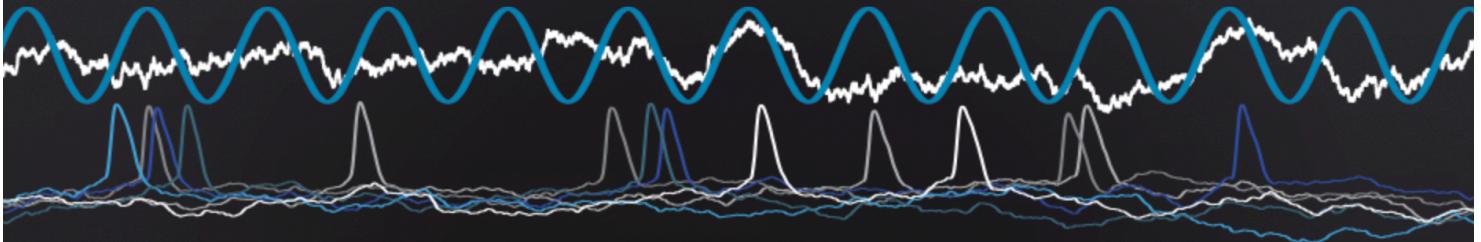


# ELECTROPHYSIOLOGICAL SIGNALS



GENERATION AND CHARACTERISATION

Michele GIUGLIANO

## Origin of Extracellular Signals

ATTENDANCE TRACKING - **code GVLZB**  
(for statistical purposes only)

<https://www.unimore.it/it/servizi/unimore-app>

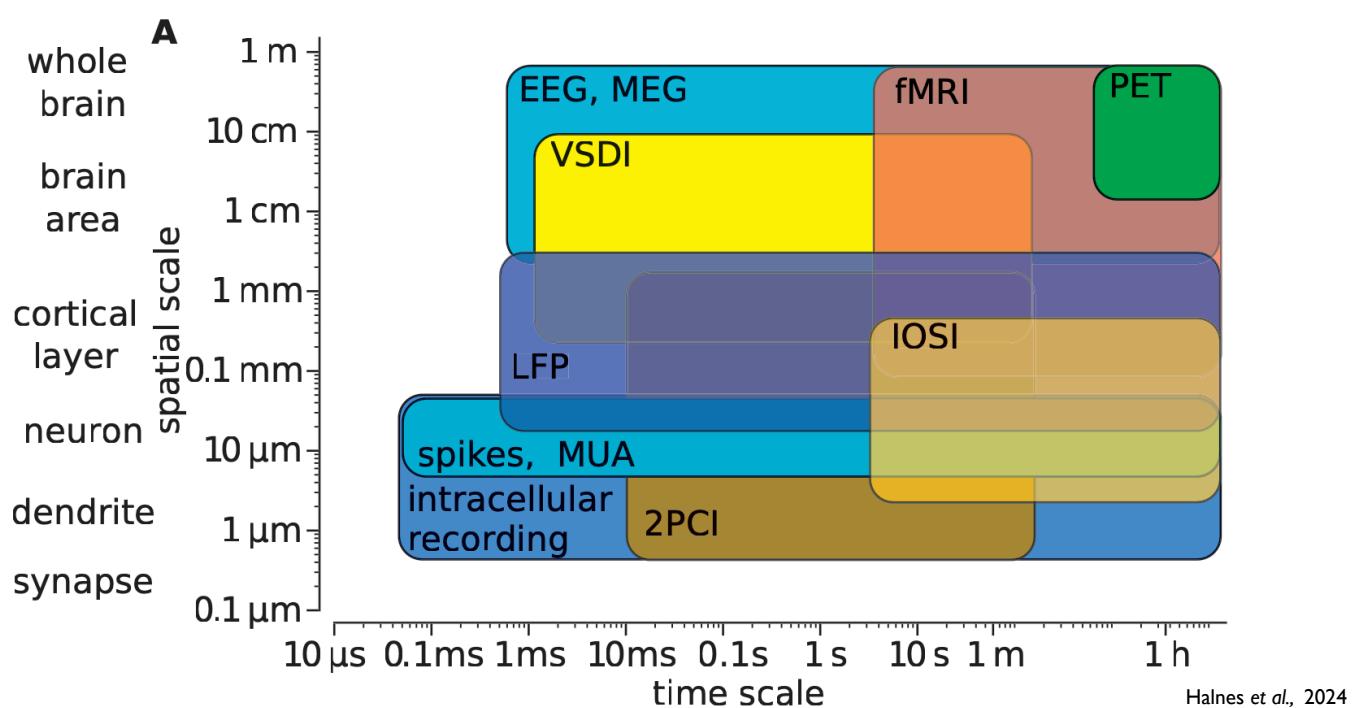
# References

supporting your study and understanding

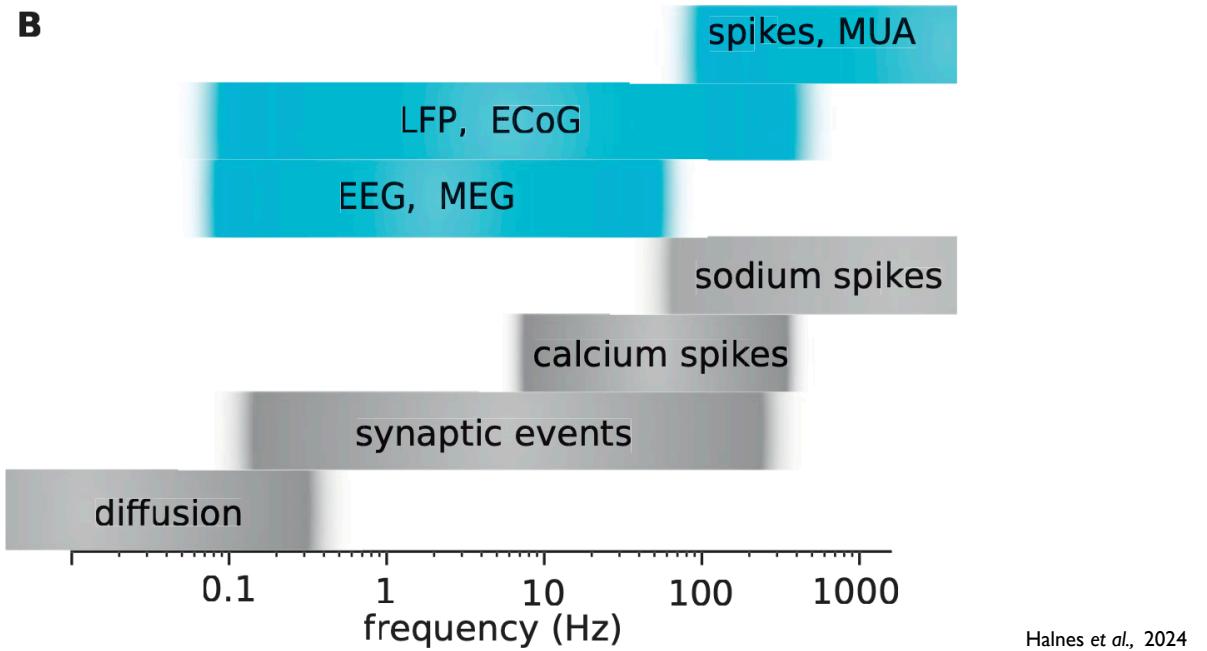
Chapters from

- Halnes et al., (2024) "Electric Brain Signals"
- Johnston & Wu (1994) "Foundations of Cellular Neurophysiology"
- Sterratt et al. (2011) "Principles of Computational Modelling..."
- Abbott LF, Dayan P (2001) "Theoretical Neuroscience"

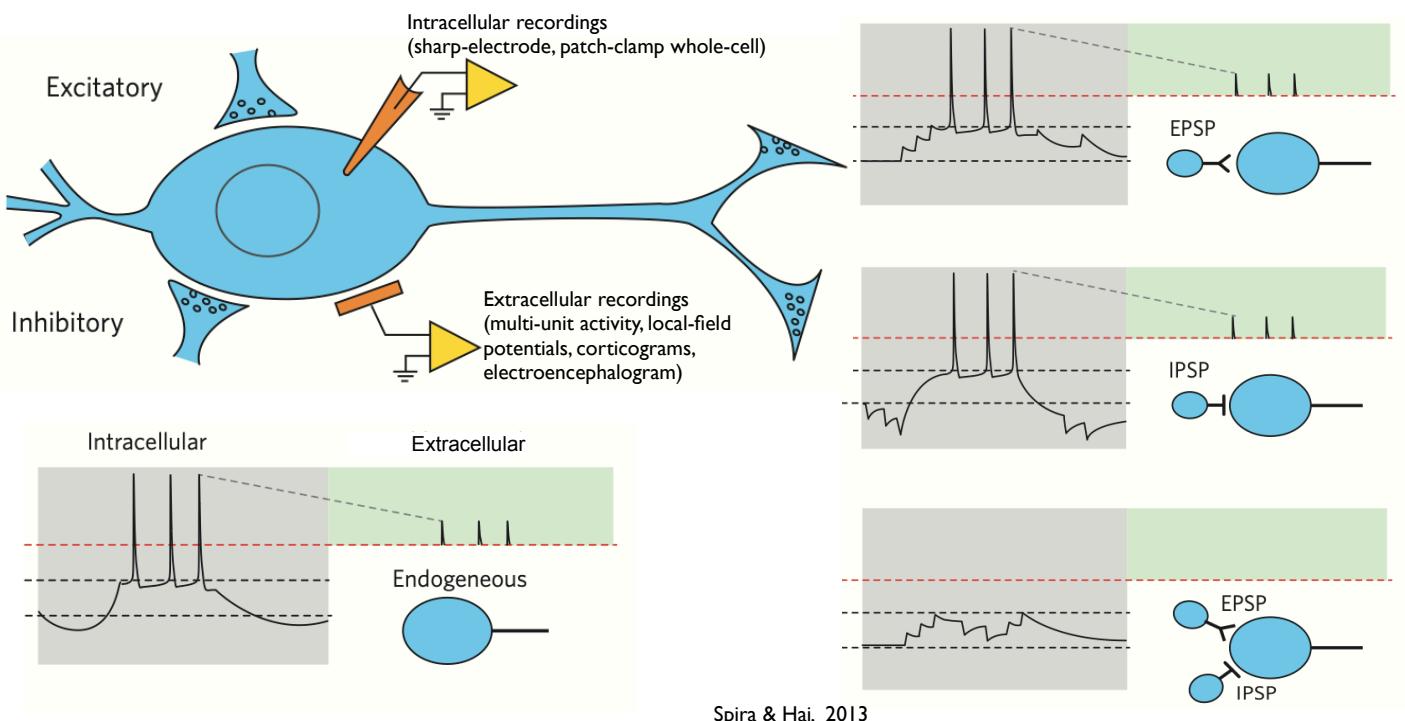
## Range of Techniques and Methods: not all the same!



# Heterogeneous (and multiple) time-scales

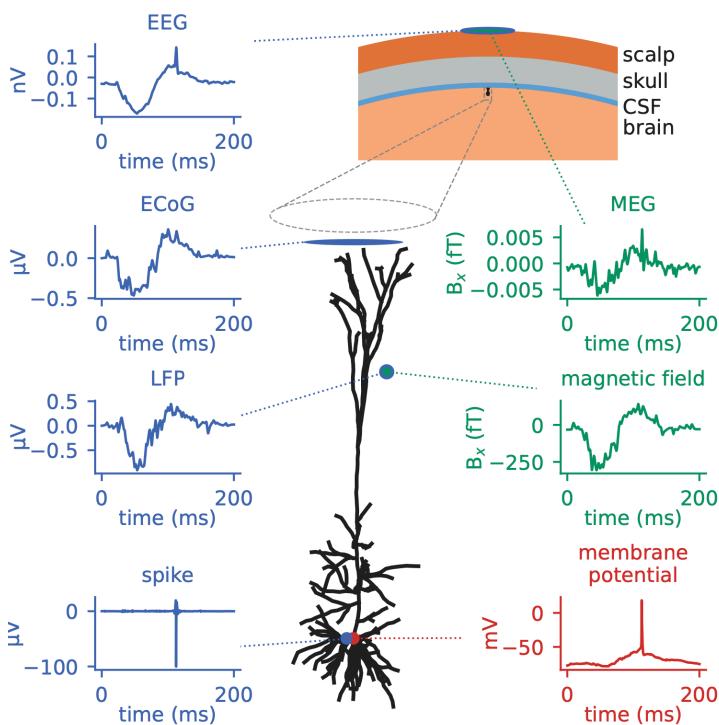


Extracellular signals: only the “fast/strong part”?



# Extracellular signals: not so elementary!

1) **Where** are you recording?



2) From **how far** in space is your recording technique sensitive too? Are you “listening” to one cell? To multiple cells?

3) How cells are **shaped**, in 3d?

4) **Where are**, if any, the synaptic **inputs** impinging to?

5) **What** (physical signals) are you recording?

