Neuronal Cable Theory (NCT) on Graphs: A Synopsis of Some Forward and Inverse Problems

by

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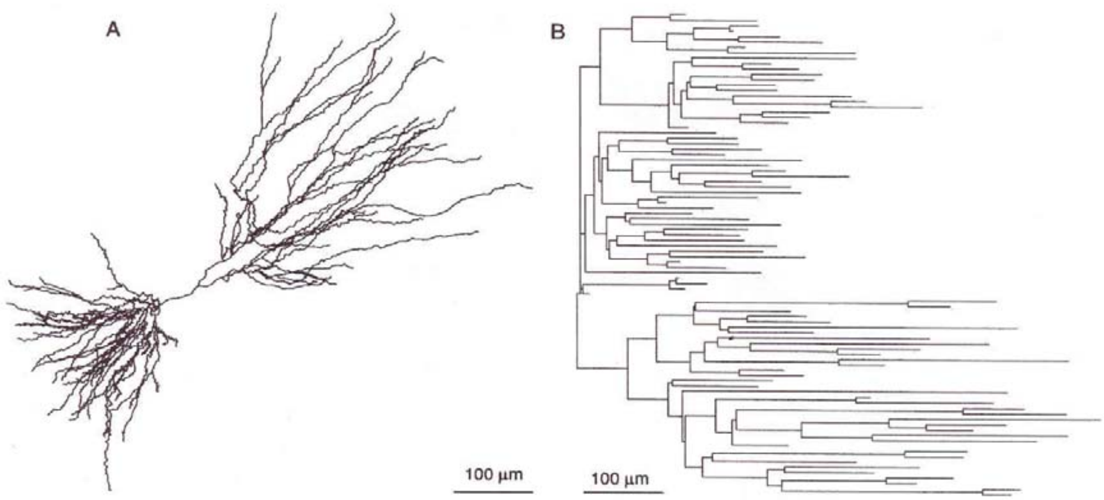
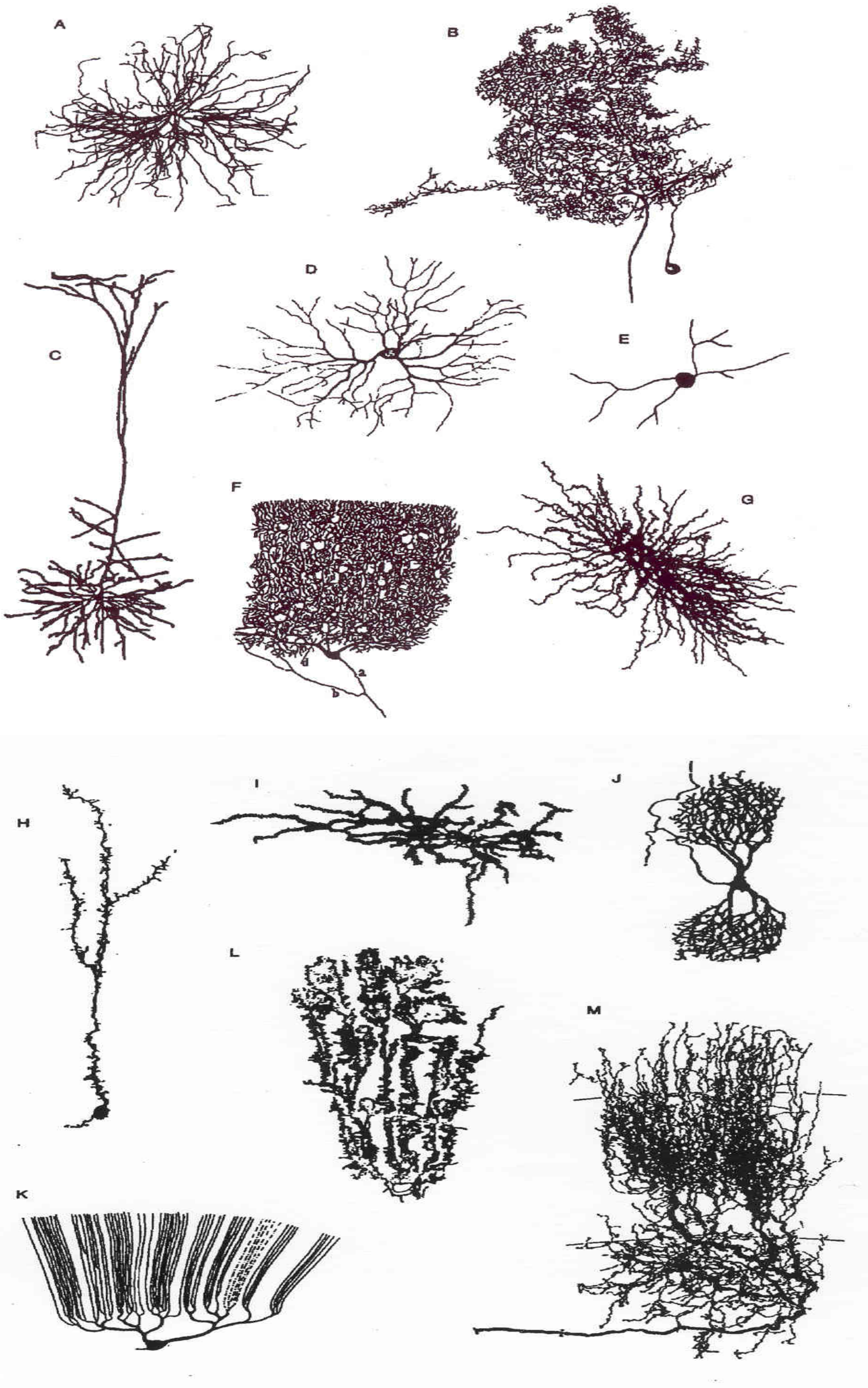


Fig. 4. Different views of the CA3 cell 148b, as for Fig. 3.

