THE UNIVERSITY OF WARWICK

complexity

Spatially extended models of single neurons: the role of dendrites

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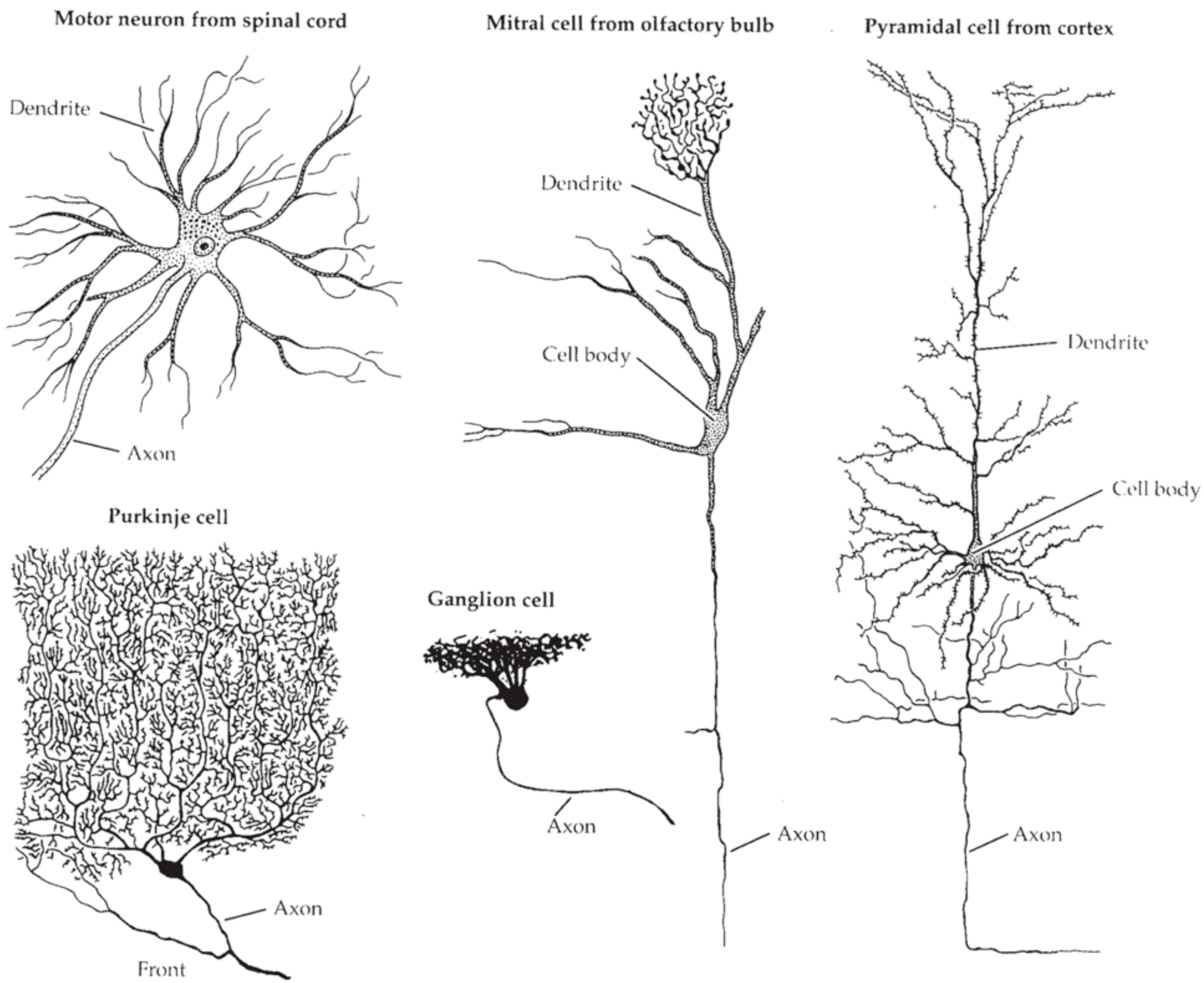
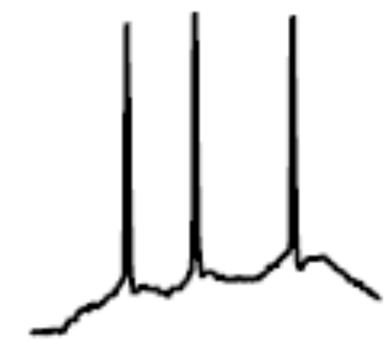
Mathematical Neuroscience Training Workshop 2010

Overview

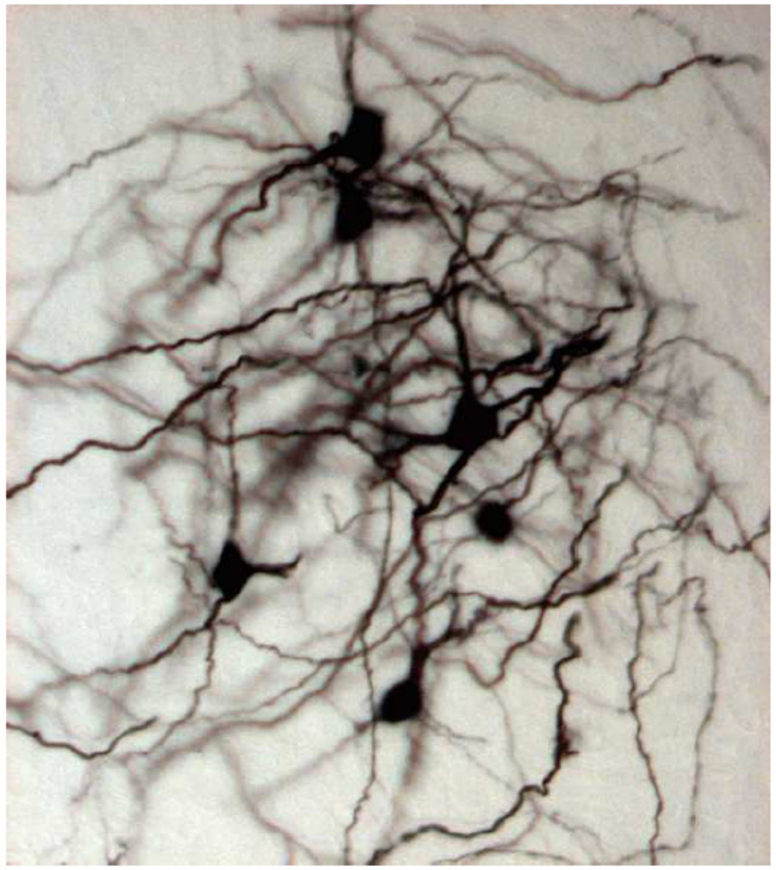
- The conductance-based membrane model
- Spatially extended models

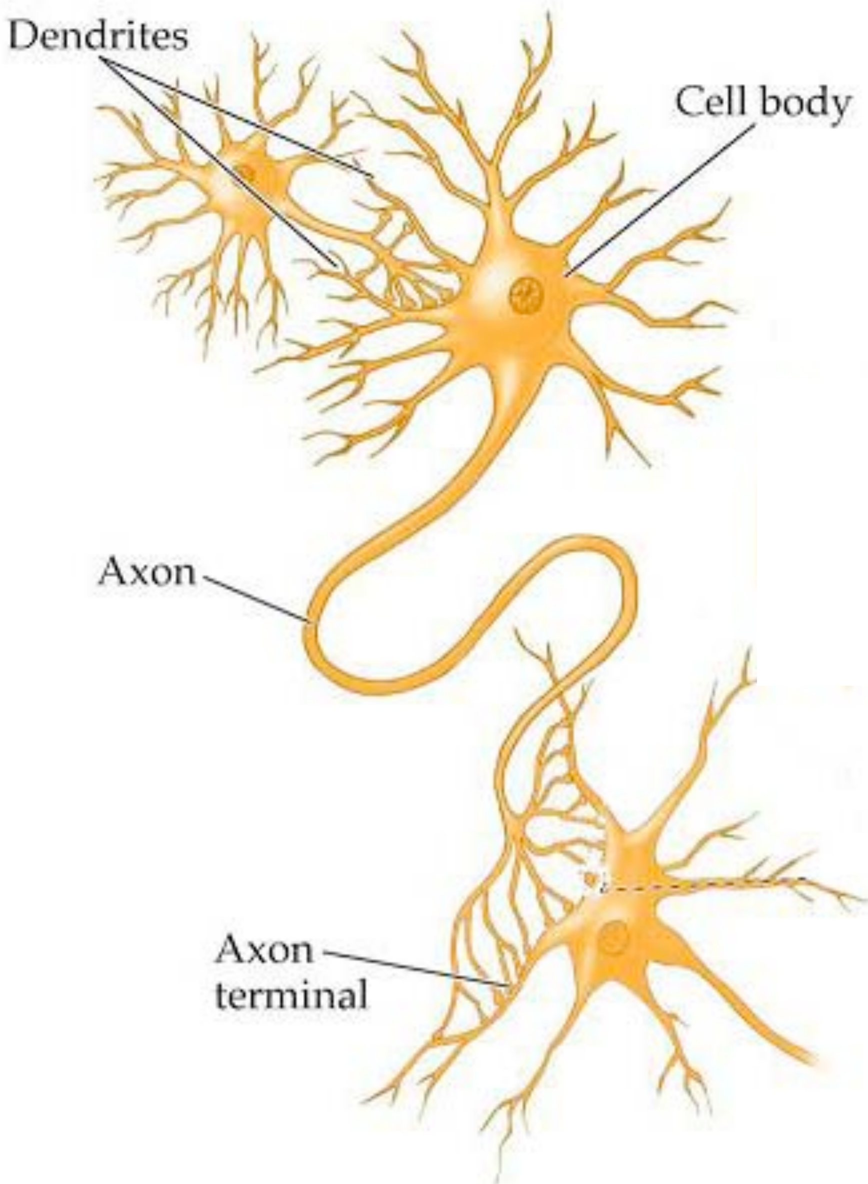
Complex spatial structure

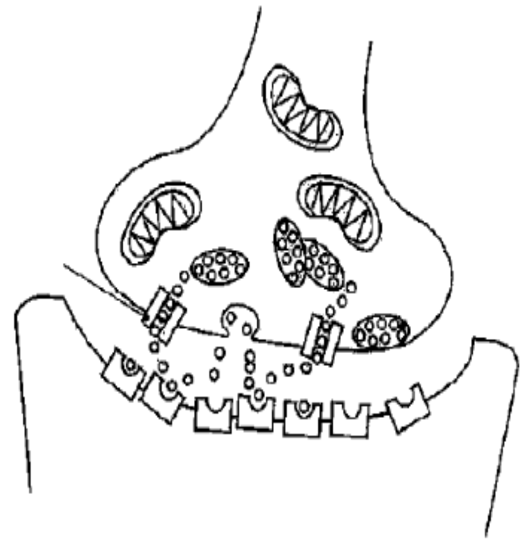




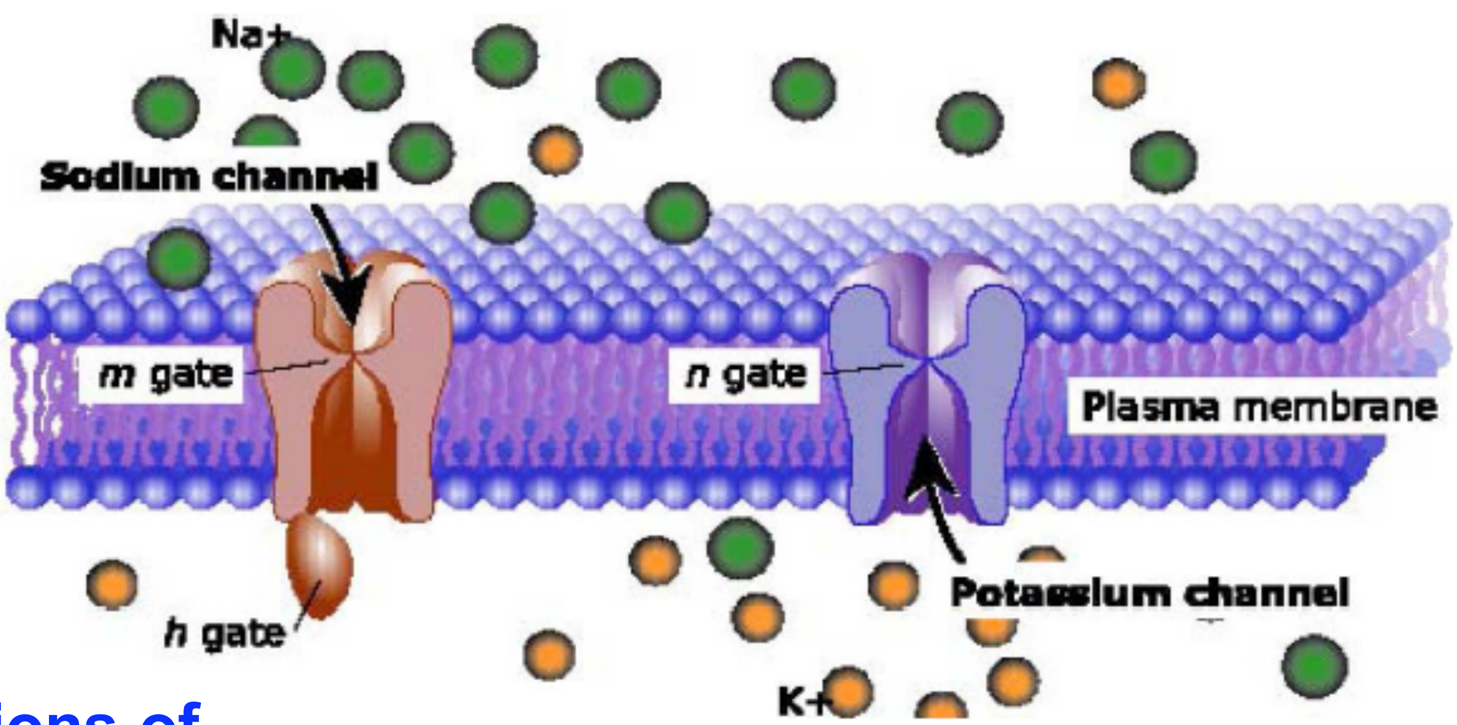
Action potentials
(short electrical spikes)





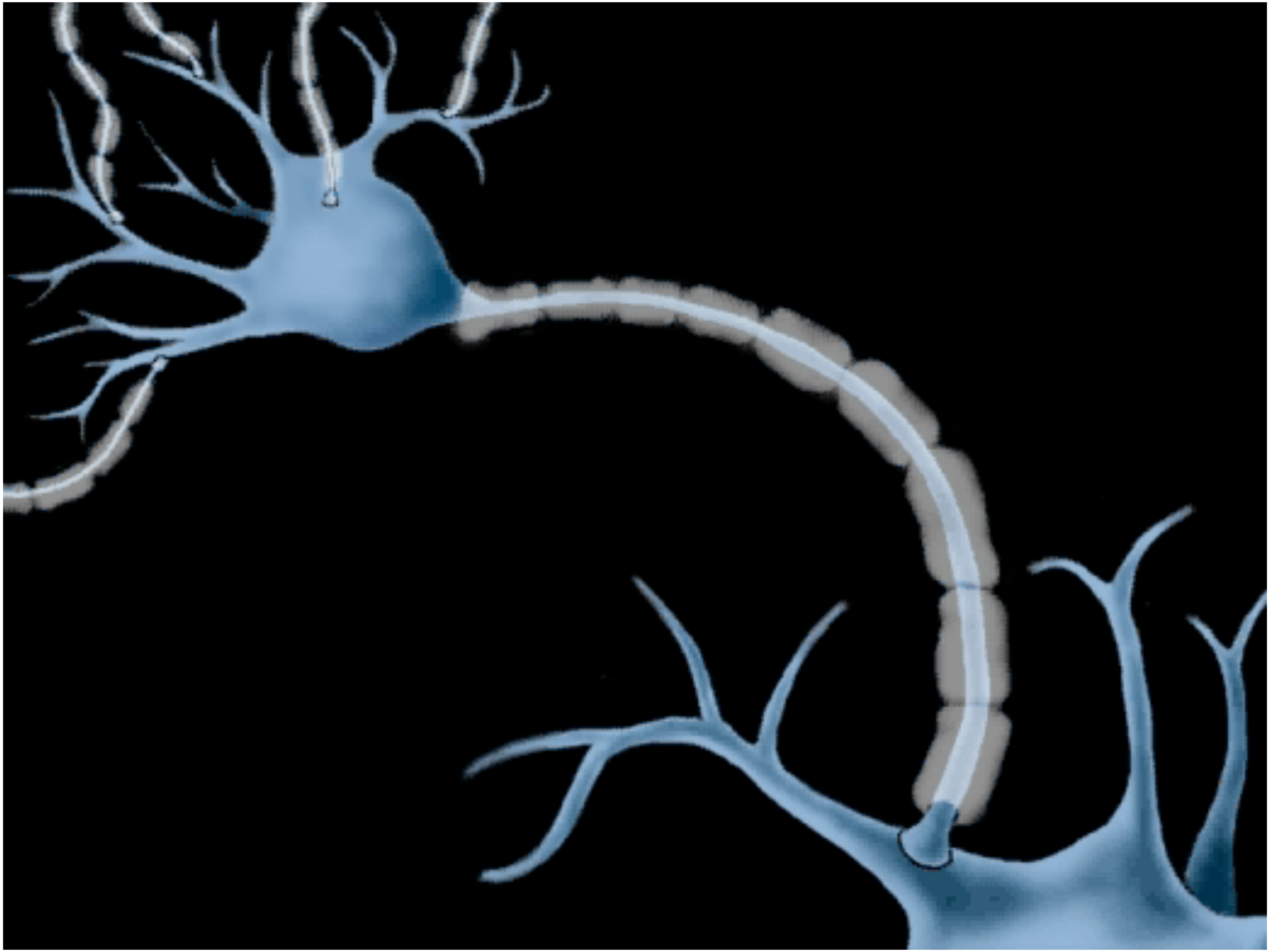


The contacts of the axon to target neurons are either located on the dendritic tree or directly on the soma, and are known as synapses

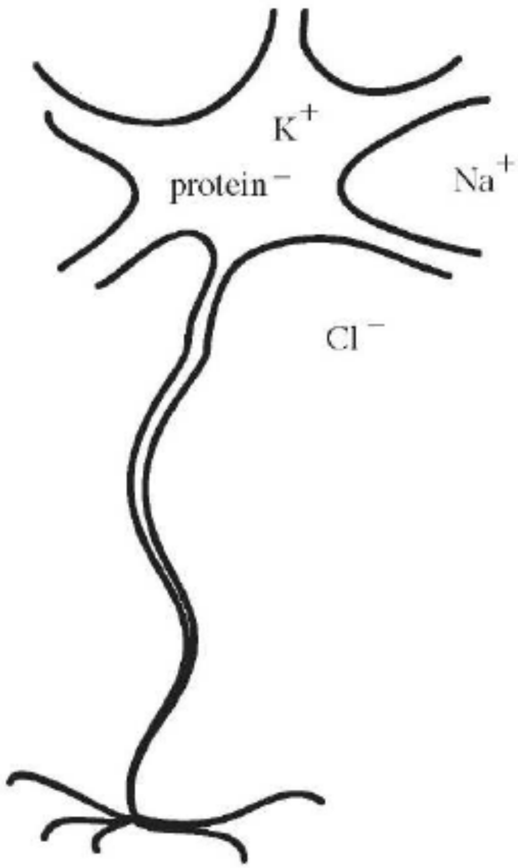


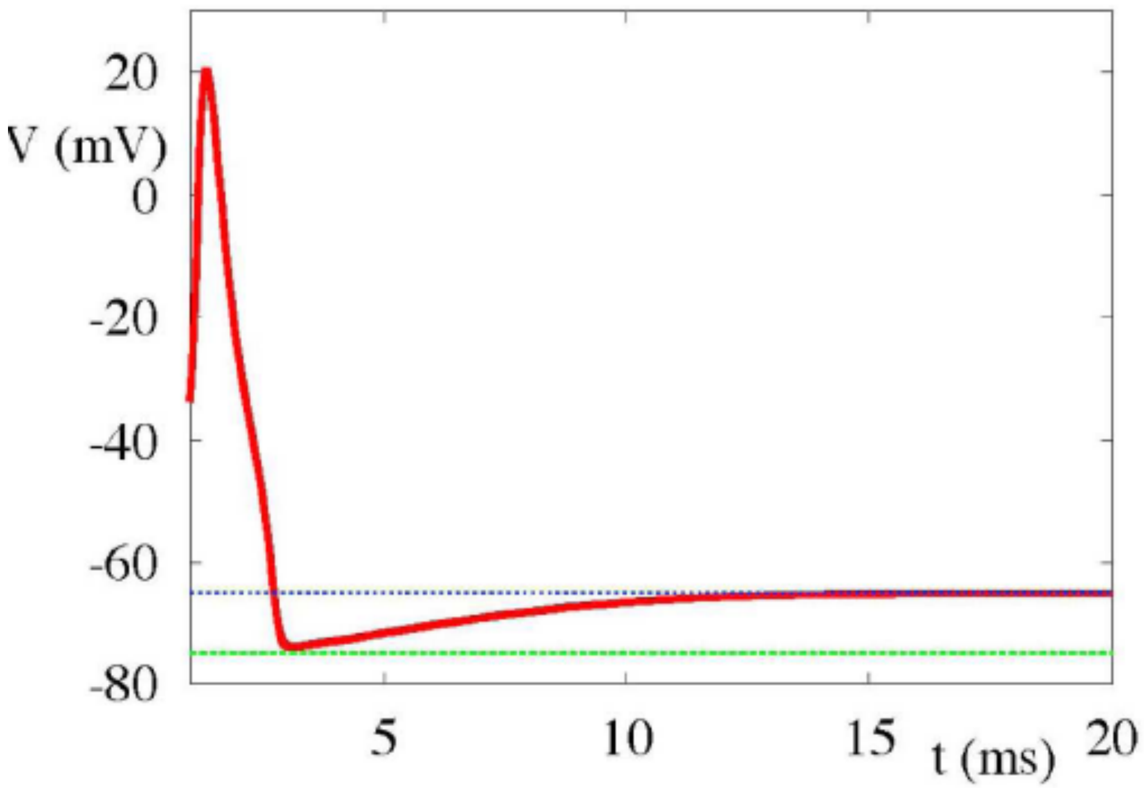
Differences in the ionic concentrations of the intra/extracellular fluids create a potential difference across the cell