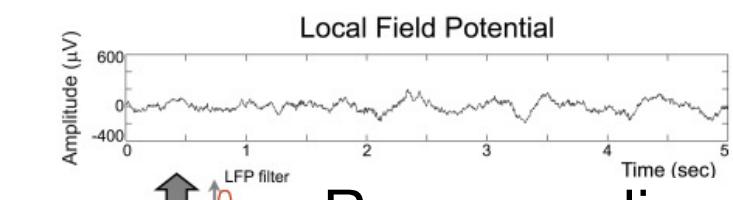
Halnes et al., 2024

## Low Frequency Parts/components

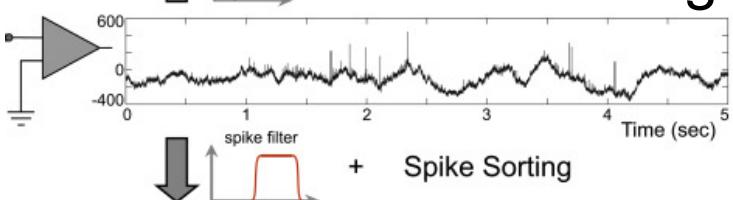
1 - 100 cycle/s

### LFP

Local Field Potential



Raw recording

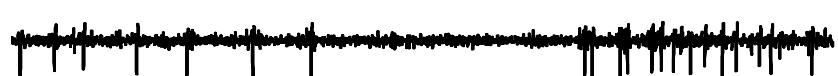


High-freq. components

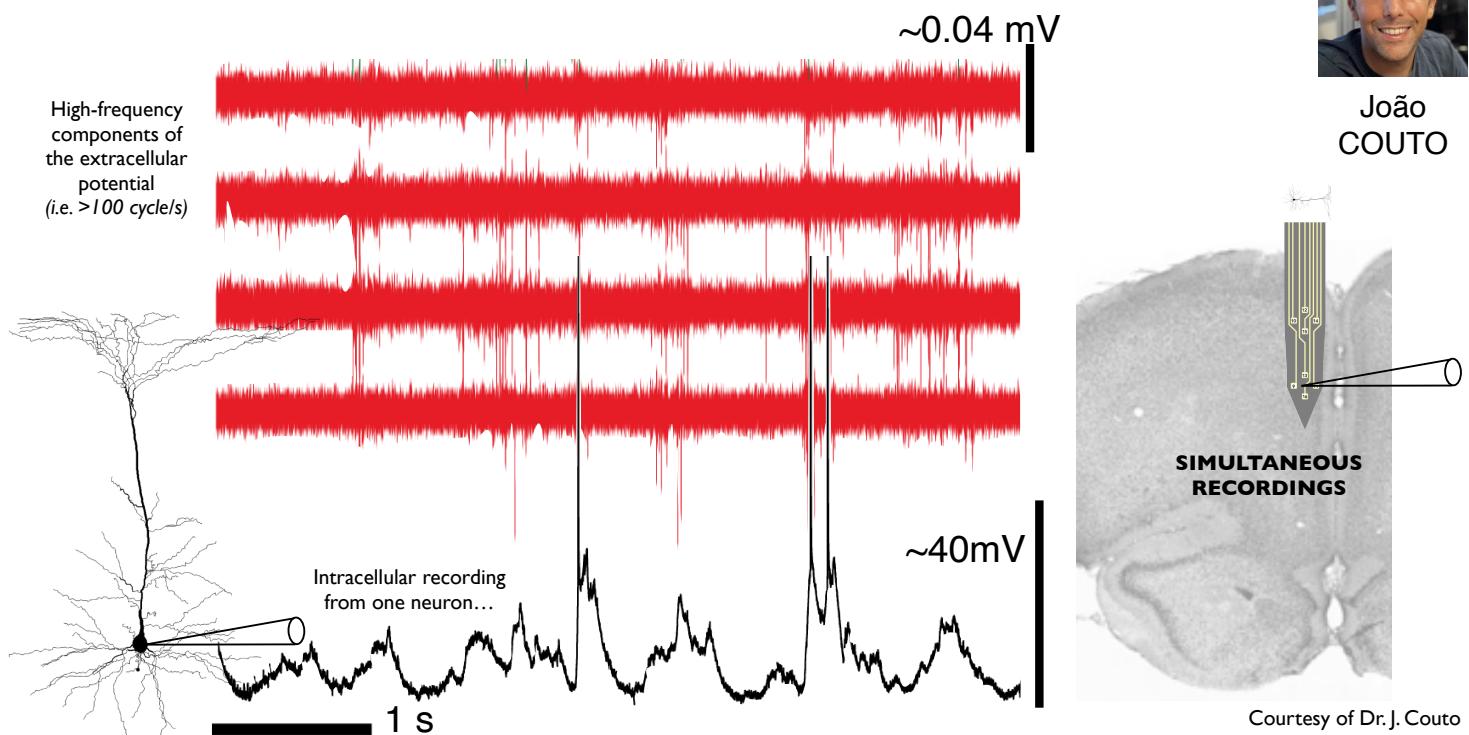
100 - 5000 cycle/s

### MUA SUA

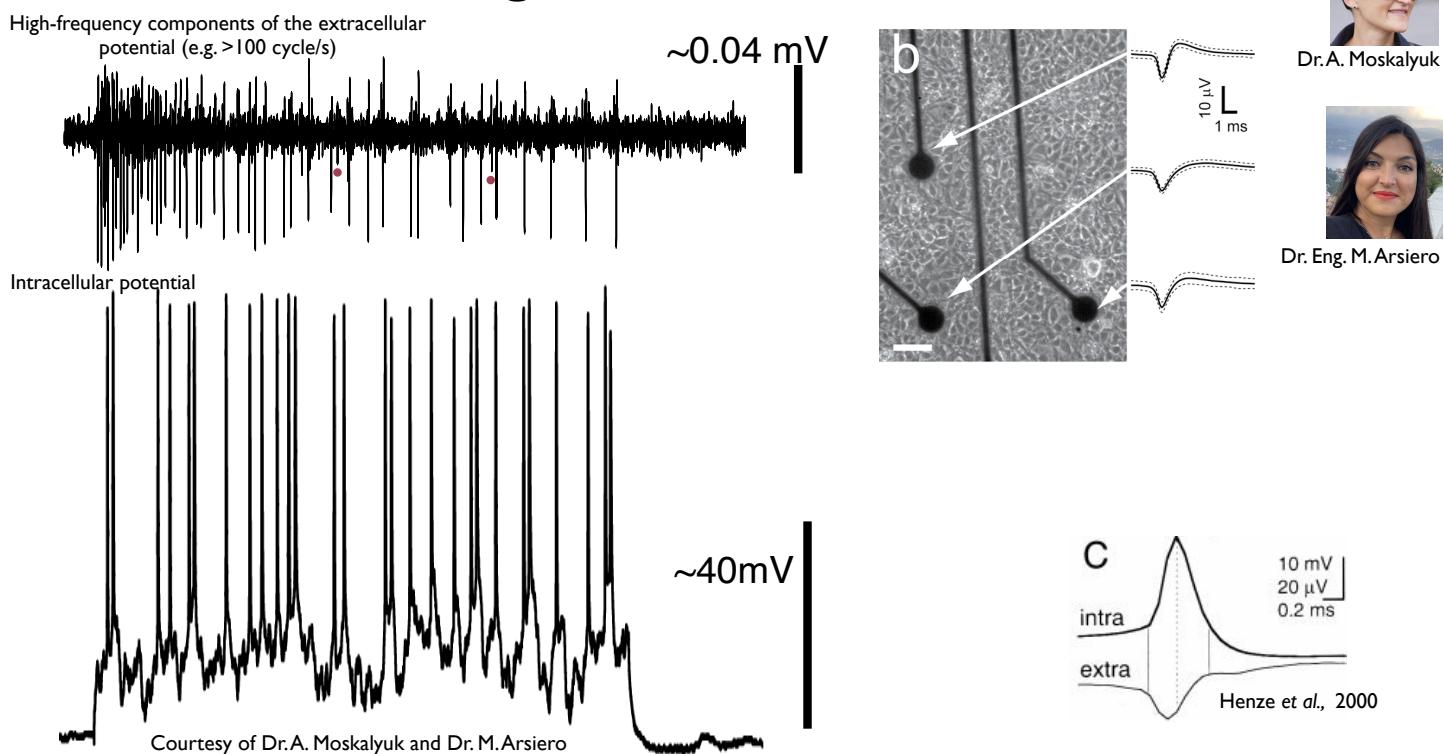
Multi-unit  
Single-unit  
Activity



# Extracellular signals: APs, near the soma?

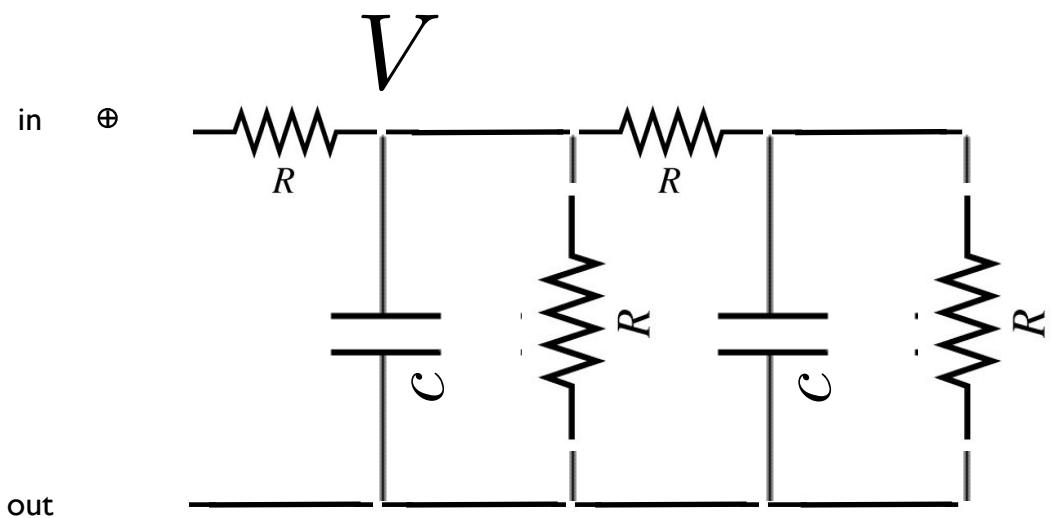
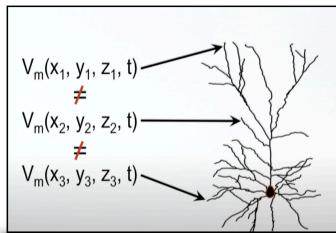


# Extracellular signals: APs, near the soma?



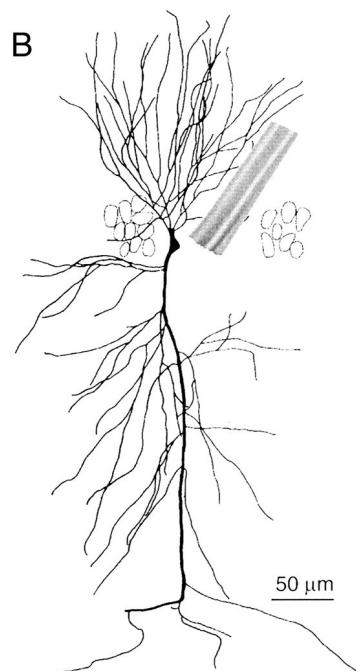
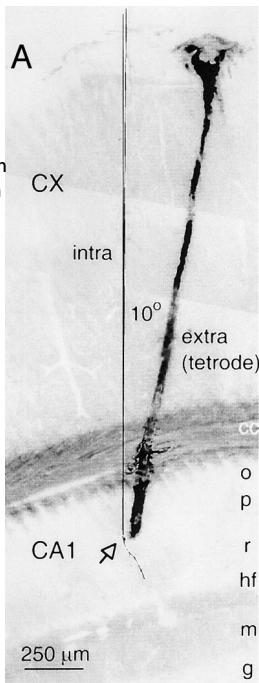
# How to make sense of this?

*Dendrites are **non-isopotential** portions of the neuron!*

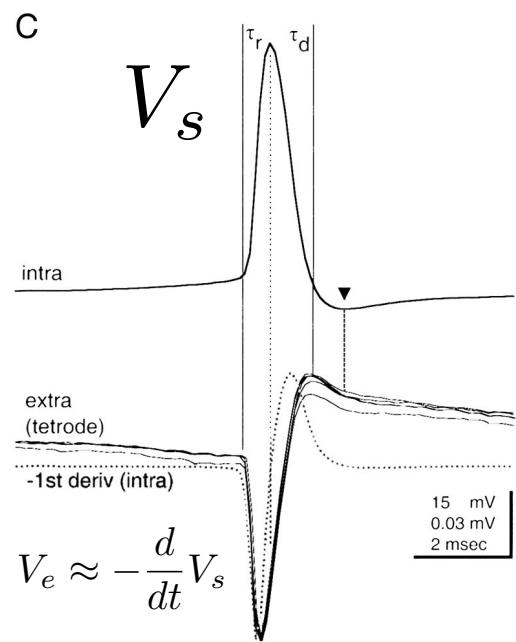


Extracellular signals: APs, near the soma

*In vivo recordings from rat hippocampus, with both tungsten wire(s) and sharp electrodes.*

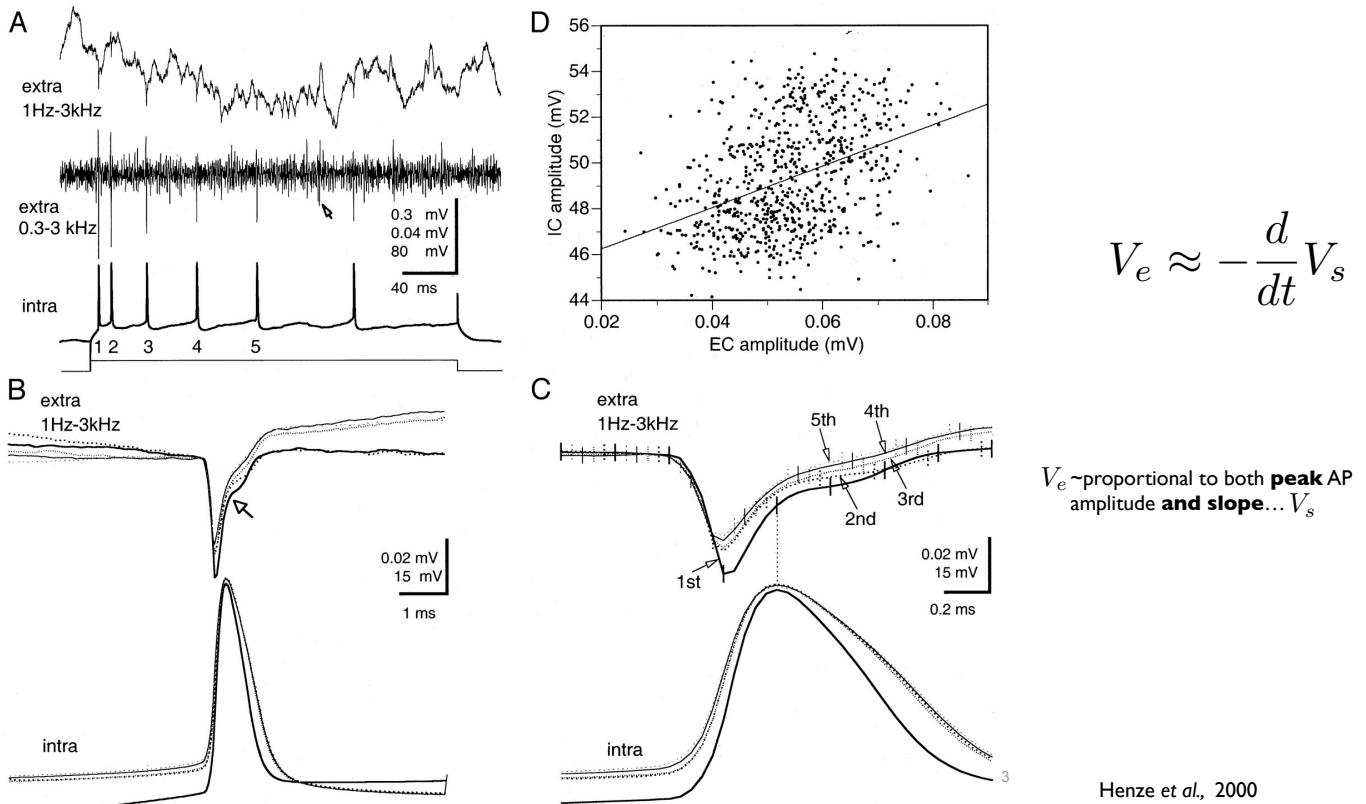


CA1, hippocampal pyramidal cell

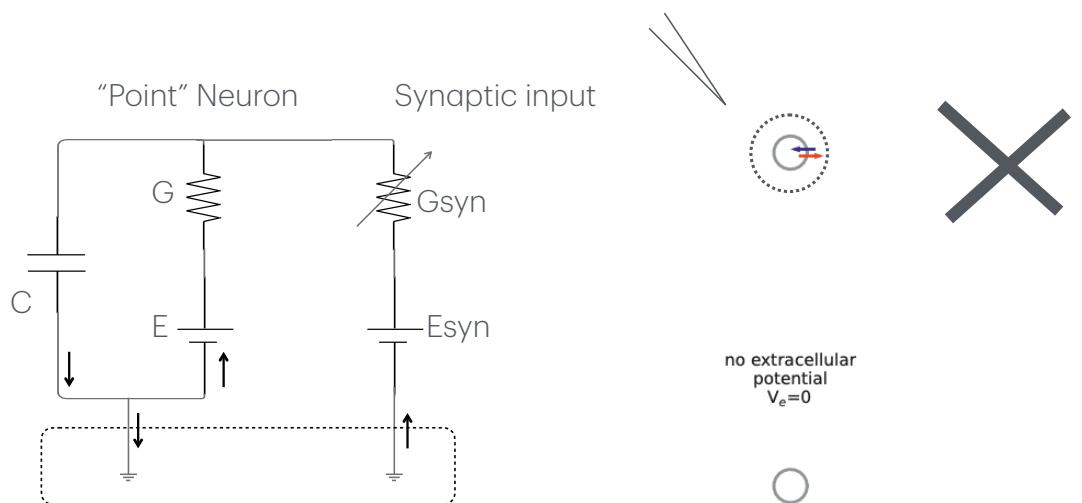


György Buzsáki

Henze et al., 2000



## Extracellular signals: APs, near the soma?



Currents, flowing in and out, cancel (at the same point in space).  
 No extracellular (difference of) potential(s) is generated.

