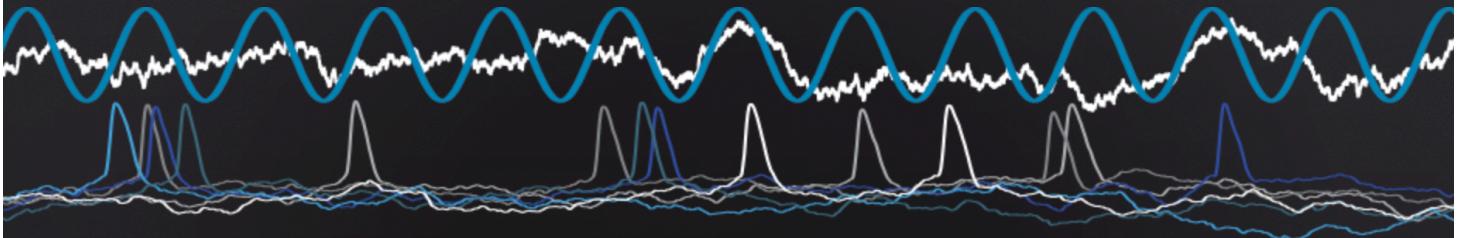


ELECTROPHYSIOLOGICAL SIGNALS



GENERATION AND CHARACTERISATION

Michele GIUGLIANO

Origin of Extracellular Signals

ATTENDANCE TRACKING - **code LCON5**
(for statistical purposes only)