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



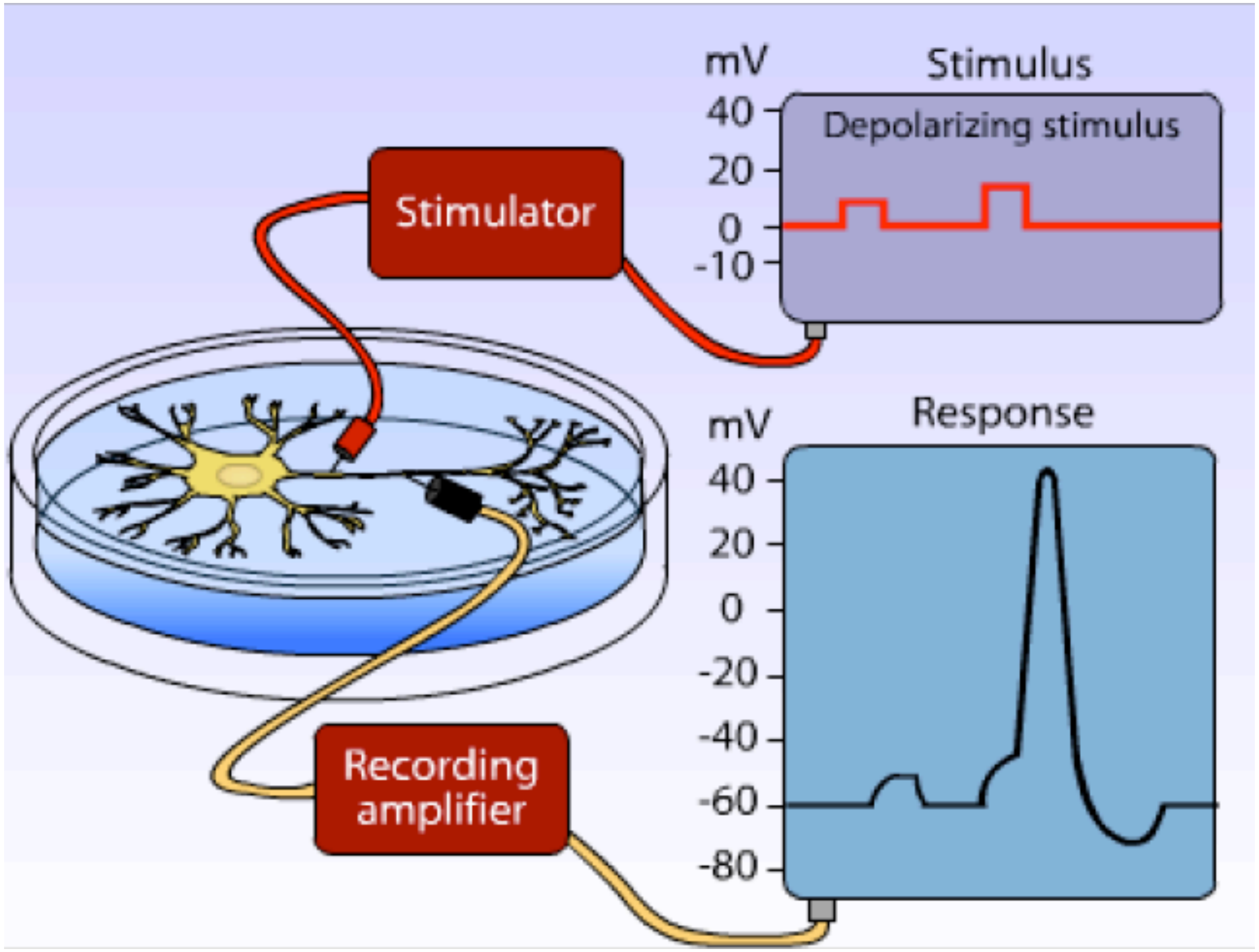
Action potential





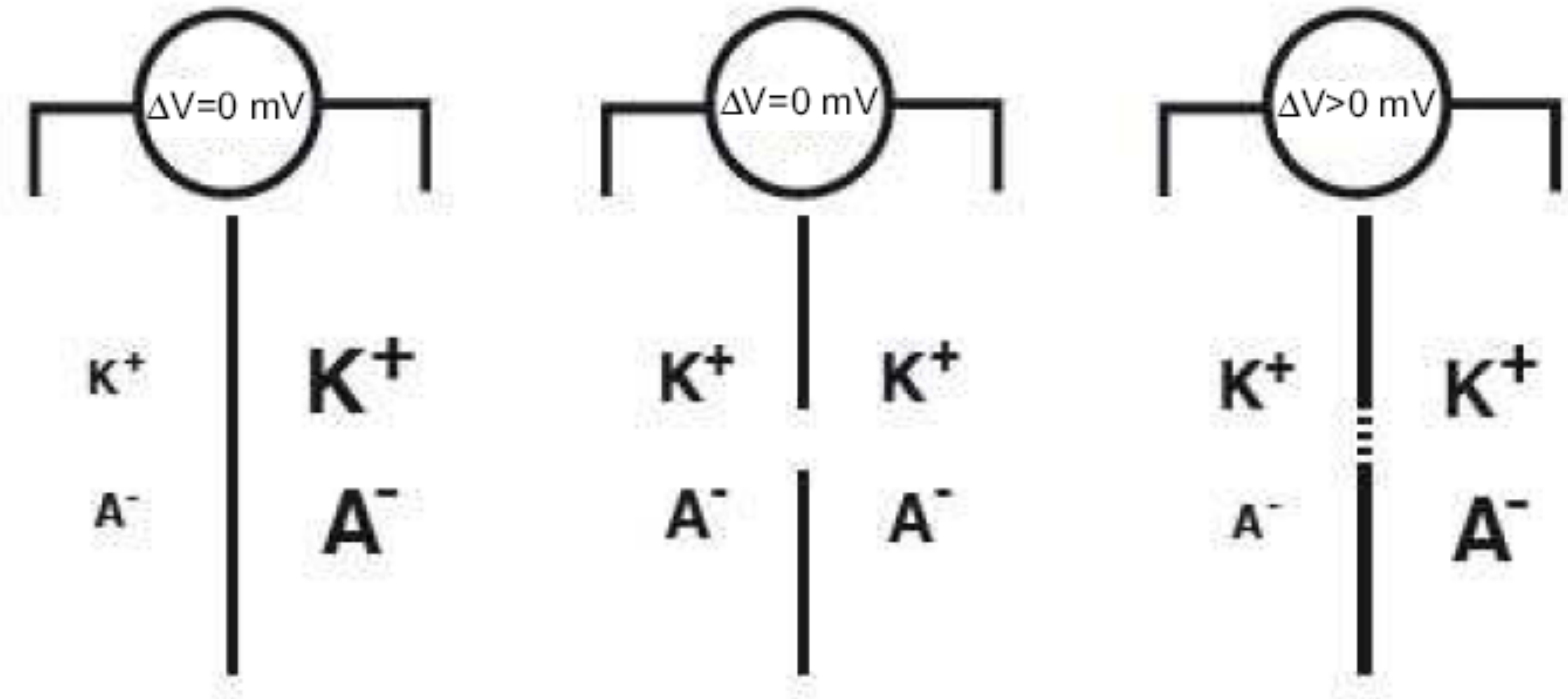
- In the absence of a signal, there is a resting potential of ~ -65mV.
- During an action potential, the membrane potential increase rapidly to ~ 20mV, returns slowly to ~ -75mV and then slowly relaxes to the resting potential.
- The rapid membrane depolarisation corresponds to an influx of Na^+ across 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.

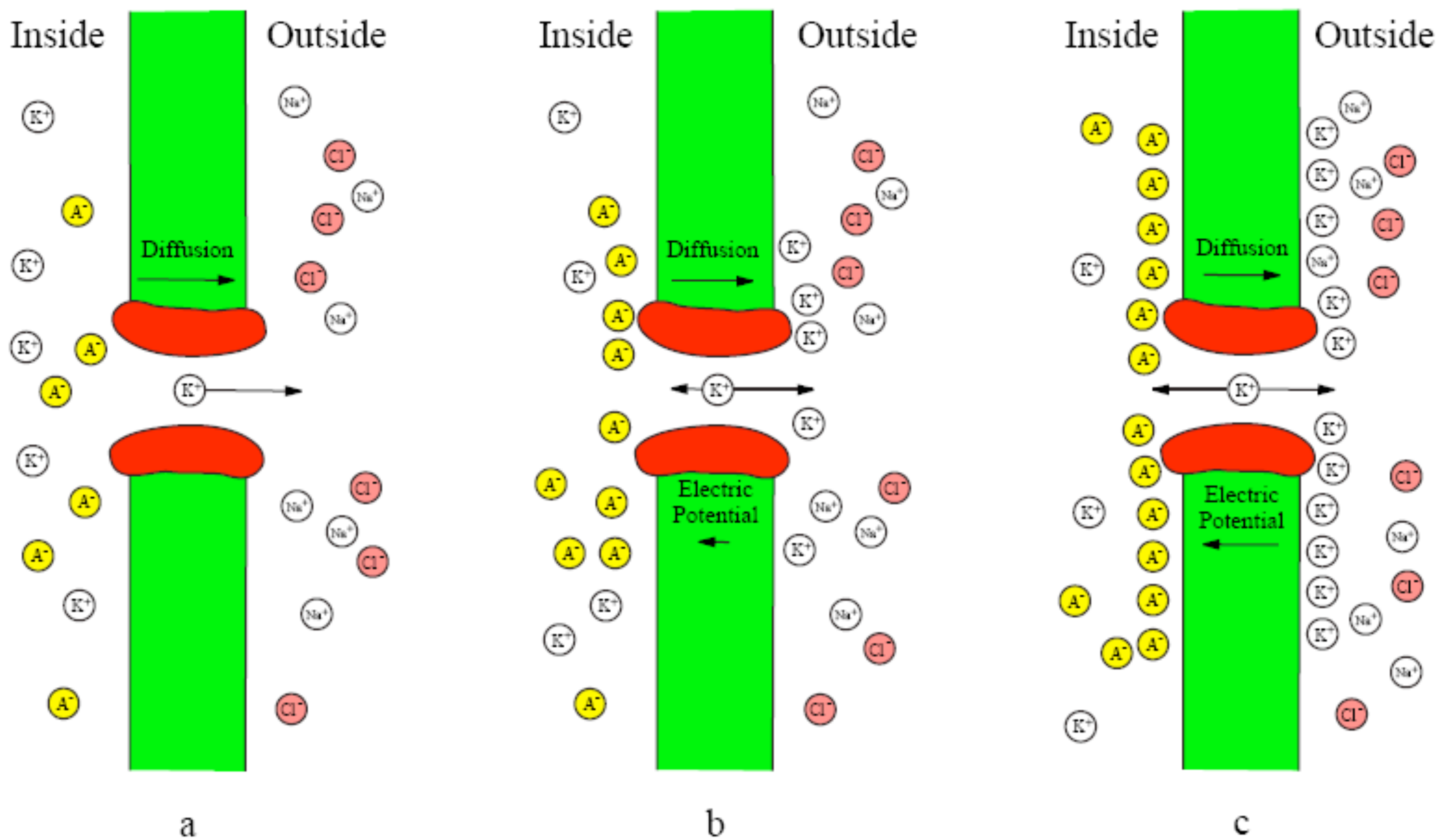
Experimental setup in vitro



Single-compartment models

The Nernst potential

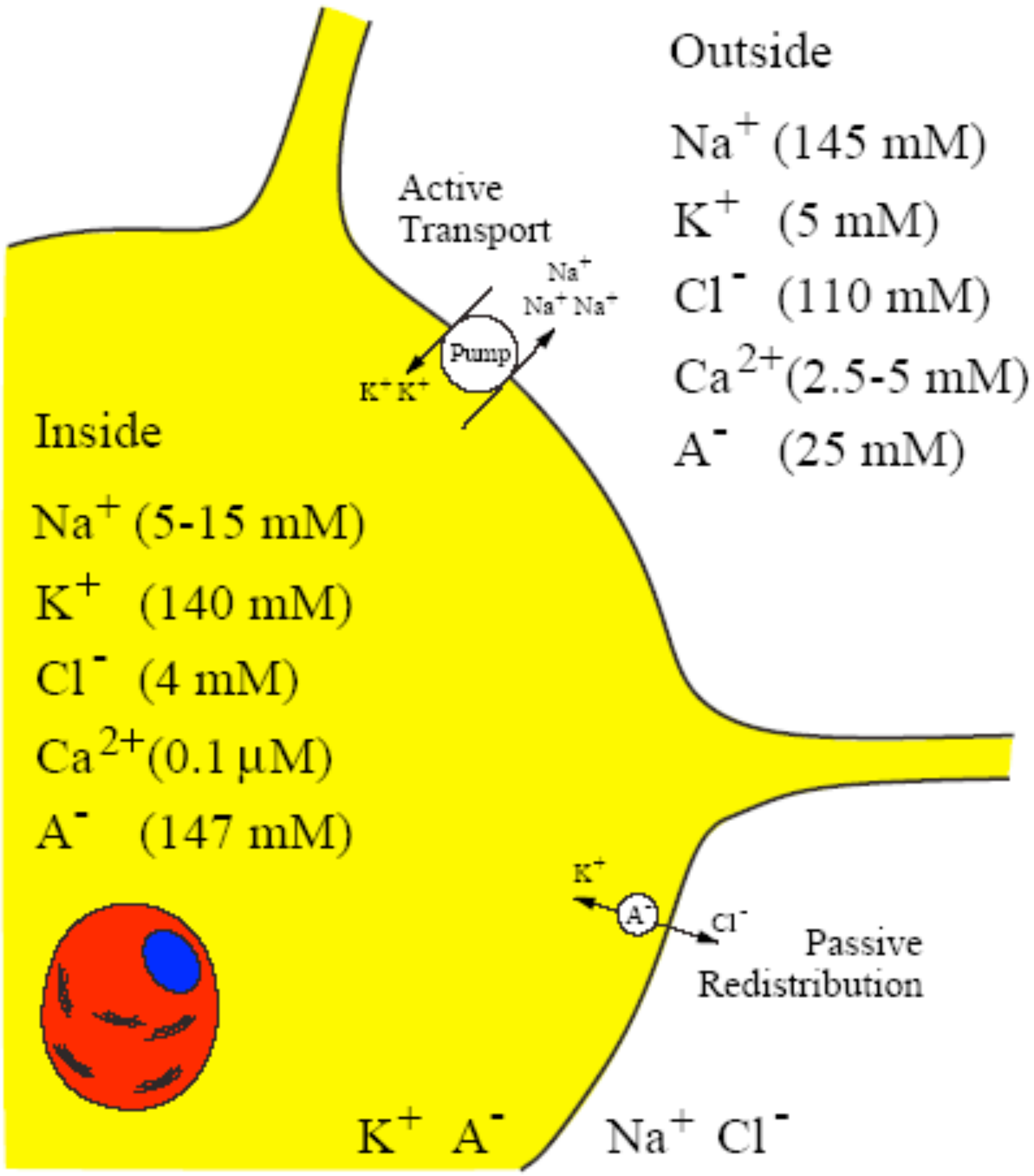




Diffusion of K^+ ions down the concentration gradient through the membrane (a) creates an electric potential force directed at the opposite direction (b) until the diffusion and electrical forces counter each other (c) resulting in the Nernst equilibrium potential for K^+

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

Nernst potentials = Reversal potentials

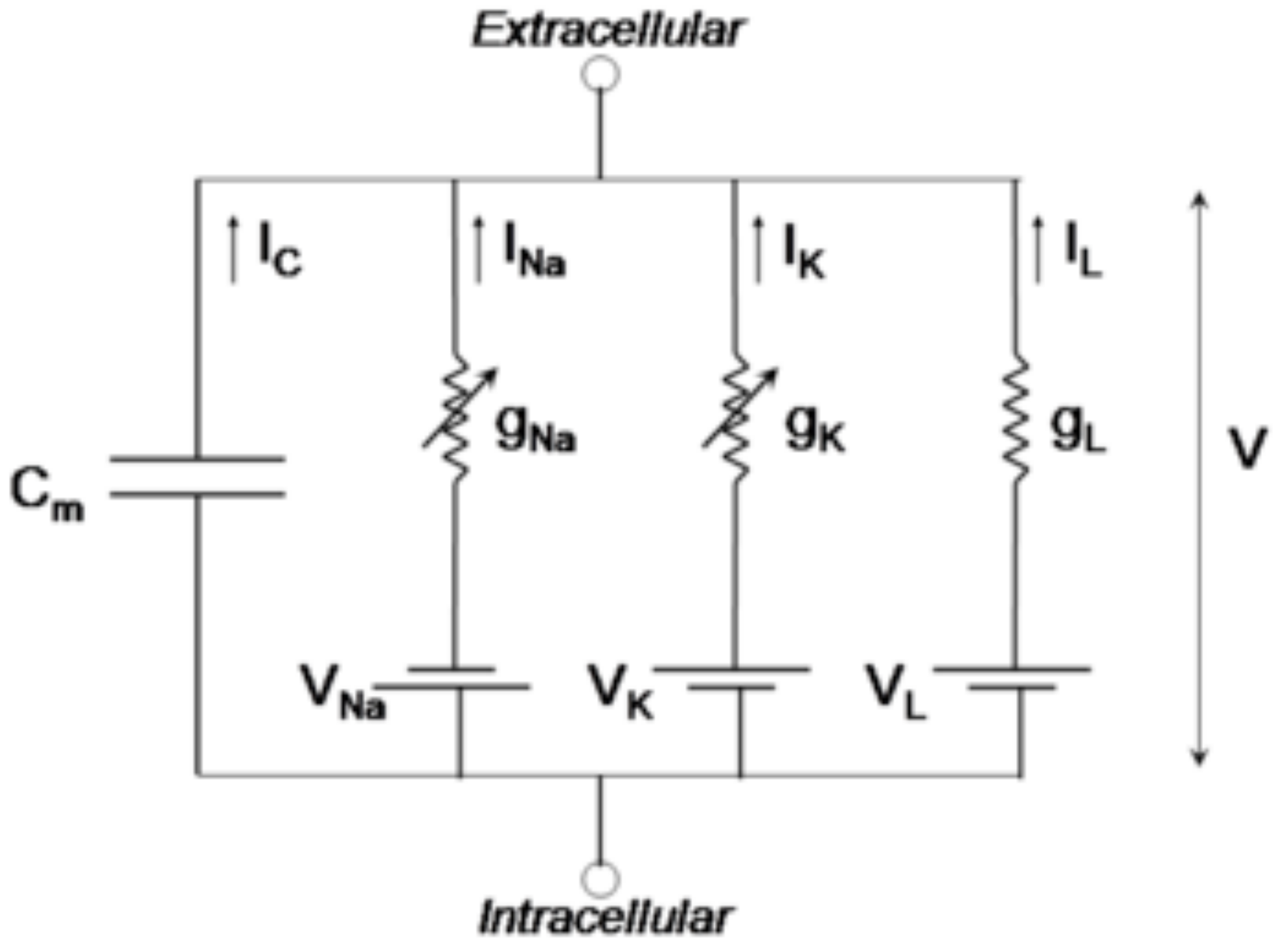


Equilibrium Potentials

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

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

$$I_K = g_K(V - V_K)$$

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

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

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

the capacitive current across the membrane

$$I_{\text{cap}} = C_m \frac{\mathrm{d}V}{\mathrm{d}t}$$

$$I_{\text{app}} = C_m \frac{\mathrm{d}V}{\mathrm{d}t} + I_{\text{ion}}$$

The main equation of the membrane model

$$C_m \frac{\mathrm{d}V}{\mathrm{d}t} = -\sum_i g_i(V - V_i) + I_{\mathrm{app}}$$

The Hodgkin-Huxley model


1949, Plymouth

Andrew Huxley Alan Hodgkin

$$g_K(V - V_K)$$

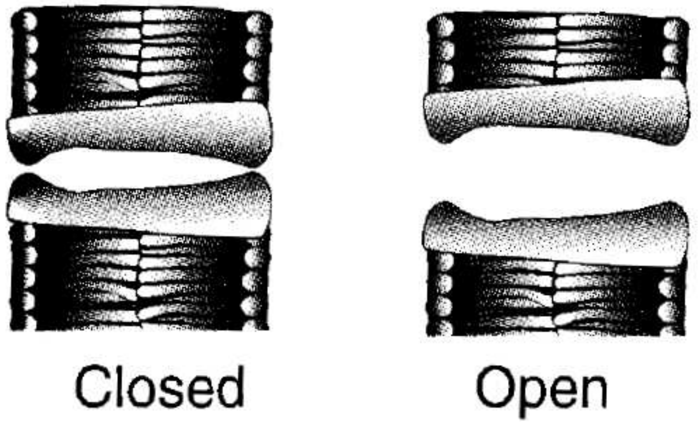
$$g_{Na}(V - V_{Na})$$

$$g_L(V - V_L)$$

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

A gated ionic channel

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



f_O - the fraction of open channels

$$f_O = N_O/N$$
$$f_C = N_C/N$$
$$f_O + f_C = 1$$

the transition from state O to state C $\quad J_- = k^- f_O$

the transition from state C to state O $\quad J_+ = k^+ f_C = k^+(1 - f_O)$

rate of change = inflow rate - outflow rate

$$\frac{\mathrm{d}f_O}{\mathrm{d}t} = J_+ - J_-$$

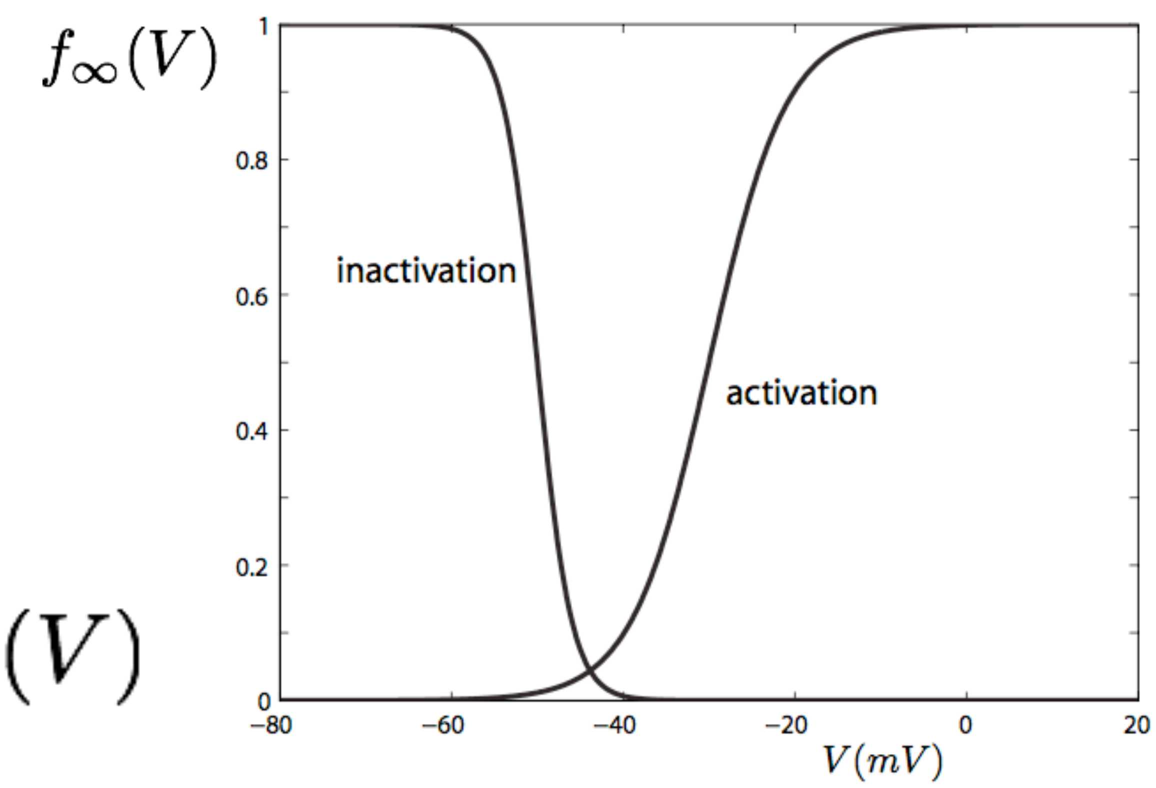
$$\boxed{\frac{\mathrm{d}f_O}{\mathrm{d}t} = \frac{f_\infty - f_O}{\tau}}$$