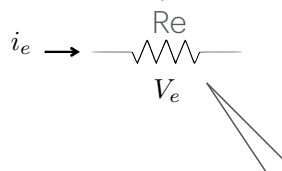
# Extracellular signals: APs, near the soma?

We must take the spatial extension of neurons into account!

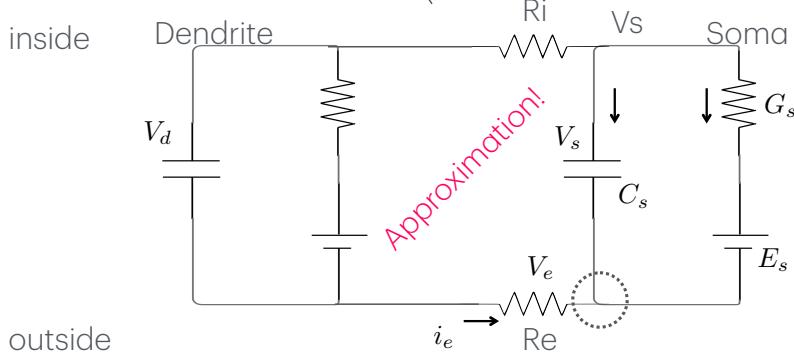


$$V_d \neq V_s$$

.....extracellular space.....



$$V_e = R_e i_e$$



$$i_e + i_c + i_m = 0$$

$$i_e + C_s \frac{d}{dt} V_s + G_s(V_s - E_s) = 0$$

$$V_e = R_e \left( -C_s \frac{d}{dt} V_s + G_s(E_s - V_s) \right)$$

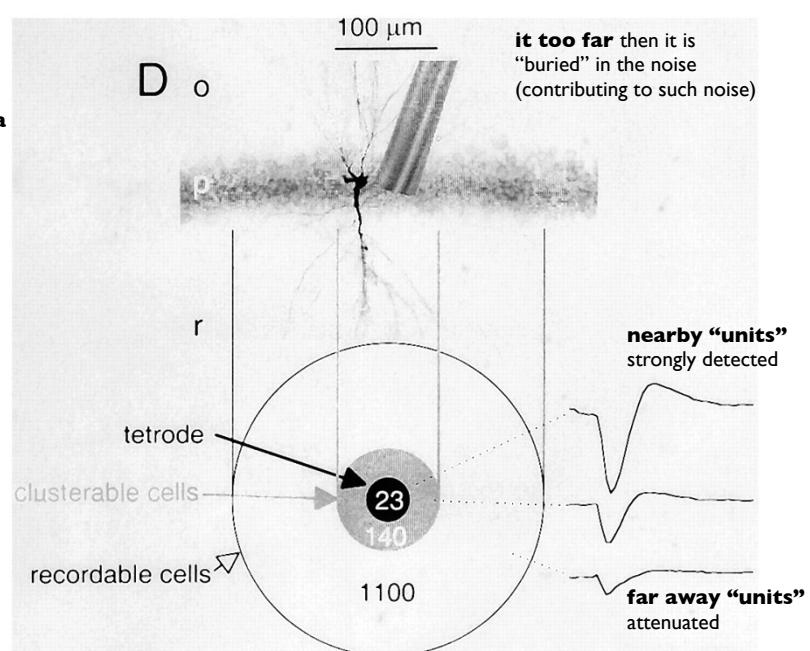
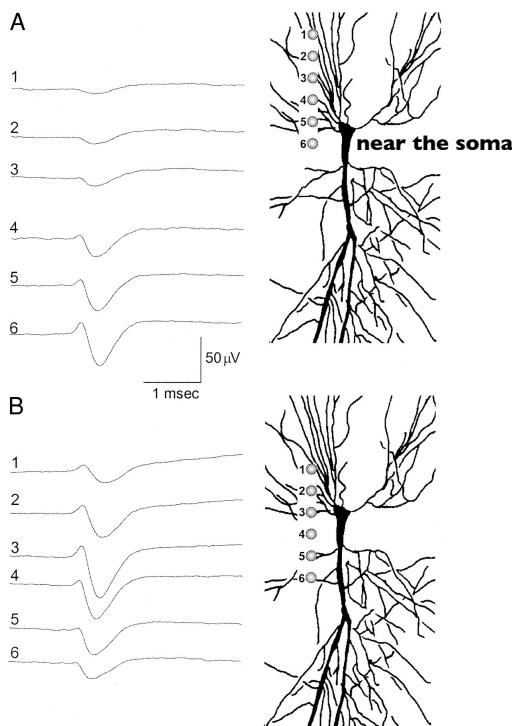
$$C_s \frac{d}{dt} V_s \gg G_s(E_s - V_s)$$

$$V_e \approx -\frac{d}{dt} V_s$$

## Extracellular signals: position and distance

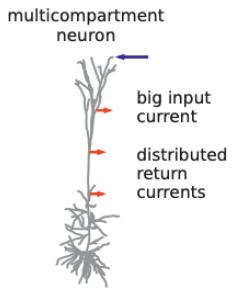
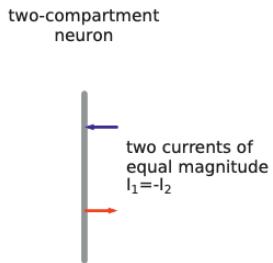
where are you recording?

how far are you recording?



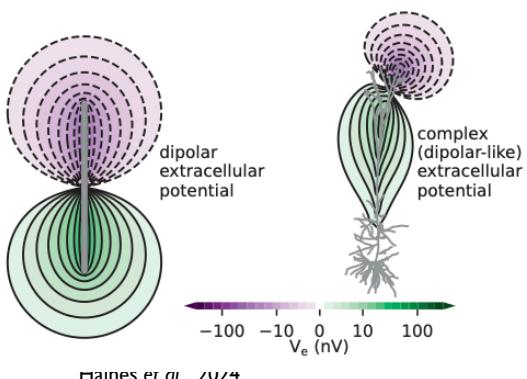
Henze et al., 2000

# Extracellular signals: more in general, how to?



- Describing, **across space**, ionic currents changes.  
**(cable theory)**

$$\lambda^2 \frac{\partial^2 v(x, t)}{\partial x^2} = \tau_m \frac{\partial v(x, t)}{\partial t} + v(x, t)$$



Haines et al., 2024

- Computing extracellular potentials, from the **spatial distribution of transmembrane currents**.  
**(volume-conductor theory)**

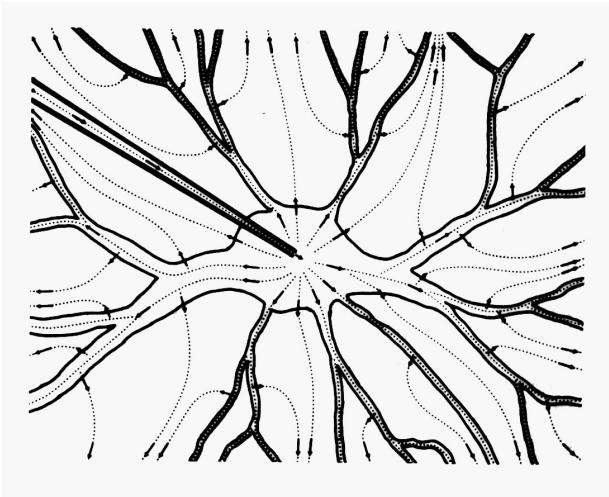
$$V_e(\mathbf{r}) = \sum_{\mathbf{n}} \frac{\mathbf{i}_n}{4\pi\sigma_t |\mathbf{r} - \mathbf{r}_n|}$$

Let's put on hold our discussion on extracellular signals (and volume-conductor theory).

Let's focus on space-dependent electrical properties and electrical phenomena of neurons.  
**(cable theory)**

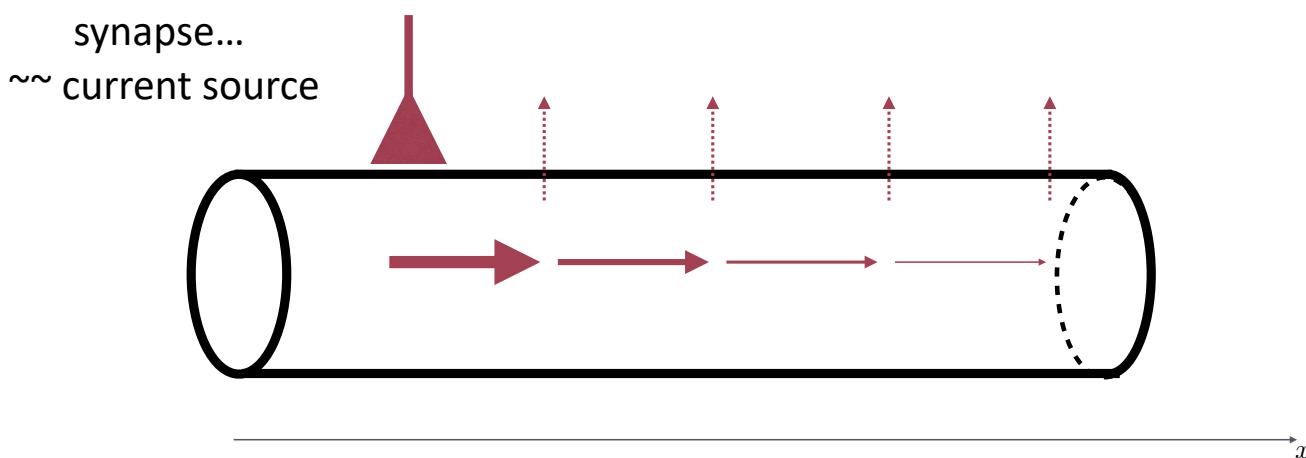
# 1959 Rall's Cable Theory for Neurites: motivations

- Most of the input current flows into the dendrites (not directly into soma)!
- Anyway, current have to flow outside the cell for “closing the circuit”.



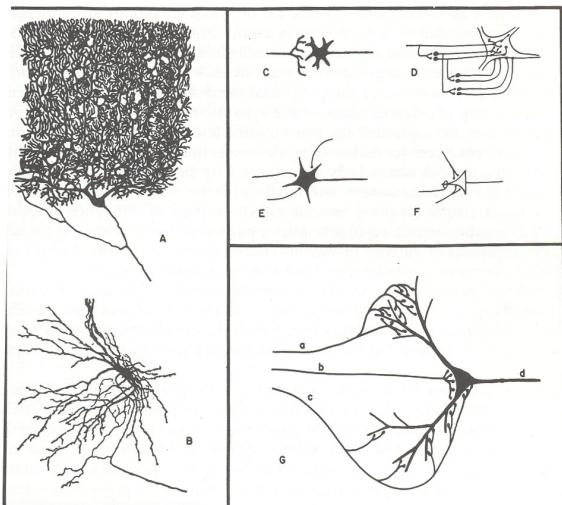
Wilfried Rall

# 1959 Rall's Cable Theory for Neurites: intuition



# 1959 Rall's Cable Theory for Neurites: motivations

- Understanding the **impact** of (**remote**) **dendritic** synapses activation (i.e. inputs) on the membrane potential of the **soma/axon** (i.e. output) region.



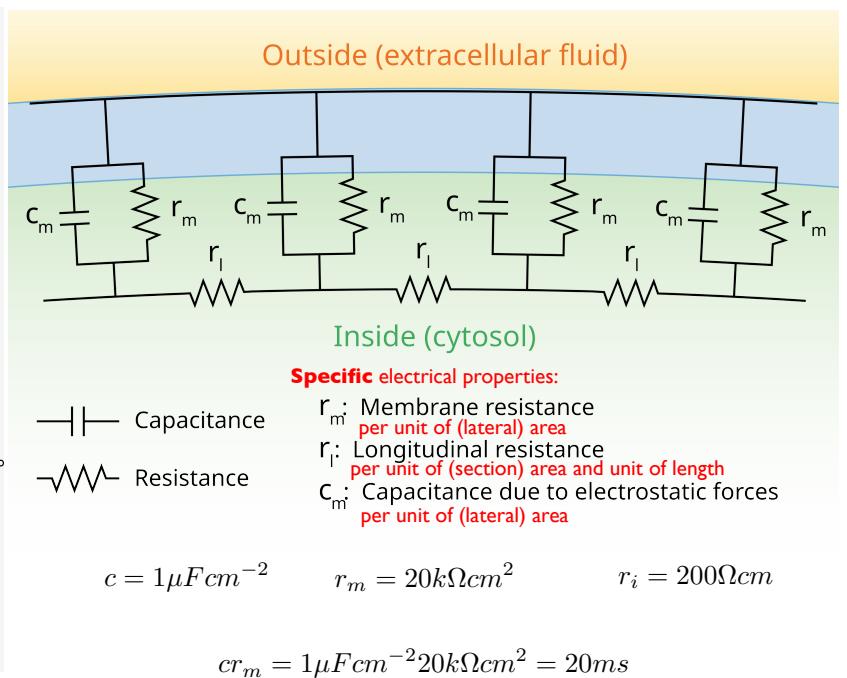
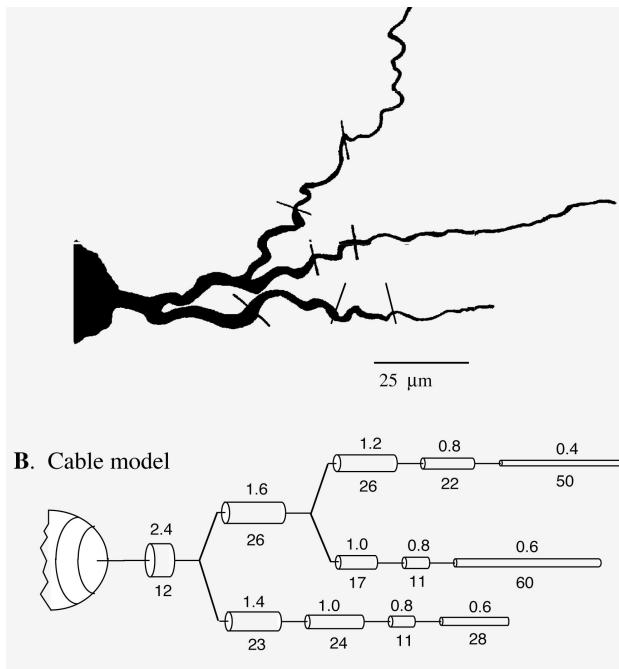
## RESULTS:

- Dendrites are non-isopotential portions of a neuron!
  - (i) voltages **attenuate** from synapse to soma!
  - (ii) it takes **time** for distal PSPs to reach the soma
  - (iii) the **shape** of EPSP/IPSP detected at the soma, **changes with** synaptic **distance**.

ATTENDANCE TRACKING - **code ???**  
(for statistical purposes only)

<https://www.unimore.it/it/servizi/unimore-app>

cylindrical symmetry, 1-d situation, thus 1-d cable!