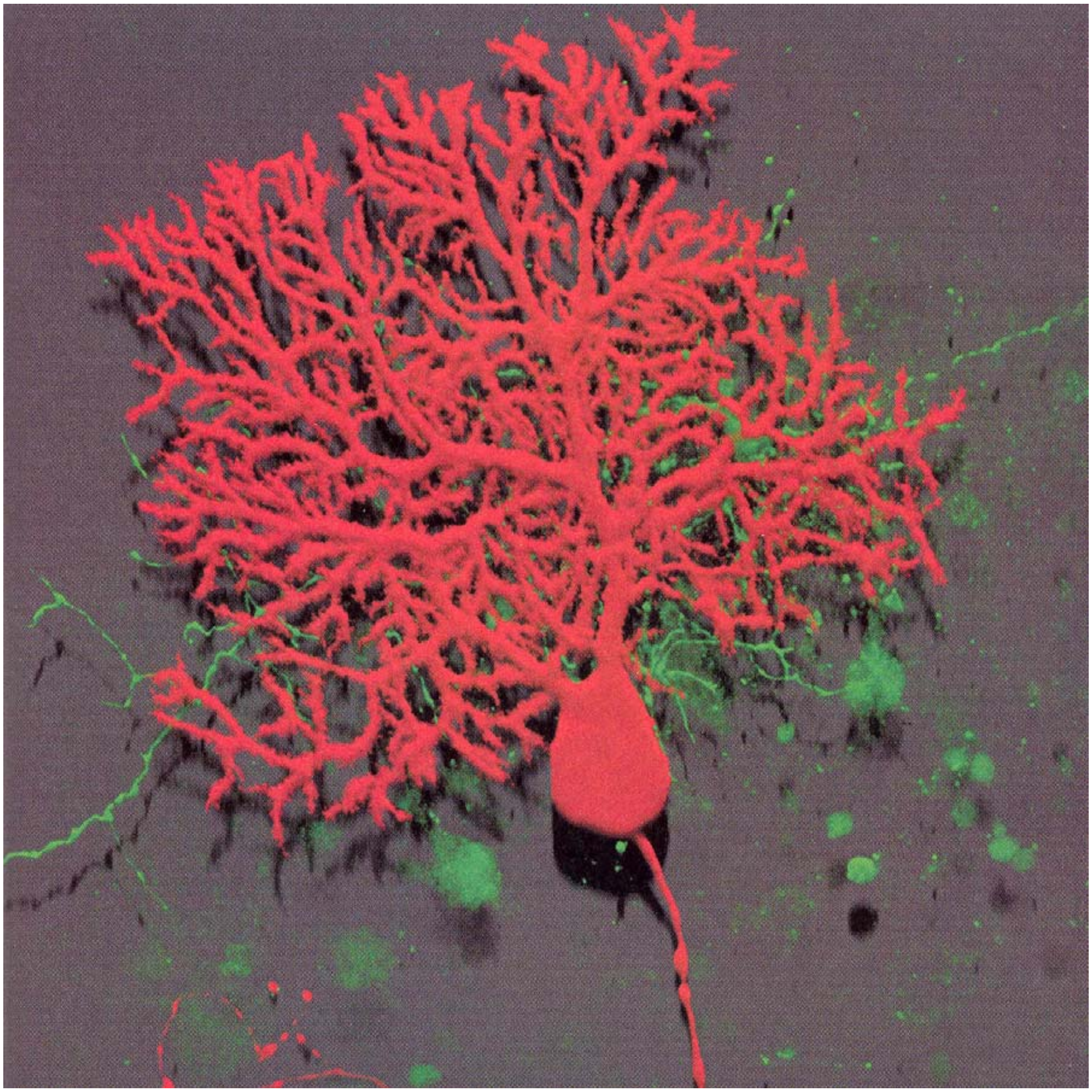
Outline

- Motivation: Some comments on dendritic trees and neural transmission
- NCT forward problems: aspects of threshold behavior, bounds on propagation speed, and conduction block
- NCT inverse problems: somatic response to distal input, ion channel densities, conductances and branch radii, and determining tree morphology from boundary measurements