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

Voltage-gated channel

$$k^+ = k^+(V) \qquad k^- = k^-(V)$$

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



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

$$g_K = \bar{g}_K n^4$$

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

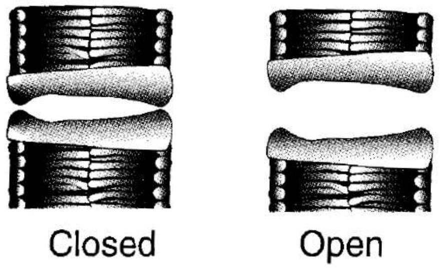
$$g_{Na} = \bar{g}_{Na} m^3 h$$

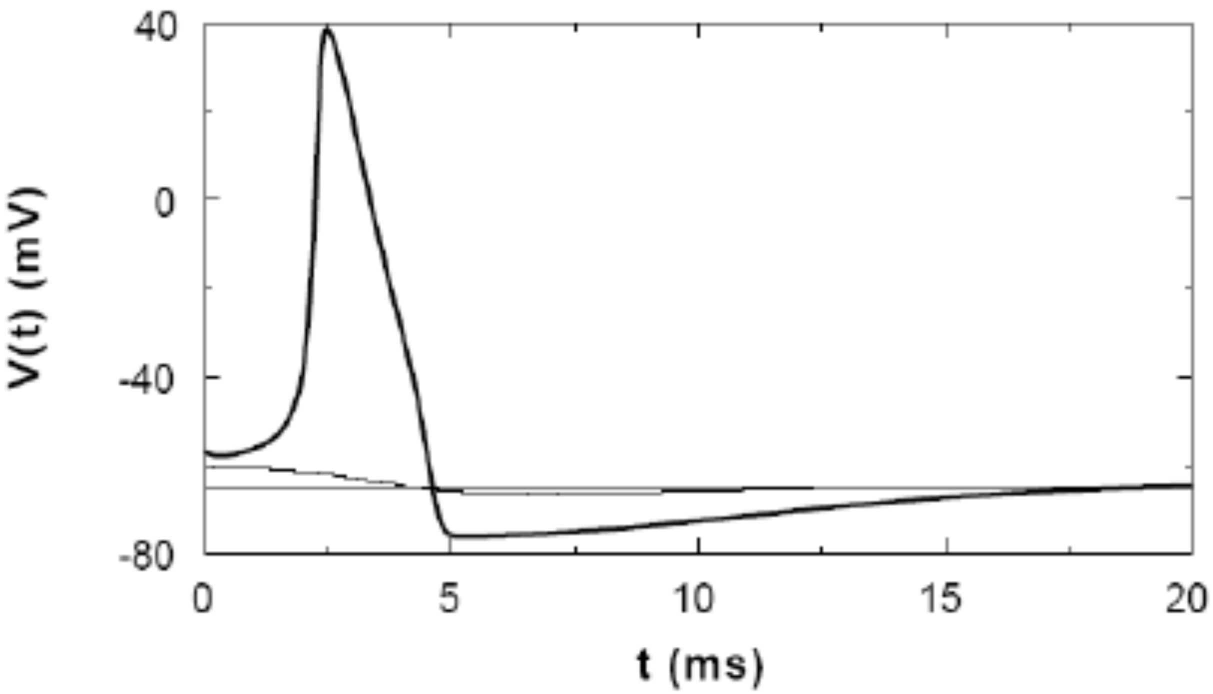
The Hodgkin-Huxley model

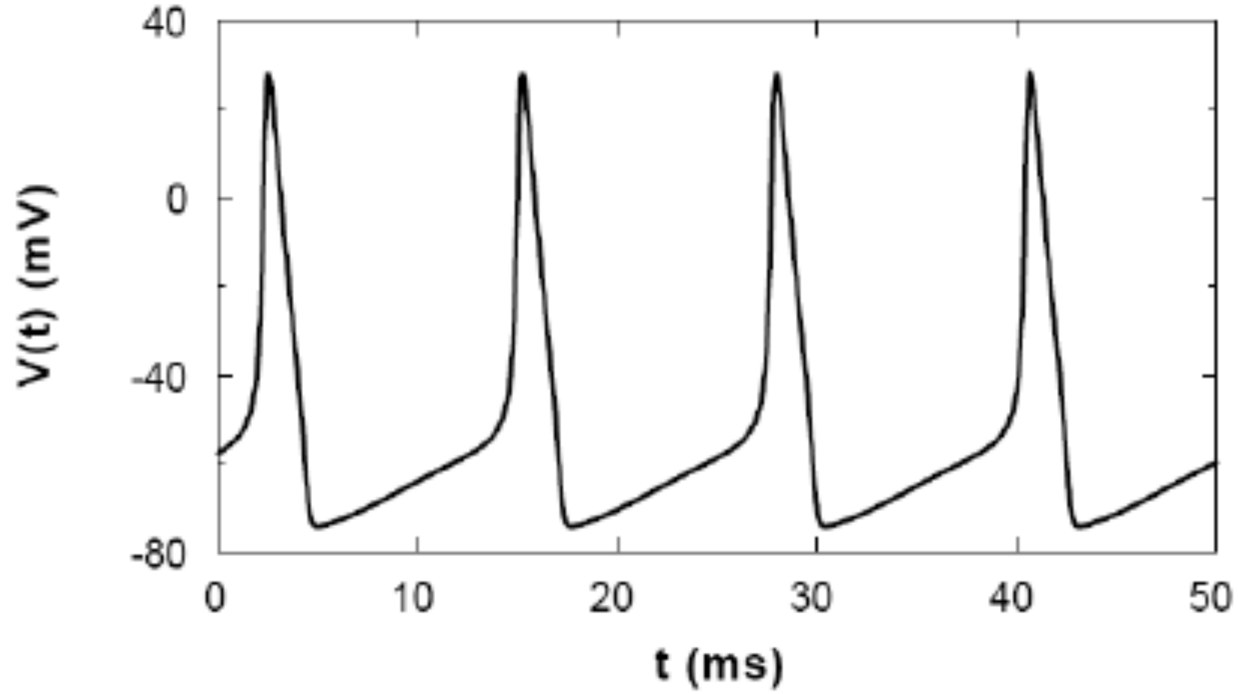
$$C_m \frac{\mathrm{d}V}{\mathrm{d}t} = -\bar{g}_K n^4 (V - V_K) - \bar{g}_{Na} m^3 h (V - V_{Na}) - \bar{g}_L (V - V_L) + I_{\mathrm{app}}$$

$$\frac{\mathrm{d}y}{\mathrm{d}t} = \frac{y_\infty(V) - y}{\tau_y(V)} \qquad y = \{m, n, h\}$$

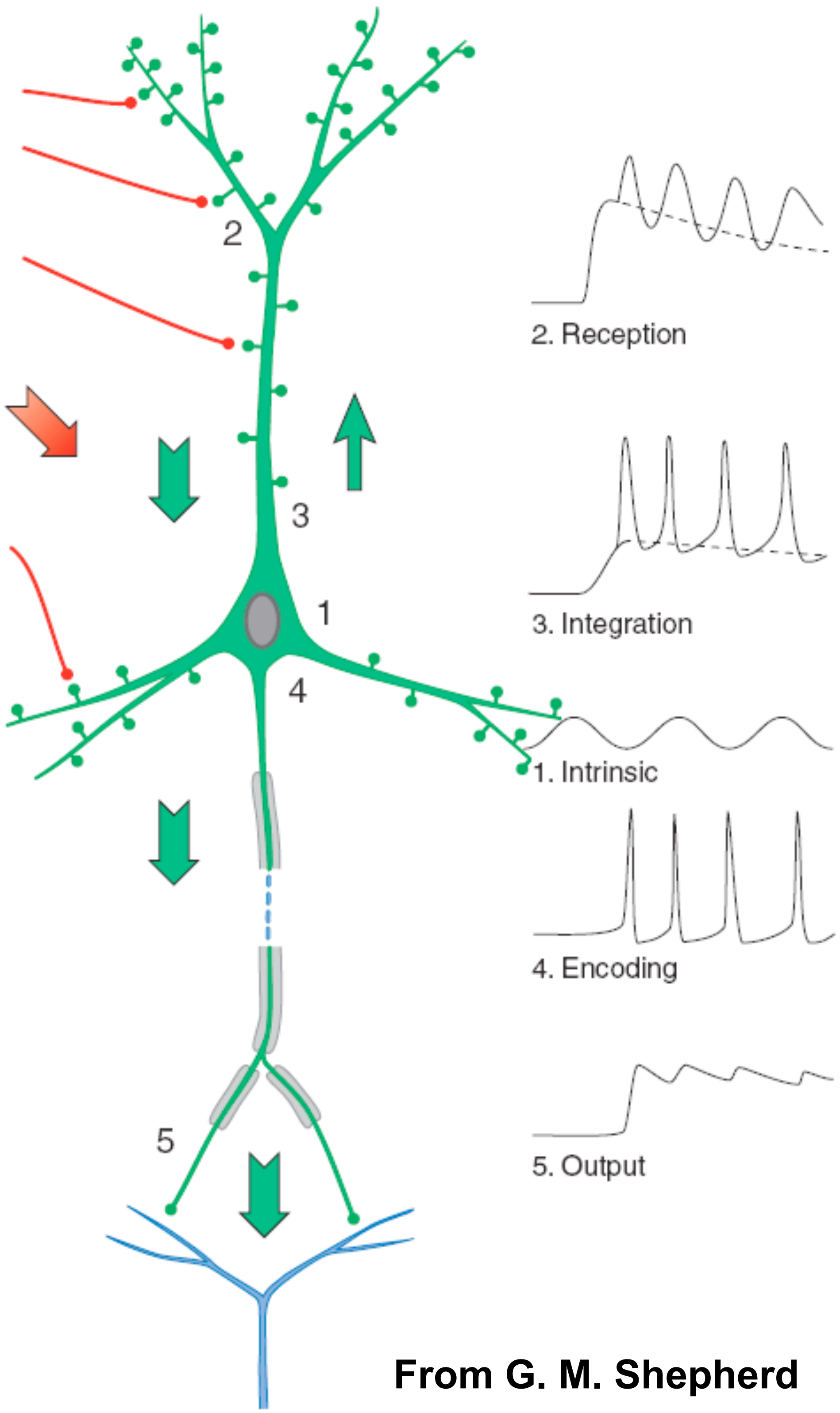
$$\frac{\mathrm{d}f_O}{\mathrm{d}t} = \frac{f_\infty - f_O}{\tau}$$







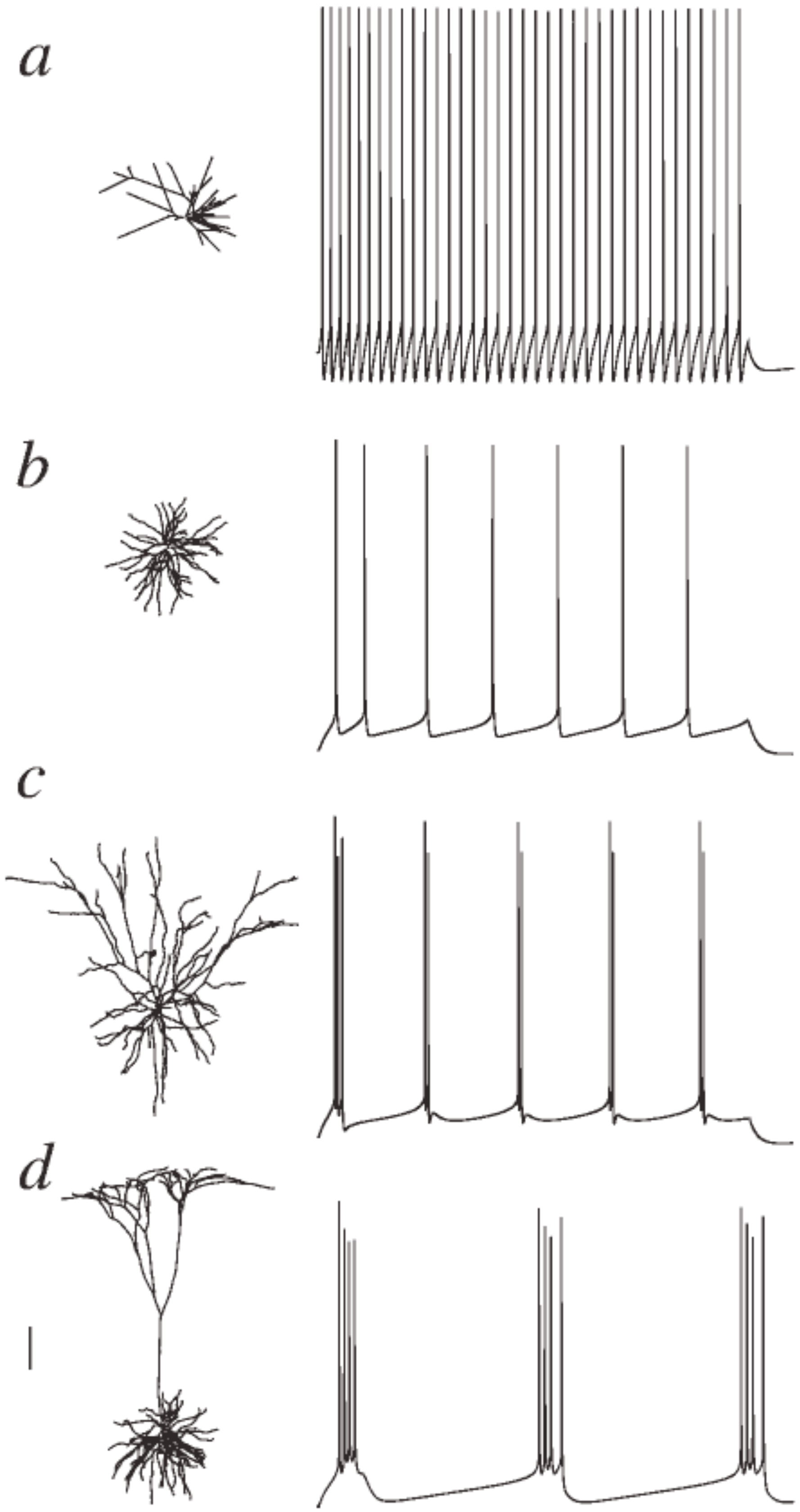
Basic functions of neurons



From G. M. Shepherd

1. Generate intrinsic activity
2. Receive synaptic inputs
3. Integrate signals
4. Encode output patterns
5. Distribute synaptic outputs

Distinct firing patterns



Layer 3 spiny stellate

Layer 4 spiny stellate

Layer 3 pyramidal

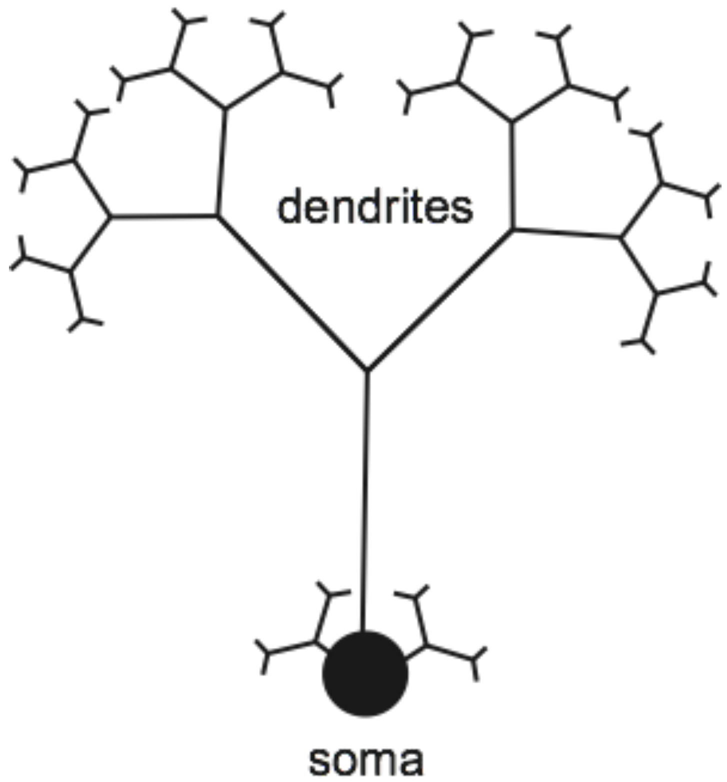
Layer 5 pyramidal

From Mainen and Sejnowski, 1996

Spatially extended models

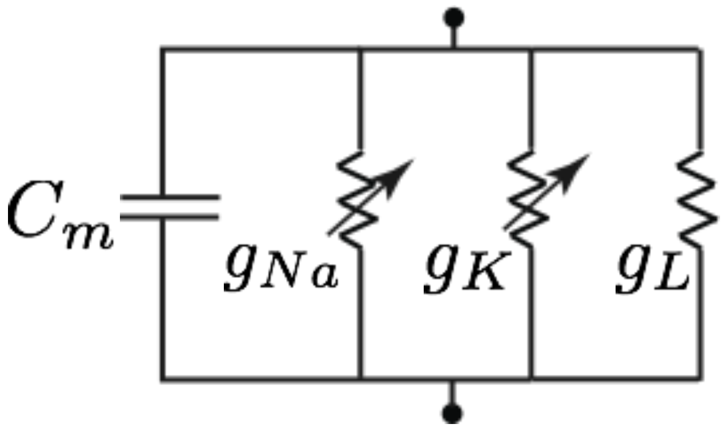
Isopotential soma

Non-isopotential structure

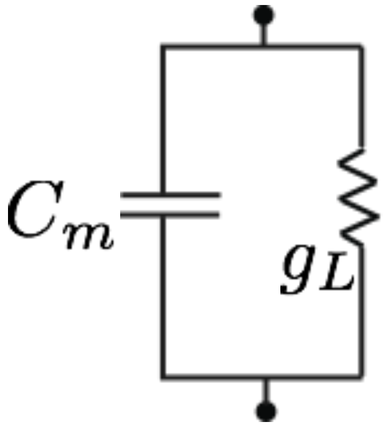


Wilfrid Rall

Active membrane



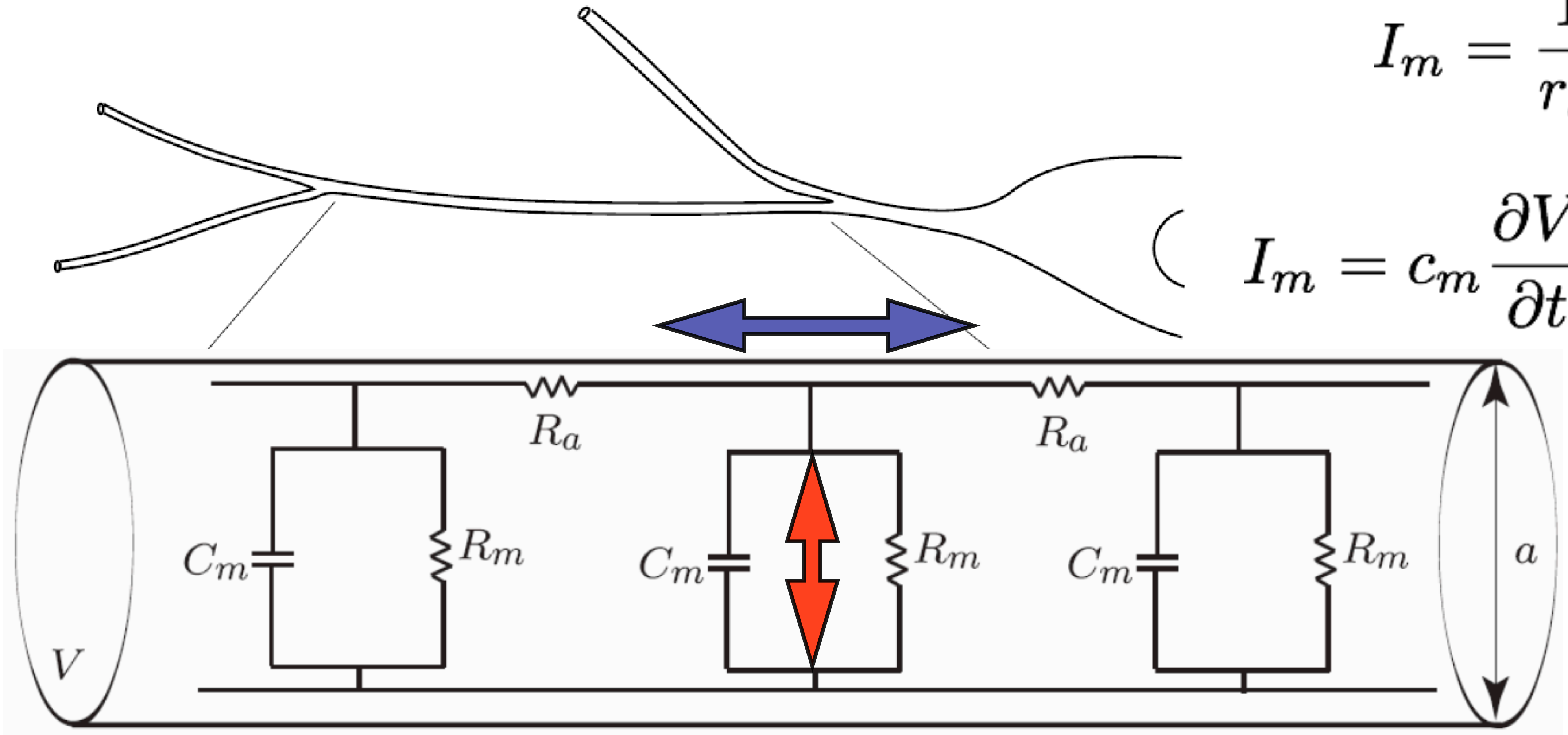
Passive membrane



Linear cable theory

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

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



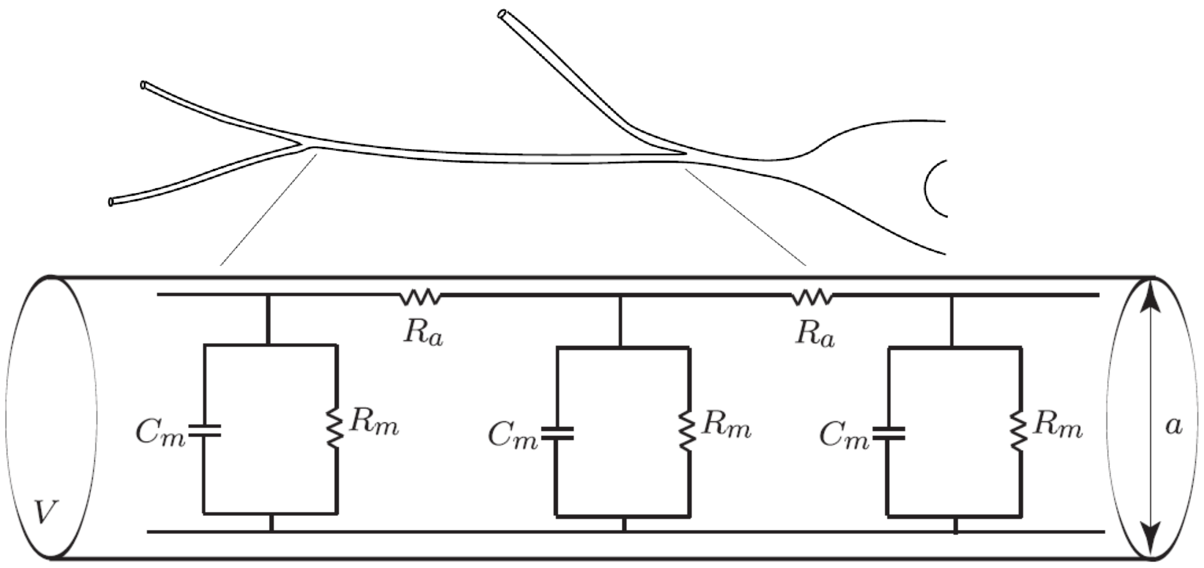
Using current balance

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

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

$$r_m = \frac{R_m}{\pi a}$$

$$c_m = \pi a C_m$$



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

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

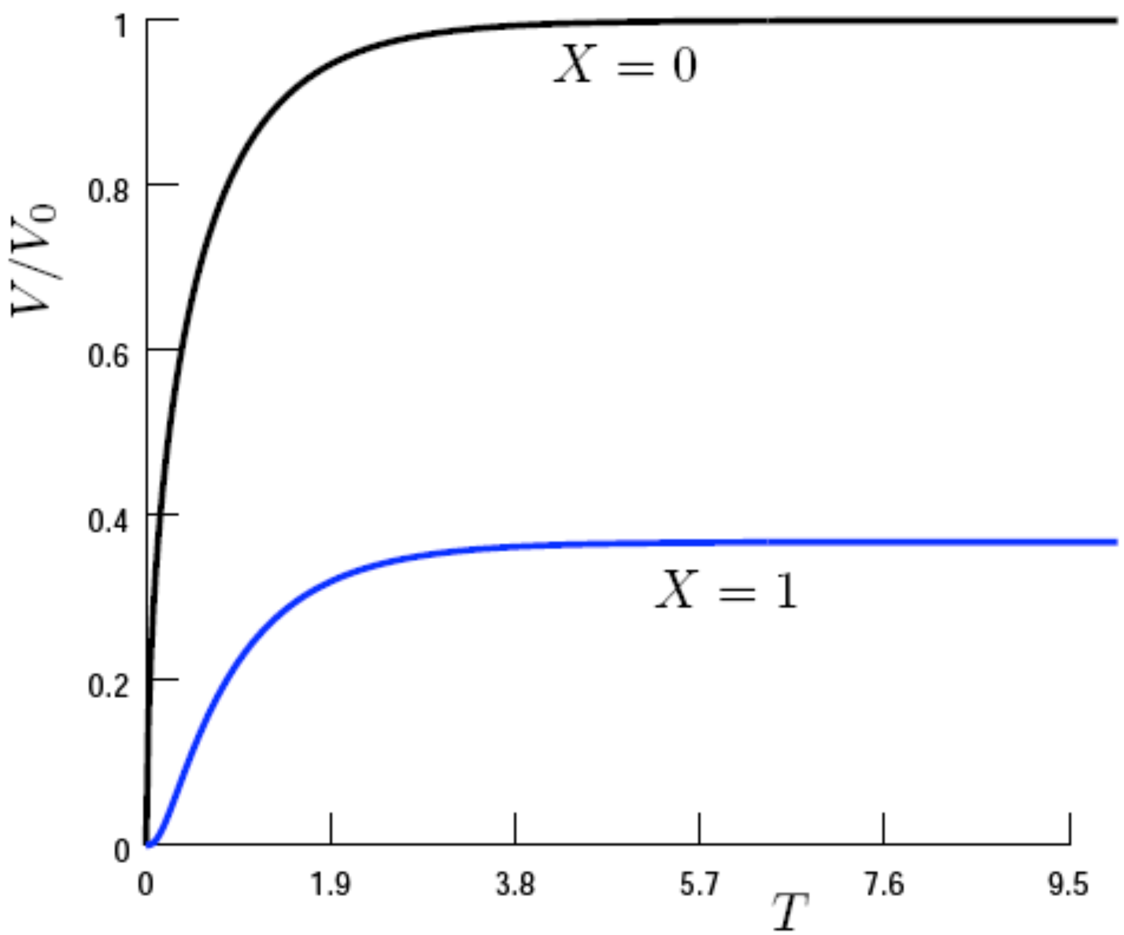
space constant $\lambda = \sqrt{r_m / r_a}$