## Cable Theory for Dendrites (and Axons)

Let's take an infinitesimal section...

$$V(x, t)$$

**Total electrical properties:**

$$R_m = r_m/S = r_m/(2\pi a \Delta x)$$

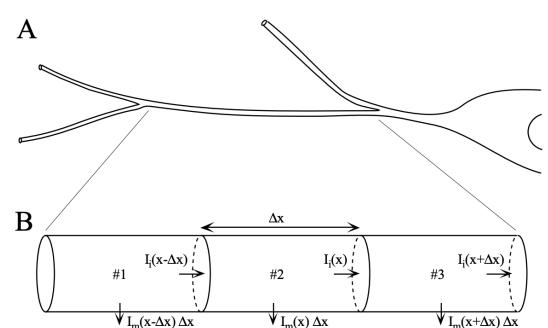
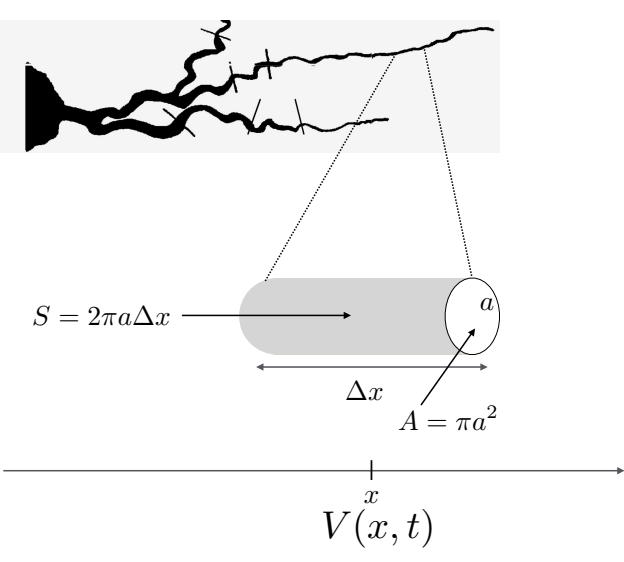
$$r_m = 20 k\Omega cm^2$$

$$C = cS = c(2\pi a \Delta x)$$

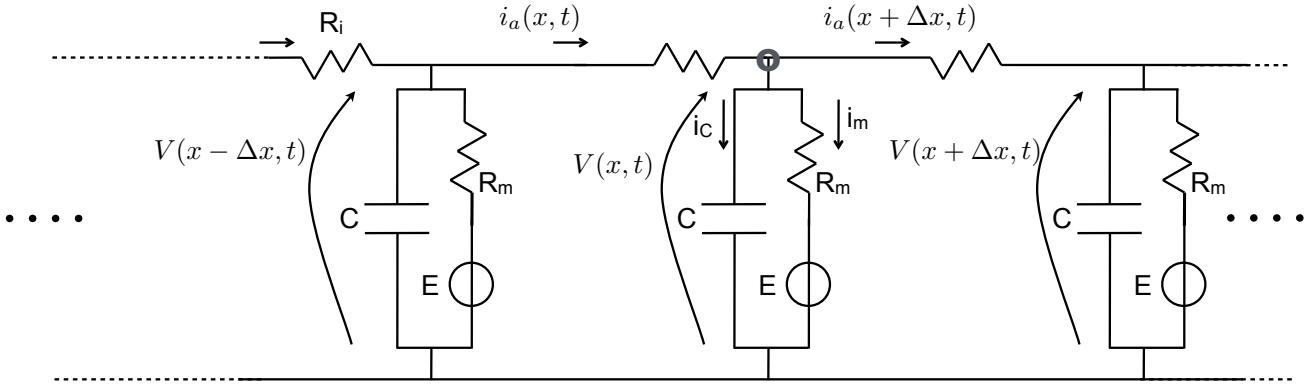
$$c = 1 \mu F cm^{-2}$$

$$R_i = r_i \Delta x / (a^2 \pi)$$

$$r_i = 200 \Omega cm$$



# Cable Theory for Dendrites (and Axons)



$$i_a(x, t) = i_C(x, t) + i_m(x, t) + i_a(x + \Delta x, t)$$

$$i_a(x, t) = \frac{V(x - \Delta x, t) - V(x, t)}{R_i} \quad i_m(x, t) = \frac{V(x, t) - E}{R_m}$$

$$i_a(x + \Delta x, t) = \frac{V(x, t) - V(x + \Delta x, t)}{R_i} \quad i_C(x, t) = C \frac{dV(x, t)}{dt}$$

$$\frac{V(x - \Delta x, t) - V(x, t)}{R_i} = C \frac{dV(x, t)}{dt} + \frac{V(x, t) - E}{R_m} + \frac{V(x, t) - V(x + \Delta x, t)}{R_i}$$

# Cable Theory for Dendrites (and Axons)

$$\frac{V(x - \Delta x, t) - V(x, t)}{R_i} = C \frac{dV(x, t)}{dt} + \frac{V(x, t) - E}{R_m} + \frac{V(x, t) - V(x + \Delta x, t)}{R_i}$$

$$v(x, t) = V(x, t) - E$$

$$\frac{v(x - \Delta x, t) - 2v(x, t) + v(x + \Delta x, t)}{R_i} = C \frac{dv(x, t)}{dt} + \frac{v(x, t)}{R_m}$$

$$\frac{R_m}{R_i} (v(x - \Delta x, t) - 2v(x, t) + v(x + \Delta x, t)) = R_m C \frac{dv(x, t)}{dt} + v(x, t)$$

$$v(x - \Delta x, t) \approx v(x, t) - \Delta x \quad \frac{dv(x, t)}{dx} + \frac{1}{2} \Delta x^2 \frac{d^2 v(x, t)}{dx^2} \quad +$$

$$v(x + \Delta x, t) \approx v(x, t) + \Delta x \quad \frac{dv(x, t)}{dx} + \frac{1}{2} \Delta x^2 \frac{d^2 v(x, t)}{dx^2}$$


---

...Invoking Taylor's...

$$v(x - \Delta x, t) + v(x + \Delta x, t) \approx 2v(x, t) + \Delta x^2 \frac{d^2 v(x, t)}{dx^2}$$

$$\frac{R_m}{R_i} (v(x - \Delta x, t) - 2v(x, t) + v(x + \Delta x, t)) = R_m C \frac{dv(x, t)}{dt} + v(x, t)$$

$$\frac{R_m}{R_i} \left( \Delta x^2 \frac{d^2 v(x, t)}{dx^2} \right) = R_m C \frac{dv(x, t)}{dt} + v(x, t)$$

PDE!

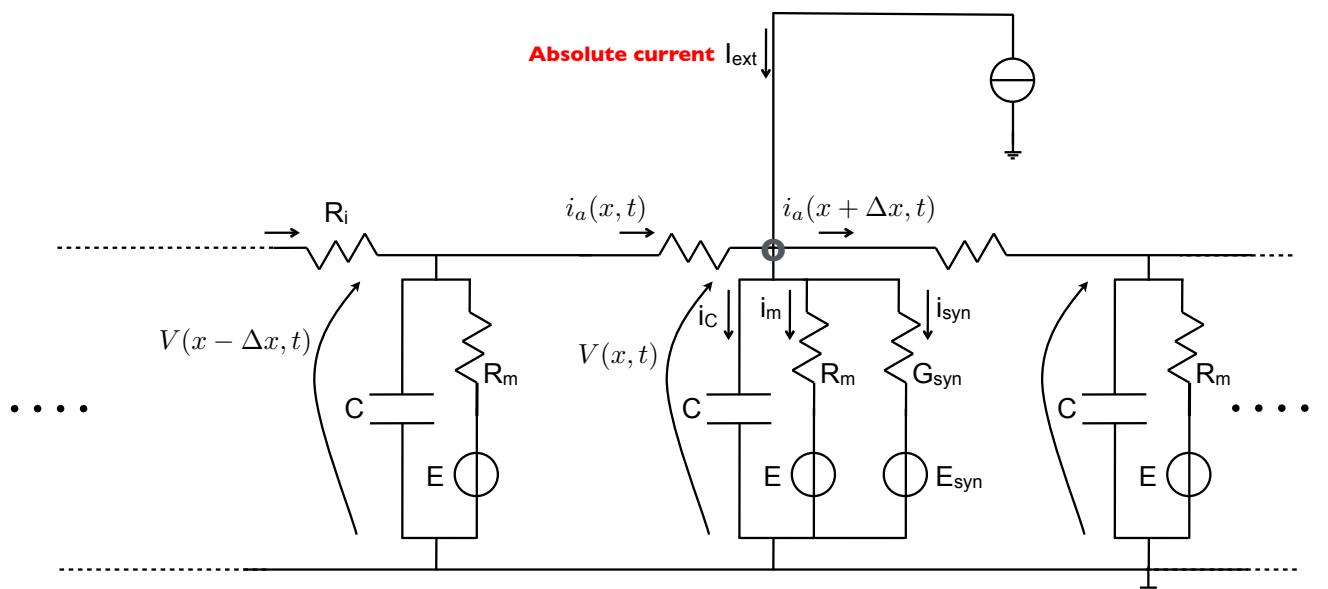
$$R_m = r_m/S = r_m/(2\pi a \Delta x)$$

$$C = cS = c(2\pi a \Delta x)$$

$$R_i = r_i \Delta x / (a^2 \pi)$$

$$\frac{a}{2} \frac{r_m}{r_i} \frac{\partial^2 v(x, t)}{\partial x^2} = r_m c \frac{\partial v(x, t)}{\partial t} + v(x, t)$$

...with synaptic and external current densities.



$$i_a(x, t) + I_{ext}(x, t) = i_C(x, t) + i_m(x, t) + i_{syn}(x, t) + i_a(x + \Delta x, t)$$

$$i_{syn}(x, t) = G_{syn} (V(x, t) - E_{syn})$$

$$i_{ext} = \frac{I_{ext}(x, t)}{2\pi a \Delta x}$$

$$\lambda^2 \frac{\partial^2 v(x, t)}{\partial x^2} = \tau_m \frac{\partial v(x, t)}{\partial t} + v(x, t)$$

$$\tau_m = r_m c$$

$$\lambda = \sqrt{\frac{a}{2} \frac{r_m}{r_i}}$$

$$\lambda^2 \frac{\partial^2 V(x, t)}{\partial x^2} = \tau_m \frac{\partial V(x, t)}{\partial t} + (V(x, t) - E)$$

$$\lambda^2 \frac{\partial^2 V(x, t)}{\partial x^2} = \tau_m \frac{\partial V(x, t)}{\partial t} + (V(x, t) - E) + r_m [g_{syn}(x, t)(V(x, t) - E) - i_{ext}(x, t)]$$

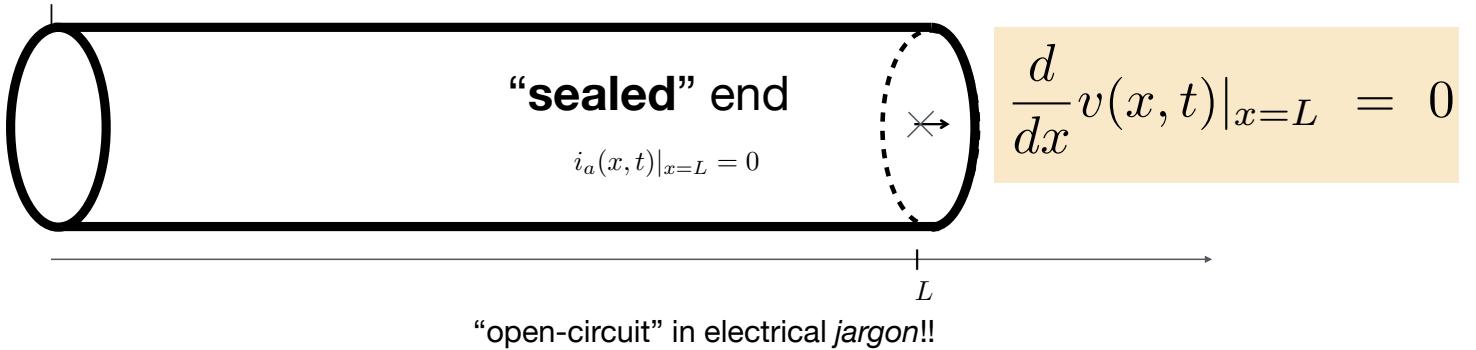
2 x Boundary conditions  
1 x Initial condition  
needed

$$i_{ext} = \frac{I_{ext}(x, t)}{2\pi a \Delta x}$$

Boundary conditions: 1

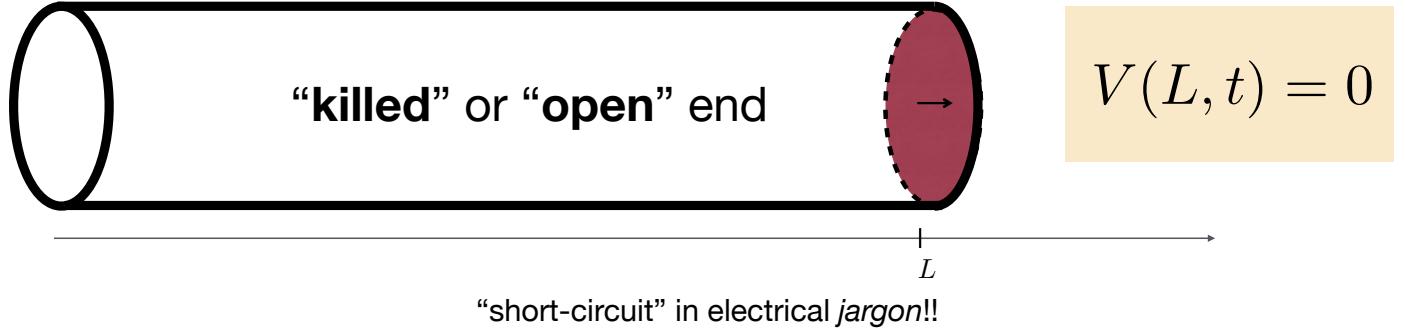
$$i_a(x, t) = \frac{v(x - \Delta x, t) - v(x, t)}{R_i} \quad i_a(x + \Delta x, t) = \frac{v(x, t) - v(x + \Delta x, t)}{R_i}$$

$$i_a(x, t)|_{x=L} = \frac{a^2 \pi}{r_i} \frac{v(x, t) - v(x + \Delta x, t)}{\Delta x}|_{x=L} = -\frac{a^2 \pi}{r_i} \frac{d}{dx} v(x, t)|_{x=L}$$