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

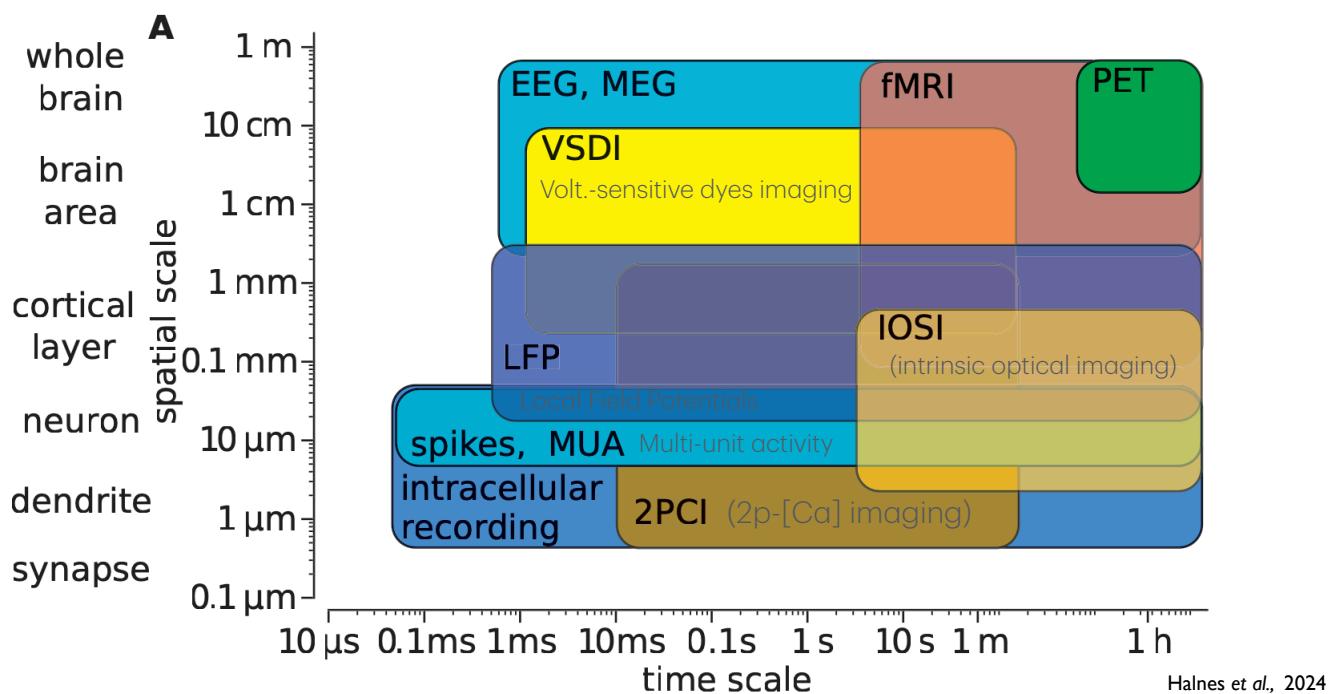
References

supporting your study and understanding

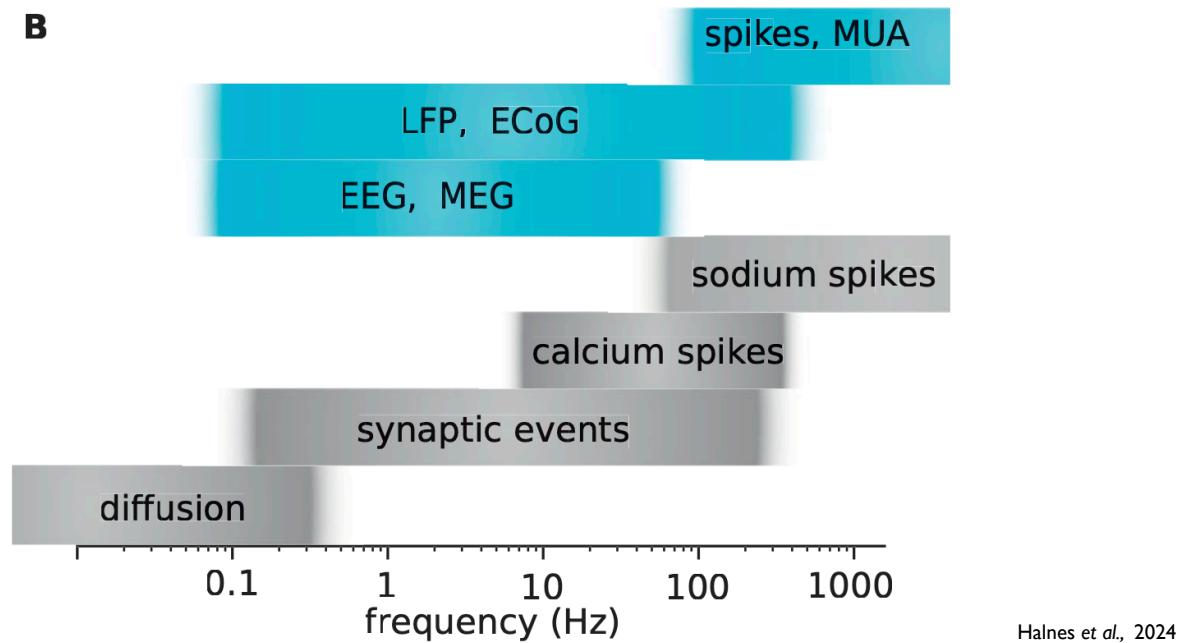
Chapters from

- 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*”

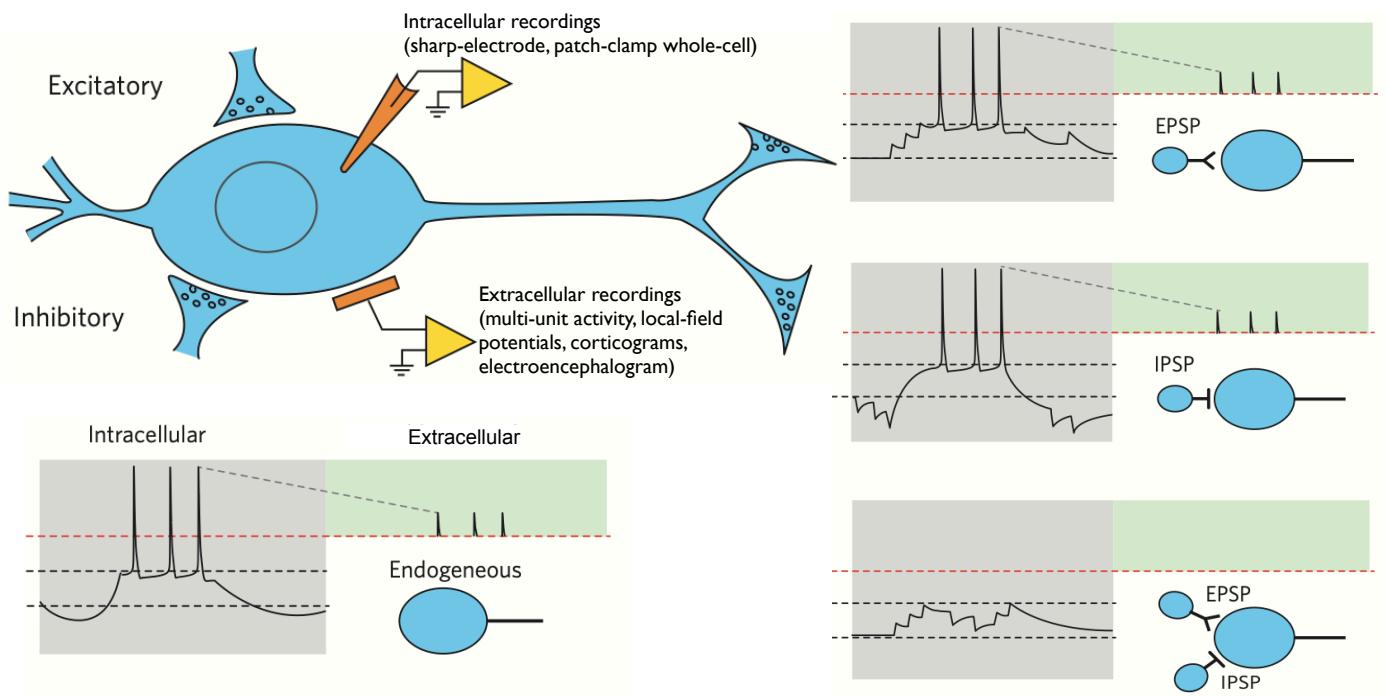
Range of Techniques and Methods: not all the same!