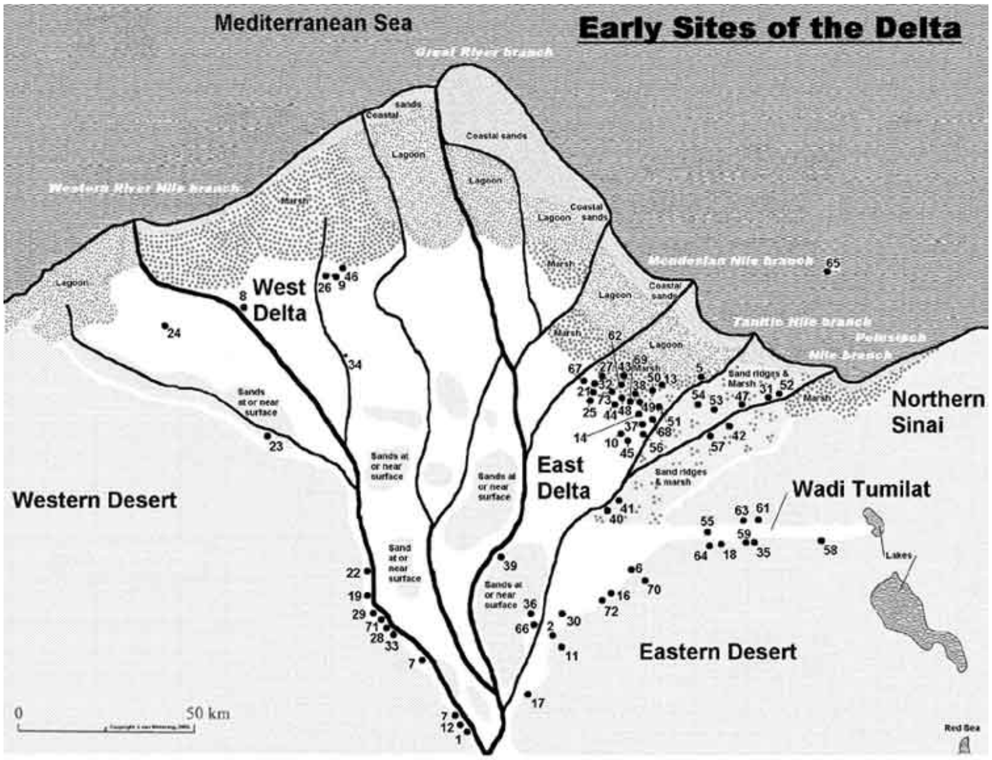
Dendritic Tree Examples

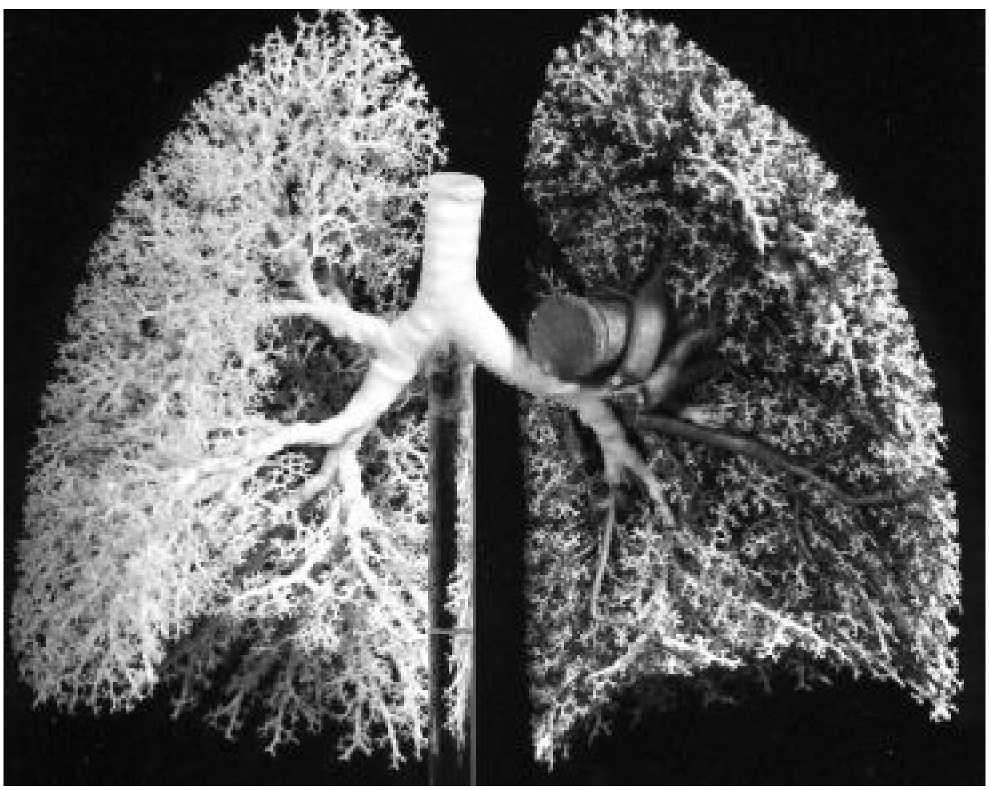


Purkinje cell with red fluorescent dye injected into it (and another cell with green dye. (From Technology Review, Dec. 2009)



Other Branching Systems





Comments on Dendrites

Dendrites account for more than 99% of surface area of some neurons, and can be studded with up to 200,000 synaptic inputs

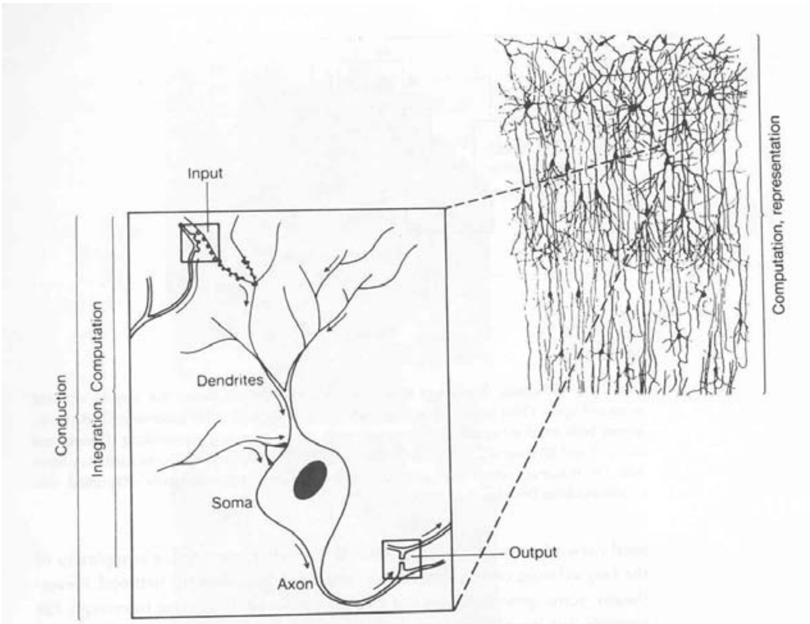
They are the largest volumetric component of nervous tissue and consume more than 60% of the brain's energy

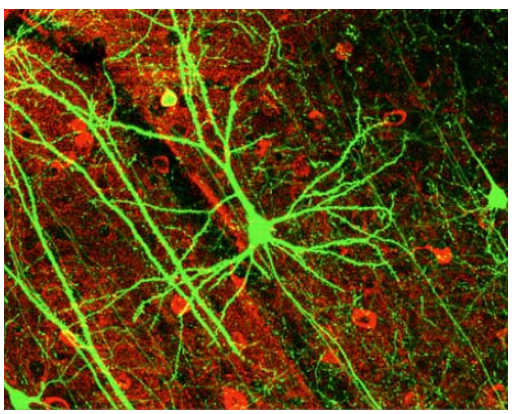
They are computing workhorses of the brain

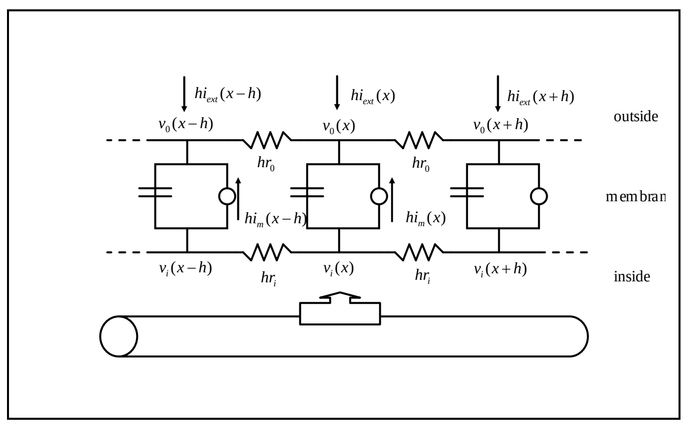
A bit of history of ideas about dendrites:

- Before electrophysiology, dendrites were considered to play a strictly nutritive role to neurons (like tree roots)
- The "classical" picture emerged in the 1930s and 40s which held that the exclusive spike trigger zone in nerve was the axon initial segment, while dendrites simply collected and summated synaptic inputs
- Now many dendrites are known to be replete with complex voltage-dependent membrane conductances capable of action potential production and other highly nonlinear behaviors.

Cable Equation(s)





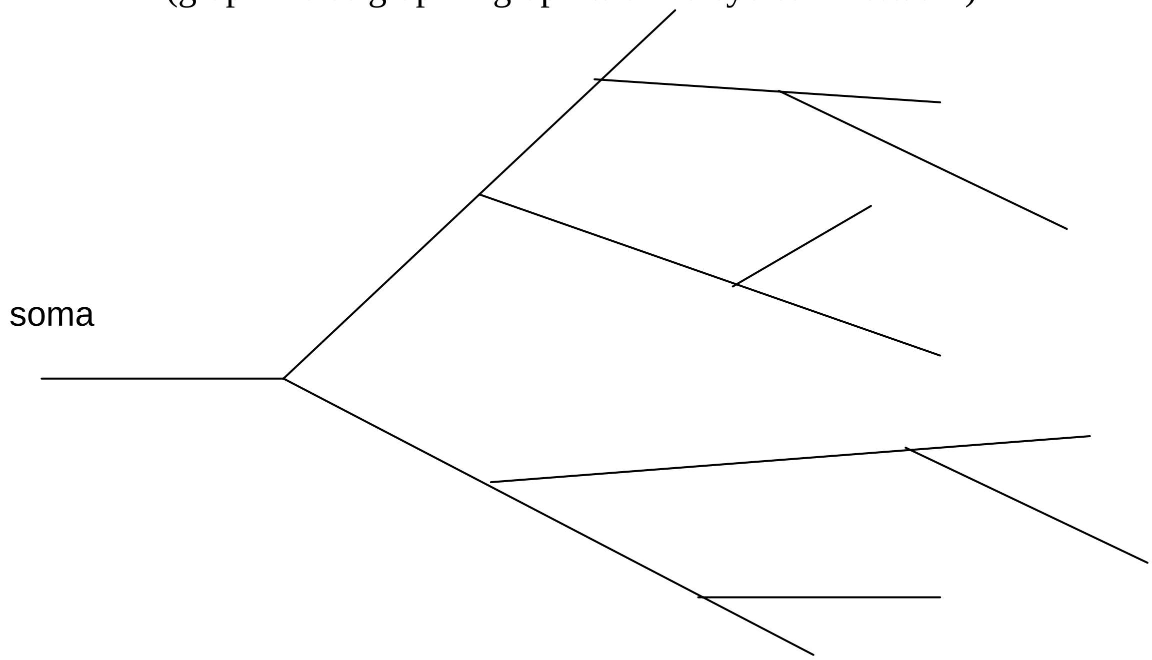


Single branch circuit model $\Rightarrow$ continuum model:

$$\frac{a}{2R_i}\frac{\partial^2 v}{\partial x^2} = C_m \frac{\partial v}{\partial t} + I_{ion}(v,\ldots) = C_m \frac{\partial v}{\partial t} + \begin{cases} \sum_{ion-j} g_j(\underline{w})(v - E_j) \\ \dfrac{v}{R_m} \end{cases}$$

Idealized Dendritic Tree Graph

(graph = tree graph = graph with no cycles = network)



1. Trees are planar, binary; if one terminal vertex identified as a soma, then $|\partial\Omega| = n+1$
2. If one can go from the soma to any one terminal node traversing **N** branch points, the tree is *complete* and has *order* **N**. The tree example above is *incomplete*, but has "bounded order" $\mathbf{N_b}$= 4. Tree complete $\Rightarrow n = 2^N$.
3. Most of time, graph = compact, metric tree graph
   $\Omega = \{E, V\}$
   $E = \{e_j \mid j = 1, \ldots, N\}$, $e_j \cong [0, l_j]$
   $V = \{\gamma_i \mid i = 1, \ldots, M\} = \partial\Omega \cup V_r$

Dendrogram of a CA1 Pyramidal Cell

R.C. Cannon et al. / Journal of Neuroscience Methods 84 (1998) 49–54 53

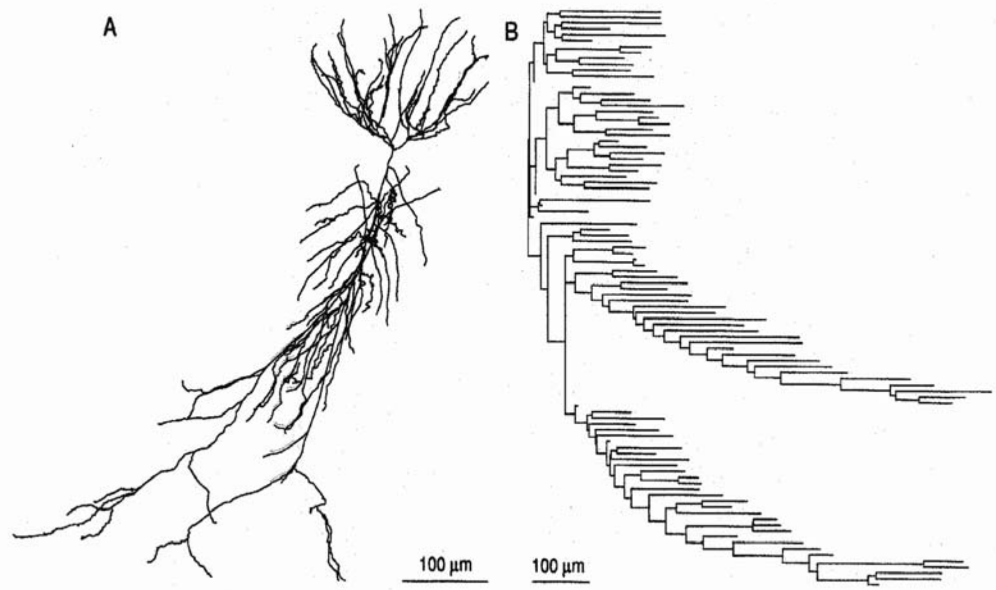


Fig. 3. A sample of representations available with the morphology editor as applied to the CA1 cell n184. A: a simple skeleton projection. B: the appropriate lengths and connections of all branches without direction information, in the form of a dendrogram.

In this example, $n = 95$, $N_b = 33$.

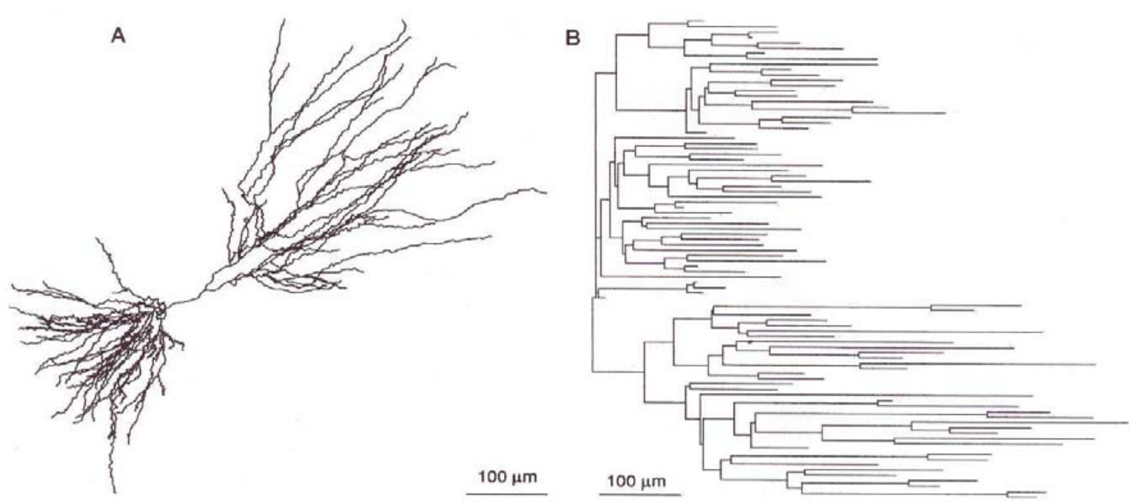


Fig. 4. Different views of the CA3 cell 148b, as for Fig. 3.

In this example, $n = 90$, $N_b = 11$.