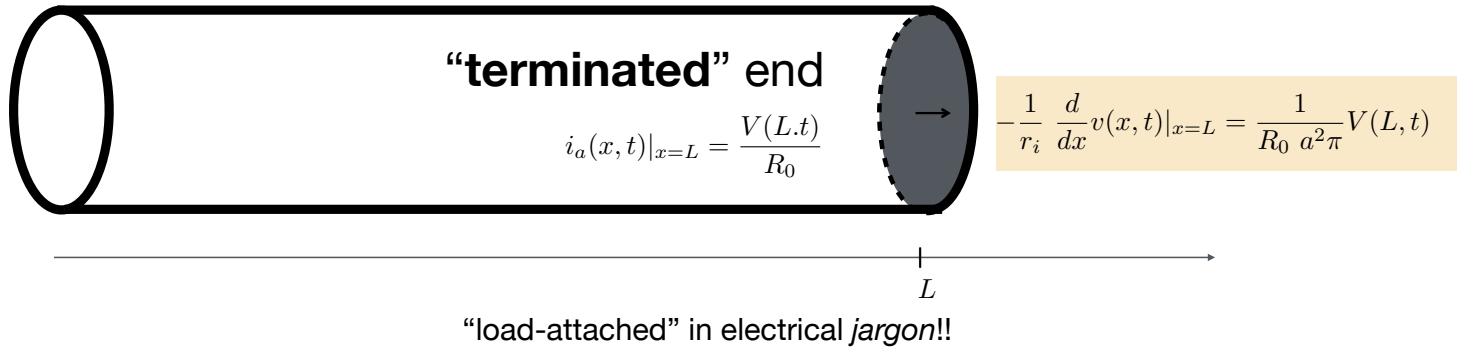


## Boundary conditions: 2

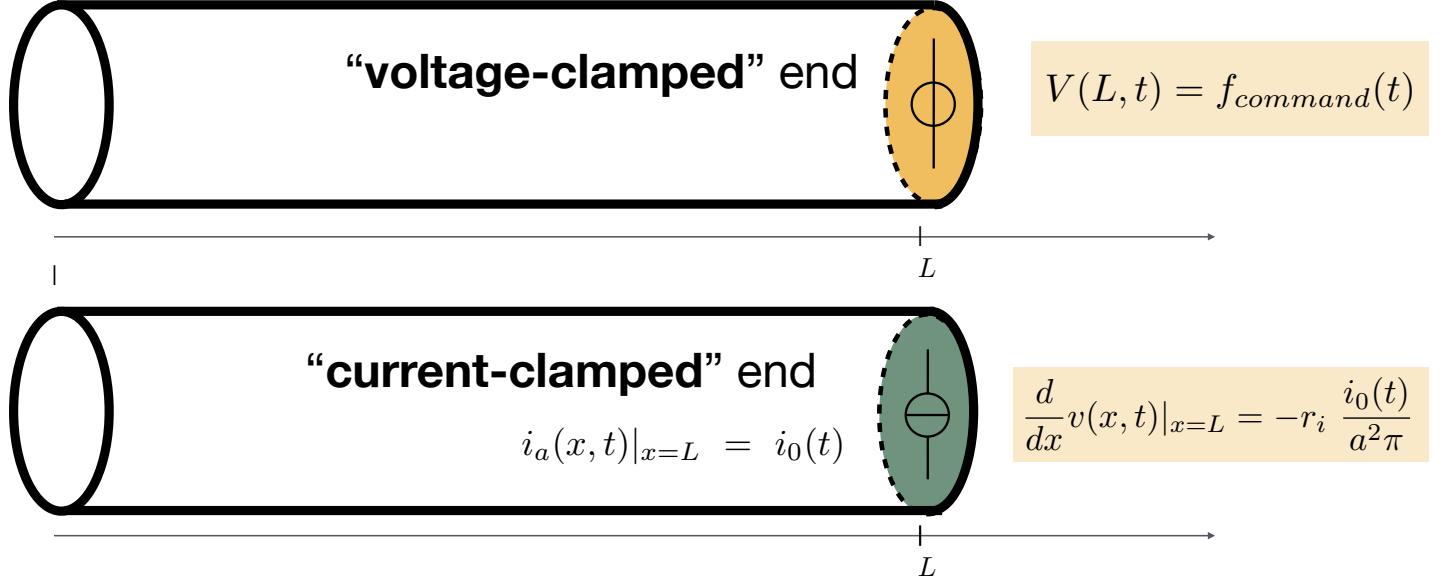
$$V_{in}(L, t) = V_{out} = 0$$



## Boundary conditions: 3



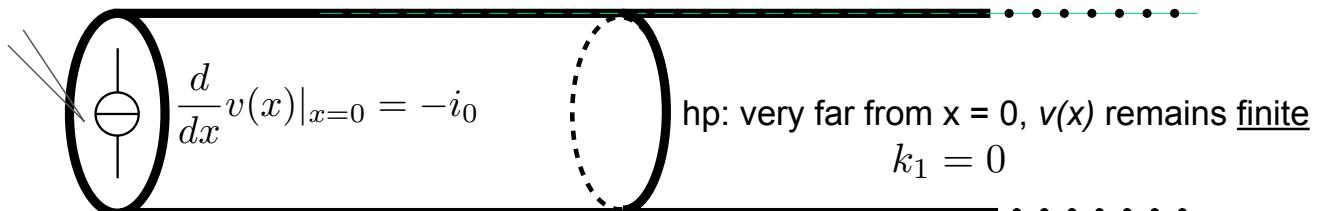
## Boundary conditions 4



**Steady-state (w.r.t. time) - DC regime**       $\frac{\partial v(x, t)}{\partial t} = 0$   
**semi-infinite cable...**       $v(x, t) \rightarrow v(x)$

$$\lambda^2 \frac{\partial^2 v(x, t)}{\partial x^2} = \tau_m \frac{\partial v(x, t)}{\partial t} + v(x, t) \quad \lambda^2 \frac{d^2 v(x)}{dx^2} = v(x) \quad \lambda^2 s^2 = 1$$

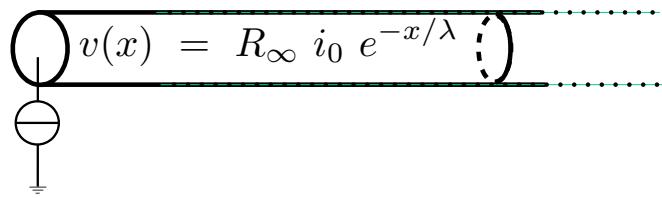
$$v(x) = k_1 e^{x/\lambda} + k_2 e^{-x/\lambda} \quad s_1 = +\frac{1}{\lambda} \quad s_2 = -\frac{1}{\lambda}$$



$$-\frac{a^2\pi}{r_i\lambda}k_2 = i_0 \quad k_2 = \sqrt{\frac{r_m r_i}{2a^3\pi^2}} i_0 \quad v(x) = \sqrt{\frac{r_m r_i}{2a^3\pi^2}} i_0 e^{-x/\lambda} = R_\infty i_0 e^{-x/\lambda}$$

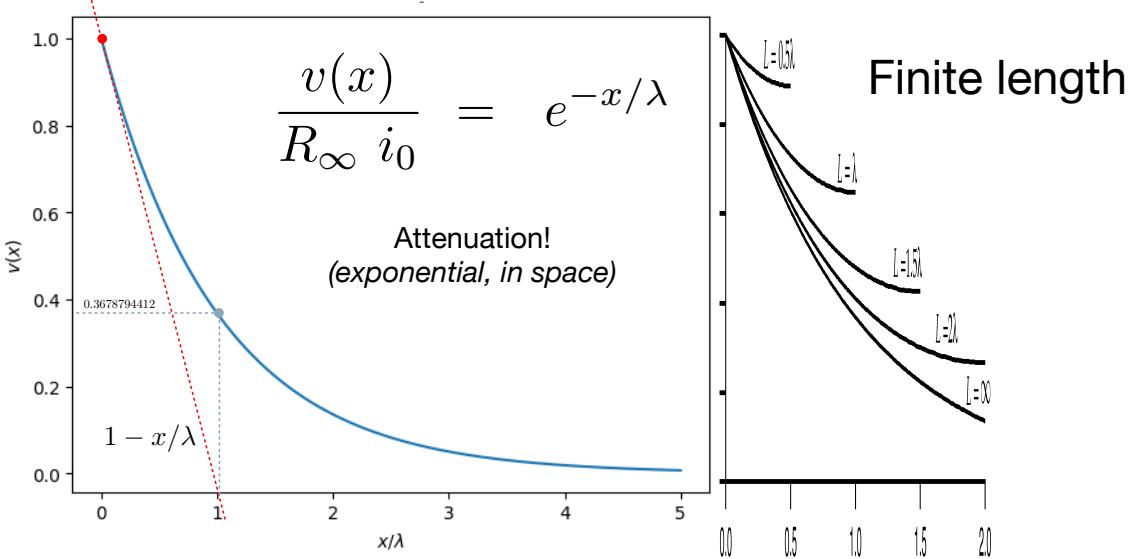
input resistance

## Steady-state (i.e. time) - semi-infinite cable

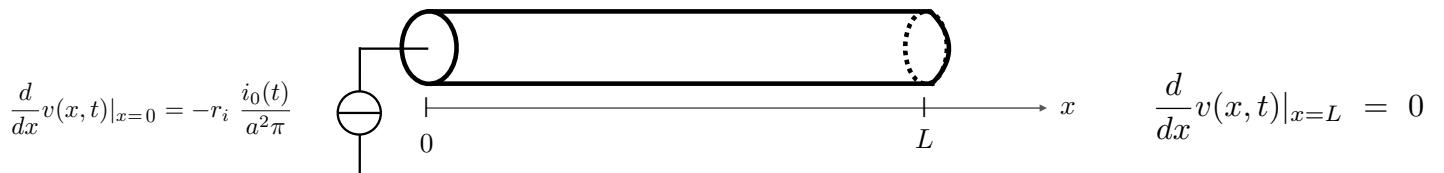


$$d = 4\mu m$$

$$\lambda = 500\mu m$$



## Steady-state (i.e. time) - finite cable



$$v(x) = k_1 e^{x/\lambda} + k_2 e^{-x/\lambda}$$

$$v(x) = \frac{a+b}{2} e^{x/\lambda} + \frac{a-b}{2} e^{-x/\lambda}$$

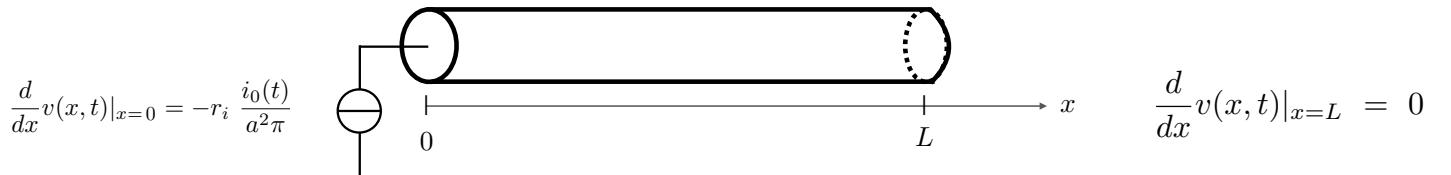
$$v(x) = \frac{a}{2} \left( e^{x/\lambda} + e^{-x/\lambda} \right) + \frac{b}{2} \left( e^{x/\lambda} - e^{-x/\lambda} \right)$$

$$\sinh x = \frac{e^x - e^{-x}}{2} \quad \cosh x = \frac{e^x + e^{-x}}{2} \quad \frac{d}{dx} \cosh(x) = \sinh(x) \quad \frac{d}{dx} \sinh(x) = \cosh(x)$$

$$v(x) = a \cosh(x/\lambda) + b \sinh(x/\lambda)$$

$$\frac{d}{dx} v(x) = \frac{a}{\lambda} \sinh(x/\lambda) + \frac{b}{\lambda} \cosh(x/\lambda)$$

## Steady-state (i.e. time) - finite cable



$$v(x) = a \cosh(x/\lambda) + b \sinh(x/\lambda)$$

$$\frac{d}{dx}v(x) = \frac{a}{\lambda} \sinh(x/\lambda) + \frac{b}{\lambda} \cosh(x/\lambda)$$

$$\frac{b}{\lambda} = -r_i \frac{i_0}{a^2\pi} \quad a \cosh(L/\lambda) + b \sinh(L/\lambda) = 0 \quad a = -b \frac{\sinh(L/\lambda)}{\cosh(L/\lambda)}$$

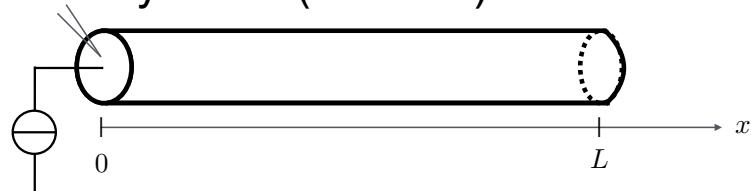
$$v(x) = -\frac{b}{\lambda} \frac{\sinh(L/\lambda) \cosh(x/\lambda) - \cosh(L/\lambda) \sinh(x/\lambda)}{\cosh(L/\lambda)}$$

$$v(x) = r_i \frac{i_0}{a^2\pi\lambda} \frac{\sinh[(L-x)/\lambda]}{\sinh(L/\lambda)}$$

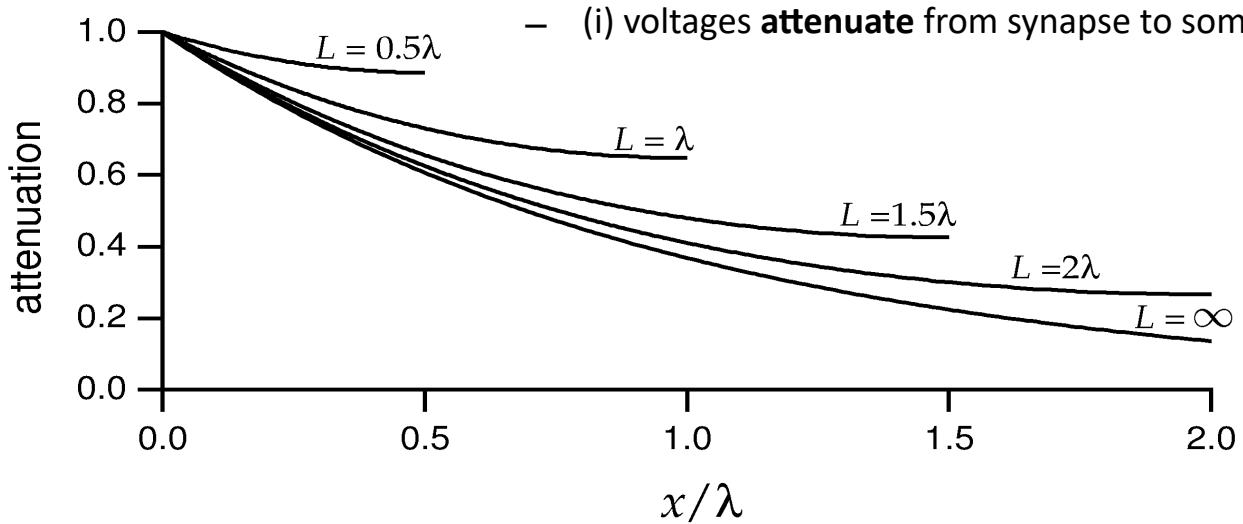
## Steady-state (i.e. time) - finite cable

$$d = 4\mu m$$

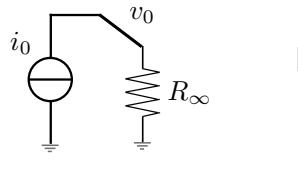
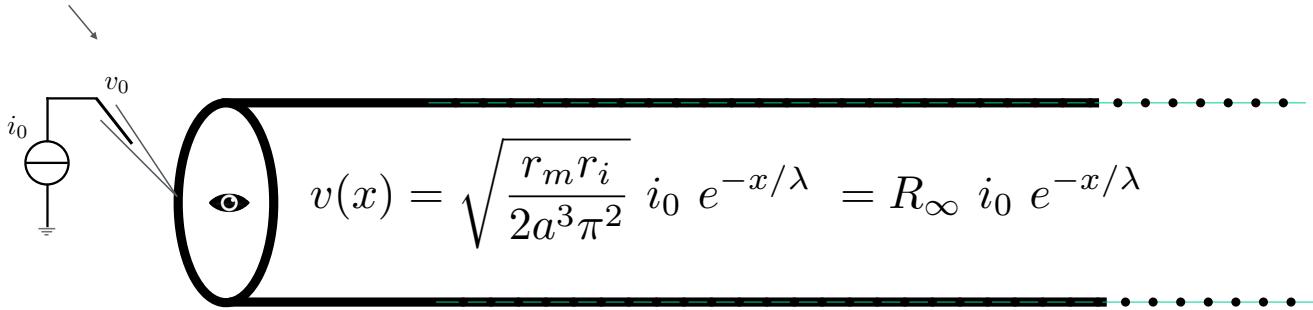
$$\lambda = 500\mu m$$



- Dendrites are non-isopotential portions of a neuron!
  - (i) voltages **attenuate** from synapse to soma!