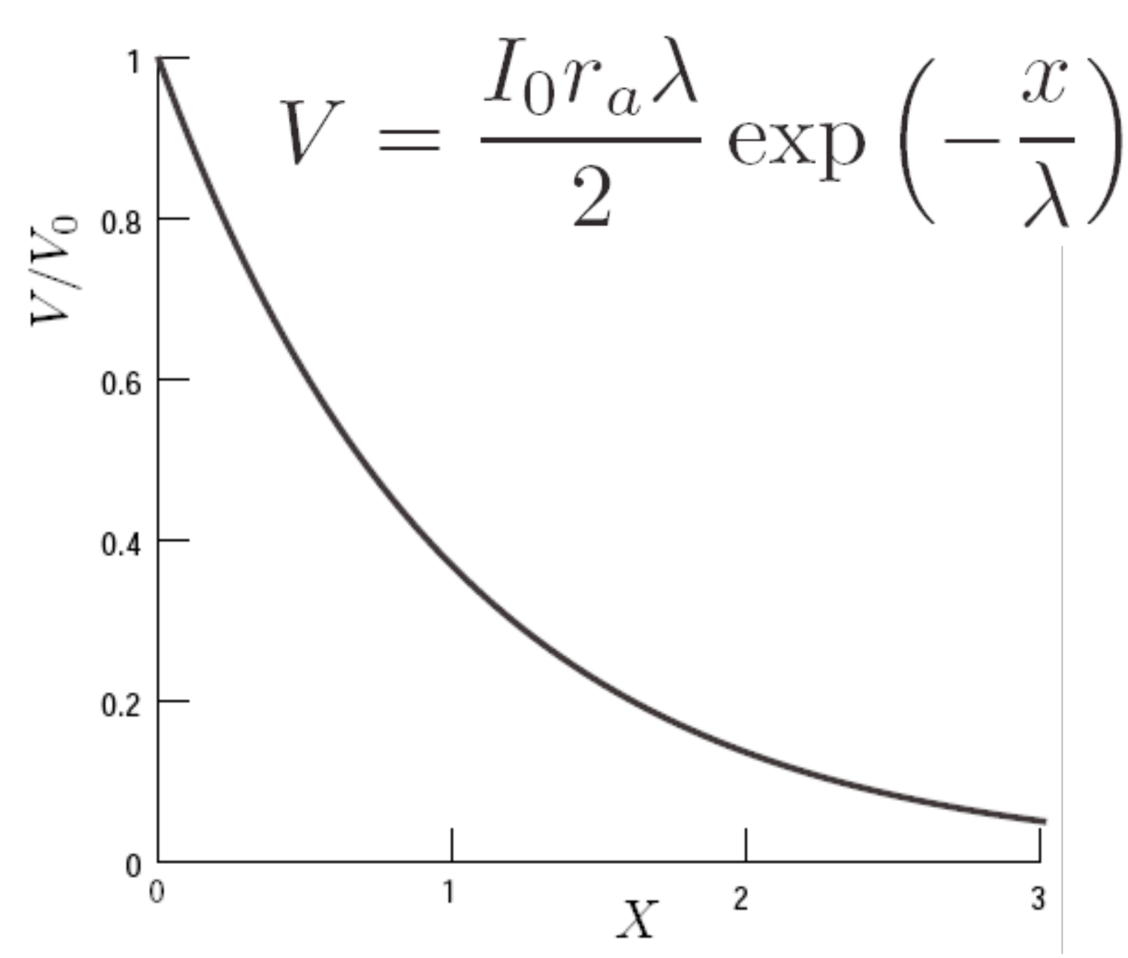
membrane time constant $\tau = r_m c_m$

$$X = x/\lambda$$
$$T = t/\tau$$

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

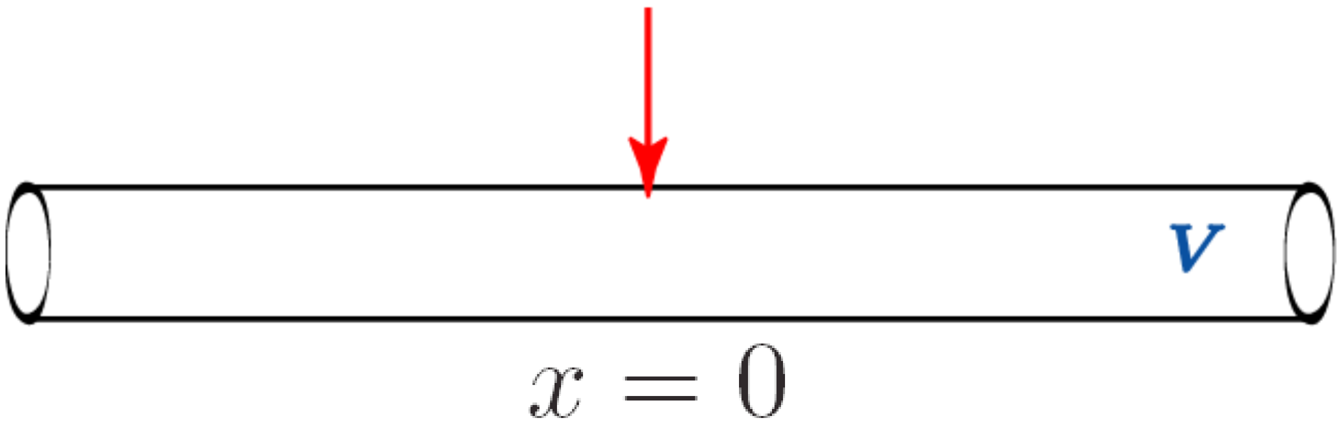
Infinite cable and constant current I_0 at $X = 0$





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

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



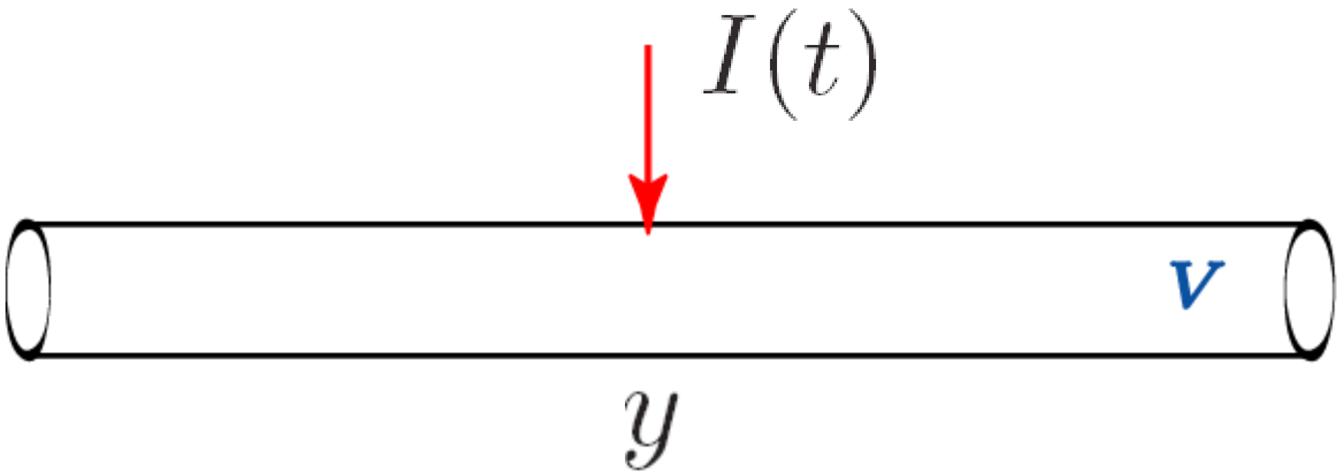
$$\tau \frac{\partial V}{\partial t} = \lambda^2 \frac{\partial^2 V}{\partial x^2} - V$$

Solution – Green's function

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

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

Infinite cable and an arbitrary stimulus



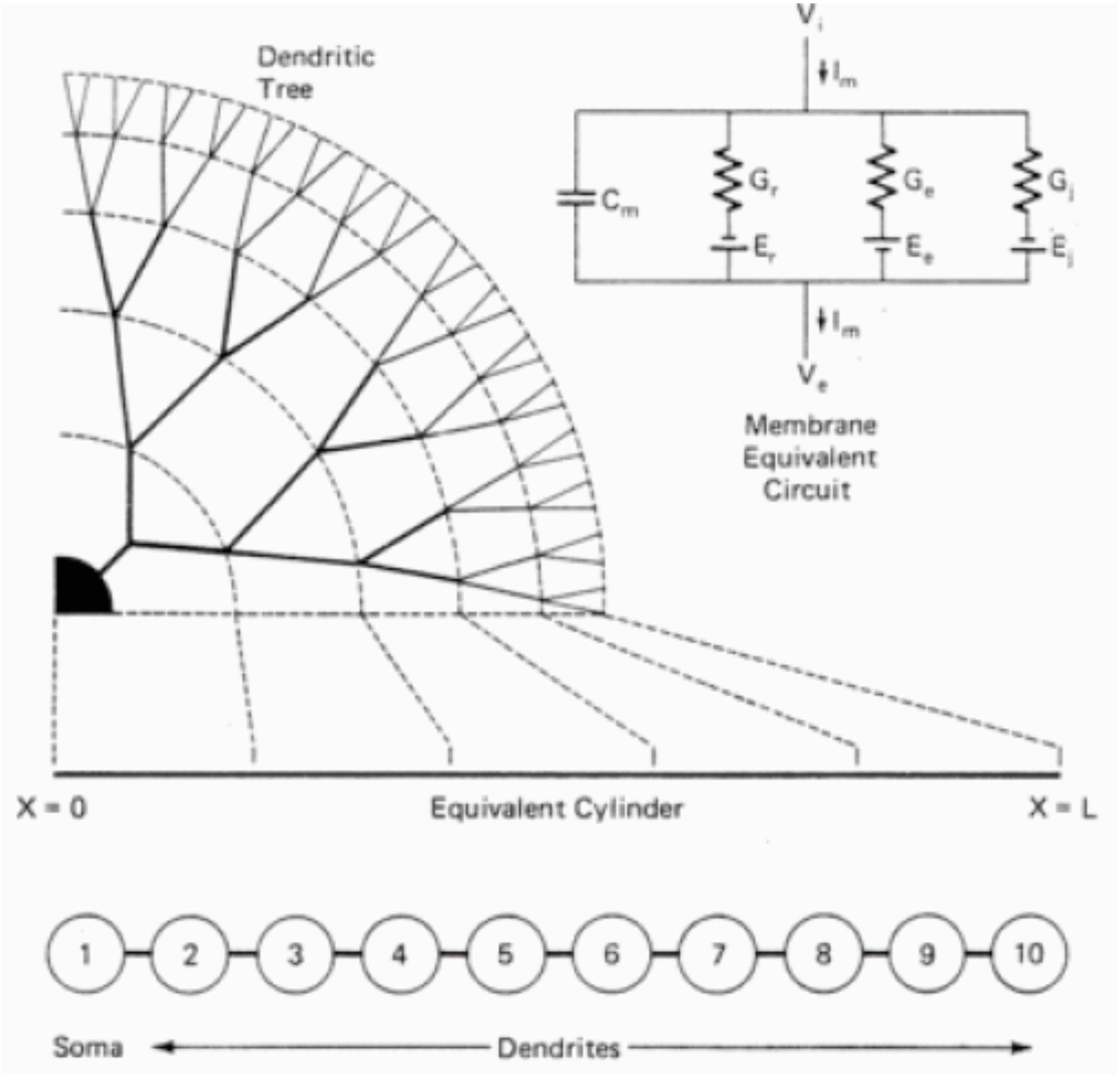
$V(x,t) =$ **convolution of initial data**

$+$

convolution of stimulus

$$V(x,t) = \int_{-\infty}^{\infty} G_{\infty}(x-x',t)V_0(x')\mathrm{d}x' + \int_0^t G_{\infty}(x-y,t-s)I(s)\mathrm{d}s$$

The Rall model

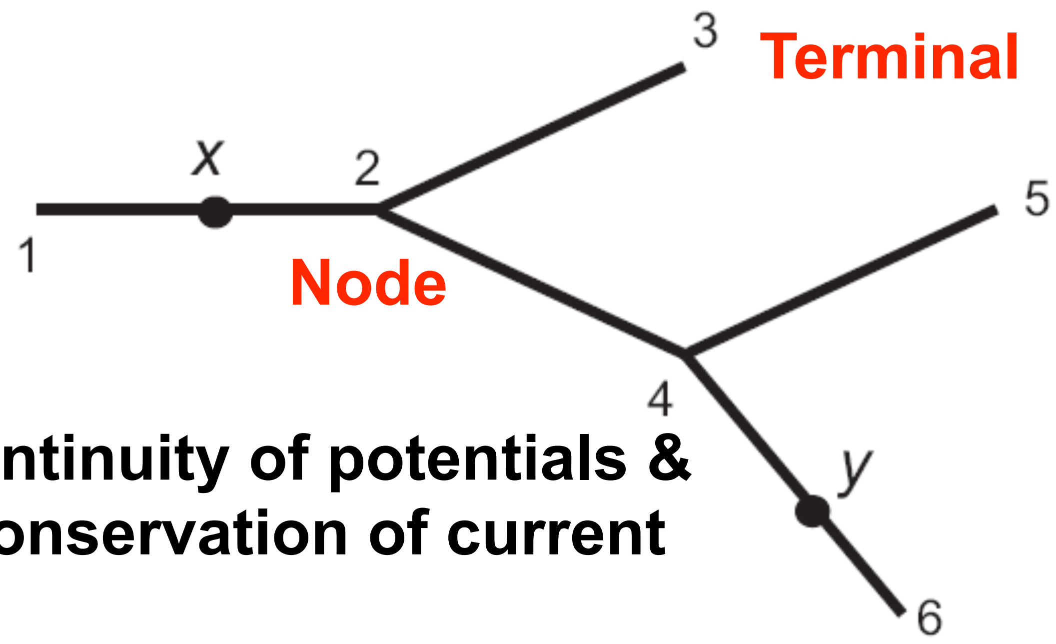


Equivalent cable

3/2 law

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

An arbitrary tree



continuity of potentials &
conservation of current

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

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

Trips

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

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

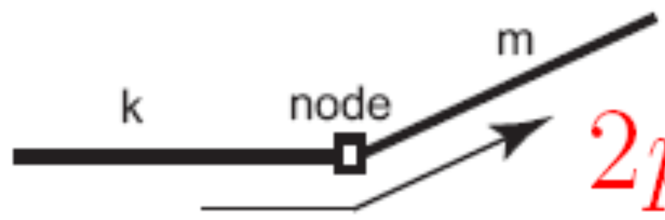
$x \longrightarrow 2 \longrightarrow 4 \longrightarrow 6 \longrightarrow y$

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

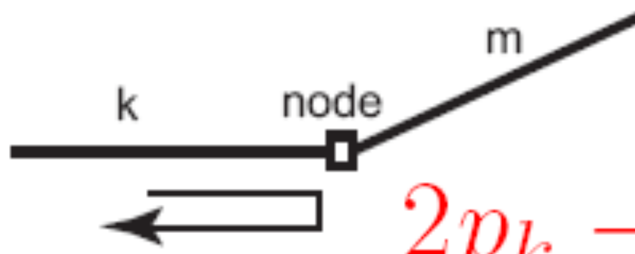
$$G_{ij}(x, y, t) = \sum A_{trip} G_{\infty}(L_{trip}, t)$$

Coefficients A_{trip}

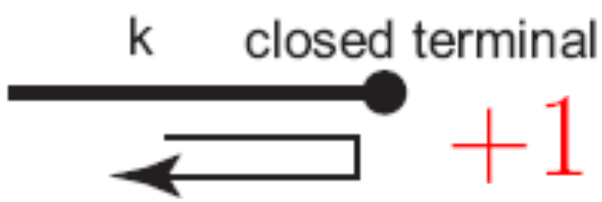
Factor of segment $p_m = \frac{a_m^{3/2}}{\sum_{k\ on\ node} a_k^{3/2}}$



$2p_m$

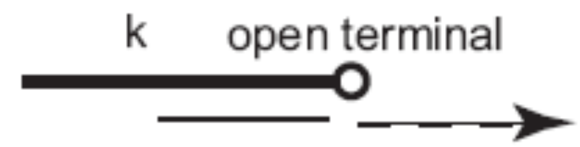


$2p_k - 1$



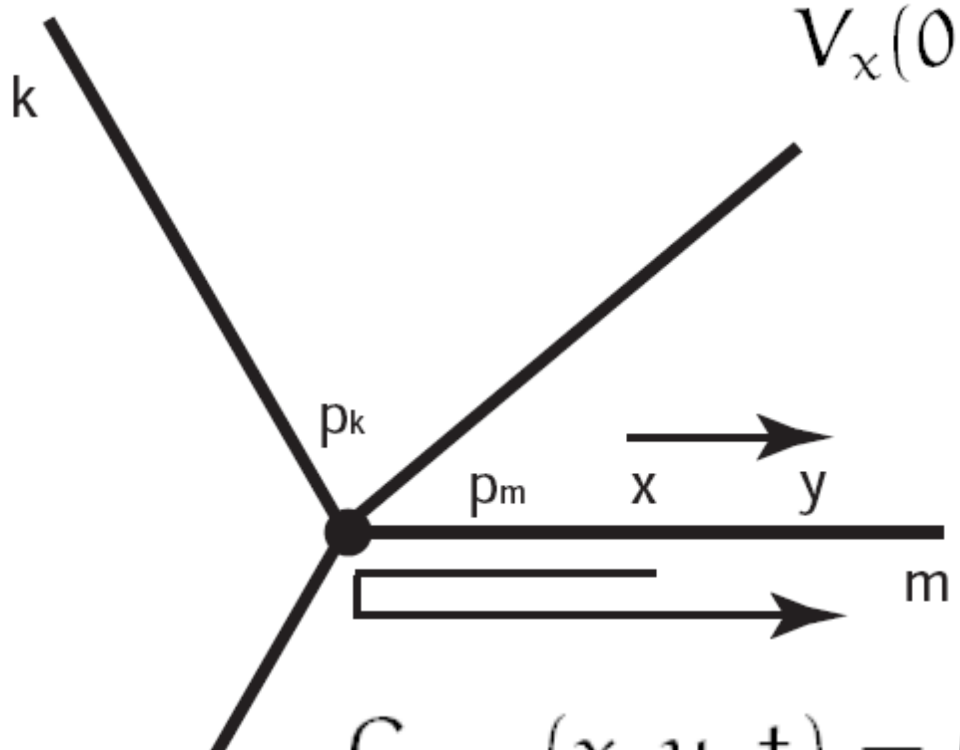
$+1$

$V_x(0, t) = 0$



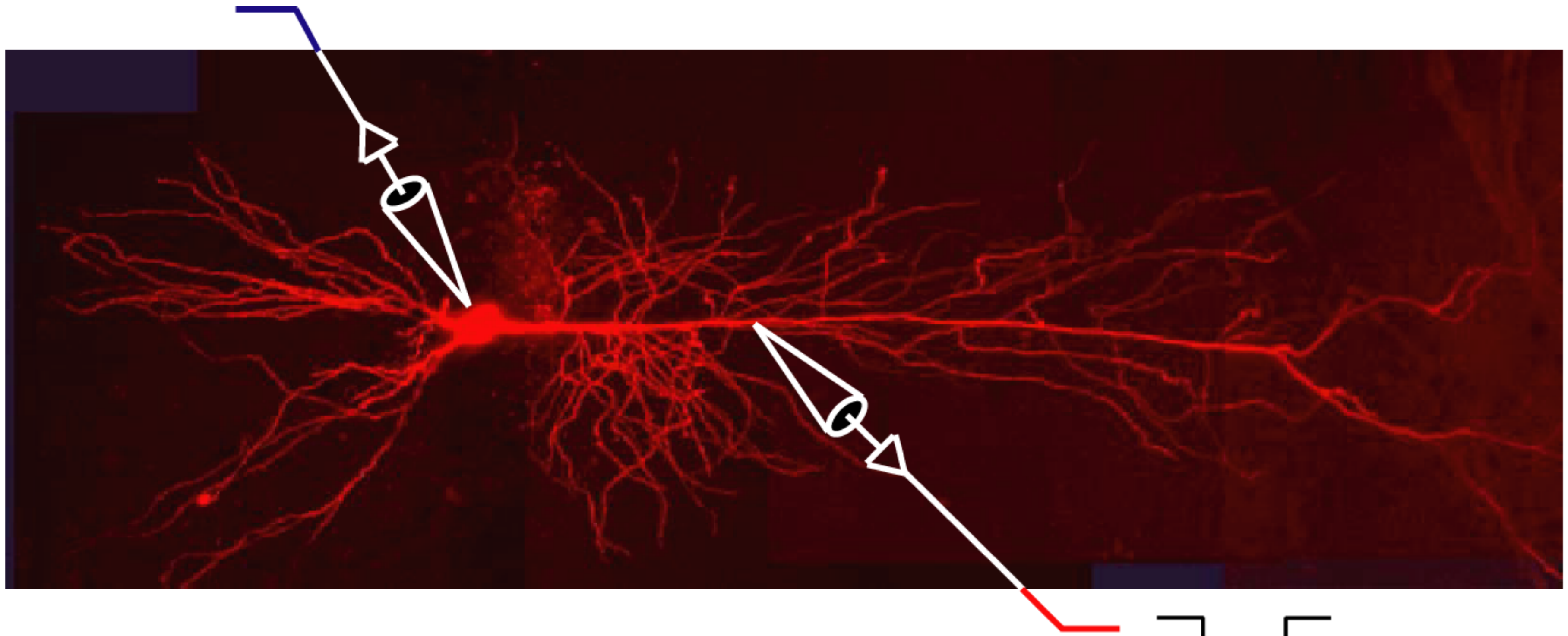
-1

$V(0, t) = 0$



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

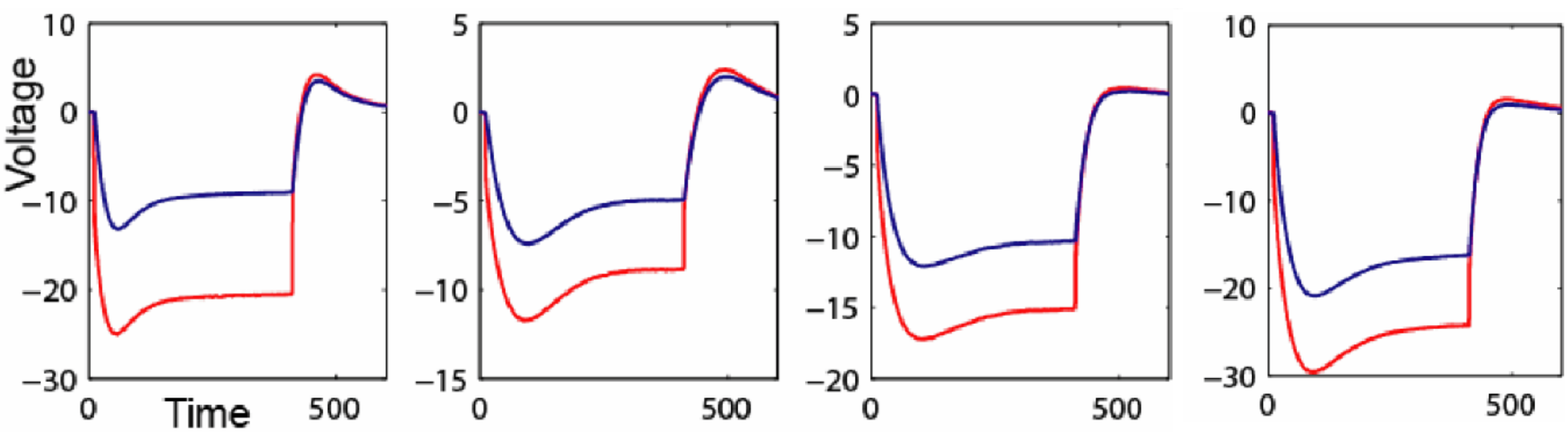
Quasi-active dendrites. Motivation



A rat CA1 hippocampal pyramidal cell visualised with differential interference contrast optics using infrared illumination

Dual simultaneous whole-cell patch-clamp recordings

Dendritic & somatic recordings with respect to rest (at about -70 mV)