Some Notation and Example System

$$\Omega_T := \left(\bigcup_{j=1}^{N} (0, l_j) \right) \times (0, T]$$

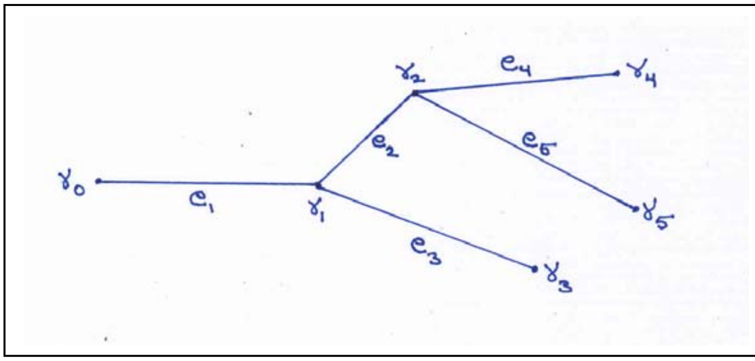
$$\Omega_{jT} := (0, l_j) \times (0, T]$$

$$\Omega_{j0} := e_j \times \{0\}$$

D = incident matrix = (d_{ij}),

$$d_{ij} = \begin{cases} 1 & if \quad \gamma_i = l_j \\ -1 & if \quad \gamma_i = 0 \\ 0 & otherwise \end{cases}$$

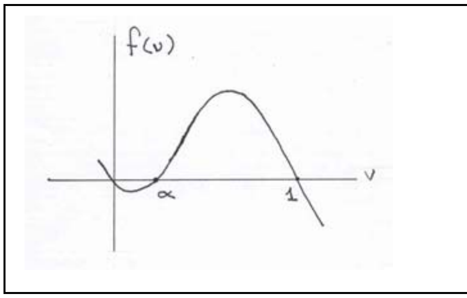
All edges have the same "radius"



$$D = \begin{bmatrix} -1 & 0 & 0 & 0 & 0 \\ 1 & -1 & -1 & 0 & 0 \\ 0 & 1 & 0 & -1 & -1 \\ 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 1 \\ 0 & 0 & 1 & 0 & 0 \end{bmatrix}$$

Example Problem: FitzHugh-Nagumo

$$H_f := \begin{cases} f \in C^1[0, A] \qquad A > 1 \\ f(0) = f(1) = 0 \\ f(v) < 0 \quad for \quad 0 < v < \alpha \\ f(v) > 0 \quad for \quad \alpha < v < 1 \\ \int_0^1 f(s)ds > 0 \end{cases}$$



Dynamics: $$\begin{cases} \dfrac{\partial v_j}{\partial t} = \dfrac{\partial^2 v_j}{\partial x^2} + f(v_j) - w_j \\ \dfrac{\partial w_j}{\partial t} = \sigma v_j - \eta w_j \\ in \qquad \Omega_{jT},\ j = 1, \dots, N, \quad \sigma, \eta > 0 \end{cases}$$

IC: $v_j = 0, w_j = 0 \quad on \quad \Omega_{j0}$

BC: $$\begin{aligned} -v_{1x}(\gamma_0, t) &= I(t) && t \in (0, T] \\ v_{jx}(\gamma, t) &= 0, && \gamma \in \partial\Omega \setminus \{\gamma_0\}, \quad e_j \sim \gamma, \quad j > 1 \end{aligned}$$ (sealed-end b.c.s)

K (Kirchhoff condition): $\gamma_i \in V_r, \quad \sum_{j, e_j \sim \gamma_i} d_{ij} v_{jx}(\gamma_i, t) = 0, \quad t \in (0, T]$

Threshold Idea: Motivation through Energy Arguments

Example: let $f(v) = v(v-\alpha)(1-v),\ 0 < \alpha < 1/2$, so

$$F(v) := \int_0^v f(s)ds = -v^2\left[\frac{v^2}{4} - \frac{1+\alpha}{3}v + \frac{\alpha}{4}\right]$$

So
$$F(v) < 0 \quad for \quad 0 < v < a_1,$$
$$F(v) > 0 \quad for \quad a_1 < v < a_2, \quad \alpha < a_1 < 1 < a_2$$

Let

$$E_1(t) := \sum_{j=1}^N \int_0^{l_j} \left\{ \frac{k}{2}\left(\frac{\partial v_j}{\partial x}\right)^2 - kF(v_j) + \frac{d}{2}(v_j)^2 + \frac{k}{2}(v_j + w_j)^2 + \frac{K}{2}(v_j{}^2 + w_j{}^2) \right\} dx_j$$

Lemma: There are *k*, *d*, *K* such that if, for some $t_0 \geq 0$, every j = 1, …, N, $\sup_{x \in e_j} |v_j(x,t_0)| < \alpha,\ \sqrt{E_1(t_0)} < \alpha,$ then $\lim_{t\to\infty}\big(v_j(x,t), w_j(x,t)\big) = (0,0)$.

Let

$$E_2(t) := \sum_{j=1}^N \int_0^{l_j} \left\{ \frac{1}{2}\left(\frac{\partial v_j}{\partial x}\right)^2 - F(v_j) + BL(v_j, w_j) \right\} dx_j, \quad BL(v,w) := \frac{1}{2}Av^2 - Bvw + \frac{1}{2}Cw^2$$

By a proper choice of *A*, *B*, *C*, $BL(v_j, w_j) \geq 0$, for j = 1, …, N, and for solution (*v*,*w*), $dE_2/dt \leq 0$. Then,

Lemma: Assume $v^2 \geq \sigma > 0$, and for some $t_0 \geq 0$, $E_2(t_0) < 0$. Then $E_2(t) < 0$ for all $t \geq t_0$ and this implies for every $t \geq t_0$, there is a $k \in \{1, \dots, N\}$, $x = x_k(t)$ such that $v_k(x_k(t), t) > a_1 > \alpha$.

Bottom Line: (0,0) is locally stable, but not globally stable.

Threshold Behavior: Scalar Dynamics Case

FitzHugh-Nagumo model, but with $w_j \equiv 0$, plus assume

H_{f1}: There exists $u_0, f_0 > 0$ such that for $0 \le u \le u_0$,

$f(u) \le -f_0 u$.

From a comparison principle…

Theorem: *f* satisfies H_f, H_{f1}; let $u \in Z_T := C(\Omega \times [0,T]) \cap C^{2,1}(\Omega_T)$ be a solution, for any $T > 0$,

(1) $u_{jt} = u_{jxx} + f(u_j) \quad in \quad \Omega_{jT}$

(2) $-u_{ix}(\gamma_0, t) = I(t) = \begin{cases} I_0 & for \quad 0 < t < t_0 \\ I_1 e^{-\delta(t-t_0)} & for \quad t \ge t_0 \end{cases}$

(3) $u_{jx}(\gamma, t) = 0 \quad for \quad \gamma \in \partial\Omega \setminus \{\gamma_0\}$, j is such that $e_j \sim \gamma$

(4) $K(u, t; \gamma) = 0 \quad for \quad \gamma \in V_r$

(5) $u_j = 0 \quad in \quad \Omega_{j0}$.

Here $I_0 \ge I_1 > 0, \quad 0 < \delta < f_0$. Then $\lim_{t \to \infty} u_j(x,t) = 0$ for all $x \in e_j$, all $j = 1, \ldots, N$.