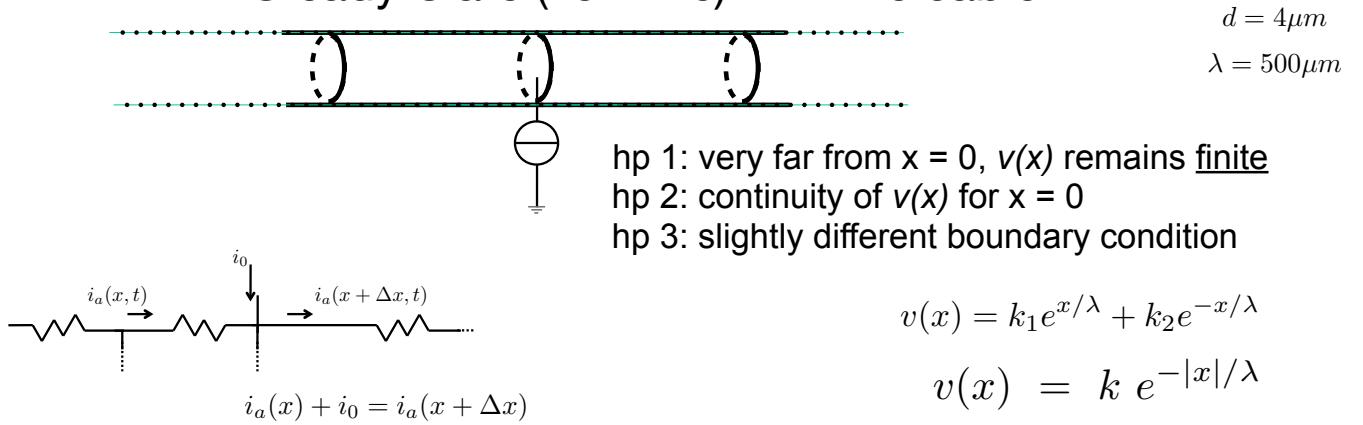
## Steady-state (w.r.t. time) - DC regime equivalent (Thevenin) circuit



I see just an equivalent resistor/conductance from this point of the “circuit”...

$$v_0 = R_\infty i_0$$

## Steady-state (i.e. time) - infinite cable



$$i_a(x, t) = \frac{V(x - \Delta x, t) - V(x, t)}{R_i}$$

$$\frac{\Delta x}{r_i} \frac{d^2 v(x, t)}{dx^2} \Big|_{x=0} = -\frac{i_0}{a^2 \pi}$$

$$i_a(x + \Delta x, t) = \frac{V(x, t) - V(x + \Delta x, t)}{R_i}$$

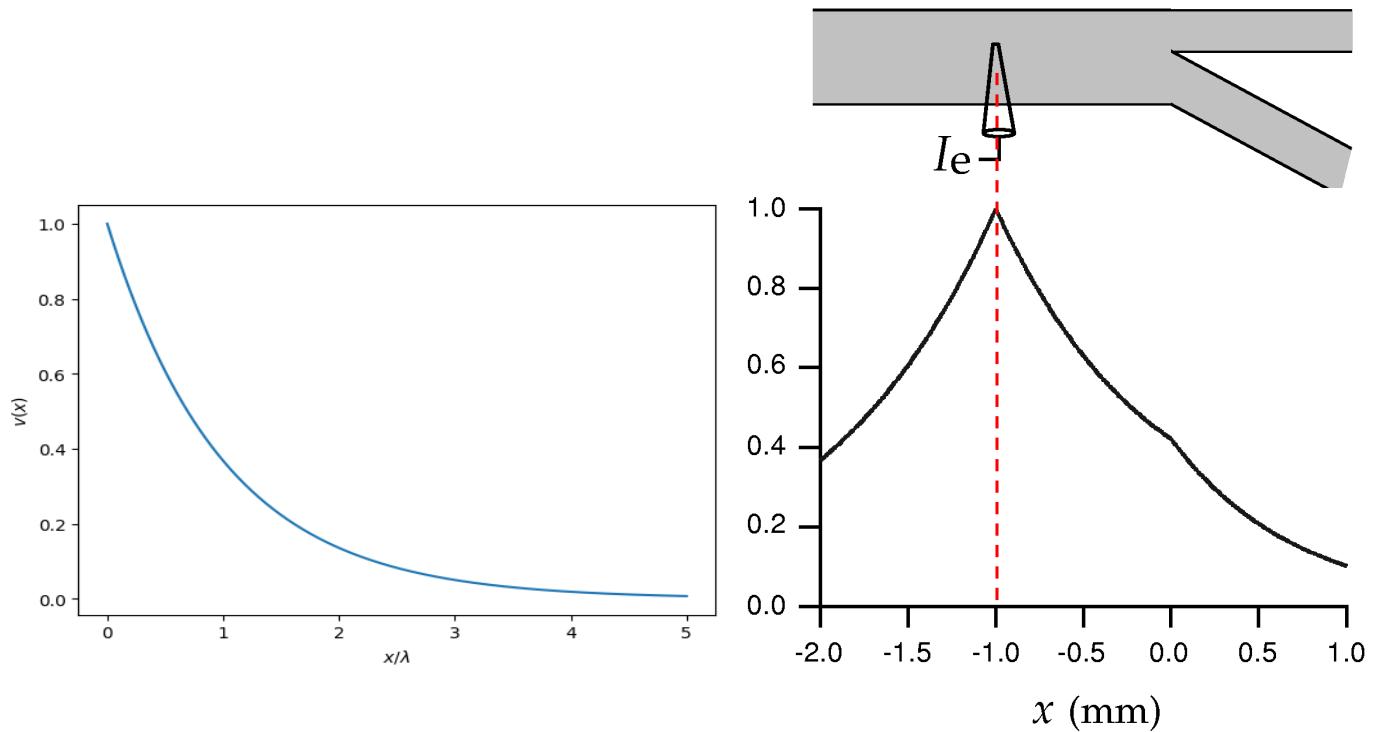
$$\frac{\Delta x}{r_i} \frac{k}{\lambda^2} = -\frac{i_0}{a^2 \pi}$$

$$v(x - \Delta x, t) + v(x + \Delta x, t) \approx 2v(x, t) + \Delta x^2 \frac{d^2 v(x, t)}{dx^2}$$

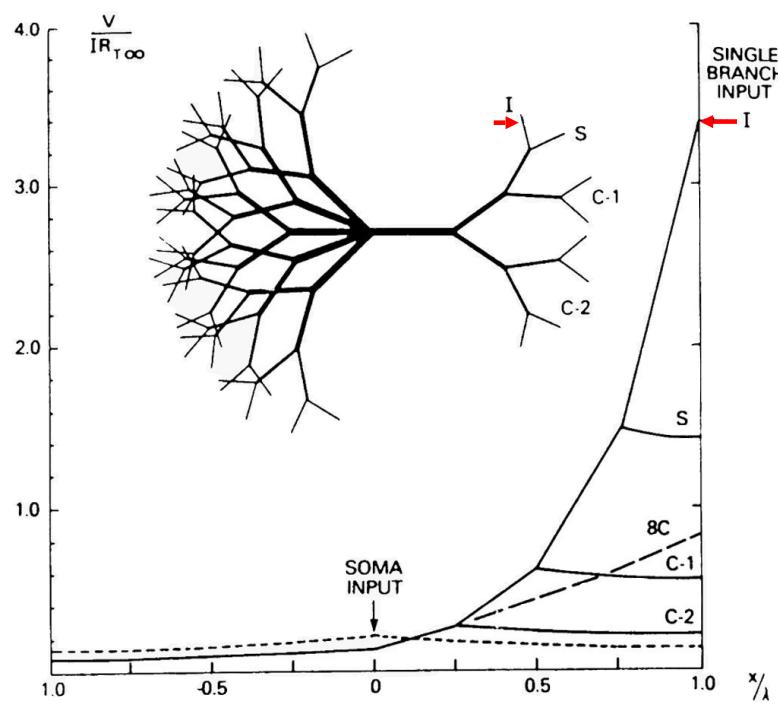
$$k = -\frac{r_m}{\Delta x} \frac{i_0}{2\pi a} \quad k = -r_m I_0$$

$$\frac{\Delta x^2}{R_i} \frac{d^2 v(x, t)}{dx^2} \Big|_{x=0} = -i_0$$

$$v(x) = -r_m I_0 e^{-|x|/\lambda}$$

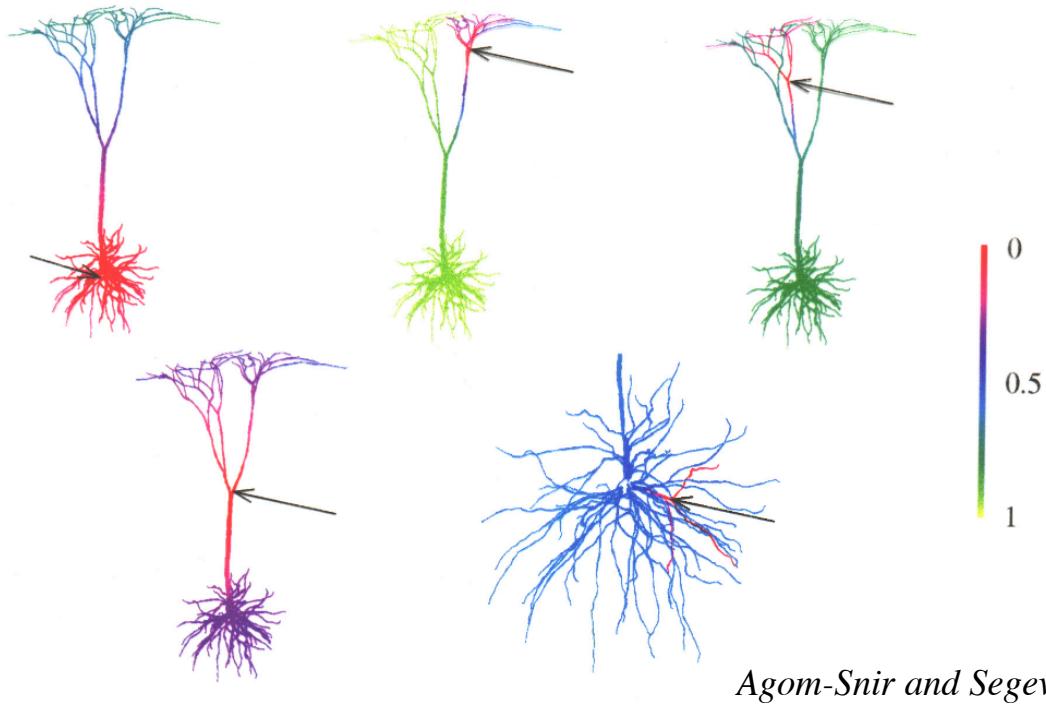


Steep and asymmetrical voltage attenuation  
(from dendrites to the soma; synaptic territories)



Rall & Rinzel, 1973

## Dendritic “functional subunits” (“synaptic territory”)



*Agom-Snir and Segev*

Sinusoidal Regime - AC regime  
semi-infinite cable...

$$\lambda^2 \frac{\partial^2 v(x, t)}{\partial x^2} = \tau_m \frac{\partial v(x, t)}{\partial t} + v(x, t)$$

$$W(x, \omega) = \frac{1}{2\pi} \int_{-\infty}^{\infty} v(x, t) e^{-j\omega t} dt \quad \text{Fourier transform: time “disappears”...}$$

$$\lambda^2 \frac{d^2 W(x, \omega)}{dx^2} = \tau_m j \omega W(x, \omega) + W(x, \omega) \quad \frac{\lambda^2}{1 + \tau_m j \omega} \frac{d^2 W(x, \omega)}{dx^2} = W(x, \omega)$$

$$W(x, \omega) = R_\infty I_0(\omega) e^{-x/\lambda^*} \quad \lambda^* = \frac{\lambda}{\sqrt{1 + \tau_m j \omega}}$$

$$W(x, \omega) = R_\infty I_0(\omega) M e^{j\Phi} \quad M = M(x, \omega) = ?$$

## Frequency-dependent and complex space-constant

$$\frac{1}{\lambda^*} = \frac{\sqrt{1 + \tau_m j\omega}}{\lambda} = A e^{j\phi}$$

$$A = \frac{\sqrt[4]{1 + \tau_m^2 \omega^2}}{\lambda}$$

$$\phi = \frac{1}{2} \arctan \tau_m \omega$$

$$e^{j\phi} = \cos(\phi) + j \sin(\phi)$$

**Euler's formula**  
*the most beautiful  
 equation in mathematics*

$$\cos(\arctan k) = \frac{1}{\sqrt{1+k^2}}$$

$$\cos(\alpha/2) = \pm \sqrt{\frac{1 + \cos(\alpha)}{2}}$$

$$\cos(0.5 \arctan k) = \pm \sqrt{\frac{1 + \frac{1}{\sqrt{1+k^2}}}{2}}$$

$$\sin(\arctan k) = \frac{k}{\sqrt{1+k^2}}$$

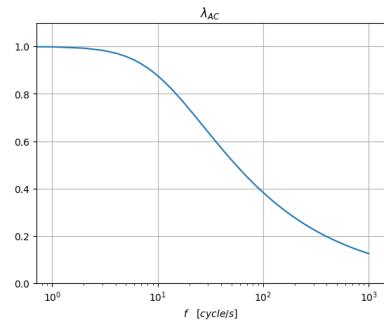
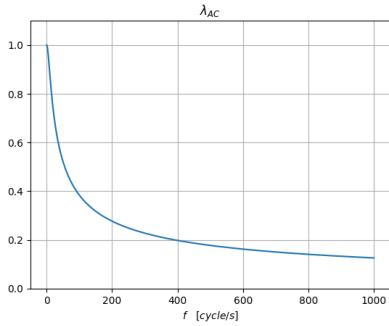
$$\sin(\alpha/2) = \pm \sqrt{\frac{1 - \cos(\alpha)}{2}}$$

$$W(x, \omega) = R_\infty I_0(\omega) M e^{j\Phi} \quad M = M(x, \omega) = ?$$

$$A = \frac{\sqrt{1 + \tau_m^2 \omega^2}}{\lambda} \quad \phi = \frac{1}{2} \arctan \tau_m \omega \quad e^{j\phi} = \cos(\phi) + j \sin(\phi)$$

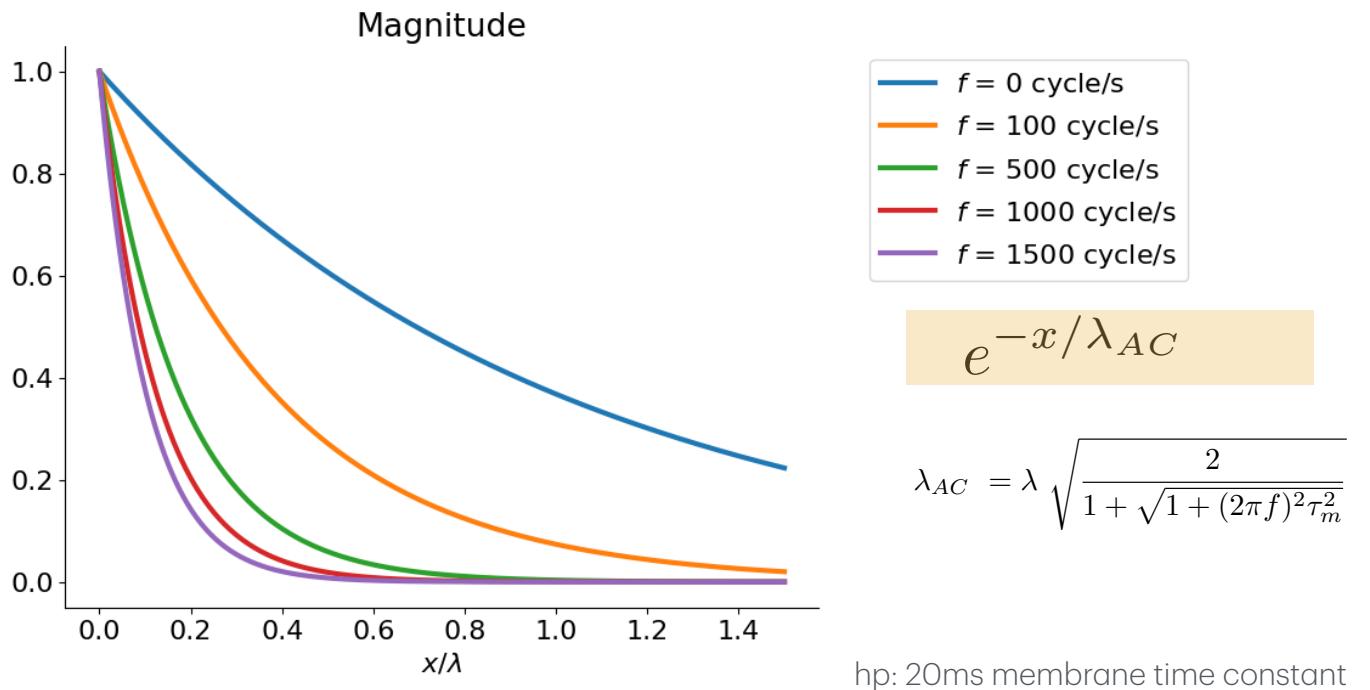
$$W(x, \omega) = R_\infty I_0(\omega) e^{-x A \cos(\phi)} e^{-j x A \sin(\phi)}$$

$$e^{-x/\lambda_{AC}} \quad \lambda_{AC} = \frac{1}{A \cos(\phi)} = \lambda \sqrt{\frac{2}{1 + \sqrt{1 + (2\pi f)^2 \tau_m^2}}}$$