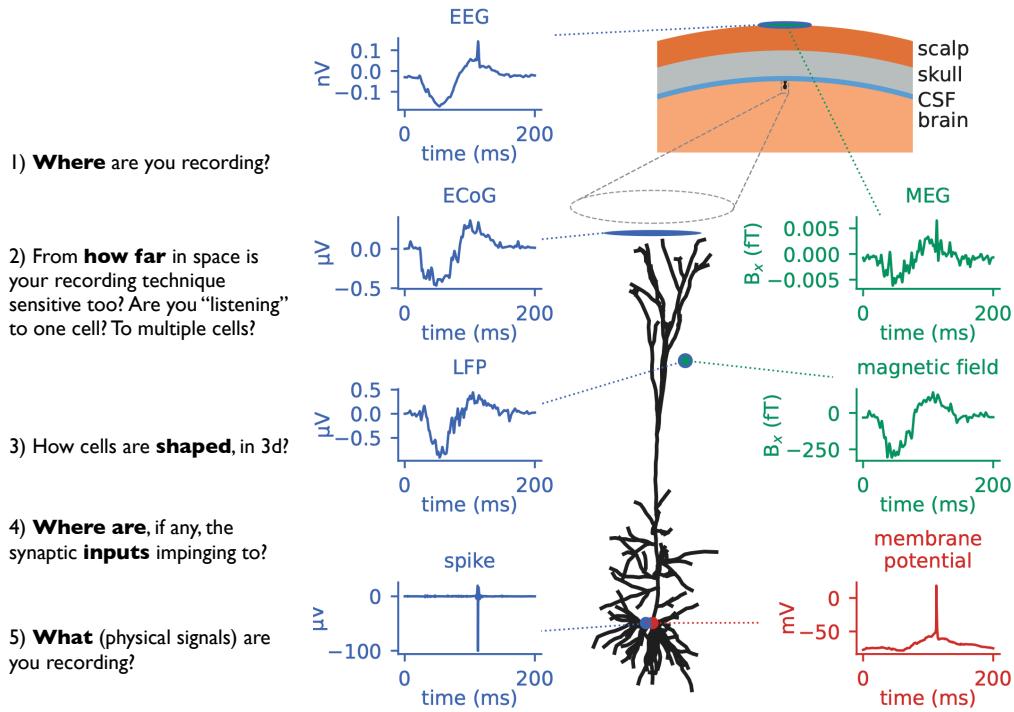
Heterogeneous (and multiple) time-scales



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



Extracellular signals: not so elementary!