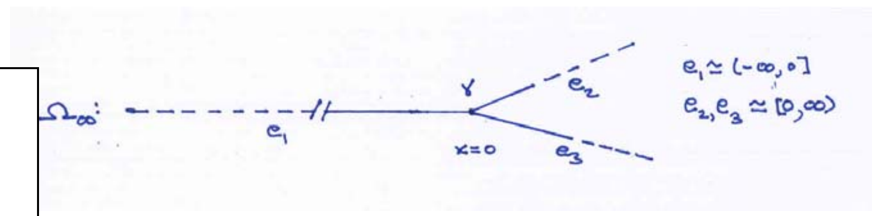
Assume

H_{f2}: for some $f_b > 0$, $f(u) \ge -f_b u$ for $u \ge 0$.

Theorem: Let $u \in Z_T$ solve (1)-(5) with $I(t)$ replaced by $\mu I^*(t)$, where $I^*(t) \ge 0$, I^* not identically zero. Then there exists a μ_0, depending on I^*, such that if $\mu > \mu_0$, for each *j*, $u_j(x,t) \ge v_j(x,t)$ and $\lim_{t \to \infty} v_j(x,t) = 1$. Here *f* satisfies H_f, H_{f2} .

Bounds on the Speed of Propagation: IVP example

Consider the problem in $\Omega_\infty \times (0,\infty)$:



(IVP) =

$$\begin{cases} v_{jt} = v_{jxx} + f(v_j) & in \quad \Omega_{jT} \\ v_j = \phi_j & in \quad \Omega_{j0} \\ K(v,t;\gamma) = 0 & for \quad t > 0 \end{cases}$$

Assume v is a solution to (IVP) such that

(6) $\lim\limits_{t\to\infty} v_j = 1$ in $\Omega_\infty \times (0,\infty)$

Write $f(u) = f'(0)u + g(u) = -au + g(u)$, g is smooth and $g(u) = O(u^2)$ as $u \to 0$.

Define $\sigma := \sup\limits_{0<u<1} \{g(u)/u\} > 0$.

Note that $\mathcal{L} v_j := v_{jt} - v_{jxx} + av_j - \sigma v_j = g(v_j) - \sigma v_j \le 0$.

Assume $0 \le \phi_j \le 1, \quad j = 1,2,3$. Then (by another comparison result), $0 \le v_j \le 1$.

Theorem: Suppose v is a solution to (IVP) satisfying (6). Let ϕ have bounded support, $\operatorname{supp}\phi \subset e_1$. If $c > \bar{c} := 2\sigma / \sqrt{a+\sigma}$, then for each j, each $x \in e_j$, $\lim\limits_{t\to\infty} v_j(x+ct,t) = 0$.

Suppose (IVP) admits a positive steady state solution $q(x)$ for $a \le x \le b < 0$, with $q(a) = q(b) = 0$. Suppose the only nonnegative global steady state τ of (IVP) with $\tau_1(x) \ge q(x)$ on $[a,b]$ is $\tau \equiv 1$. Let v be a solution to (IVP) with $\phi_1(x) \ge q(x)$ on $[a,b]$.

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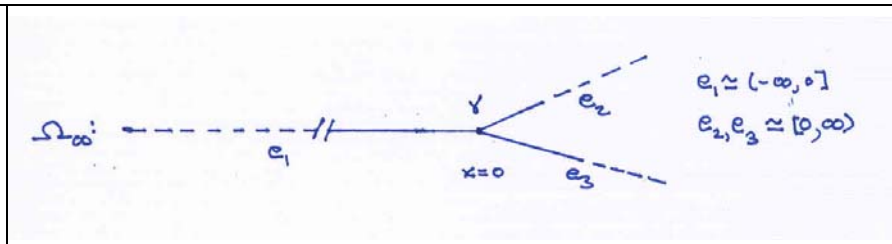
Then there is a $\underline{c} > 0$ such that for $0 < c < \underline{c}$, for any x, any $\varepsilon > 0$, there is a $T > 0$ such that for $t > T$, $v_j(x+ct,t) \ge 1-\varepsilon, \quad j = 1,2,3$.

Conduction Block

Return to (IVP) on Ω_∞ that includes "pseudo-uniform" radii:

$$\begin{cases} v_{jt} = a_j v_{jxx} + f(v_j) & in \quad \Omega_{jT} \\ v_j = \phi_j & in \quad \Omega_{j0} \\ K(v,t) = 0 & t > 0 \end{cases}$$

where, for convenience, $a_1 = 1$, and $K(v,t) := v_{1x}(0-,t) - a_2^2 v_{2x}(0+,t) - a_3^2 v_{3x}(0+,t)$



It is slightly more convenient to rescale; let $z = \begin{cases} x & in & e_1 \\ x/a_3^2 & in & e_2, e_3 \end{cases}$. Then

$v_{jt} = D_j v_{jxx} + f(v_j)$, where $D_j := \begin{cases} 1 & in & e_1 \\ \beta\varepsilon & in & e_2 \\ \varepsilon & in & e_3 \end{cases}$. Here $\beta = a_2 / a_3$ and

$\varepsilon = a_3^{-3}$. Also $K(v,t) = \left(v_{1z} - \beta^2 v_{2z} - v_{3z}\right)_{|(\gamma,t)} = 0$.

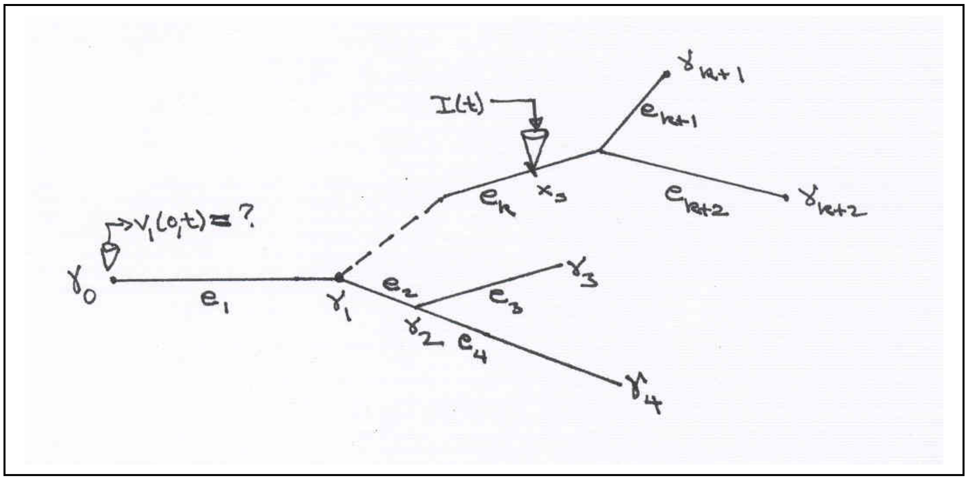
Definition: For a class $\mathcal{A}$ of admissible initial functions, let $\psi_1, \psi_2 : \Omega_\infty \to \Re$ have the property $\phi \in \mathcal{A}$ implies $\psi_{1j} \le v_j(\cdot,t;\phi) \le \psi_{2j}$ in Ω_{jT}, $j = 1,2,3$. Then $\{\psi_1, \psi_2\}$ will be called a **trap** for $\mathcal{A}$.