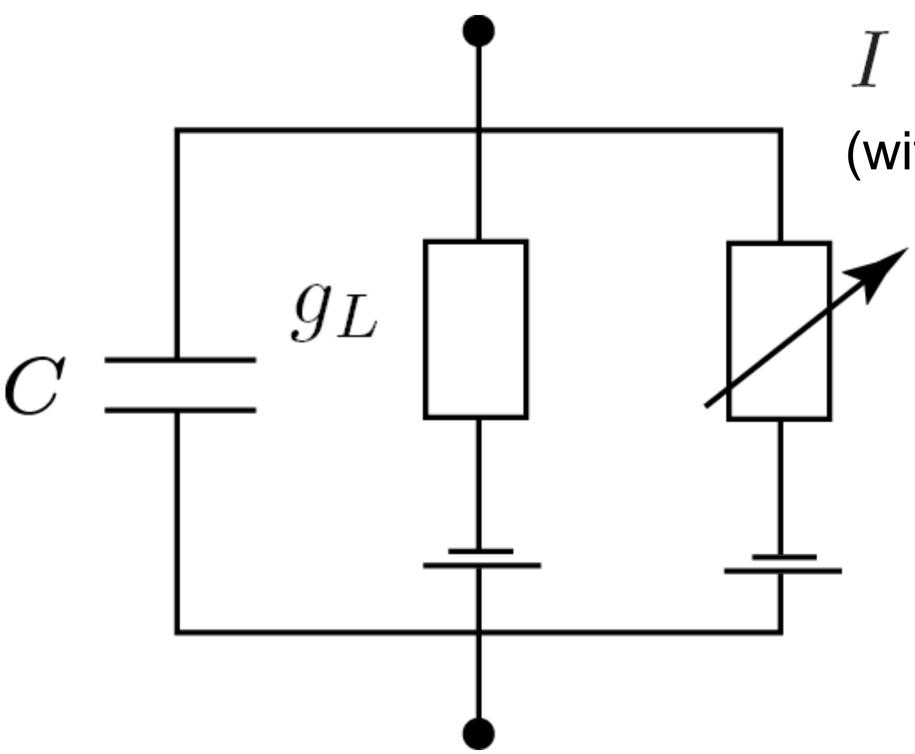
Quasi-active membrane

nonlinear current

$$C\frac{\mathrm{d}V}{\mathrm{d}t} = -g_L(V - V_\mathrm{L}) - I + I_\mathrm{inj}$$

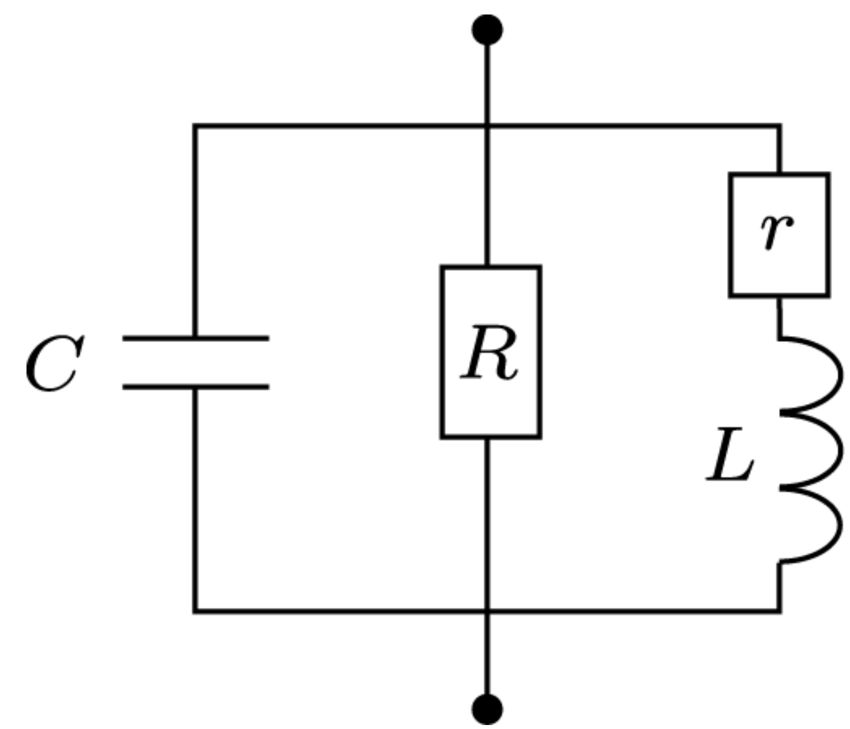
$$C\frac{\mathrm{d}V}{\mathrm{d}t} = -\frac{V}{R} - \sum_{k=1}^{N} I_k + I_\mathrm{inj}$$

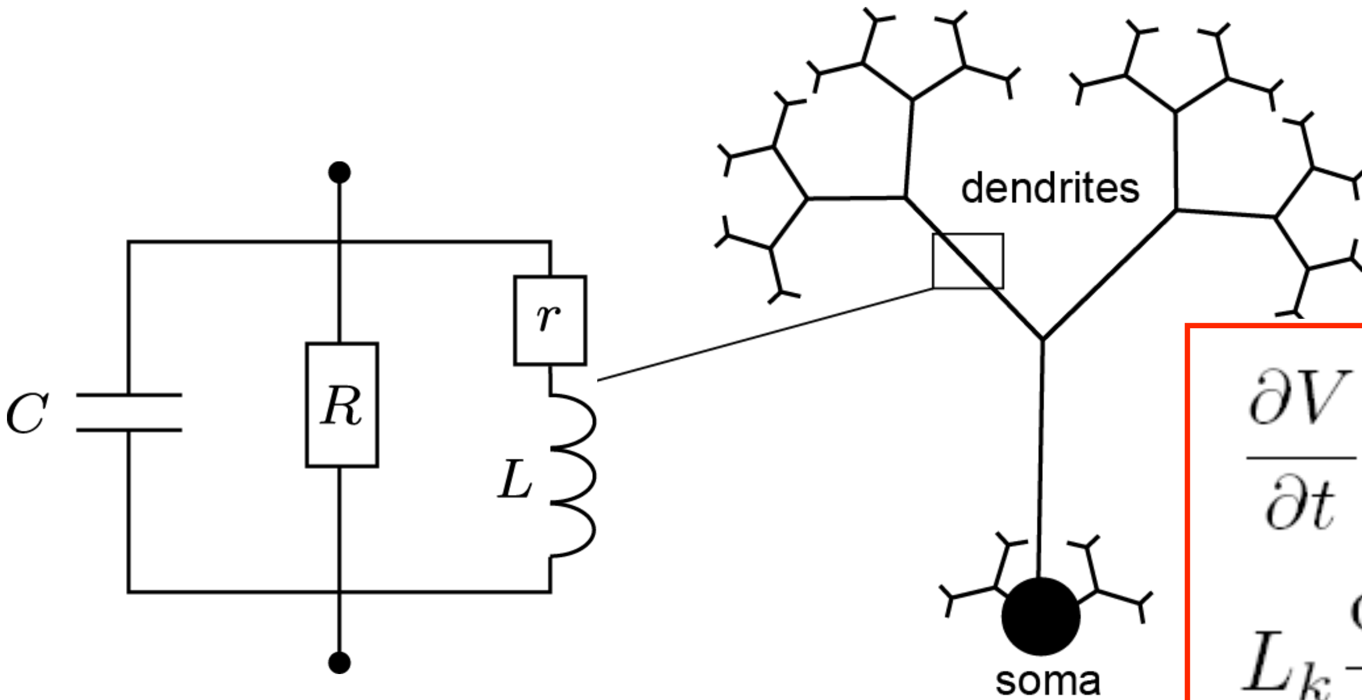
$$L_k\frac{\mathrm{d}I_k}{\mathrm{d}t} = -r_k I_k + V.$$



$$I = I(V, f)$$

(with a single gating variable)





On each branch

$$\frac{\partial V}{\partial t} = -\frac{V}{\tau} + D\frac{\partial^2 V}{\partial X^2} - \frac{1}{C}\left[\sum_k I_k - I_{\mathrm{inj}}\right]$$

$$L_k \frac{\mathrm{d}I_k}{\mathrm{d}t} = -r_k I_k + V$$

Using Laplace transform → **For example, for infinite cable**

$$G_\infty(X,\omega) = \frac{H_\infty(\gamma(\omega)X)}{D\gamma(\omega)} = \frac{\mathrm{e}^{-\gamma(\omega)|X|}}{2D\gamma(\omega)}$$

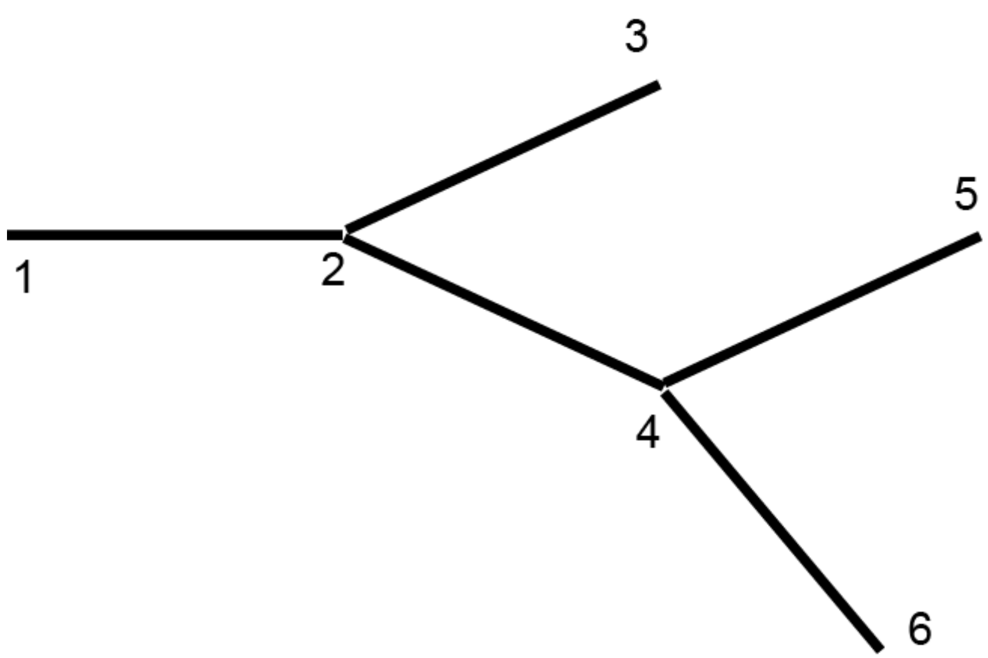
$$\gamma^2(\omega) = \frac{1}{D}\left[\frac{1}{\tau} + \omega + \frac{1}{C}\sum_k \frac{1}{r_k + \omega L_k}\right]$$

Recovers expected result as $r_k \rightarrow \infty$

Passive system

$$\gamma^2(\omega) = (1/\tau + \omega)/D$$

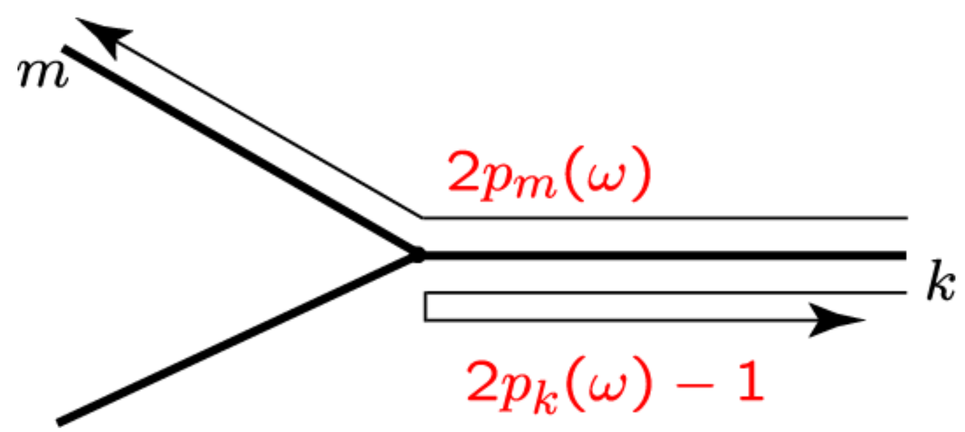
Sum-over-trips (quasi-active membrane)

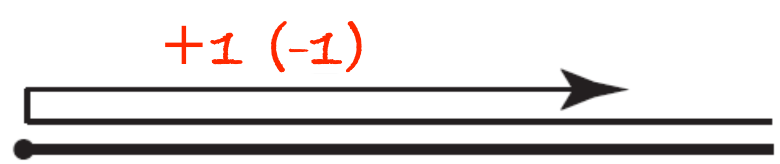


Seek a solution in terms of H_∞

$$H_{ij}(x,y,\omega) = \sum_{\text{trips}} A_{\text{trip}}(\omega) H_\infty(\mathcal{L}_{\text{trip}})$$

$$\mathcal{L}_{\text{trip}} = \mathcal{L}_{\text{trip}}(i,j,x,y,\omega)$$





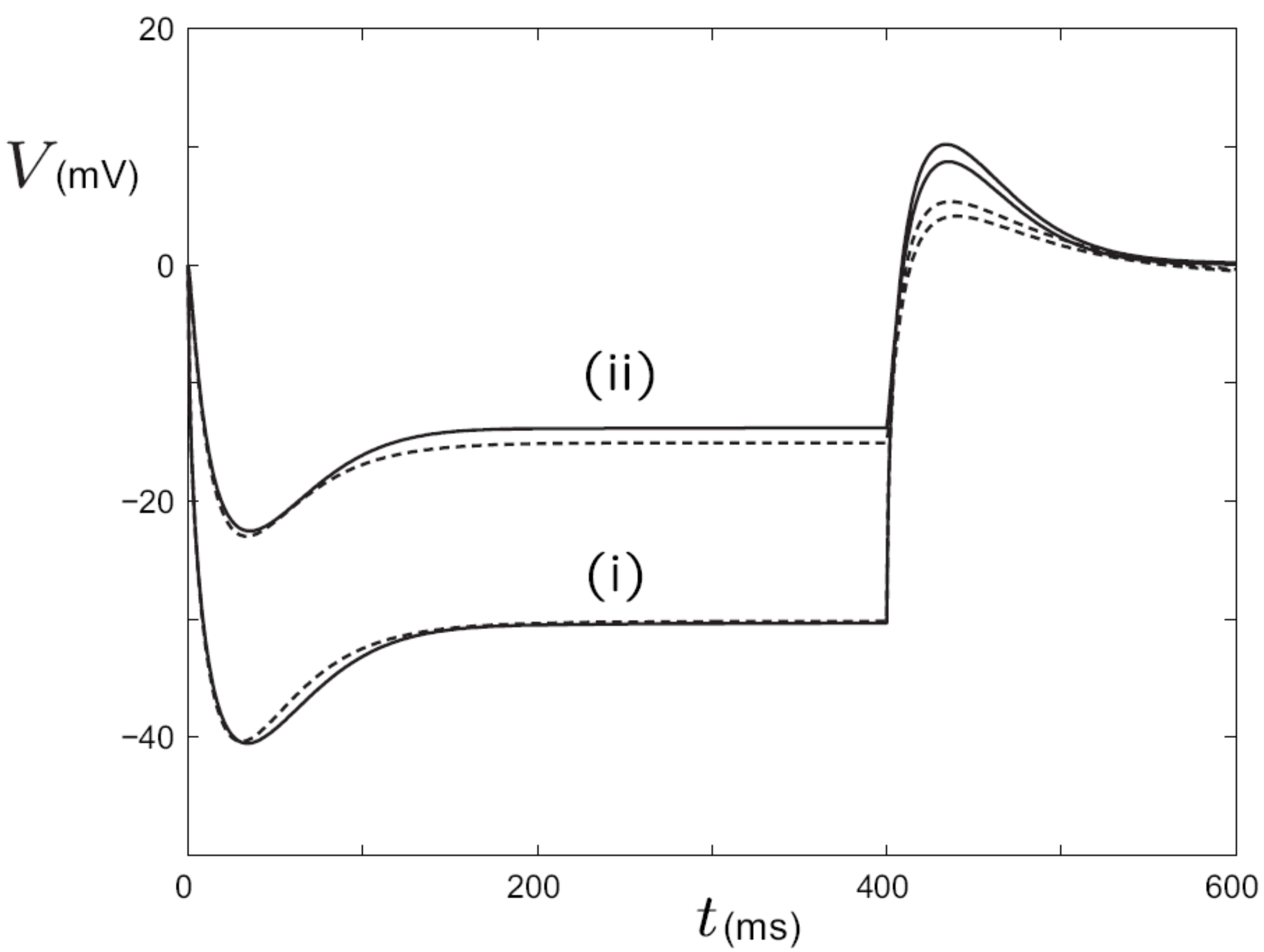
$$G_{ij}(X,Y,\omega) = H_{ij}(\gamma_i(\omega)X, \gamma_j(\omega)Y, \omega)/(D_j\gamma_j(\omega))$$

Application

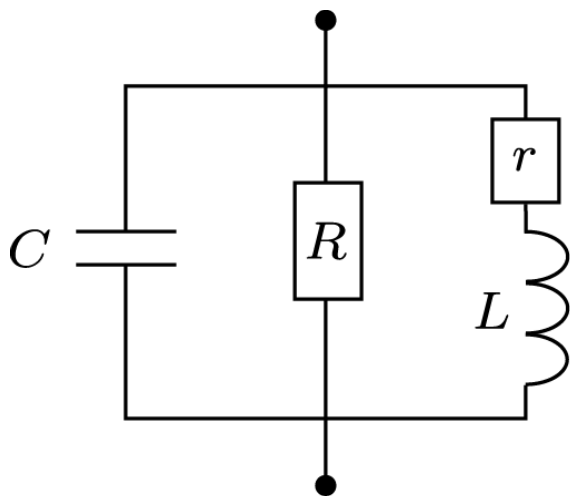
Resonance associated with I_h current

Model of nonlinear I_h current (Magee (1998) Journal of Neuroscience 18)

$I_h = g_h(V - V_h)f$ $f(V)$ **- a single gating variable**



Dashed line: Magee's current
Solid line: 'LRC' circuit



Natural frequency $\omega^* = \dfrac{\sqrt{CL} - Cr}{CL}$

$$G_\infty(X, \omega^*) = \max$$

Idealised geometry

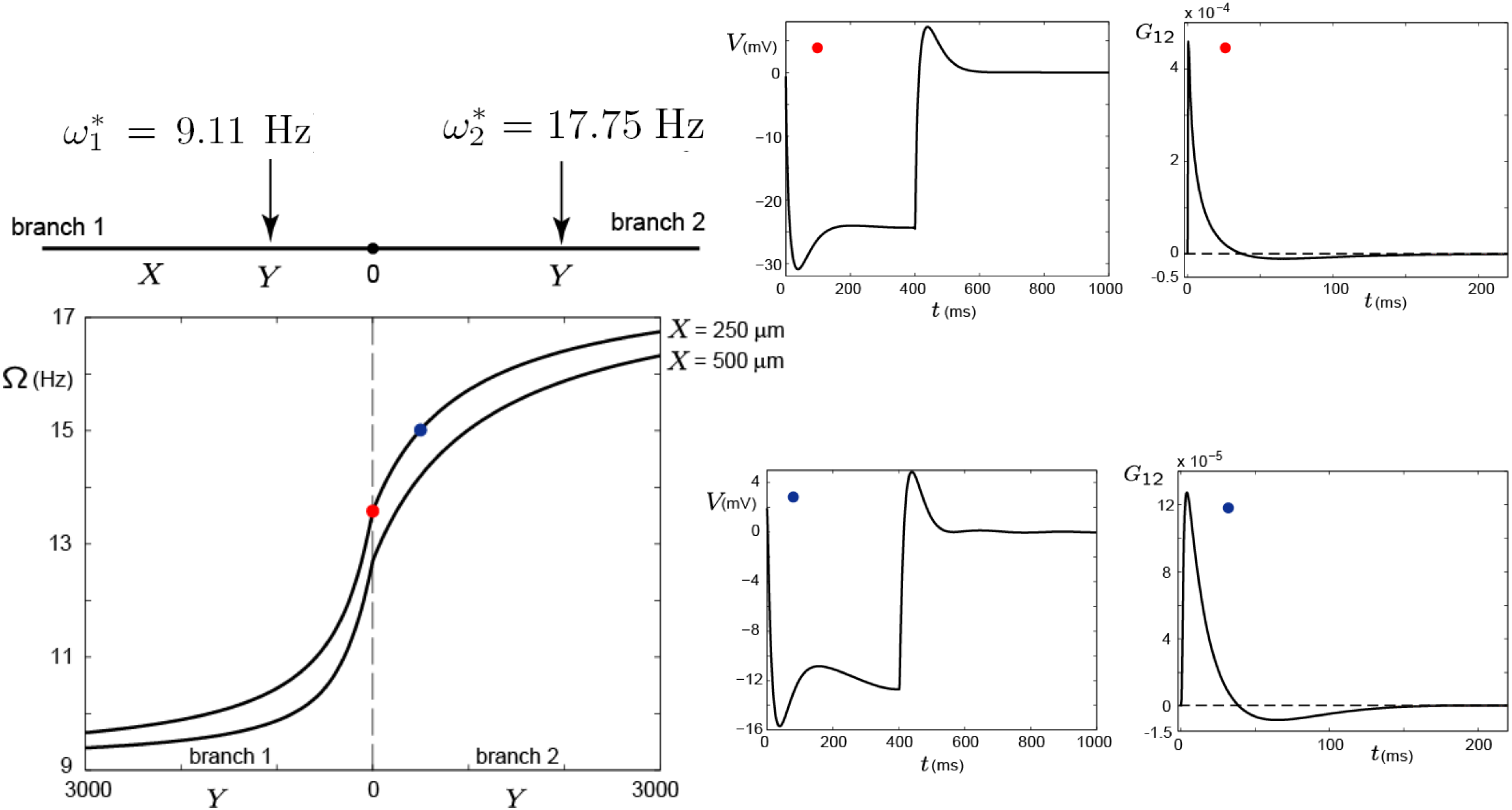
Two semi-infinite branches

$G_{11}(X, Y, \omega)$ $G_{12}(X, Y, \omega)$

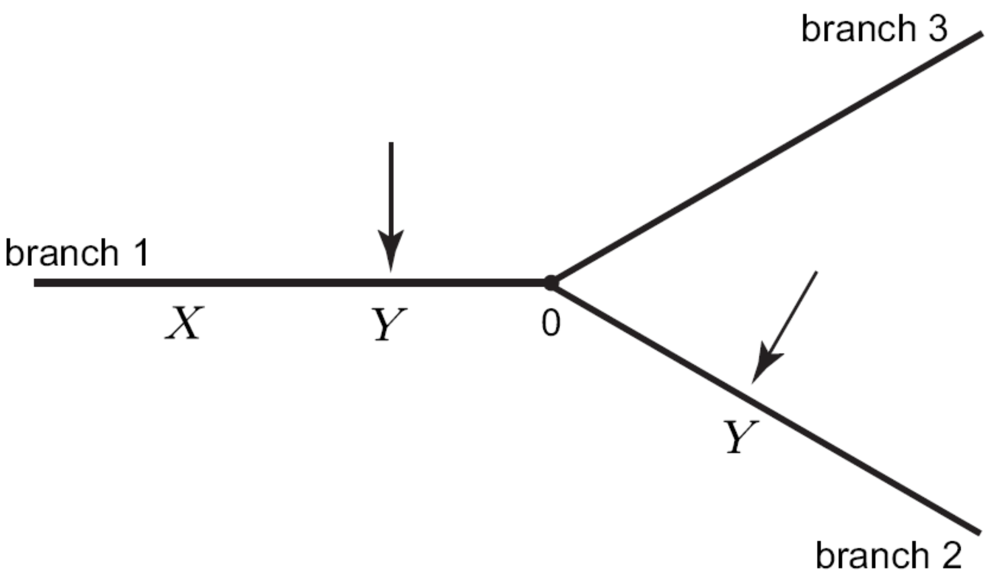
Resonant frequency Ω

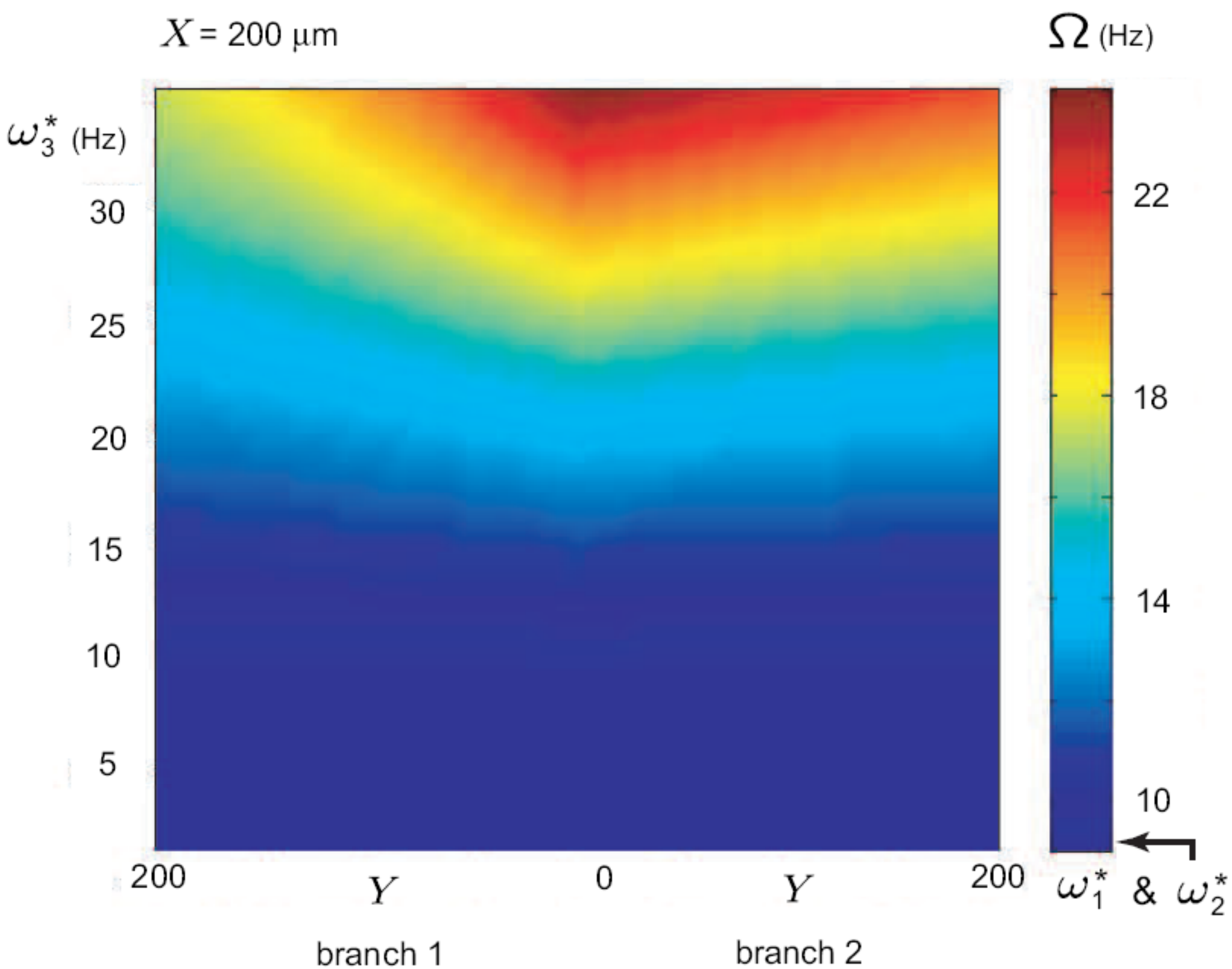
$$\partial G_{ij}(X, Y, \omega)/\partial\omega = 0$$