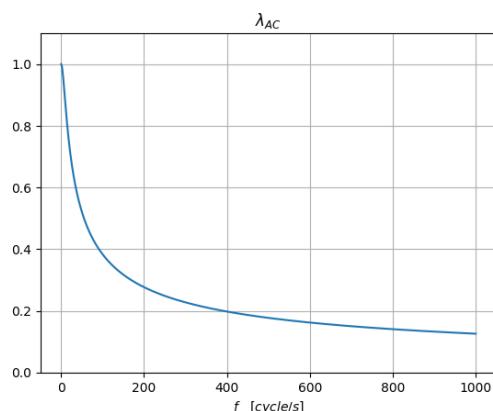
hp: 20ms membrane time constant

## Sinusoidal Regime - AC - attenuation (semi-infinite cable...)

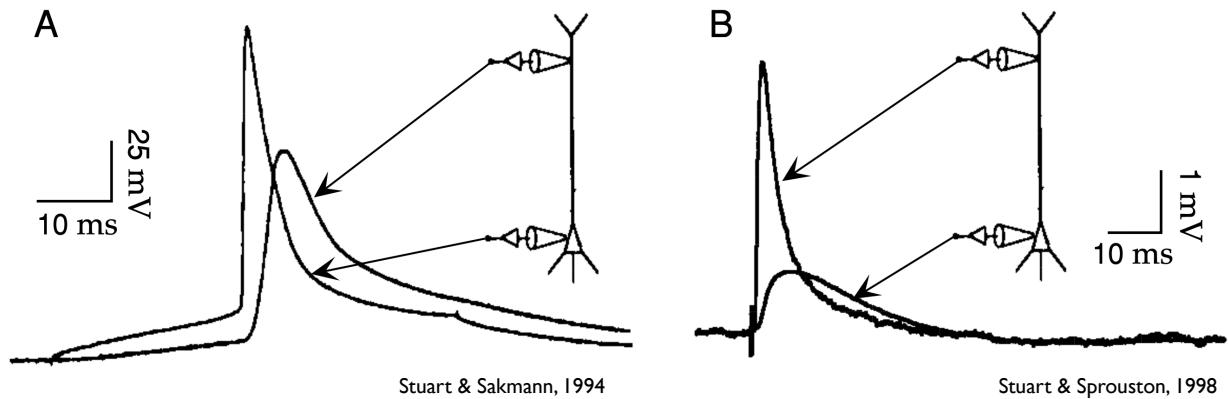


## Sinusoidal Regime - AC - attenuation (semi-infinite cable...)

- Dendrites are “filtering out” fast frequency components. (i) The (effective, equivalent) space-constant *shrinks* for fast frequencies!

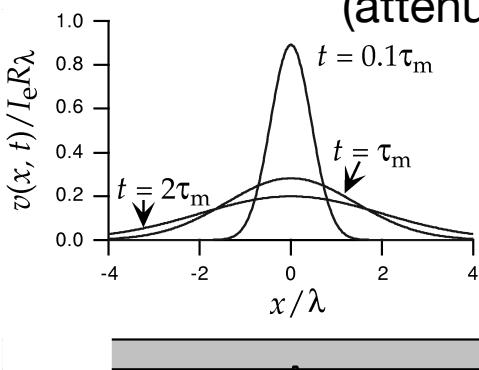


## Back-propagating AP and (forward propagating) EPSPs



### Transient solution

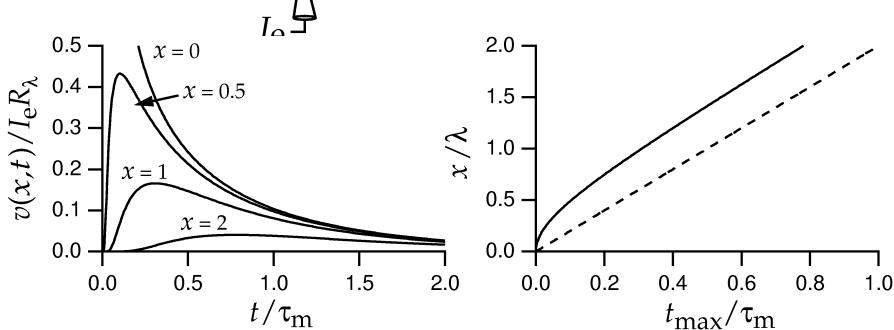
**(attenuation, shape change, delay)**



$$V(x, t) = \frac{I_e R_\lambda}{\sqrt{4\pi \lambda_m^2 t/\tau_m}} \exp\left(-\frac{\tau_m x^2}{4\lambda_m^2 t}\right) \exp\left(-\frac{t}{\tau_m}\right)$$

$$V(x, t) = \frac{A(t)}{\sqrt{2\pi \sigma^2(t)}} \exp\left(-\frac{x^2}{2\sigma^2(t)}\right)$$

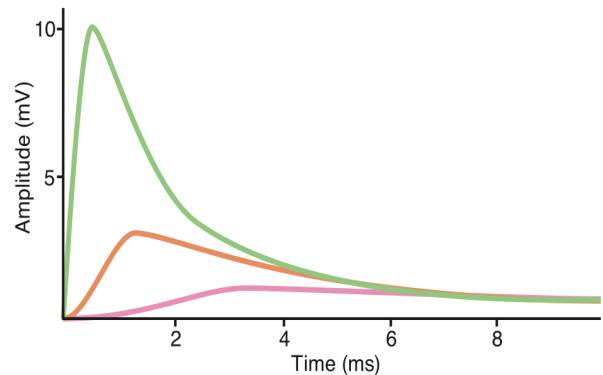
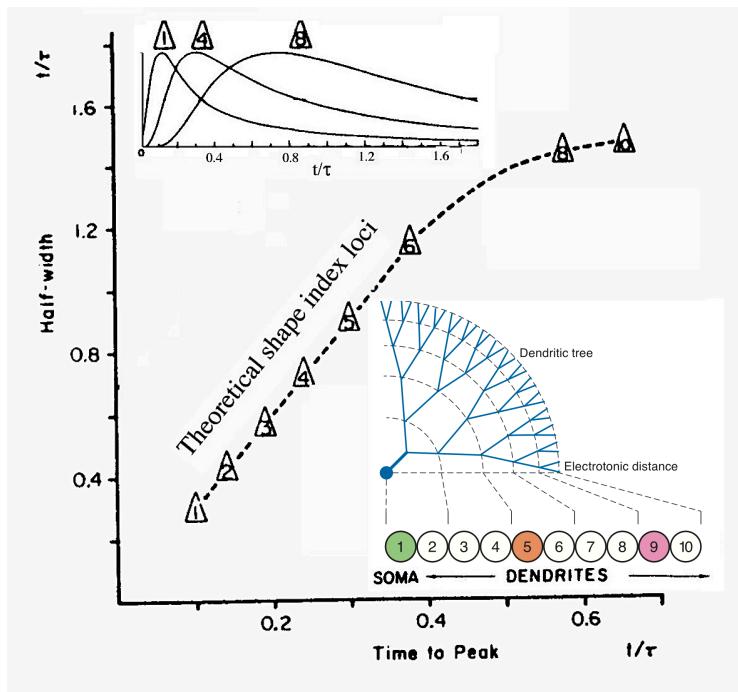
$$A(t) = I_e R_\lambda \exp\left(-\frac{t}{\tau_m}\right), \quad \sigma(t) = \lambda_m \sqrt{\frac{2t}{\tau_m}} \quad R_{\lambda_i} = \frac{r_L \lambda_i}{\pi a_i^2}$$



$$t_{max} \approx \frac{x \tau_m}{2 \lambda_m} \Rightarrow$$

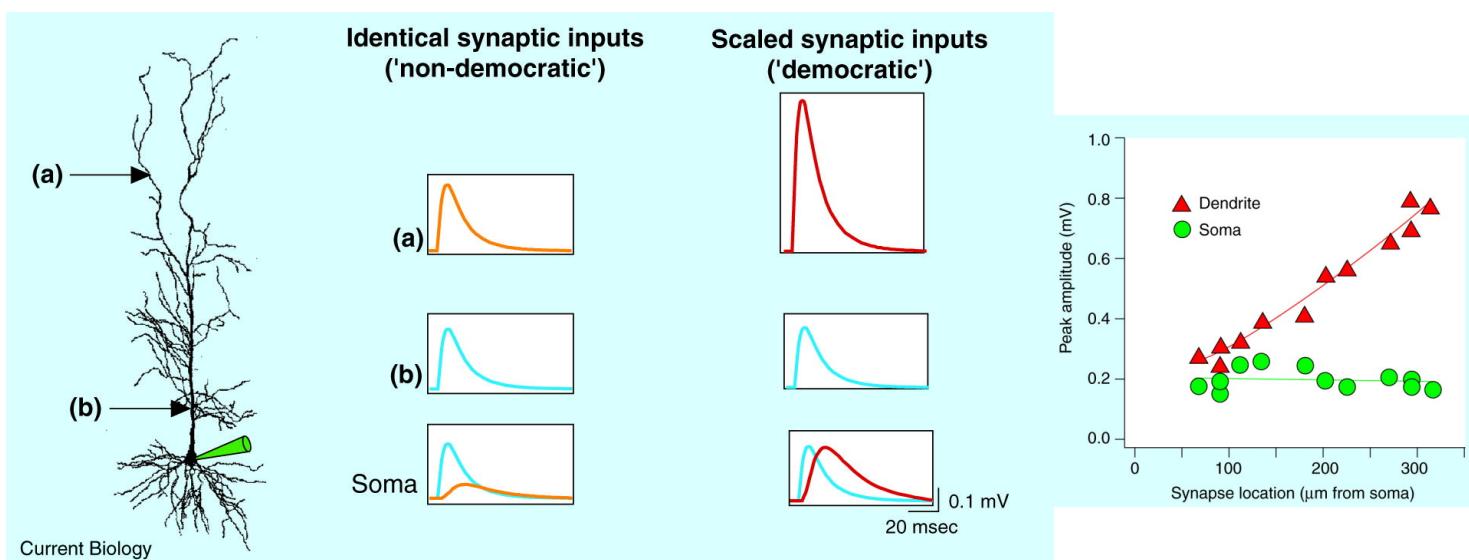
$$\Rightarrow v_{cond} \equiv \frac{x}{t_{max}} \approx 2 \frac{\lambda_m}{\tau_m}$$

## Experimental Predictions distal synapses are “broader” and “delayed”



**Synaptic potentials  
attenuate from the origin  
towards other regions of  
the dendrites/neuron**

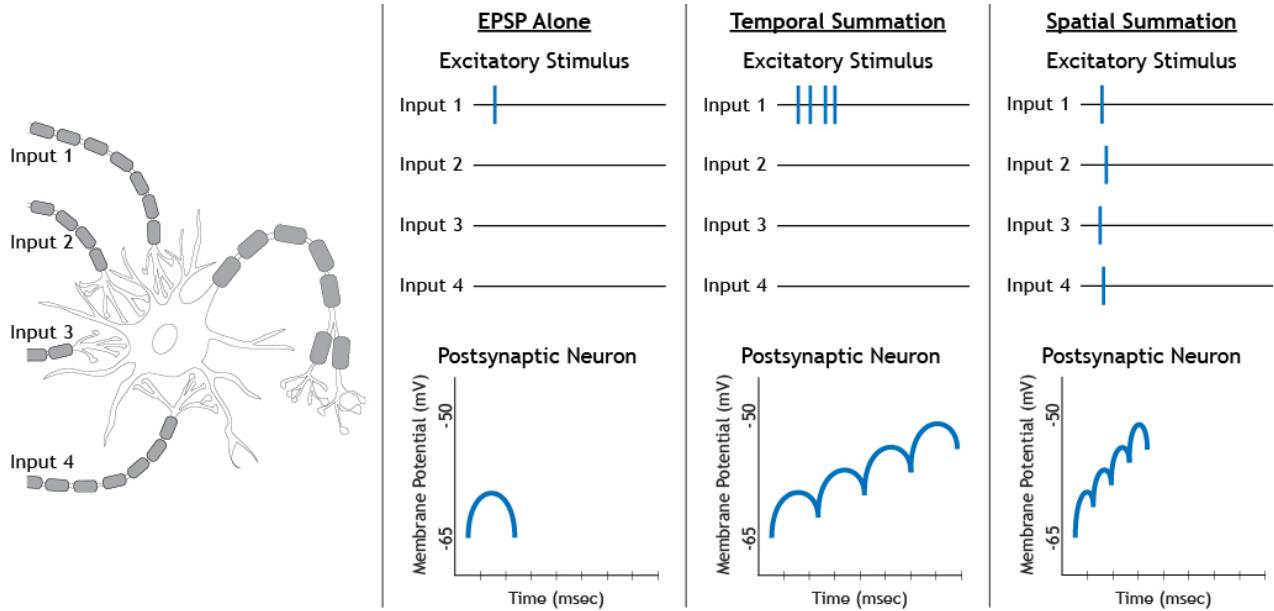
## Dendritic “democracy” (in CA1 pyramidal neurons)



CA1 pyramidal neuron

Häusser, 2001

# Temporal and Spatial summation

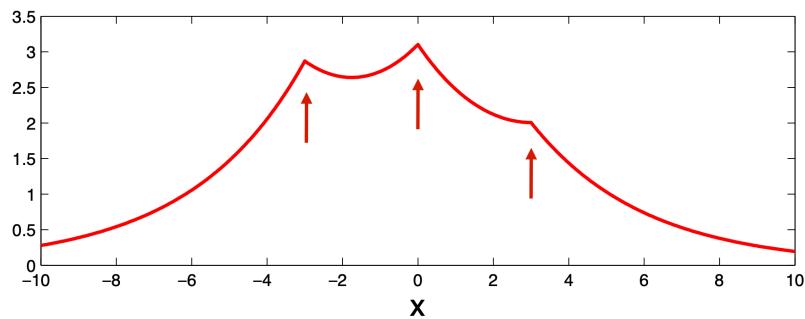
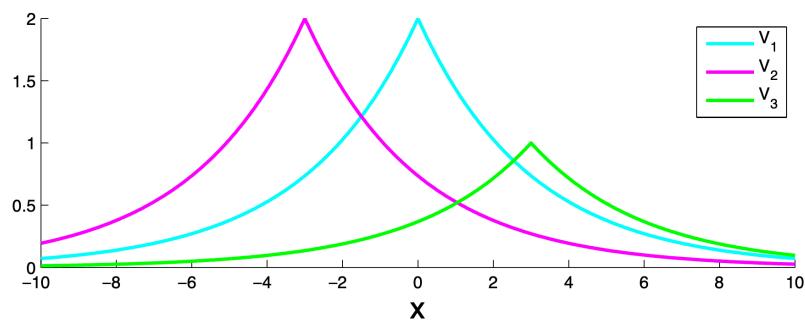


