda}{2} = \frac{\sqrt{r_m r_a}}{2} = \frac{\sqrt{R_m R_a}}{\pi a^{3/2}}$$

The Green's function method

$$V_t = DV_{xx} - \frac{V}{\tau} + I$$

$$0 < x < L, \; t > 0$$

$$D = \lambda^2/\tau$$

Initial value $V(x,0) = v_0(x)$ **and BC**

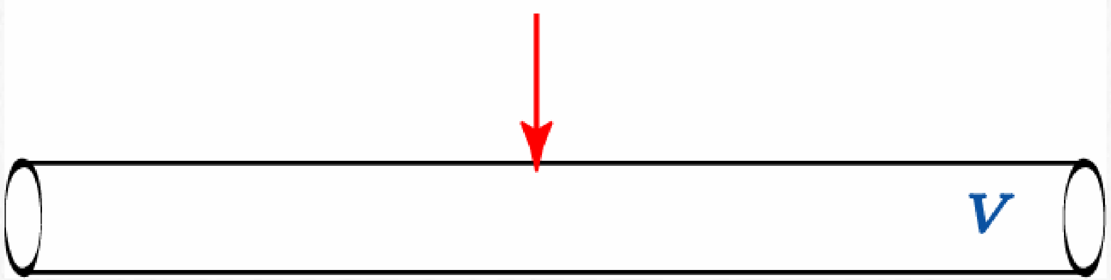
The Green's function $G(x,y,t)$ **is the solution of**

$$\boxed{G_t = DG_{xx} - \frac{G}{\tau} + \delta(x-y)\delta(t)}$$

$$0 < x < L, 0 < y < L$$

$$\boxed{V(x,t) = \int_0^L G(x,y,t)v_0(y)dy + \int_0^L \int_0^t G(x,y,t-s)I(y,s)dsdy}$$

Infinite cable and delta-pulse stimulus $I_{\text{stimulus}} = \delta(t)$



$$G_\infty(x, y, t) = \frac{1}{\sqrt{4\pi D t}} \exp\left(-\frac{t}{\tau}\right) \exp\left(-\frac{(x-y)^2}{4Dt}\right)$$