Definition: $v(x,t;\phi)$ will be said to be *blocked at* γ if there is a trap $\{\psi_1, \psi_2\}$ such that $\| \psi_i \|_{\Re^+} \le \rho(\varepsilon), \quad i = 1,2, \quad and \quad \rho(\varepsilon) \to 0 \quad as \quad \varepsilon \to 0+$.

Remark: This requires a (conditional) comparison principle to help construct such a trap. We have an approach to do this for bistable dynamics above, and believe it doable for FitzHugh-Nagumo (as a generalization of a result of Pauwelussen, 1981) and Morris-Lecar (as a generalization of a result of Zhou-Bell, 1994).

Somatic Output due to a Distal Current Source

Question: Given stimulus $I(t)$, voltages $m_j(t)$ and sealed-end b.c.s on $\partial\Omega \setminus \{\gamma_0\}$, can we estimate $v_1(0,t)$ at γ_0 (representing potential at the soma)?



Present Cases

A. Linear cable theory: $\dfrac{\partial v_j}{\partial t} + v_j = a_j \dfrac{\partial^2 v_j}{\partial x^2} + RI(t)\delta_{jk}\delta(x - x_s) \quad in \quad \Omega_{jT}$

plus zero i.c.s, sealed-end b.c.s and voltage measurements on $\partial\Omega \setminus \{\gamma_0\}$, continuity and Kirchhoff conditions at on V_r , continuity and jump conditions at $x = x_s$:

$$[\![v_k]\!]_{x_s} := v_k^+(x_s+,t) - v_k^-(x_s-,t) = 0, \quad [\![\partial_x v_k]\!]_{x_s} = -RI(t)/a_k$$

Key is use of Fourier transform in t to obtain $v_1(0,t) = \dfrac{1}{2\pi}\displaystyle\int_{-\infty}^{\infty} e^{it\omega} a_1(\omega) d\omega$.

Methodology works in principle for a finite number of point stimuli.

B. Nonlinear cable theory: $\begin{cases} \dfrac{\partial v_j}{\partial t} = a_j \dfrac{\partial^2 v_j}{\partial x^2} + f(v_j) - w_j + RI(t)\delta_{jk}\delta(x - x_s) \\ \dfrac{\partial w_j}{\partial t} = \alpha v_j - \beta w_j \end{cases}$

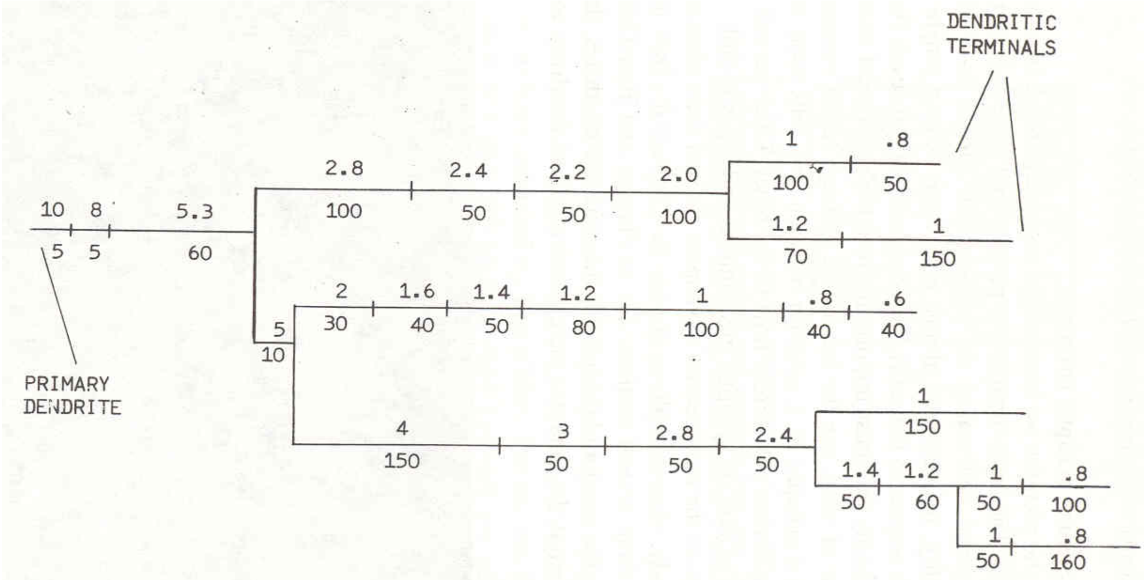
Only can address question for *steady state* case, $f(v), \alpha, \beta$ such that $f(v) - \alpha v/\beta$ satisfies hypothesis H_f .

Key here is uniqueness of trajectories through non-singular points in phase plane, and knowledge of lengths of trajectory segments (length of edges)

Problem: can not do anything with the (ill-posed) diffusion problems.

Inverse Problem for a Dendritic Tree

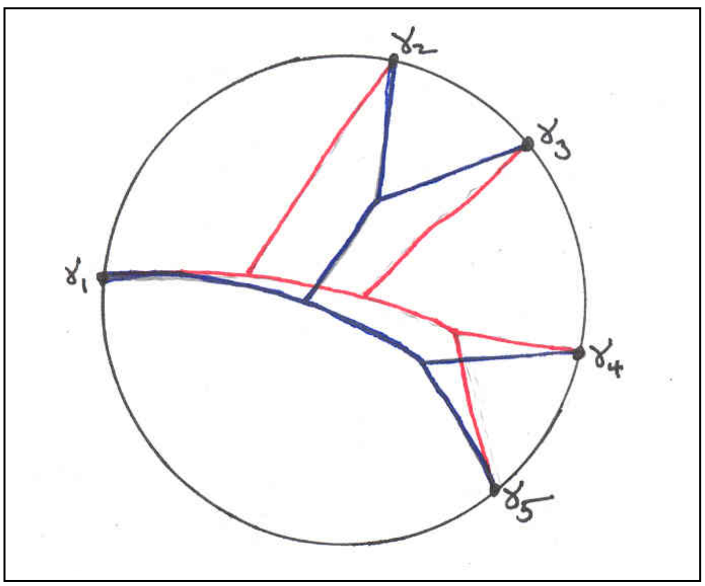
Example: Measurements of diameters (upper numbers) and segment lengths (lower numbers) of a primary dendrite and its branches from a **cat spinal motoneuron**. (Lengths are not to scale.)   (data from J. Barrett, as presented by H. Tuckwell in *Introduction to Theoretical Neurobiology*, vol. 1, Cambridge Univ. Press, 1988.)



Question

Given sufficient electrical data at the terminal ends of a dendritic tree, can we "recover the tree" in the sense of obtaining the topology of the tree (up to isometry), the lengths of the branches (edges), the diameters of the branches, and the conductances in the branches?