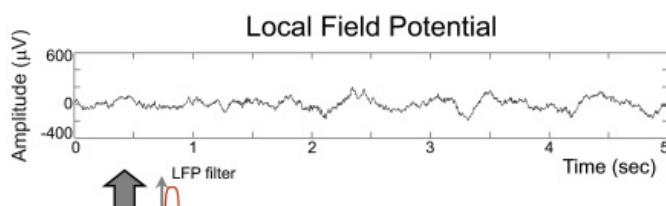
Halnes et al., 2024

Low Frequency Parts/components

1 - 100 cycle/s

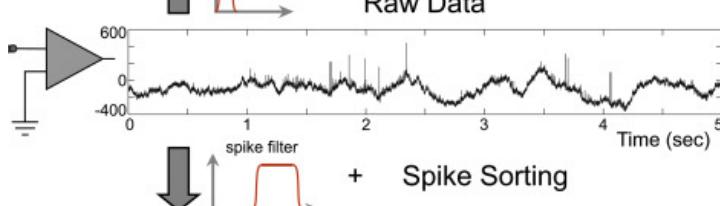
LFP

Local Field Potential



LFP filter

Raw Data



Raw recording

spike filter

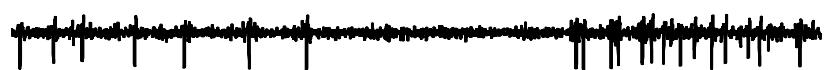
+ Spike Sorting

MUA SUA