Boundary conditions

$V_x(0, t) = 0$ **closed end at x=0**

$V(0, t) = 0$ **open end at x=0**

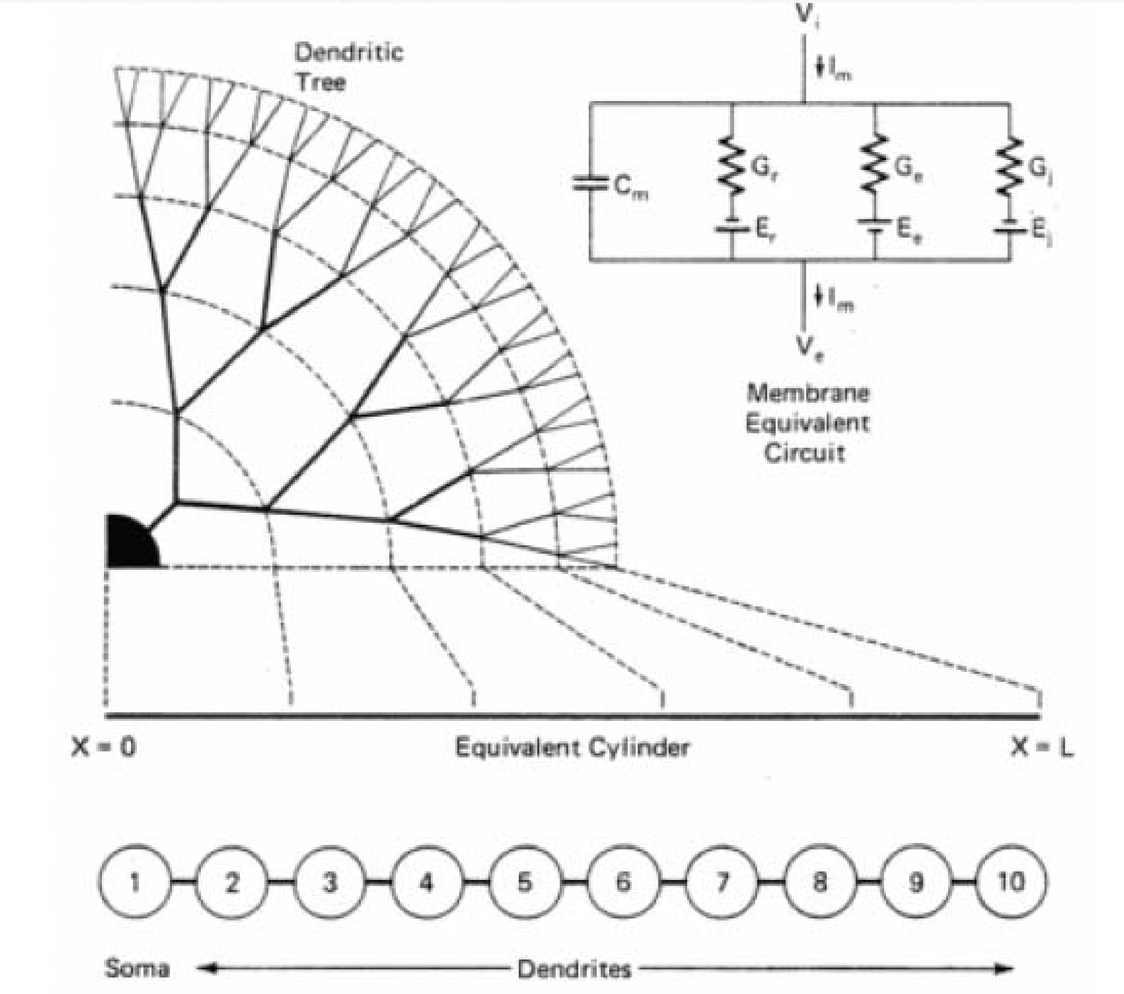
Semi-infinite cable, closed end at x=0 $G_\infty(x-y,t)+G_\infty(x+y,t)$

$$G(x,y,t)=\frac{1}{\sqrt{4\pi Dt}}\exp\left(-\frac{t}{\tau}\right)\left[\exp\left(-\frac{(x-y)^2}{4Dt}\right)+\exp\left(-\frac{(x+y)^2}{4Dt}\right)\right]$$

Semi-infinite cable, open end at x=0 $G_\infty(x-y,t)-G_\infty(x+y,t)$

$$G(x,y,t)=\frac{1}{\sqrt{4\pi Dt}}\exp\left(-\frac{t}{\tau}\right)\left[\exp\left(-\frac{(x-y)^2}{4Dt}\right)-\exp\left(-\frac{(x+y)^2}{4Dt}\right)\right]$$

The Rall model

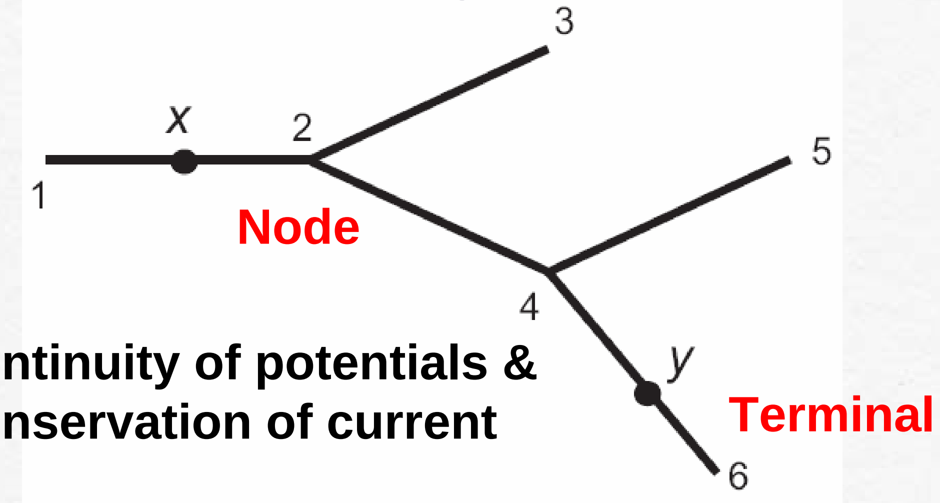


Equivalent cable

3/2 law

$$a_1^{3/2} = a_2^{3/2} + a_3^{3/2}$$

The Green's function for an arbitrary tree



continuity of potentials & conservation of current

$$G_{ij}(x, y, t)$$

'Sum-over-paths' approach (L.F. Abbott,1992)