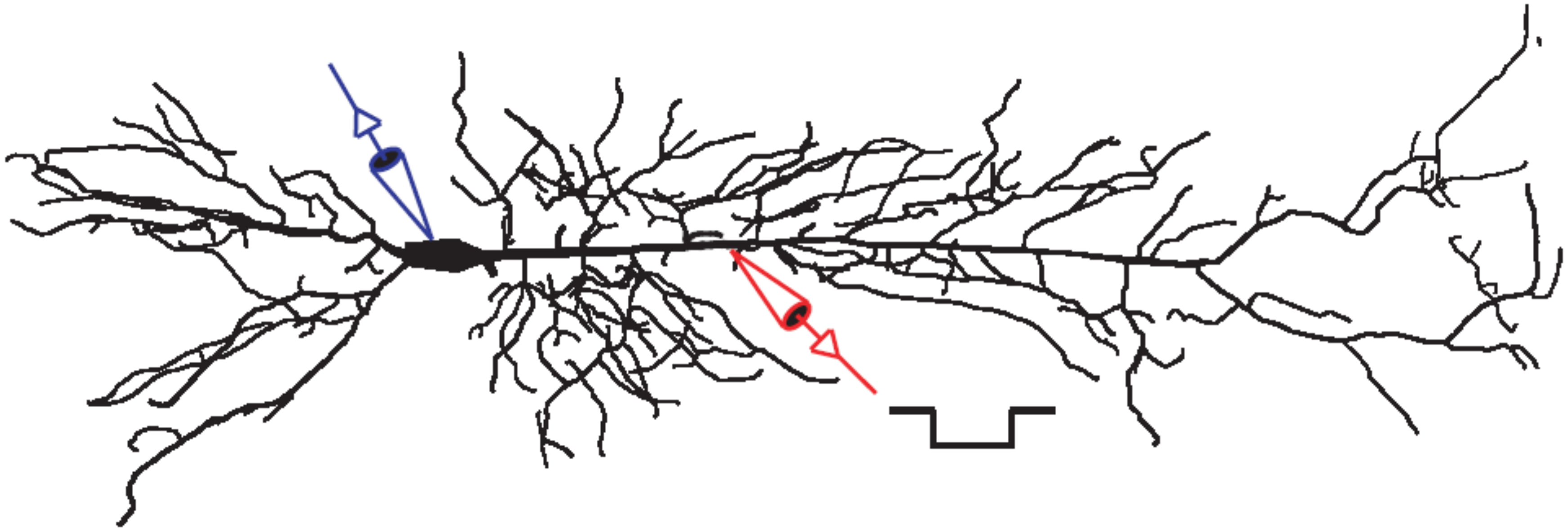
Two semi-infinite resonant branches

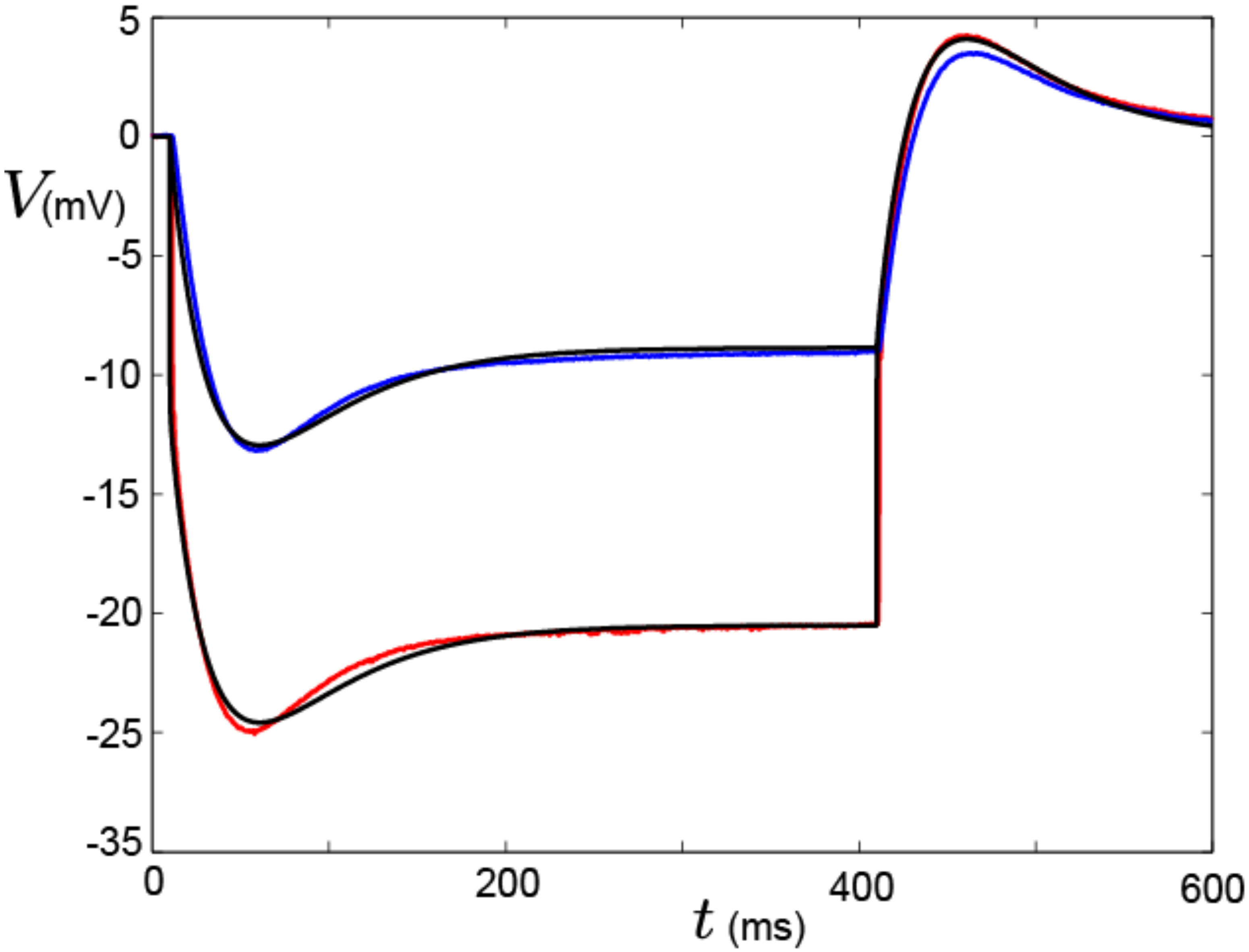


Three semi-infinite resonant branches



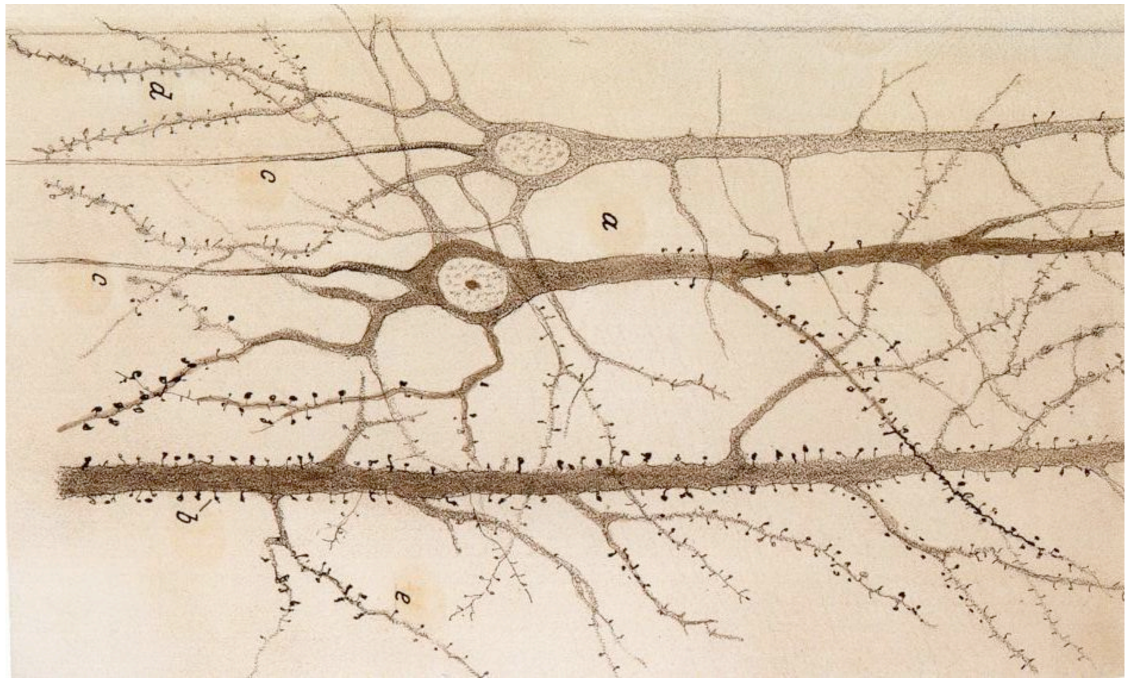




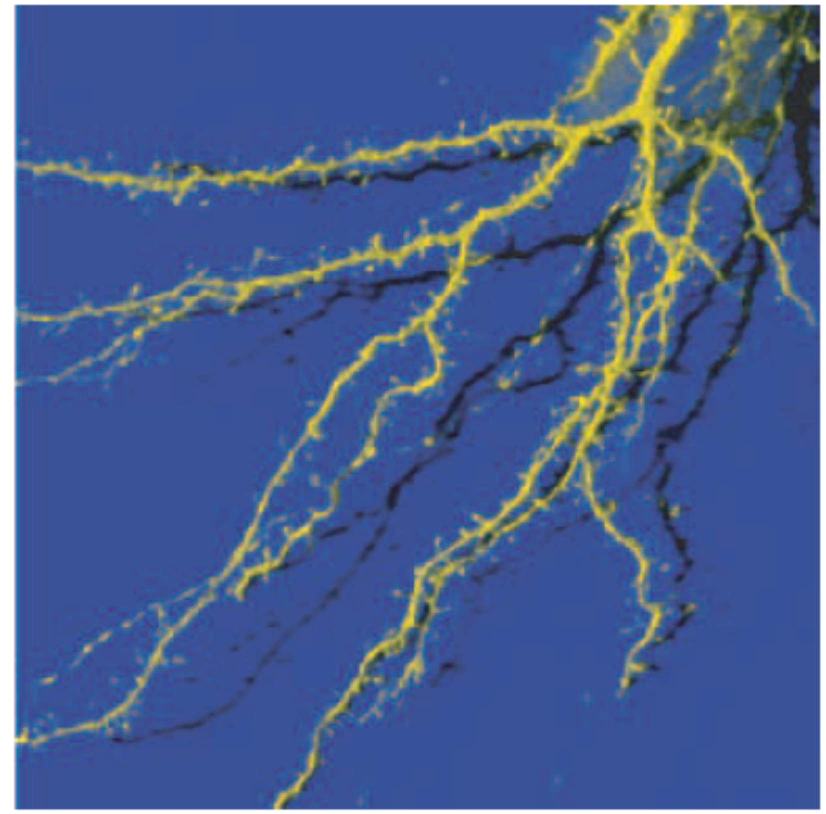


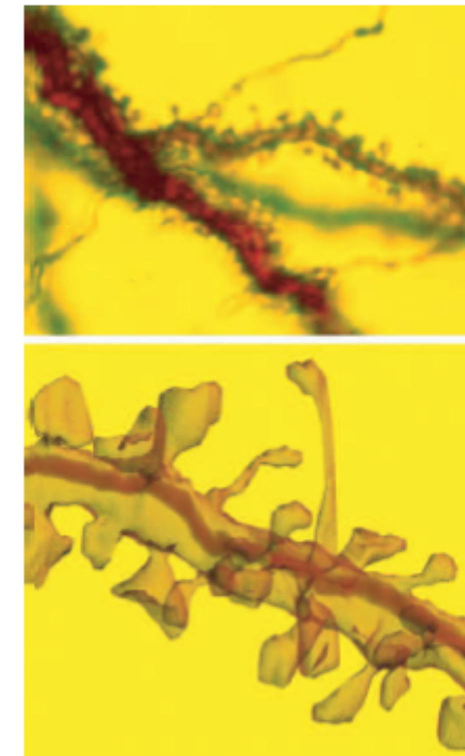
S Coombes, YT, C-M Svensson, G J Lord, K Josic, S J Cox and C M Colbert
Biological Cybernetics (2007) Vol 97, pp. 137-149

Spiny dendrites



Ramon y Cajal, 1896





Andreas Herzog http://iesk.et.uni-magdeburg.de/~herzog/

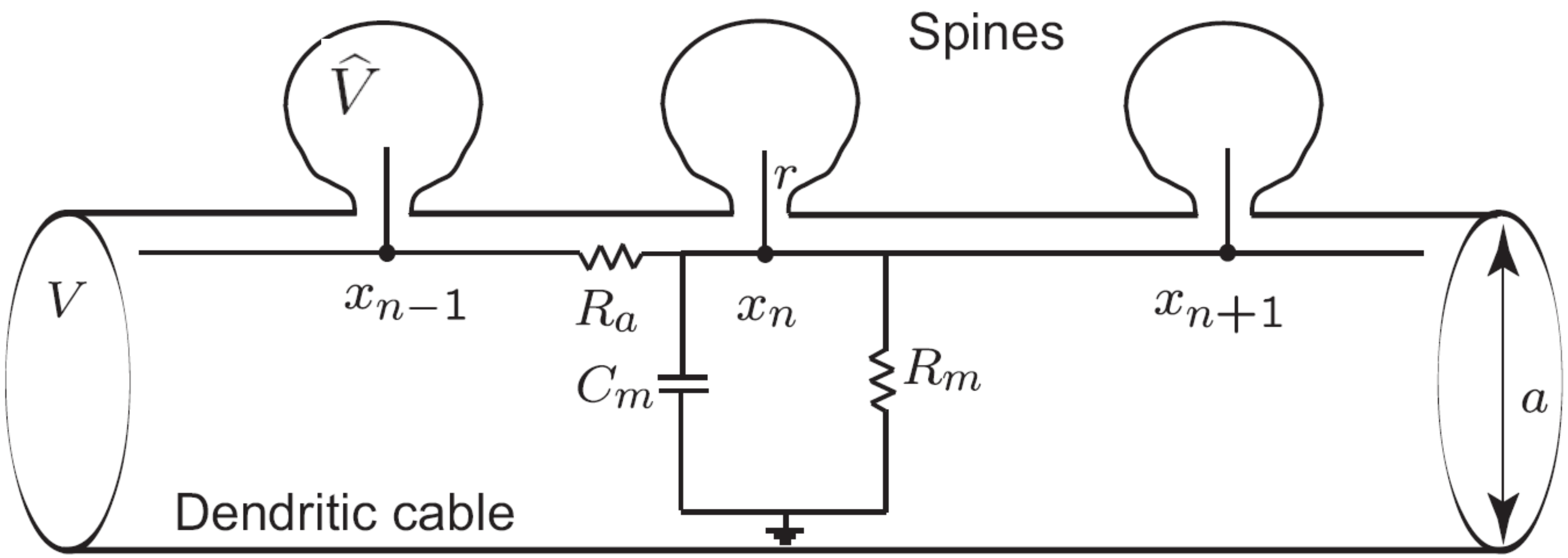
Learning and memory, logical computations, pattern matching, amplification of distal synaptic inputs, temporal filtering

Action potentials in spine apparatus seen using Calcium dyes + confocal microscopy

Experimental observations of travelling waves in distal dendritic trees

For a perspective see Segev & Rall 'Excitable dendrites and spines: earlier theoretical insights elucidate recent direct observations '*Trends in Neuroscience* 21(11), 1998

Baer&Rinzel model



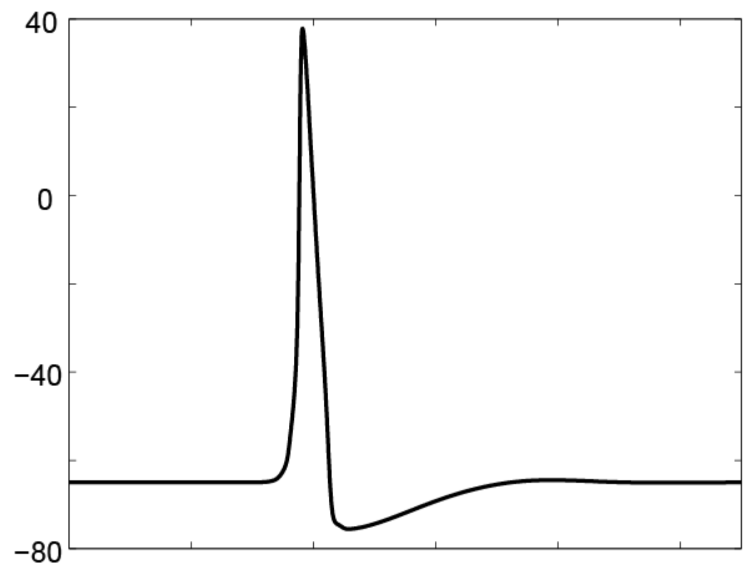
Cable eqn. + currents from spines

$$\frac{\partial V}{\partial t} = D\frac{\partial^2 V}{\partial x^2} - \frac{V}{\tau} + \rho(x) I_{\text{sp}}$$

$$I_{\text{sp}} = \frac{\hat{V} - V}{r}$$

HH dynamics at spines

$$\hat{C}\frac{\mathrm{d}\hat{V}}{\mathrm{d}t} = -I(\hat{V}, m, n, h) - \frac{\hat{V} - V}{r}$$