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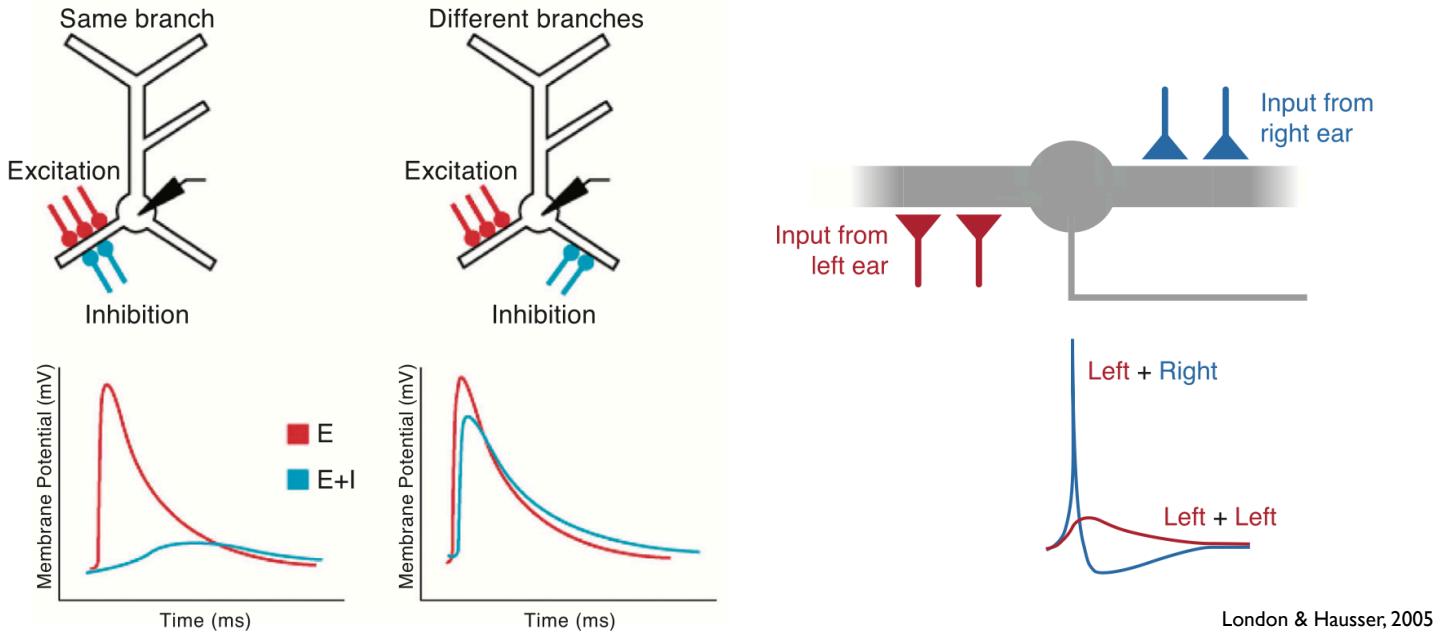
# Temporal and Spatial summation

$$I_{sum}(x) = I_1(x) + I_2(x) + I_3(x)$$

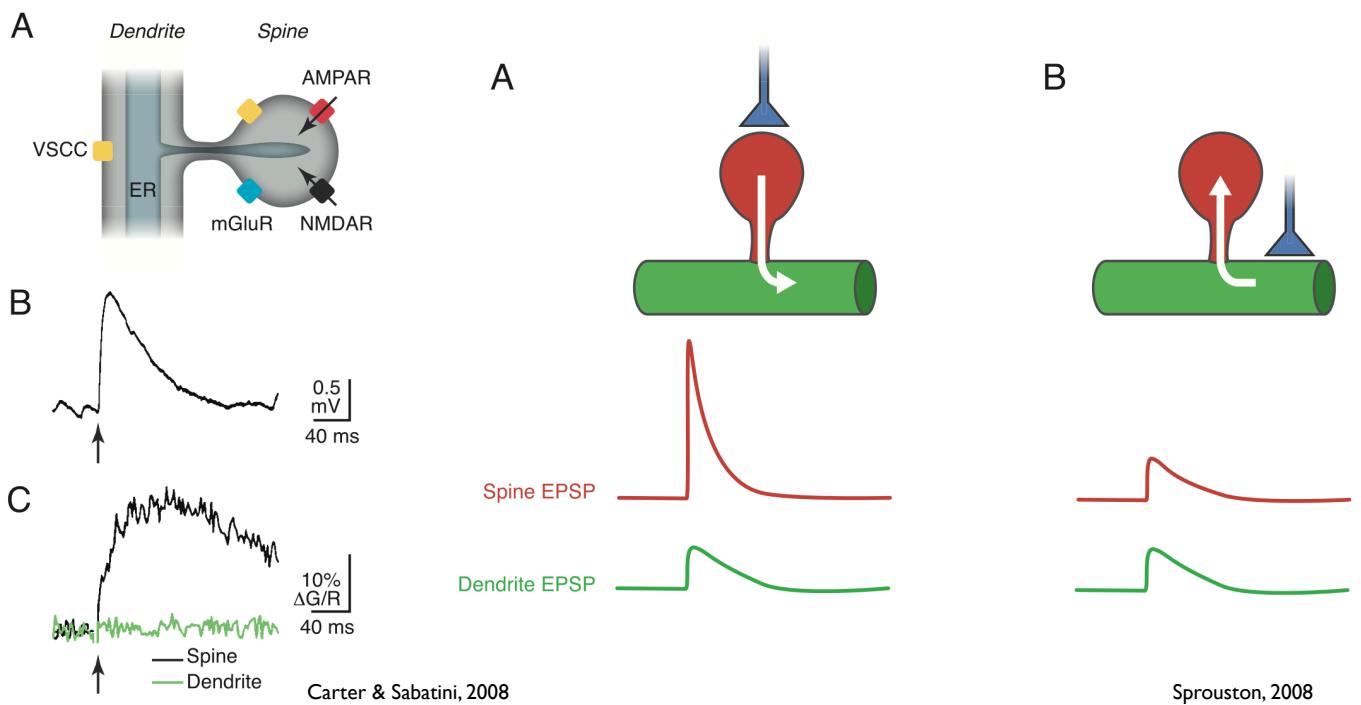
$$V_{sum} = V_1(x) + V_2(x) + V_3(x)$$



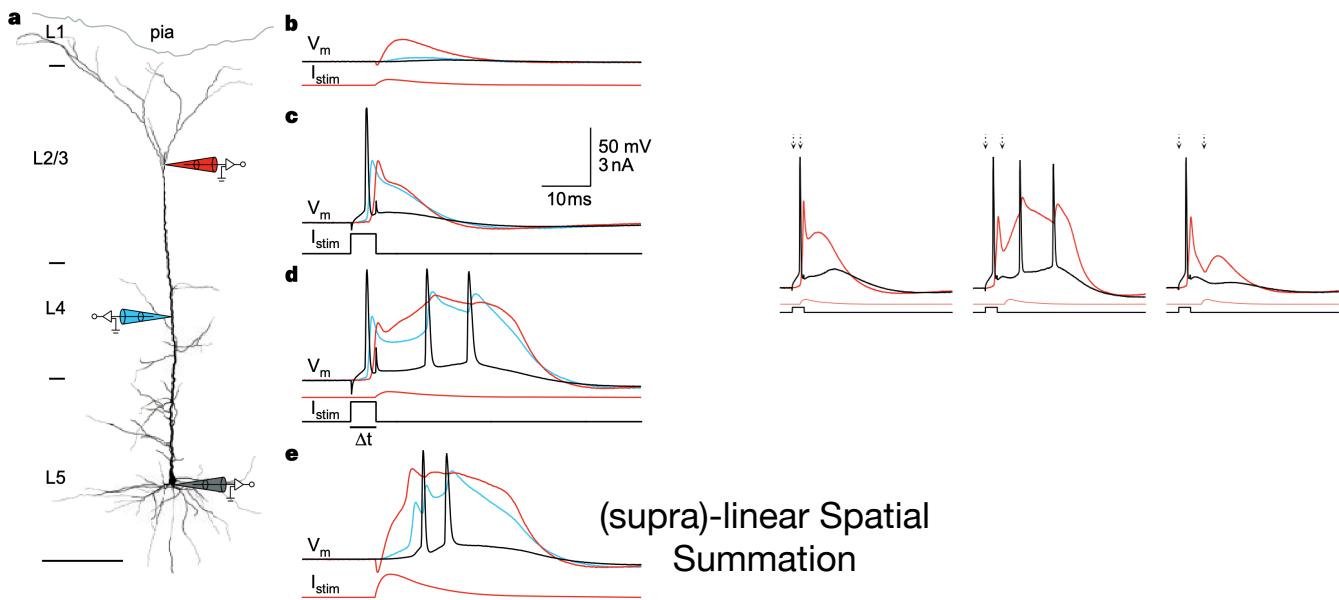
## (sub)-linear Spatial Summation



## Dendritic spines, depolarization, and Ca<sup>++</sup> influx

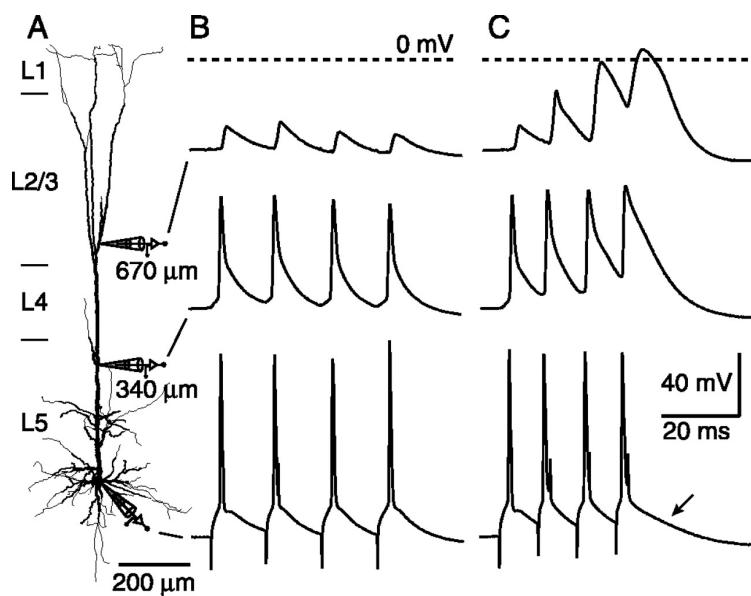


This back-propagating AP activated  $\text{Ca}^{2+}$  spike firing (BAC): coincidence detection (distal inputs & AP firing)



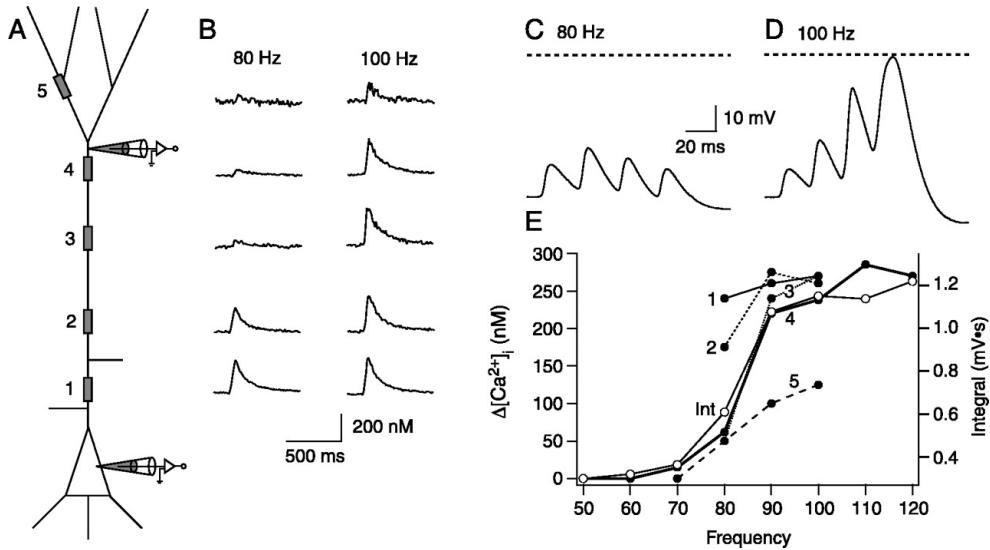
Larkum, Zhu, & Sakmann, 1999

$\text{Ca}^{++}$  electrogenesis in distal apical dendrites of L5 pyr. cells at a critical frequency of back-propagating AP



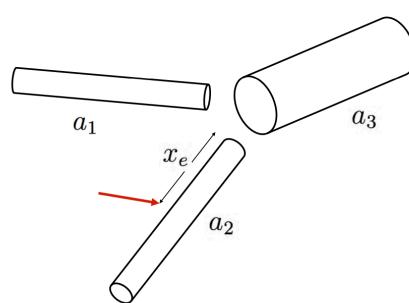
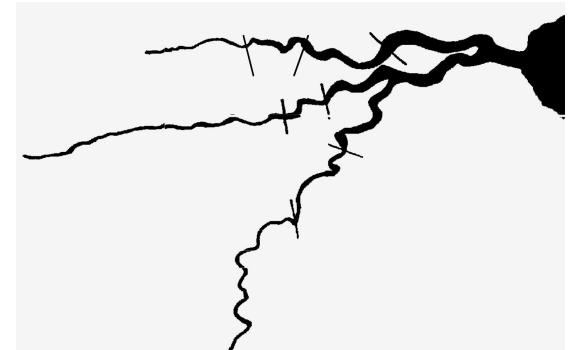
Larkum et al. 1999

# Ca<sup>++</sup> electrogenesis in distal apical dendrites of L5 pyr. cells at a critical frequency of back-propagating AP



Larkum et al. 1999

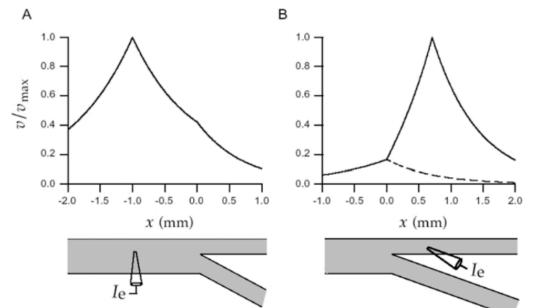
## Branching points



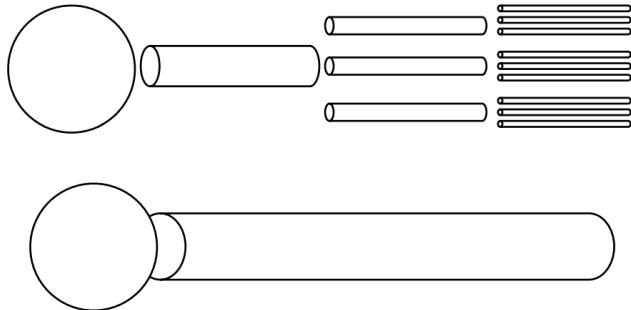
thick → thin                                    thin → thick

$$p_i = \frac{a_i^{3/2}}{a_1^{3/2} + a_2^{3/2} + a_3^{3/2}}$$

$$R_{\lambda_i} = \frac{r_L \lambda_i}{\pi a_i^2}$$



## Rall's model



Radius  $a$  and length  $L$  of the equivalent dendrite are chosen to match the properties of the actual dendritic tree:

- (i) Surface area  $2\pi L a$  is set equal to surface area of full dendritic tree.
- (ii) Electrotonic length  $L/\lambda$  is set equal to total electrotonic length of tree segments  $\sum_i \frac{L_i}{\lambda_i}$

The Rall model is exact when

$$a_1^{3/2} = a_2^{3/2} + a_3^{3/2} \quad \Rightarrow \quad p_1 = p_2 + p_3 = \frac{1}{2}$$