Trips

$$x \longrightarrow 2 \longrightarrow 4 \longrightarrow y$$

$$x \longrightarrow 1 \longrightarrow 2 \longrightarrow 4 \longrightarrow y$$

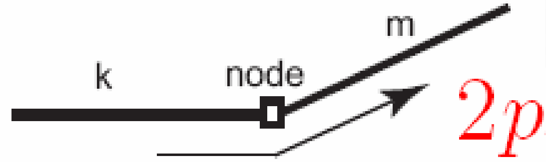
$$x \longrightarrow 2 \longrightarrow 4 \longrightarrow 6 \longrightarrow y$$

$$x \longrightarrow 1 \longrightarrow 2 \longrightarrow 4 \longrightarrow 6 \longrightarrow y$$

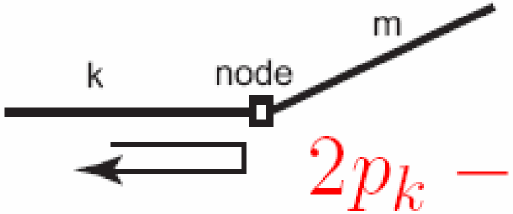
$$\boxed{G_{ij}(x, y, t) = \sum A_{\mathrm{trip}} G_{\infty}(L_{\mathrm{trip}}, t)}$$

Coefficients A_{trip}

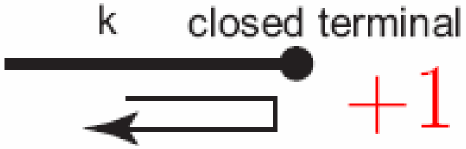
$$p_m = \frac{Z_m}{\sum_{i \text{ on node}} Z_i}, \qquad Z_i = a_i^{3/2}(R_{a_i} R_{m_i})^{-1/2}$$