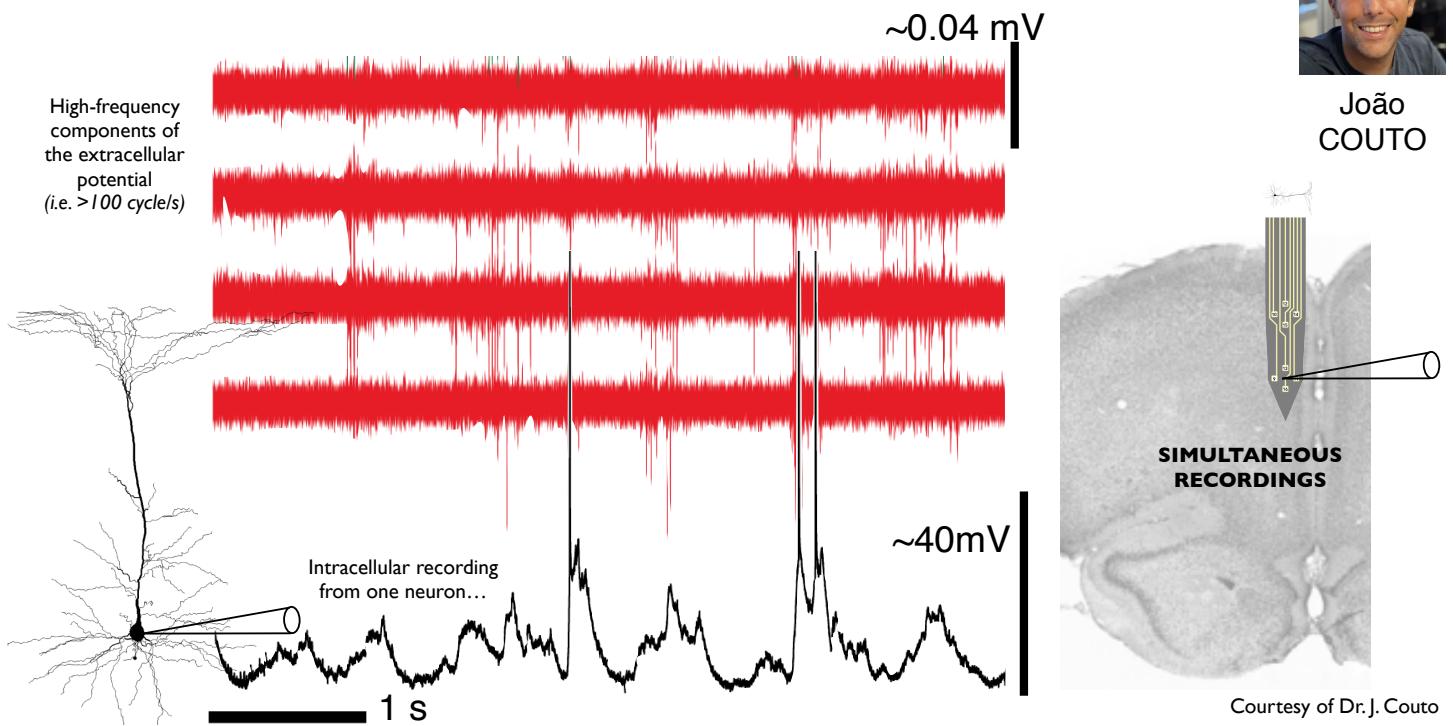
Multi-unit
Single-unit
Activity

High-freq. components

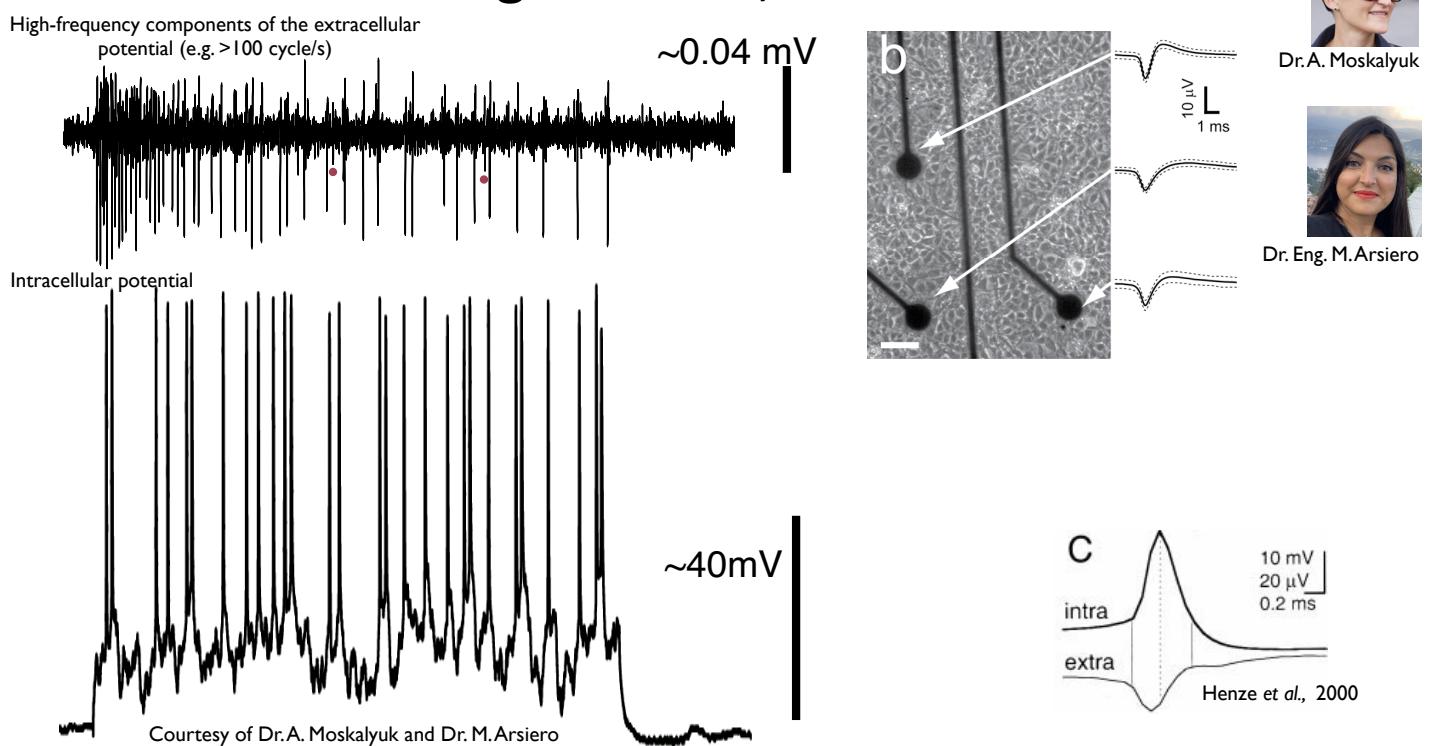
100 - 5000 cycle/s



Extracellular signals: APs, near the soma?

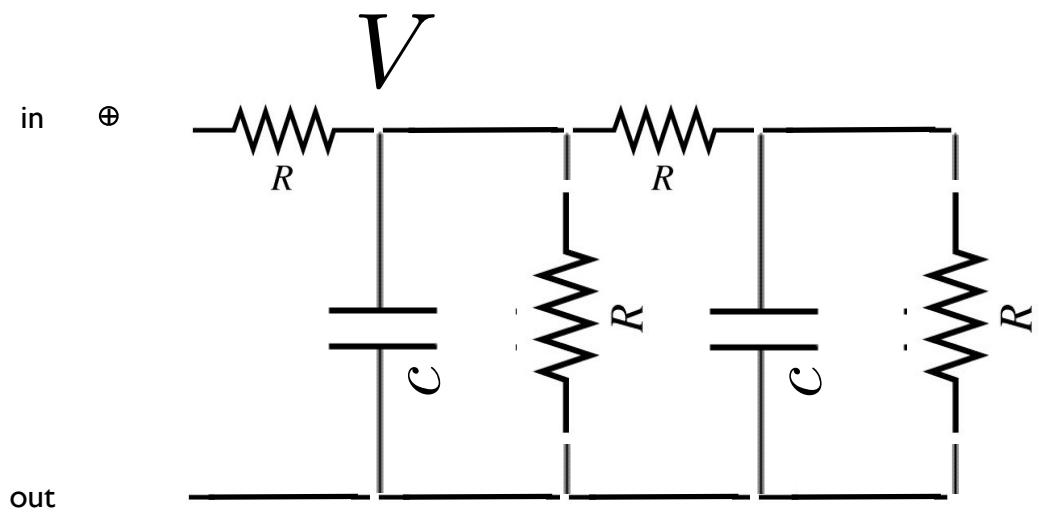
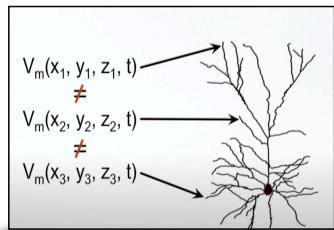


Extracellular signals: APs, near the soma?