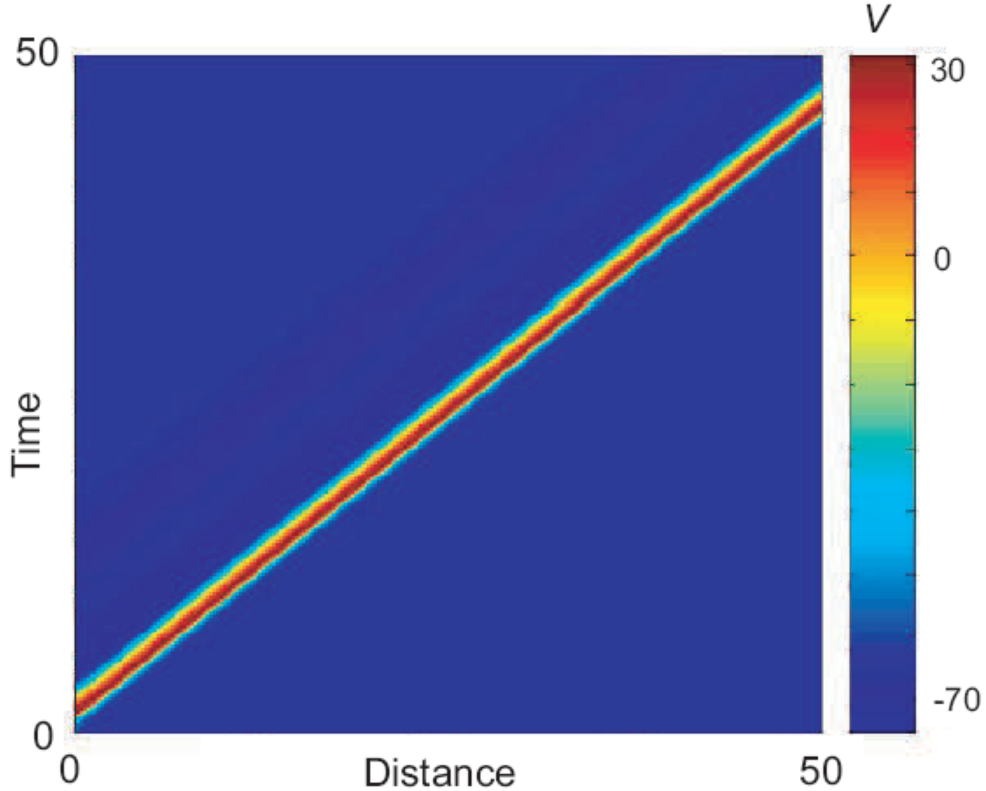


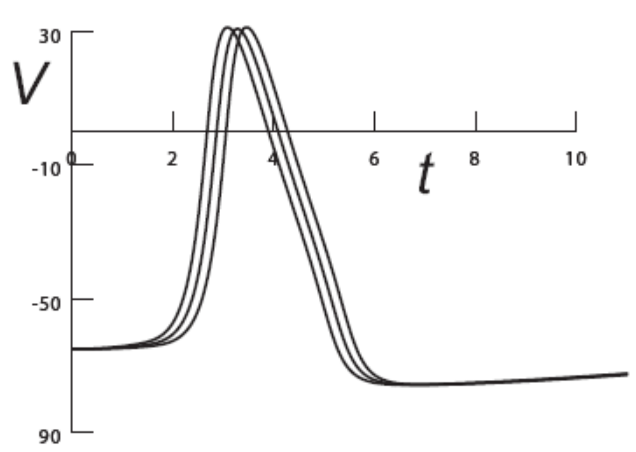
Baer & Rinzel *J.Neurophysiol.*,1991

Variations in spine distribution

Continuum model

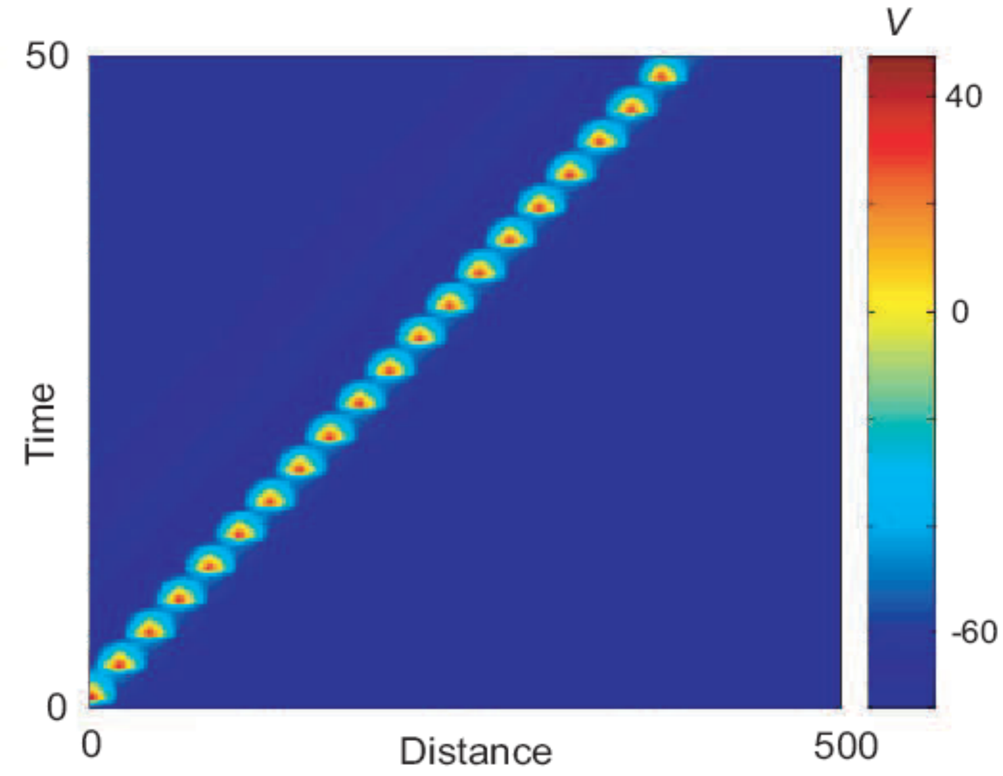
$$\rho(x) = \text{const}$$



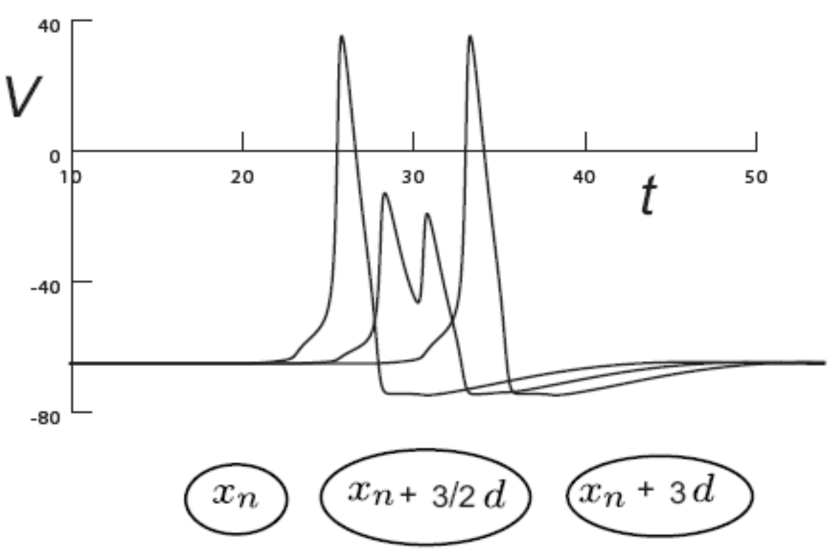


Discrete model

$$\rho(x) = \sum_n \delta(x - x_n)$$

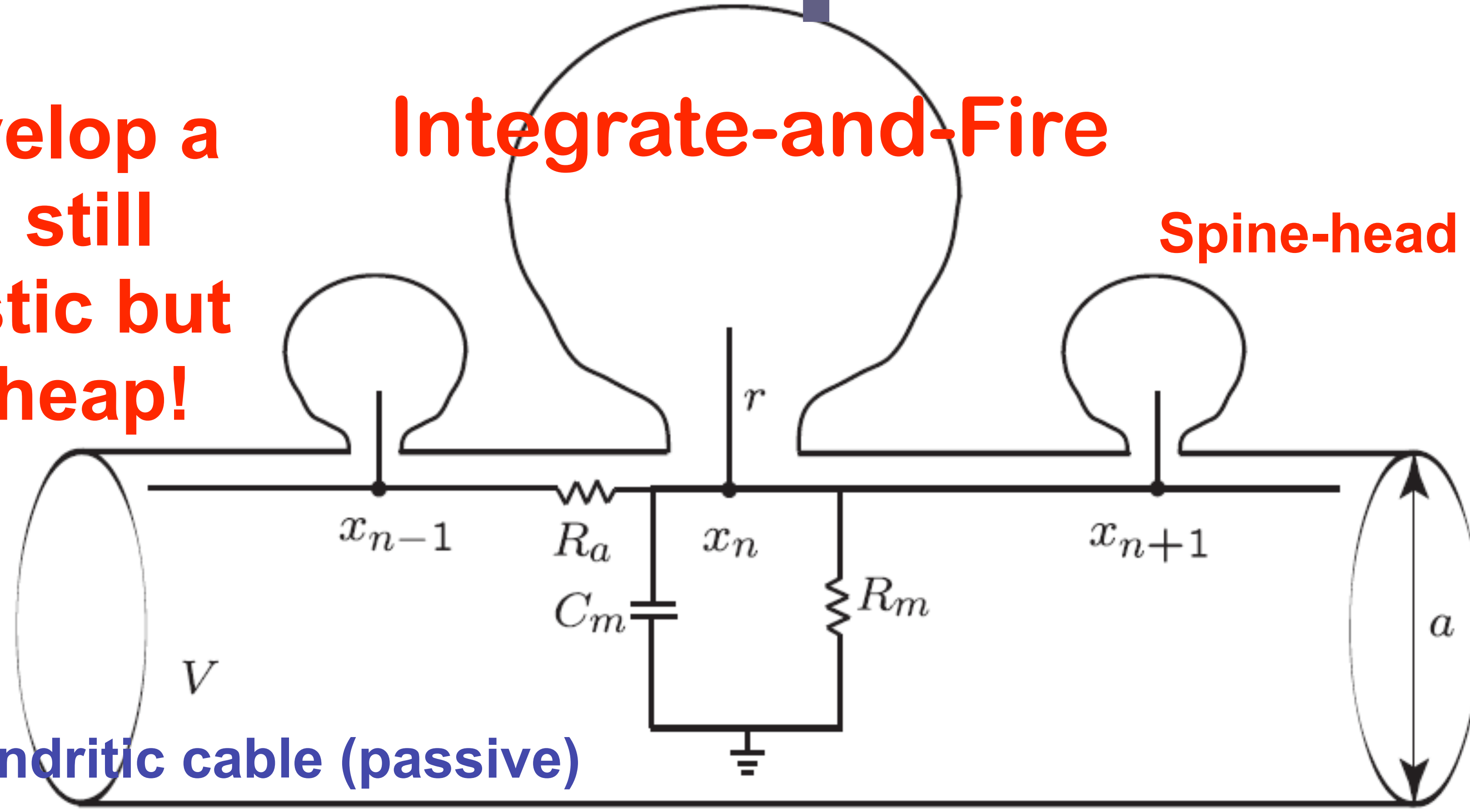


$x_n = nd$



The Spike-Diffuse-Spike model

Motivation – to develop a simplified model, still biophysically realistic but computationally cheap!

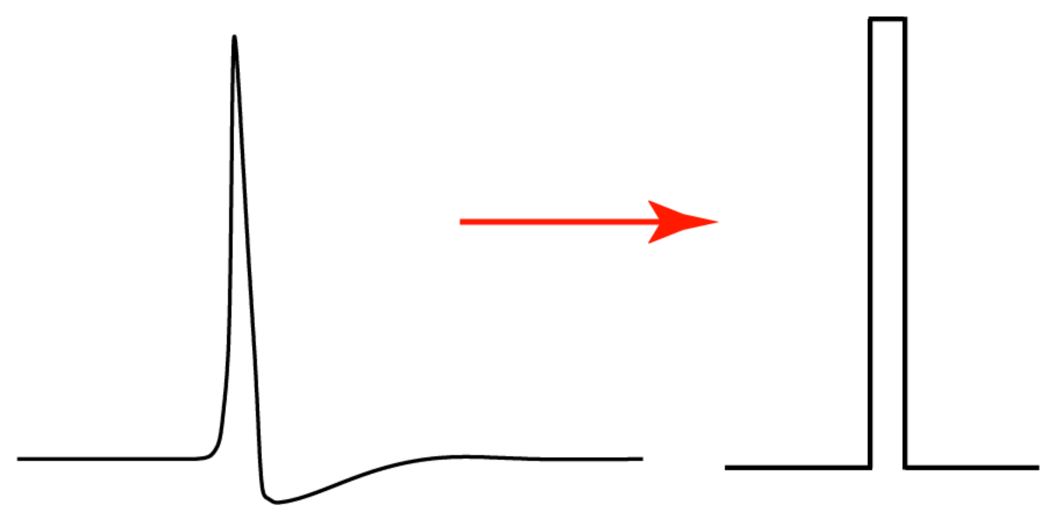


$$\frac{\partial V}{\partial t} = D\frac{\partial^2 V}{\partial x^2} - \frac{V}{\tau} + \sum_n \delta(x - x_n) I_{\text{sp}}$$

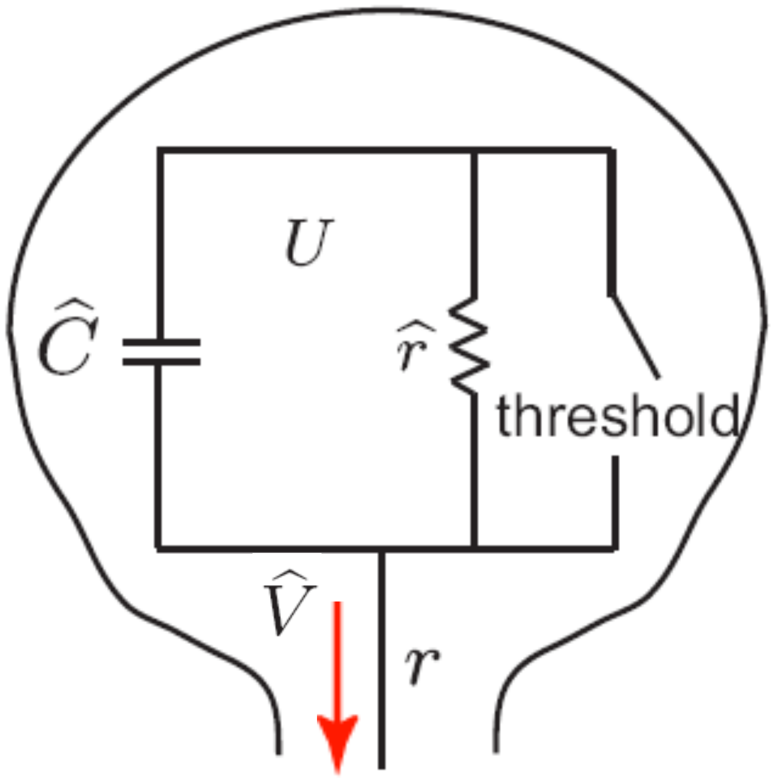
$$I_{\text{sp}} = \frac{\widehat{V} - V}{r}$$

$\widehat{V}$ - action potential from active spines

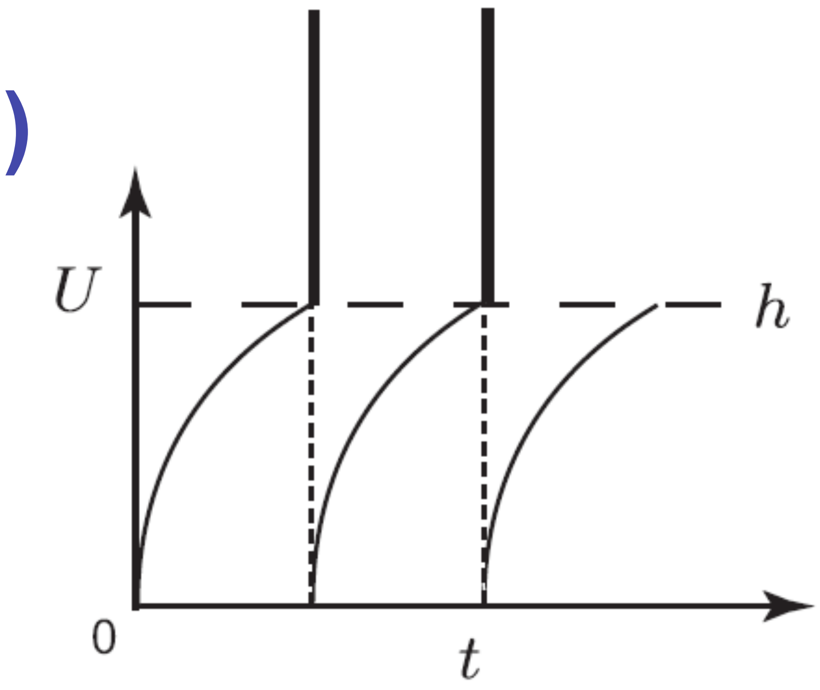
$$\widehat{V}(x_n, t) = \sum_m \eta(t - T_n^m)$$



Coombes & Bressloff *SIAM J Appl Math* 2000, *PRL* 2003



Spine-head dynamics (IF)

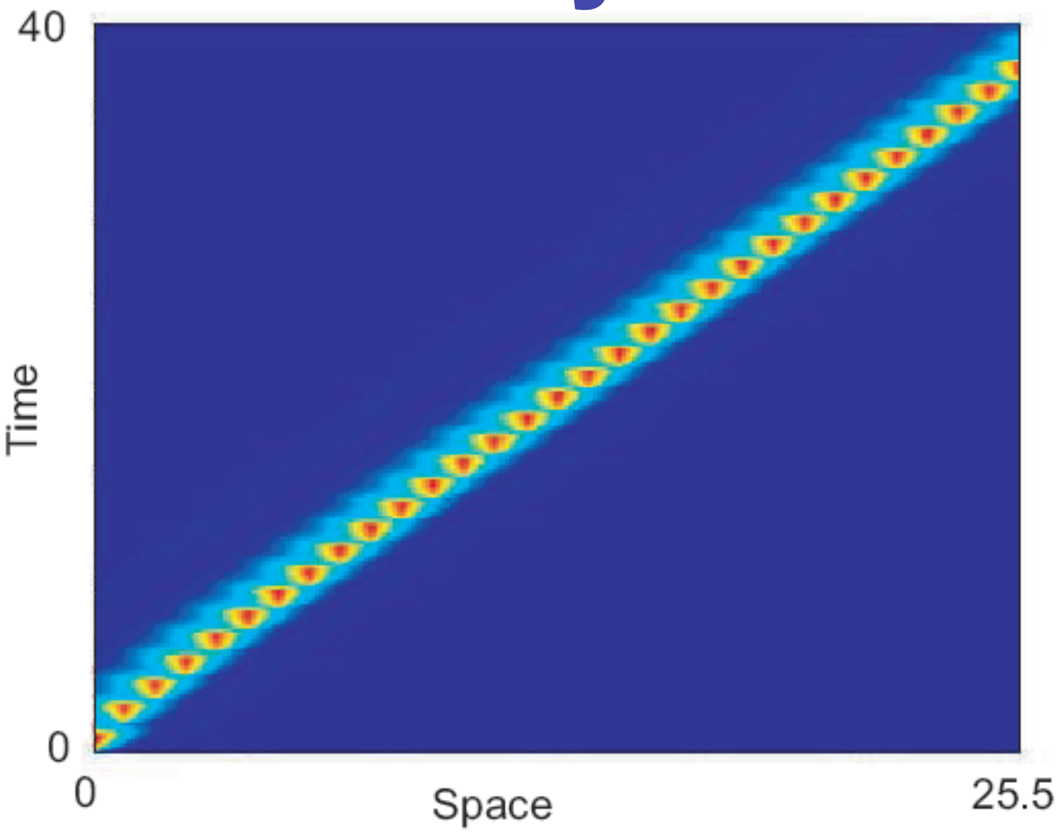


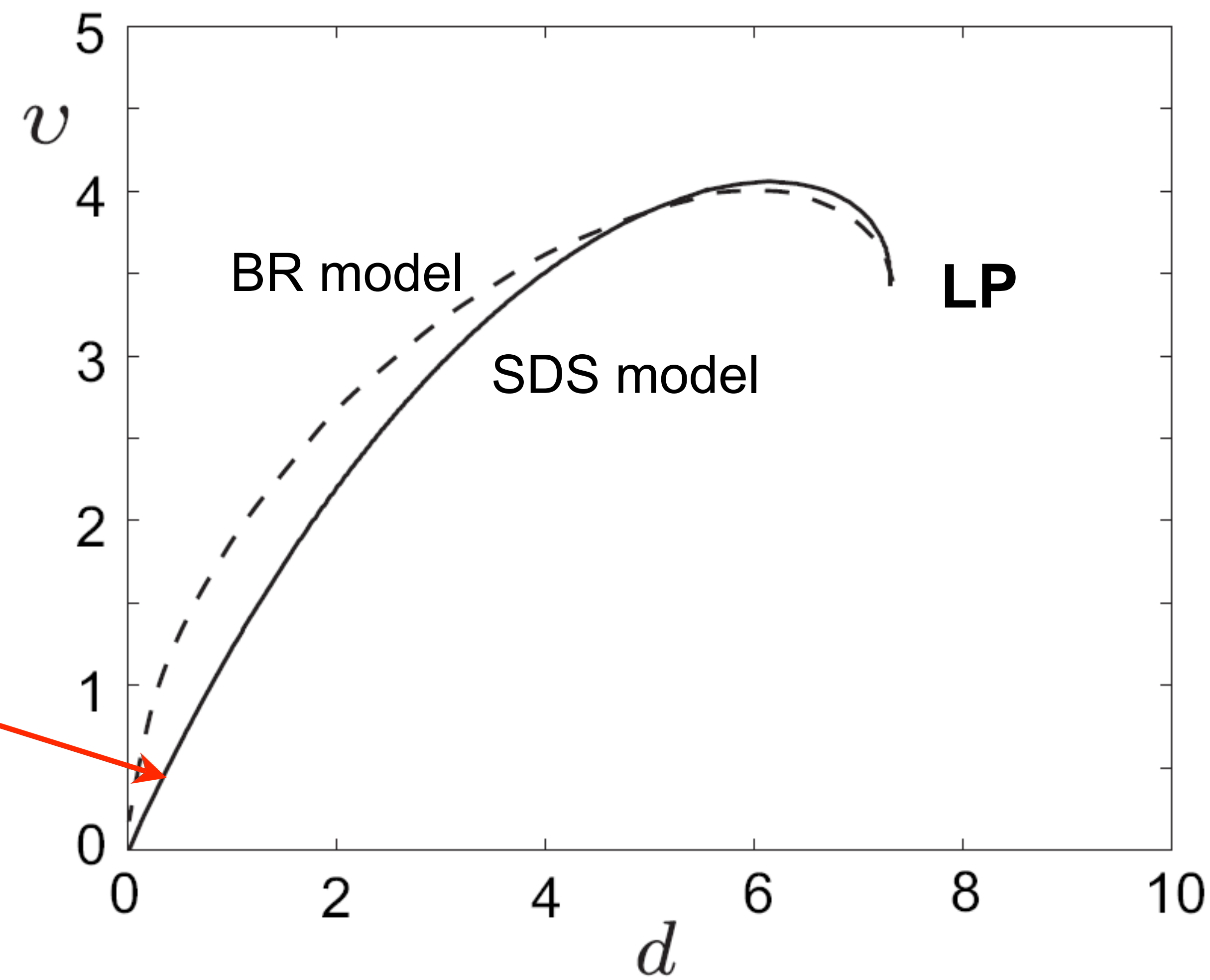
Firing times: $T_n^m = \inf\{t \mid U_n(t) \geq h,\ t > T_n^{m-1} + \tau_R\}$