$2p_m$

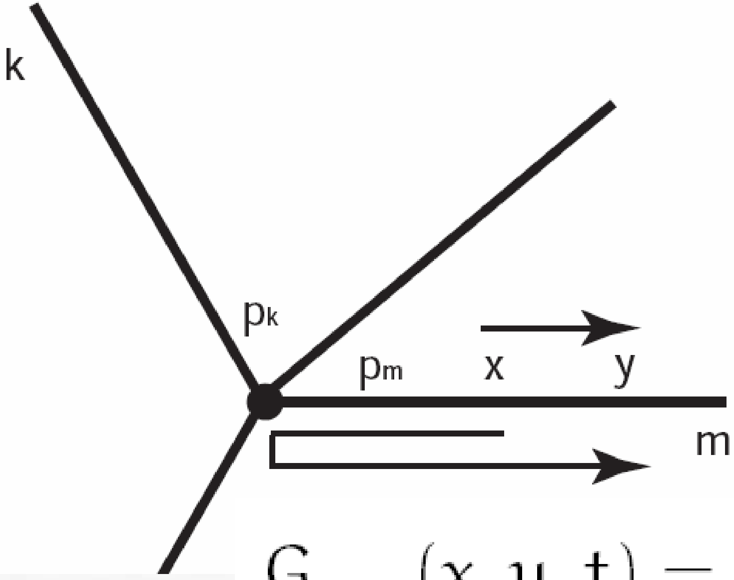


$2p_k - 1$



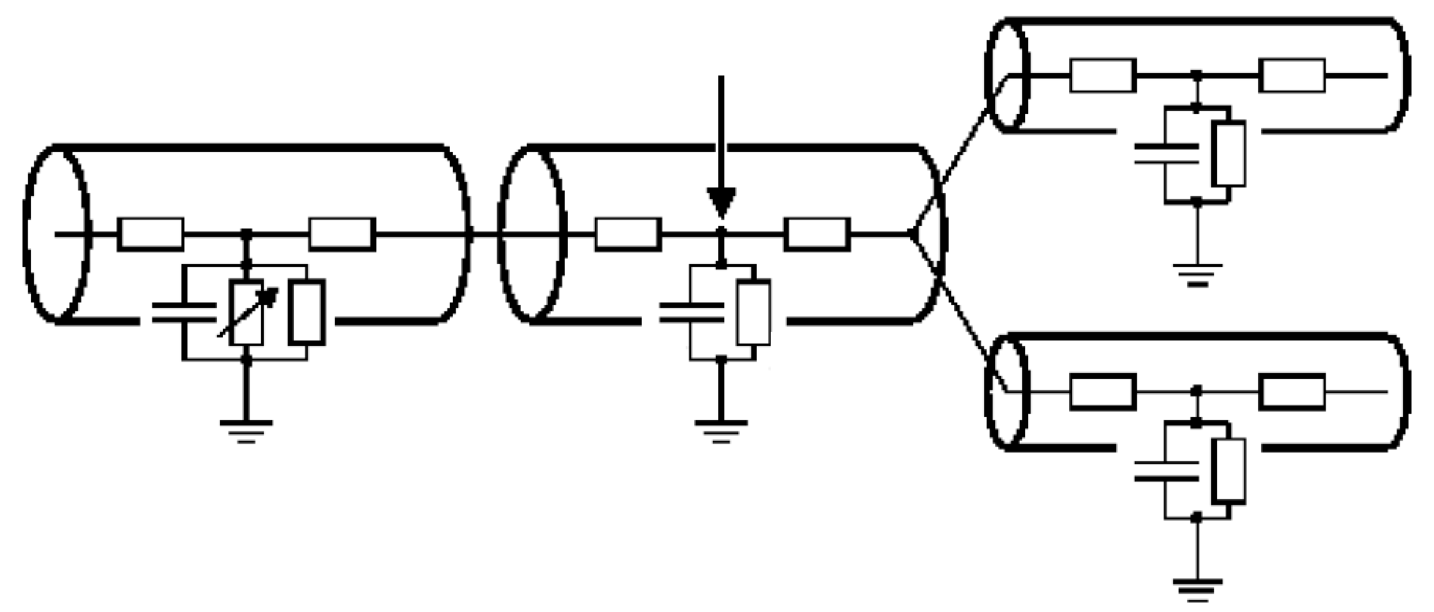
$+1$

-1



$$G_{mm}(x, y, t) = G_\infty(x - y, t) + (2p_m - 1)G_\infty(x + y, t)$$

Compartmental models

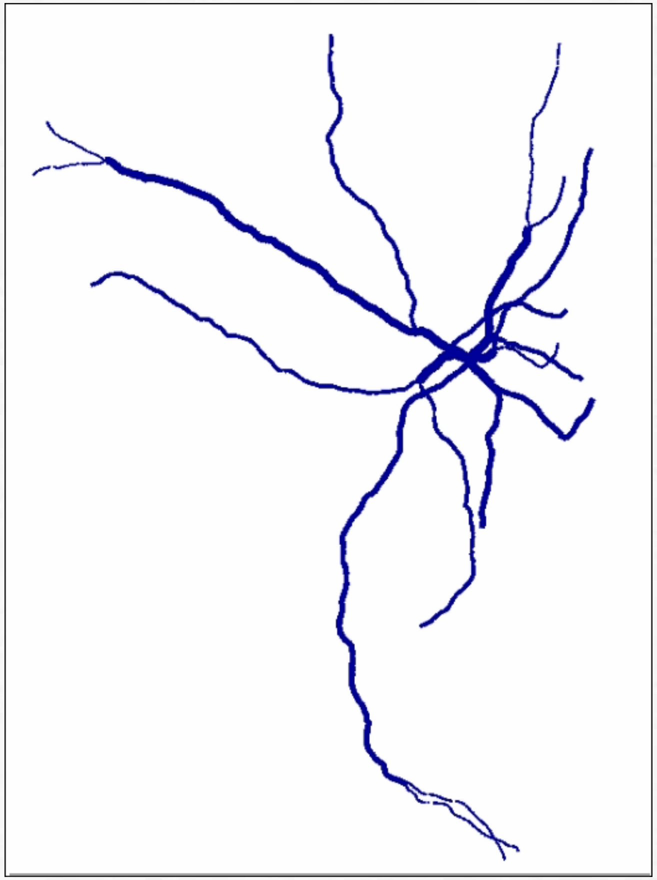