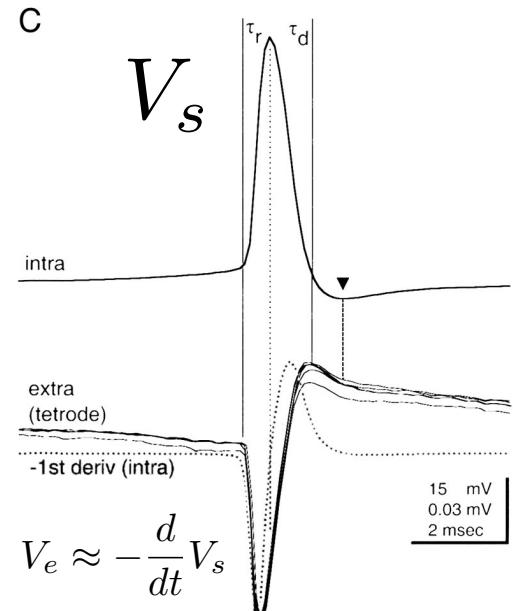
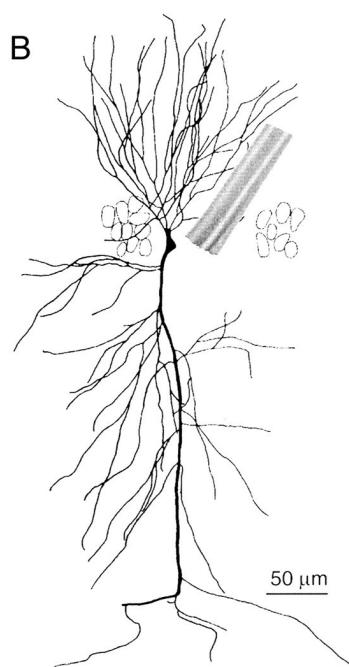
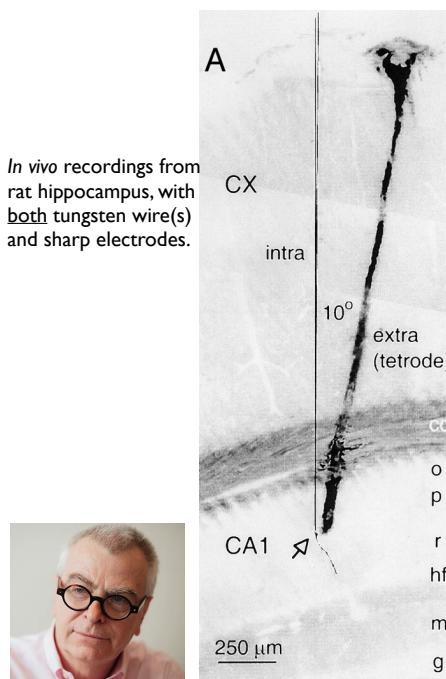


How to make sense of this?

Dendrites are non-isopotential portions of the neuron!