τ_R **- refractory time**

Reset: $U(x_n, t^+) = 0$ **whenever** $U(x_n, t) = h$

Saltatory wave





Spines: $x_n = nd$

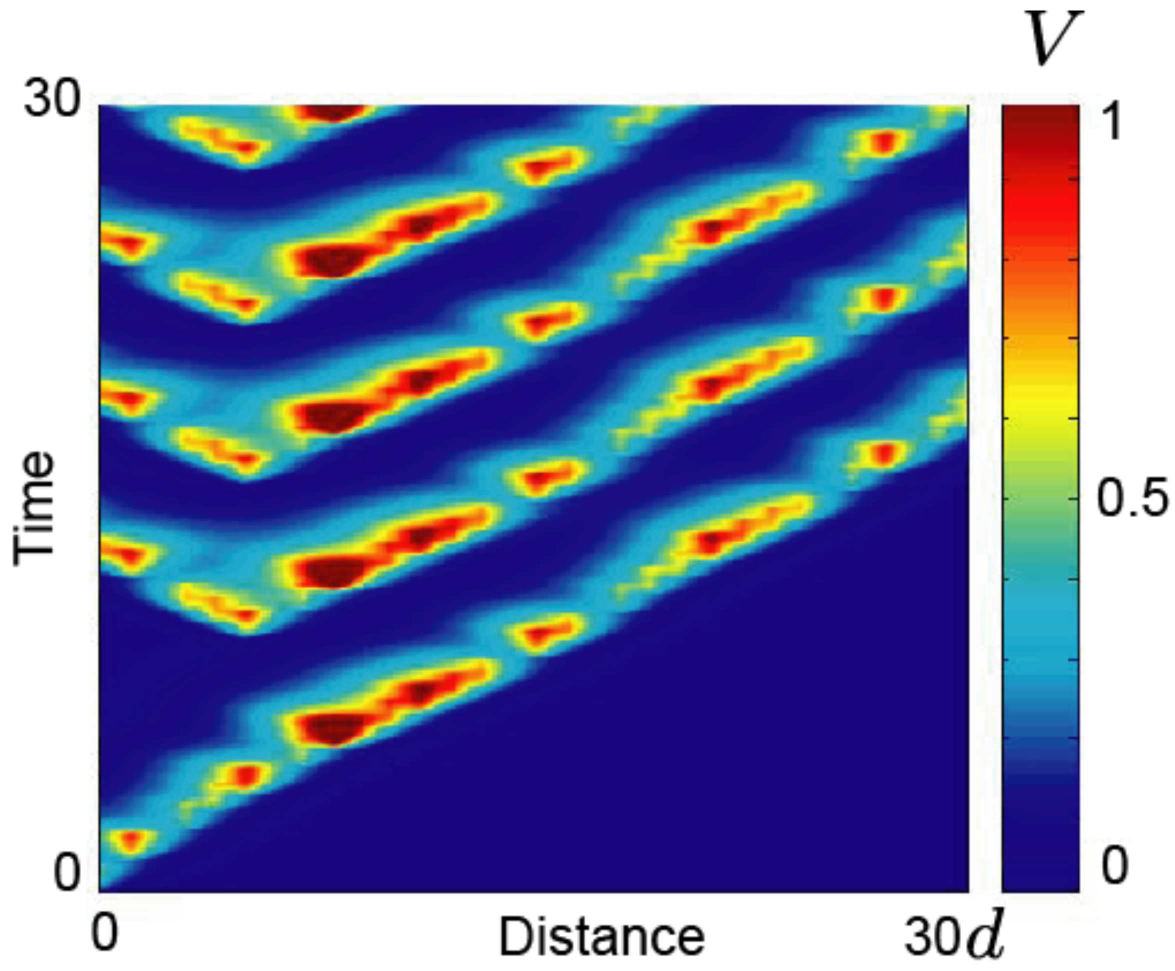
Firing events: $T_n = n\Delta$

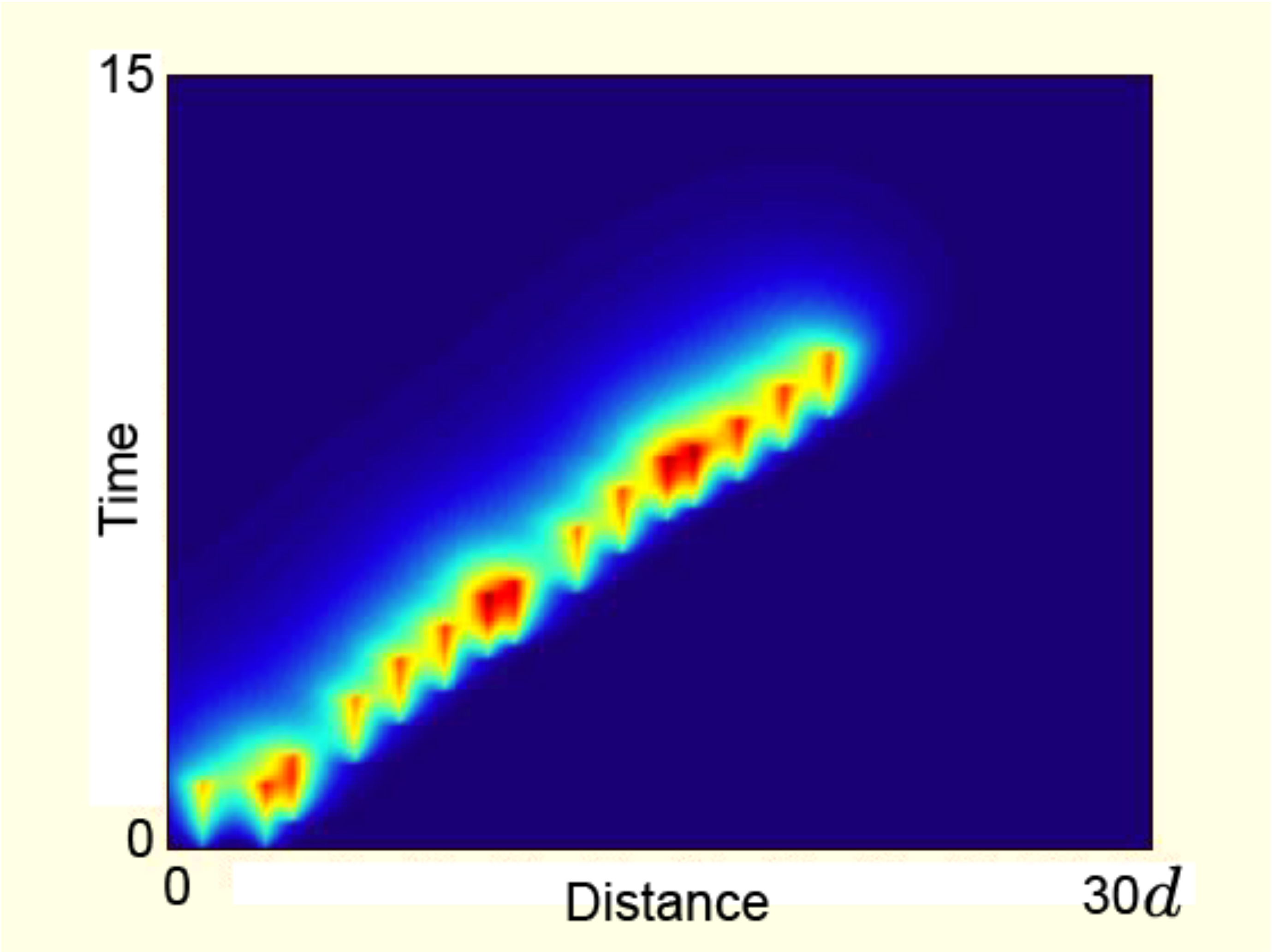
Speed: $v = d/\Delta$

Self-consistent speed

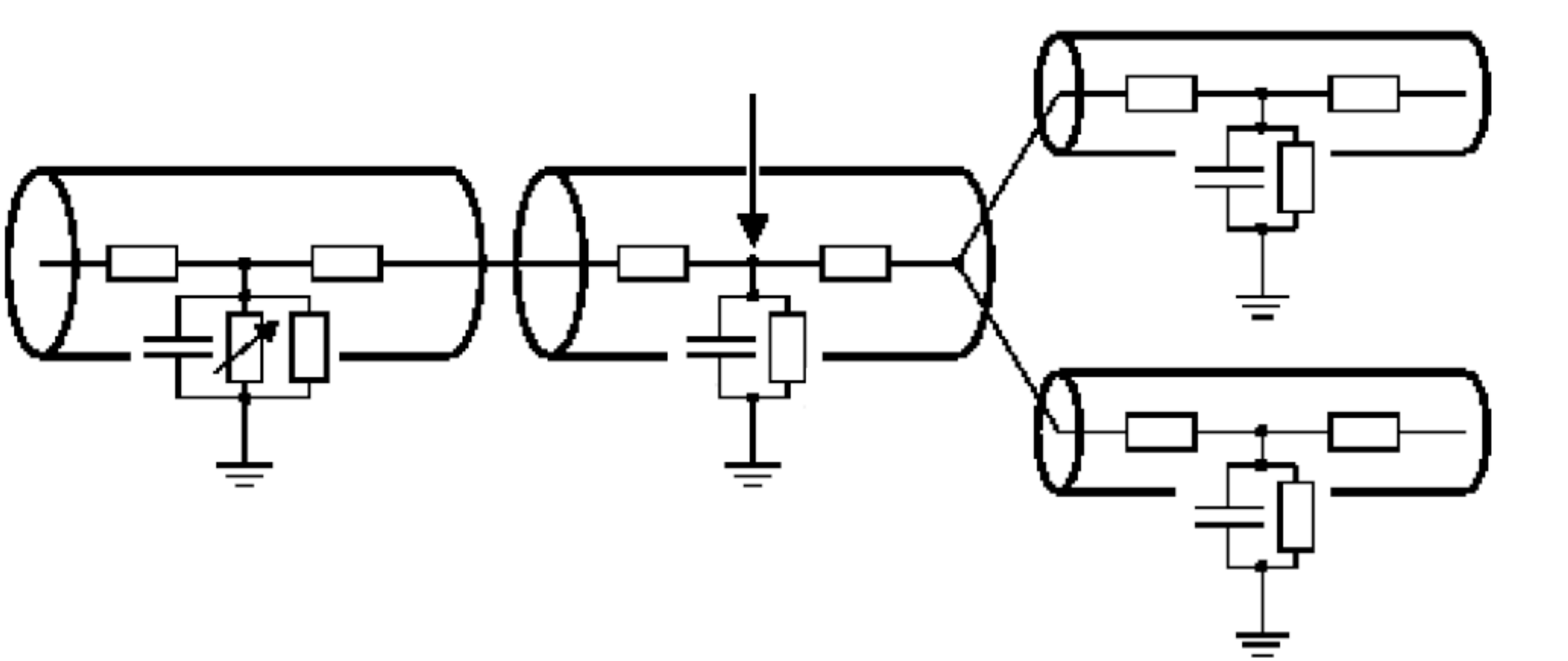
YT, Lord & Coombes 2006 *J.Comput.Neurosci.* 21

Irregular distribution of spines





Compartmental models

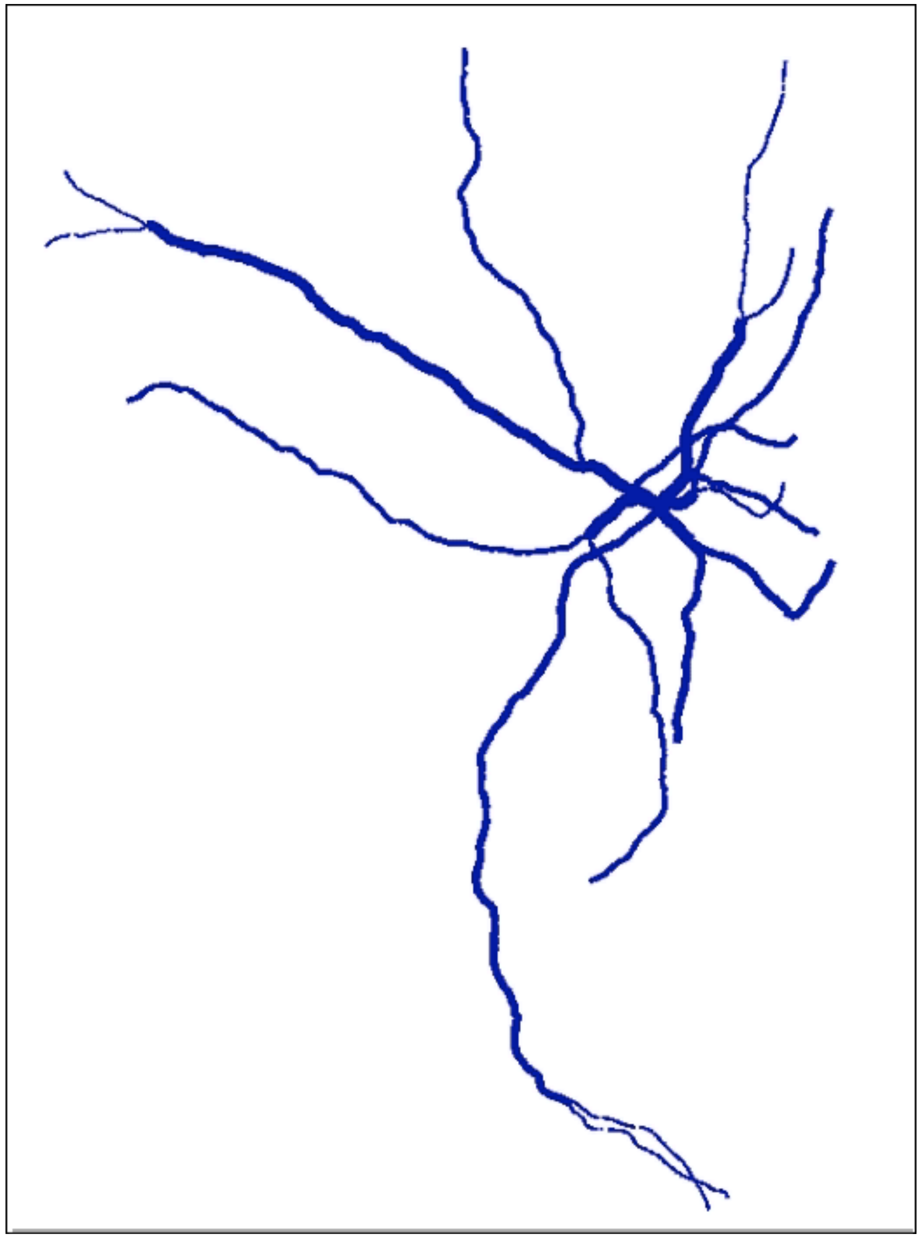


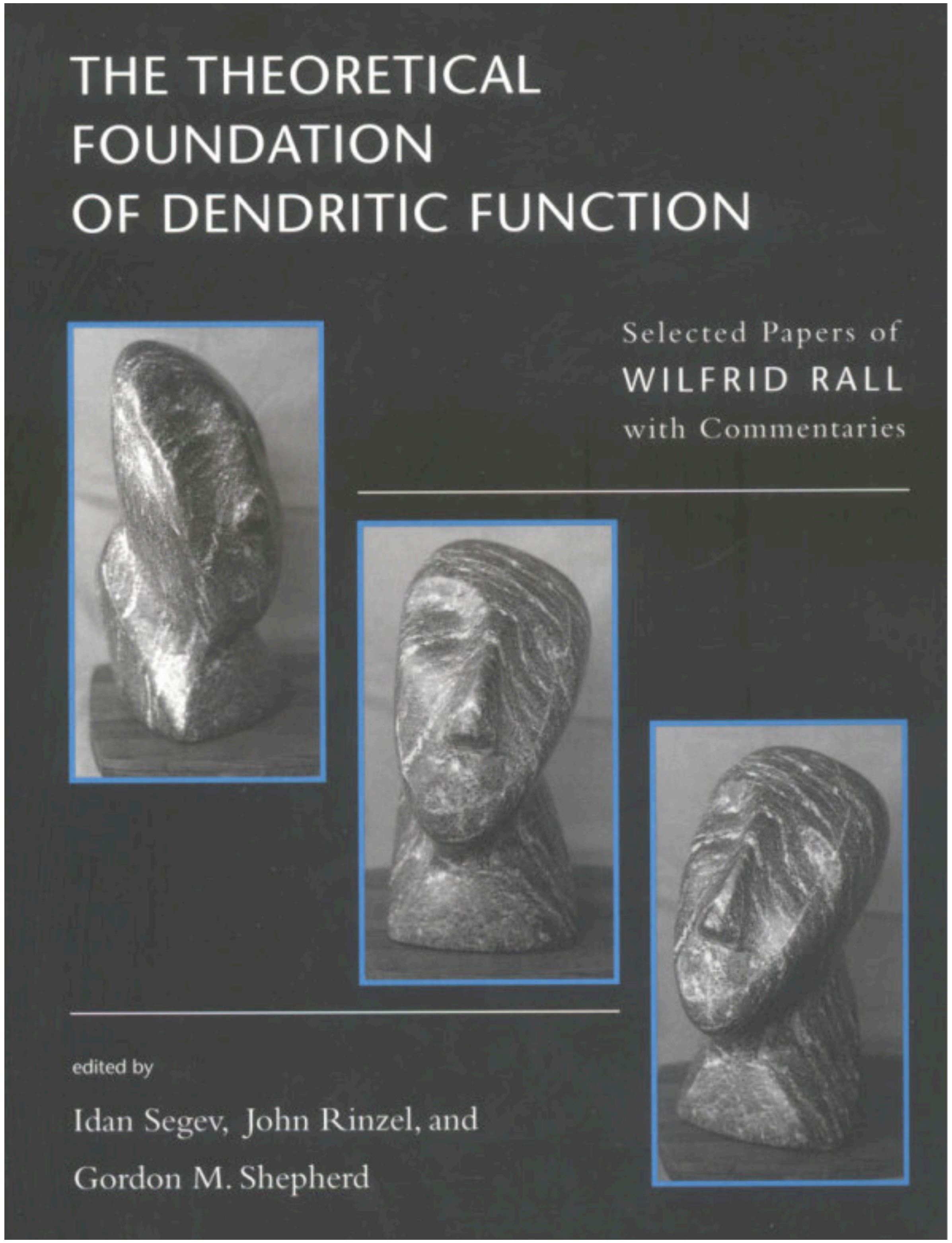
$$c_m \frac{dV_\mu}{dt} = -i_m^\mu + \frac{I_e^\mu}{A_\mu} + g_{\mu,\mu+1}(V_{\mu+1} - V_\mu) + g_{\mu,\mu-1}(V_{\mu-1} - V_\mu)$$

Simulation software tools

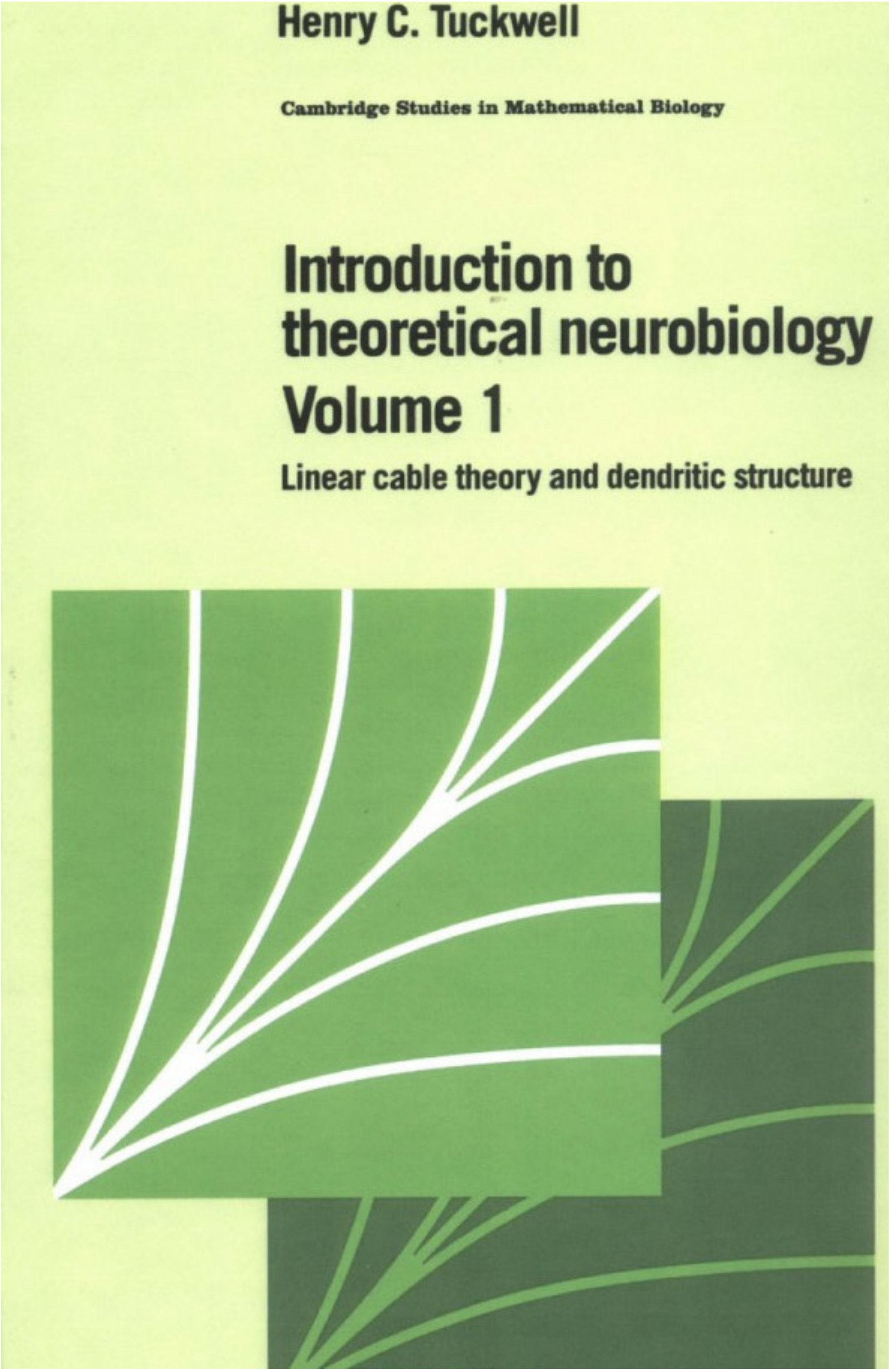
GENESIS (http://www.genesis-sim.org/GENESIS/)

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

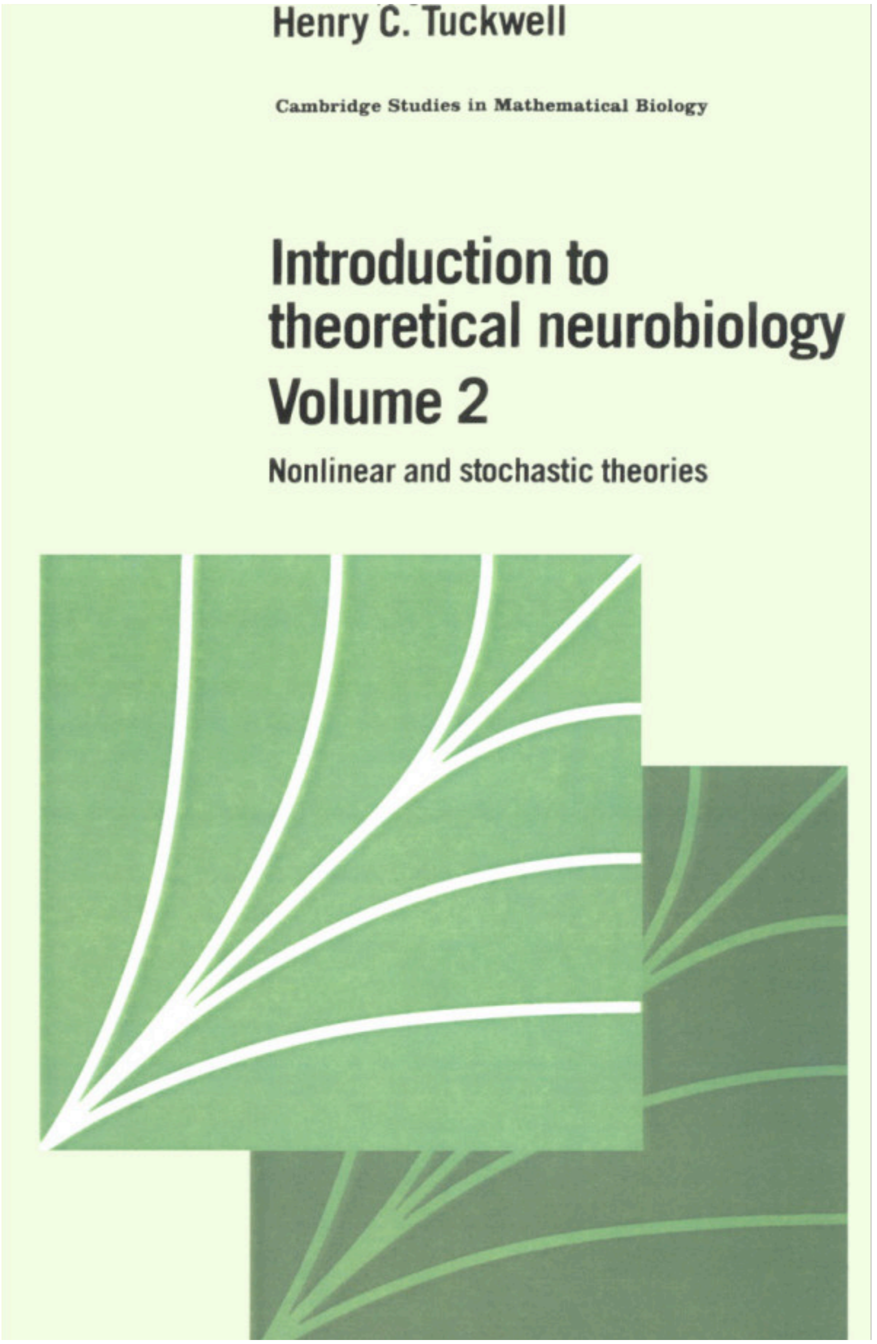


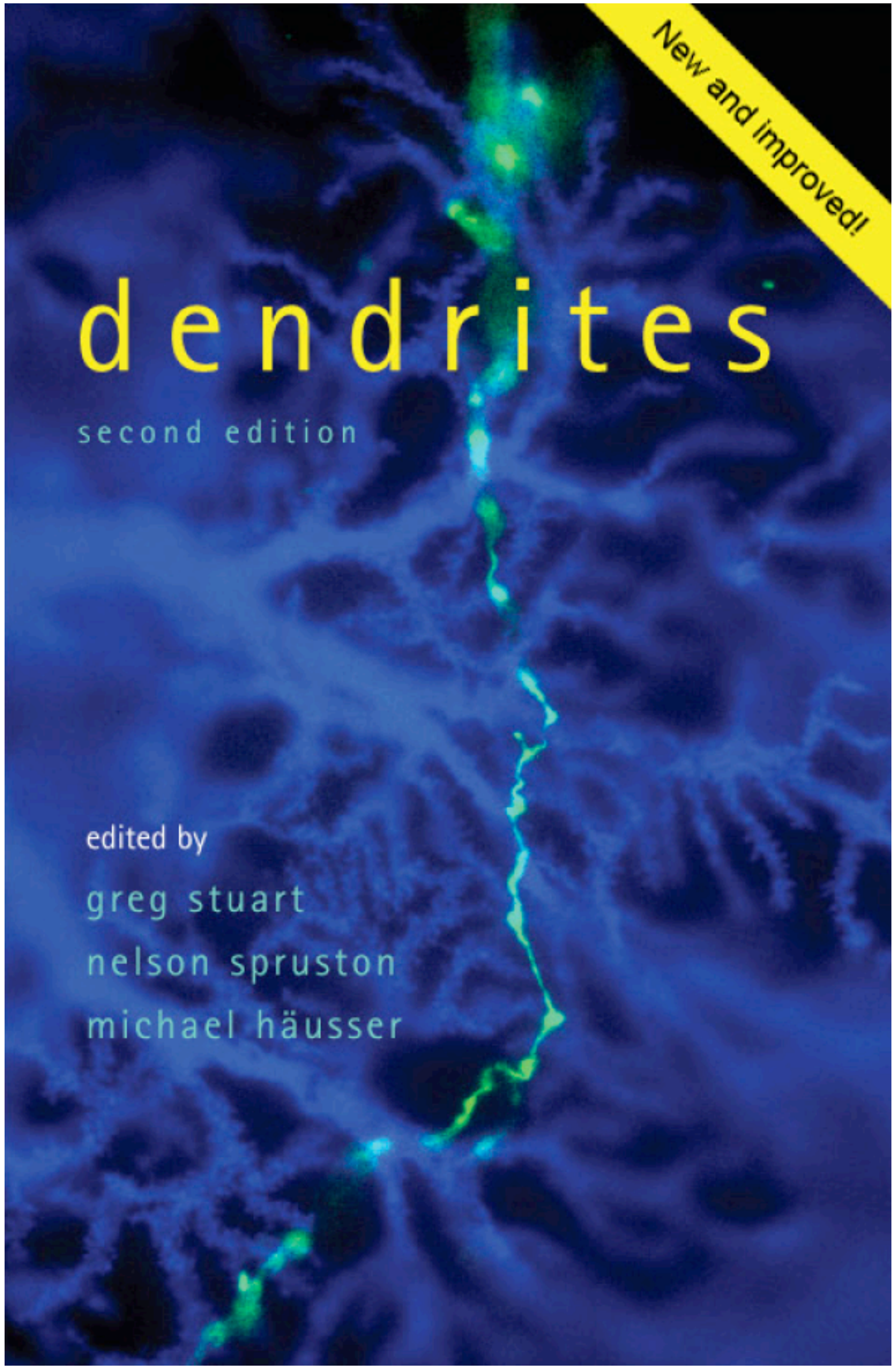


I. Segev, J. Rinzel and G. M. Shepherd, *The Theoretical Foundation of Dendritic Function: Selected Papers of Wilfrid Rall with Commentaries*, MIT Press, Cambridge, MA, 1995



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





G. Stuart, N. Spruston, M. Hausser, *Dendrites*, Oxford University Press, 2008