Example: smallest case of two non-isometric trees
(one complete, one incomplete)



A Single Branch Example: Recover a Channel Density

Assumptions: single (unbranched) passive cable
single ion channel with distributed density $N(x)$
$C_m = C_0 + N(x)C^*, \quad g = N(x)g^*$
C_0 = capacity of membrane without channels (~0.8 $\mu F/cm^2$)
C^* = capacity per channel (~ $8\times 10^{-18} F$)
g^* = maximum conductance per single channel (~ $2.5\times 10^{-12}\Omega^{-1}$)

Model Problem:

$$\begin{cases} (1+q(x))\dfrac{\partial v}{\partial t} + q(x)v = \dfrac{\partial^2 v}{\partial x^2}, & 0<x<l \qquad 0<t<T \\ v(x,0)=0 & 0<x<l \\ \dfrac{\partial v}{\partial x}(0,t) = -i(t), & \dfrac{\partial v}{\partial x}(l,t)=0 \quad v(0,t)=f(t) \end{cases}$$

Inverse Problem: Find a constructive theory for recovering $q(x)$ to this problem and its graph analogue (Avdonin & B: boundary control method…*work in progress*, along with problem on a graph)

Lemma (mentioned in B and Craciun, 2005): Let v_1, v_2 be solutions to (6) corresponding to $q_1, q_2 \in L^2[0,l]$, for some stimulus $i(t)$, where $i \in C^2(0,T)$, with $i(0)=0, \quad i'(0)\neq 0$. If $v_1(0,t)=v_2(0,t)$ on $(0,T)$, then $q_1(x)=q_2(x)$ on $[0,l]$.

Remark: One parameter, but different, more challenging, than the classical physics case of $v_t + q(x)v = v_{xx}$.

Another case (B and Craciun, 2005): Morris-Lecar…recover K^+ channel density

$$(1+q(x))\frac{\partial v}{\partial t} + g_{Ca}m_\infty(v)(v-E_{Ca}) + q(x)w(v-E_K) + g_l(v-E_l) = \frac{\partial^2 v}{\partial x^2}$$

$$\frac{\partial w}{\partial t} = \varphi\left\{\frac{w_\infty(v)-w}{\tau(v)}\right\}$$

Single Branch IPs (continued)

Another non-traditional IP:

$$\frac{\partial v}{\partial t} + g(x)v = \frac{1}{a(x)}\frac{\partial}{\partial x}\left\{a(x)^2\frac{\partial v}{\partial x}\right\} \quad , \quad 0 < x < l, \quad t > 0$$

Separate variables: $v(x,t) = T(t)\varphi(x) \Rightarrow$

$$\frac{d}{dx}\left(a^2\frac{d\varphi}{dx}\right) + (\lambda - g)a\varphi = 0 \quad .$$

Liouville transformation: $y = \frac{1}{L}\int_0^x \frac{ds}{\sqrt{a(s)}}, \quad L := \int_0^l \frac{ds}{\sqrt{a(s)}} \ , \ w := a^{3/4}\varphi$

(1) $\frac{d^2w}{dy^2} + (\mu^2 - Q(y))w = 0, \quad 0 < y < 1$ standard form of S-L operator

where $\mu^2 = \lambda L^2 \quad and \quad Q = L^2 g + \frac{3L^2}{4}\left(\frac{d^2a}{dx^2} + \frac{1}{4a}\left(\frac{da}{dx}\right)^2\right)$.

Much is known about (1). For example, if *w'(0)-hw(0) = 0 = w'(1)*, then

$$\mu_n^2 = n^2\pi^2 + \int_0^1 Q(y)dy - \int_0^1 Q(y)\cos(2n\pi y)dy + O(1/n^2) \text{ as}$$

$n \to \infty, \quad \left(Q \in L^2(0,1)\right)$

Through spectral theory there are classical (and not so classical) ways of determining Q. We assume that is done. Can not recover both $a(x)$, $g(x)$, but

A. Given a smooth $a = a(x)$, then $b(x) = \frac{3}{4}\left(\frac{d^2a}{dx^2} + \frac{1}{4a}\left(\frac{da}{dx}\right)^2\right)$ is known, so

$$g(x) = Q(x)/L^2 - b(x) .$$

B. Given $g(x)$, and assume a smooth $a(x)$, we still require two extra pieces of information (initial/boundary data). We know $B(x) = \frac{4}{3}\left(Q/L^2 - g\right)$, so we need to solve $\frac{d^2a}{dx^2} + \frac{1}{4a}\left(\frac{da}{dx}\right)^2 = B(x)$, if $h := a(x)^{5/4}$, then solve

$$\frac{d^2h}{dx^2} = \frac{5}{4}B(x)h^{1/5} .$$

Initial Considerations on Morphology Determination

1. Dendritic tree is **passive** $\Rightarrow$ $\dfrac{\partial v}{\partial t} + g(x)v = \dfrac{\partial^2 v}{\partial x^2}$ (uniform properties). Our starting point, not the wave equation.

2. This leads to the spectral problem
$$-\frac{d^2\varphi}{dx^2} + g(x)\varphi = \lambda\varphi \quad \text{in } \Omega \setminus V_r$$
3. Classically, for all $\gamma \in \partial\Omega$, $\varphi(\gamma) = 0$.

4. Associated with operator $-\dfrac{d^2}{dx^2} + g$ is the discrete spectrum $\{\lambda_k\}_{k\geq 1}$; with associated eigenfunctions $\{\varphi_k\}_{k\geq 1}$, consider the pairs $\left\{\lambda_k, \dfrac{d\varphi_k}{dx}|_\Gamma\right\}_{k\geq 1}$ = (Dirichlet) *spectral data* of graph Ω

Theorem (Belishev): If the spectral data of two trees coincide, the trees are spatially isometric.

Remark: In determining the graph and densities g on Ω, Belishev (2004) studied the boundary controllability of the wave equation defined on $\Omega \setminus V_r$ and exploited that construction to recover the tree from its spectral data.

$$\text{Dynamic Inverse Problem} \xrightarrow{BCmethod} \text{Inverse Spectral Problem}$$

Remark (with Avdonin): For our case, need Neumann-to-Dirichlet map (inverse of Belishev's), Neumann spectral data, comparable Spectral Inverse Problem, and develop BC theory from diffusion equation standpoint, rather than a wave equation standpoint. Part of the program has been done with the heat equation, recovering a diffusivity coefficient on a single interval domain (Avdonin, Belishev, Rozhkov, 1997).

Comments on “Swiss Cheese”* Project

1. Threshold behavior: special cases of conditional comparison principles for *systems*; prove stronger threshold results; propagation results for systems on tree graphs; explore relationship between upper and lower bounds on propagation speed ($\bar{c}, \underline{c}$) and model parameters

2. More general conditions with respect to graph, system dynamics for conduction block

3. Distal current sources: find a way to make progress for active networks (nonlinear cable theory), and tie to stronger propagation results

4. Finish channel recovery problem for branch and network problems; develop BC theory for cable theory on networks (new spectral inverse problem, etc.); develop numerical approach for highlighted inverse problems

* “Swiss Cheese” because so many unfinished pieces of analysis and numerical work to do