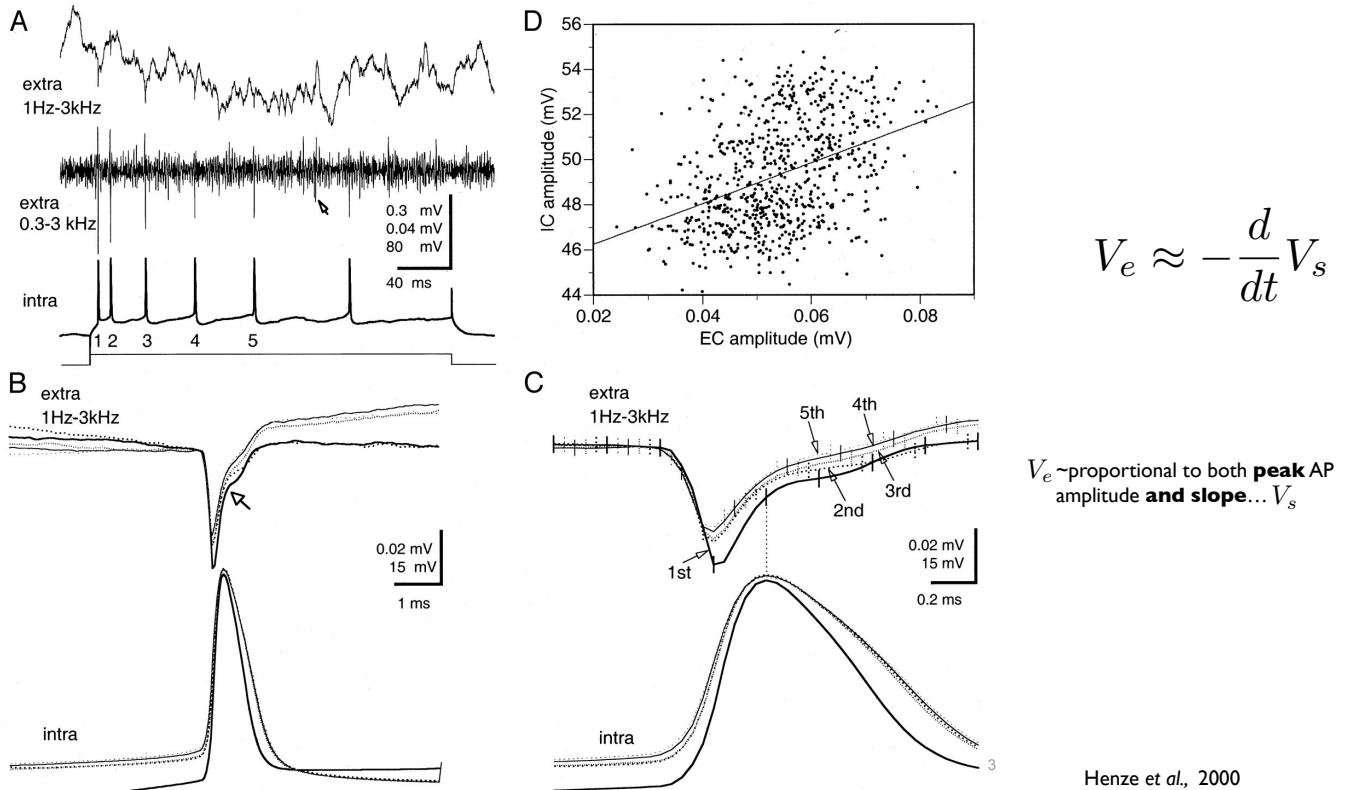


Extracellular signals: APs, near the soma

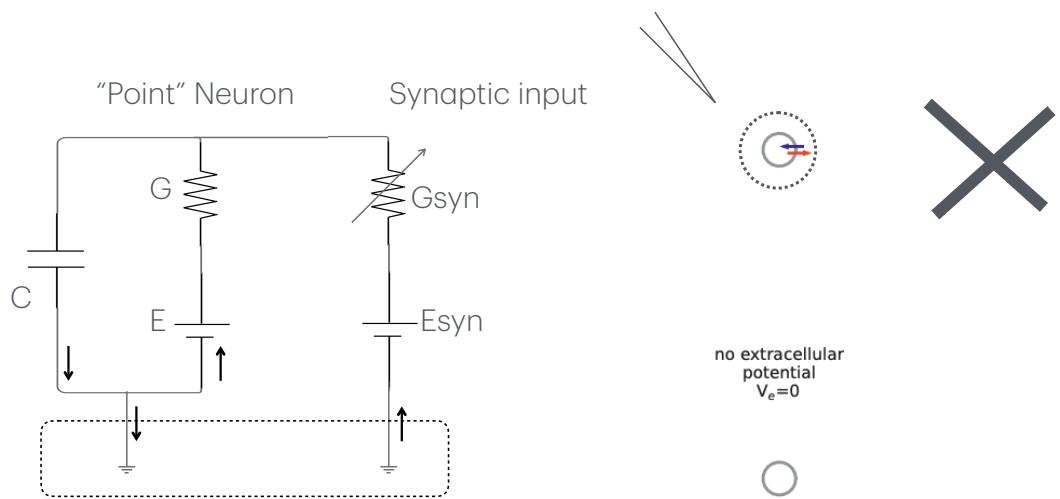


György Buzsáki

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.

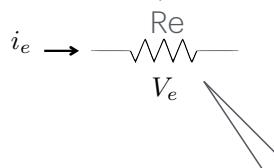
Extracellular signals: APs, near the soma?

We must take the spatial extension of neurons into account!