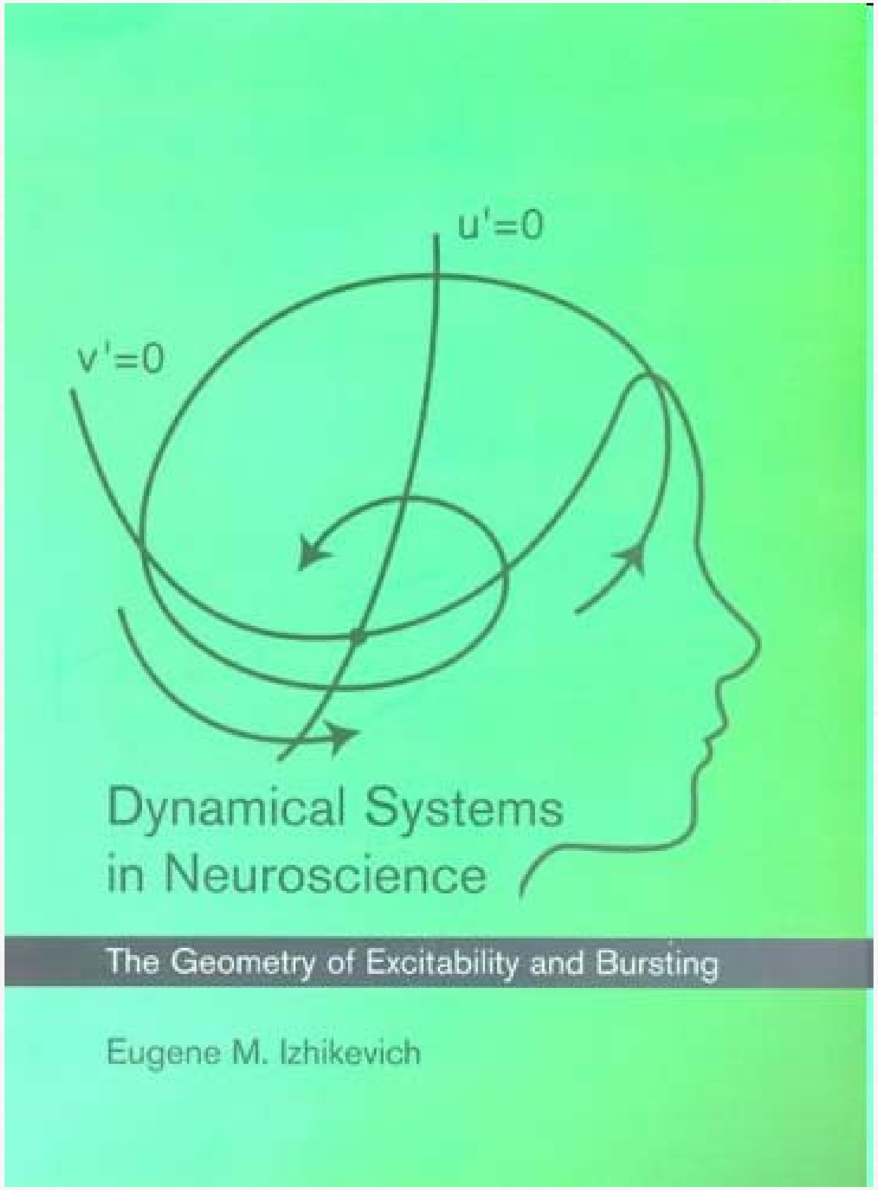
$$c_m \frac{dV_\mu}{dt} = -i_m^\mu + \frac{I_e^\mu}{A_\mu} + g_{\mu,\mu+1}(V_{\mu+1} - V_\mu) + g_{\mu,\mu-1}(V_{\mu-1} - V_\mu)$$

Simulation software tools

GENESIS (http://www.genesis-sim.org/GENESIS/)

NEURON (http://www.neuron.yale.edu/neuron/)



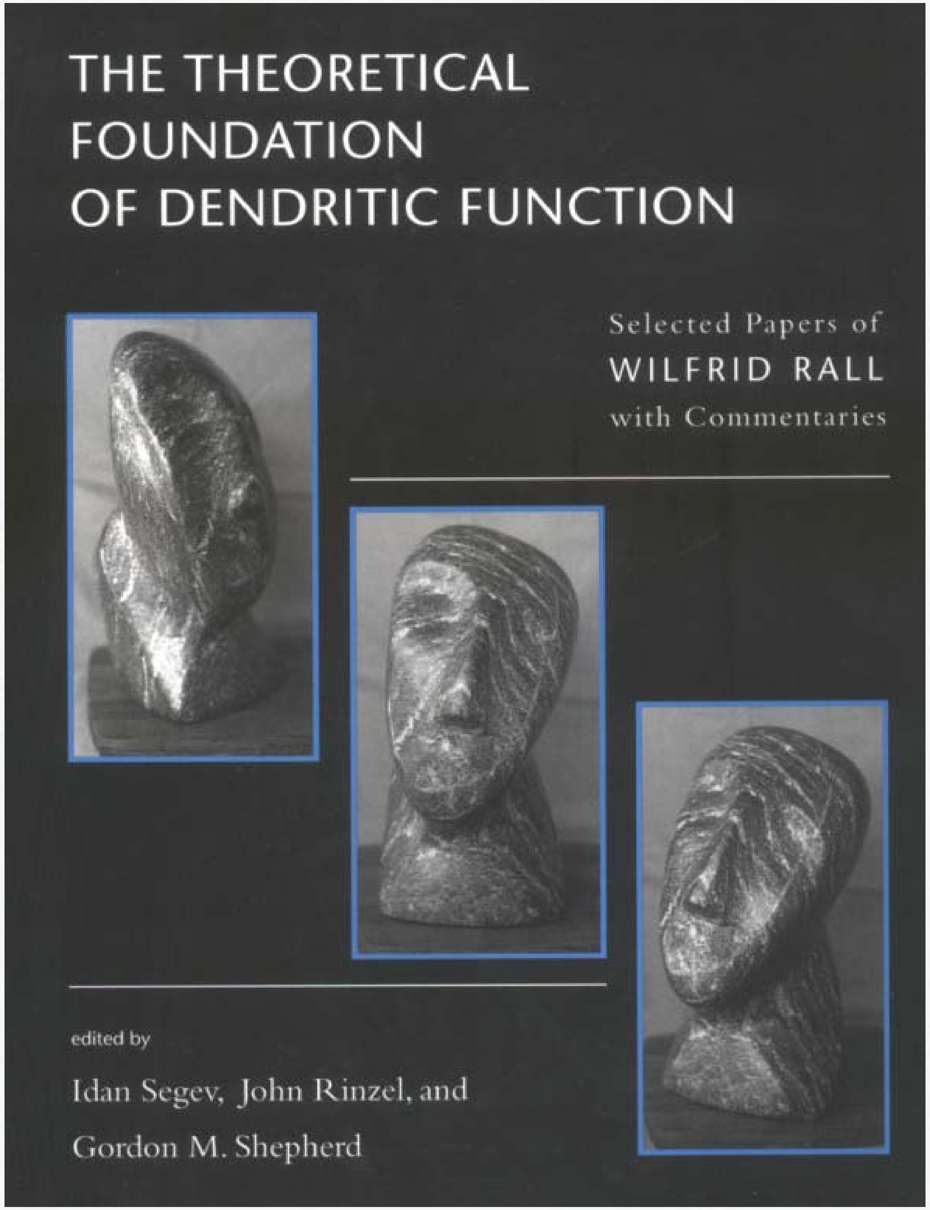


Dynamical Systems
in Neuroscience

The Geometry of Excitability and Bursting

Eugene M. Izhikevich

E. Izhikevich, *Dynamical Systems in Neuroscience*, MIT Press, 2007

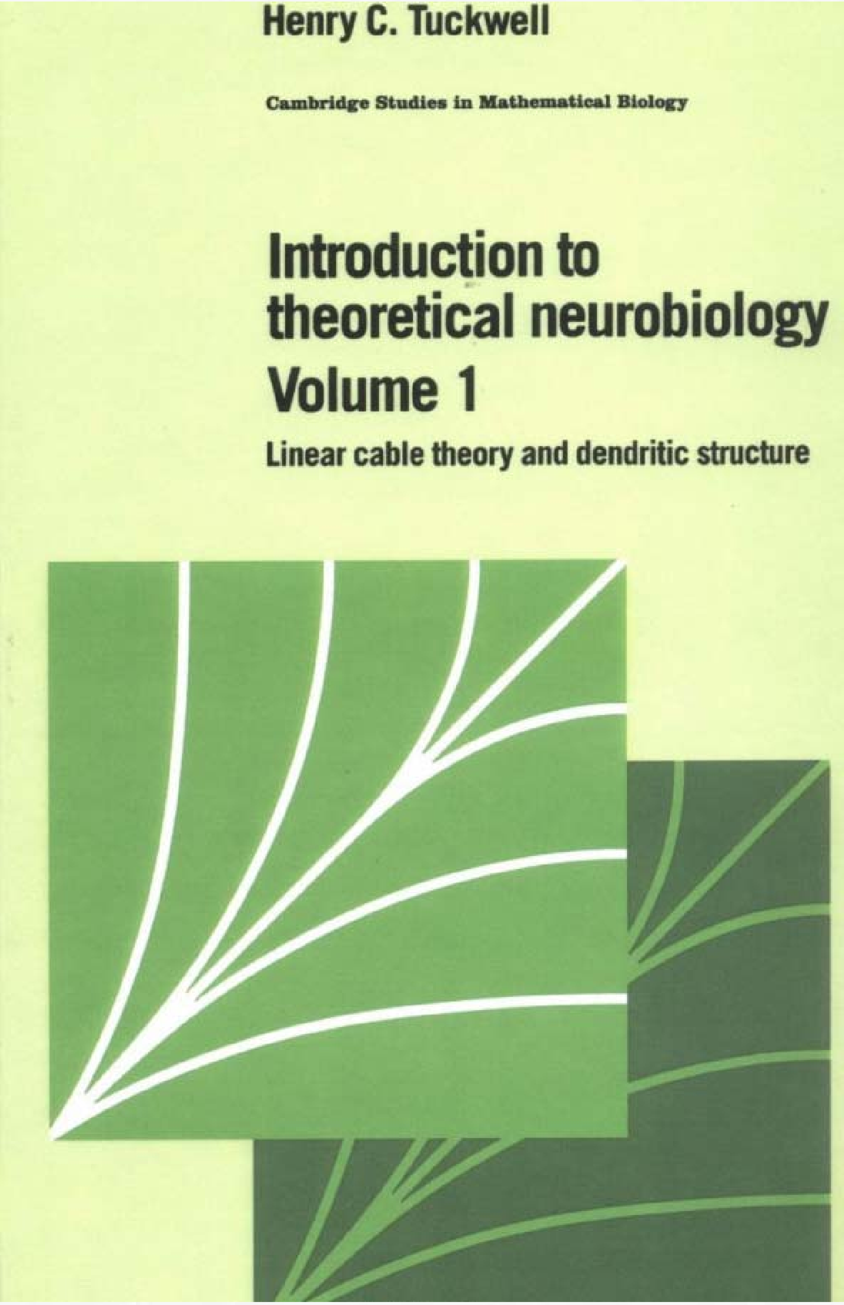


THE THEORETICAL
FOUNDATION
OF DENDRITIC FUNCTION

Selected Papers of
WILFRID RALL
with Commentaries

edited by
Idan Segev, John Rinzel, and
Gordon M. Shepherd

I. Segev, J. Rinzel and G. M. Shepherd, ***The Theoretical Foundation of Dendritic Function: Selected Papers of Wilfrid Rall with Commentaries*, MIT Press, Cambridge, MA, 1995**



Henry C. Tuckwell

Cambridge Studies in Mathematical Biology

Introduction to theoretical neurobiology Volume 1

Linear cable theory and dendritic structure

H.C. Tuckwell, *Introduction to theoretical neurobiology. Volume 1: Linear cable theory and dendritic structure*, Cambridge Studies in Mathematical Biology, 1988