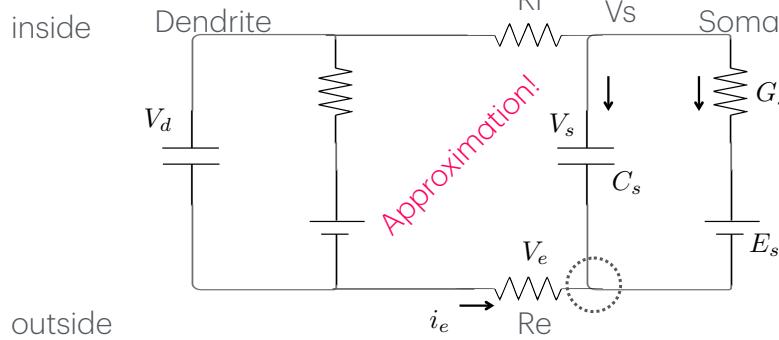
$$V_d \neq V_s$$

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



$$V_e = R_e i_e$$

$$i_e + i_c + i_m = 0$$



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

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

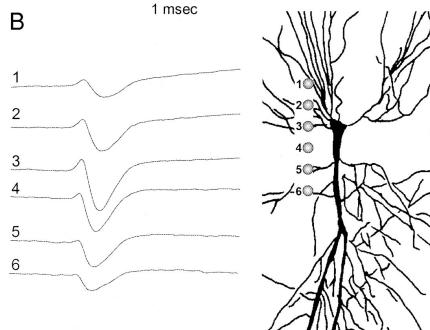
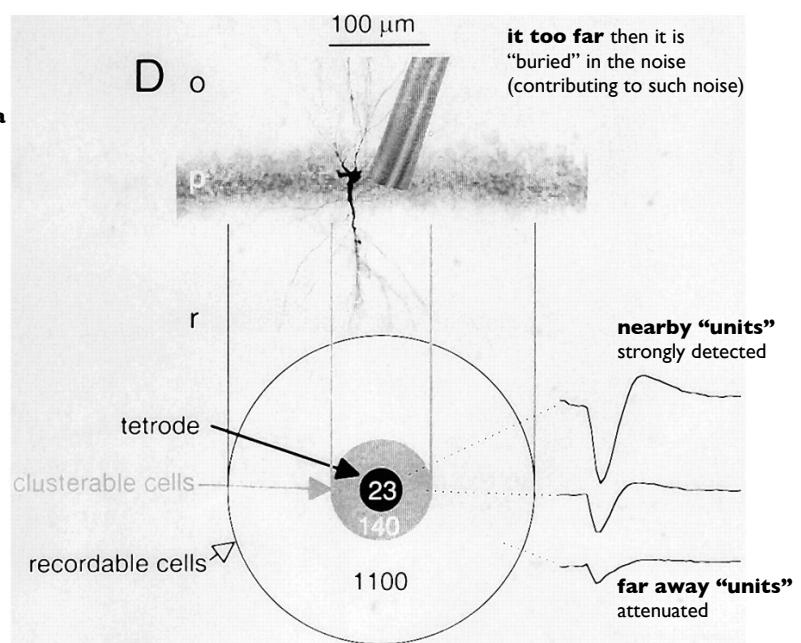
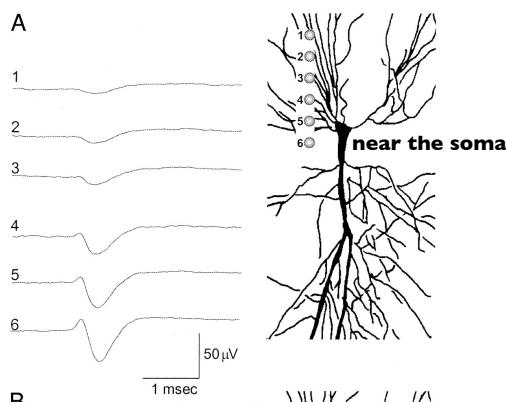
$$C_s \frac{d}{dt} V_s \gg G_s (E_s - V_s)$$

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

Extracellular signals: position and distance

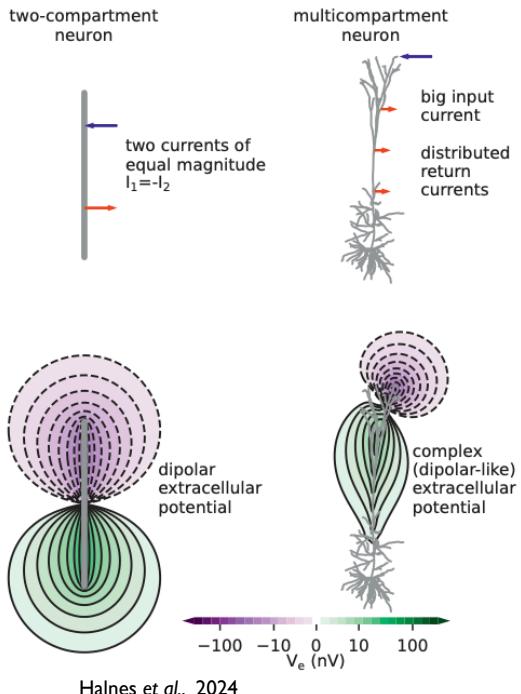
where are you recording?

how far are you recording?



Henze et al., 2000

Extracellular signals: more in general, how to?



Halnes et al., 2024

- Describing, **across space**, ionic currents changes.

(**cable theory**)

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

- Computing extracellular potentials, from the **spatial distribution of transmembrane currents**.

(**volume-conductor theory**)

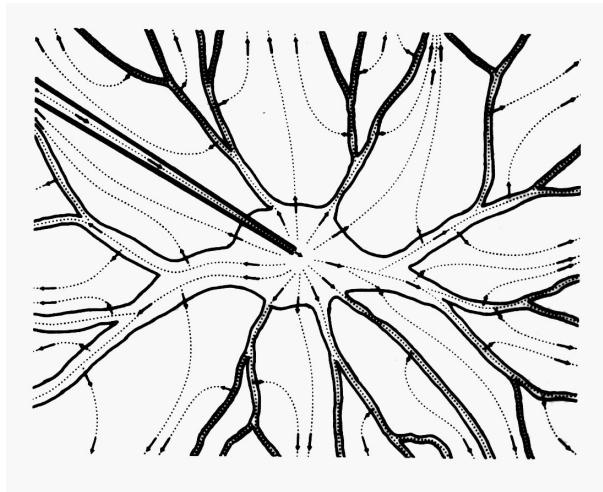
$$V_e(\mathbf{r}) = \sum_{\mathbf{n}} \frac{\mathbf{i}_{\mathbf{n}}}{4\pi\sigma_t |\mathbf{r} - \mathbf{r}_{\mathbf{n}}|}$$

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)

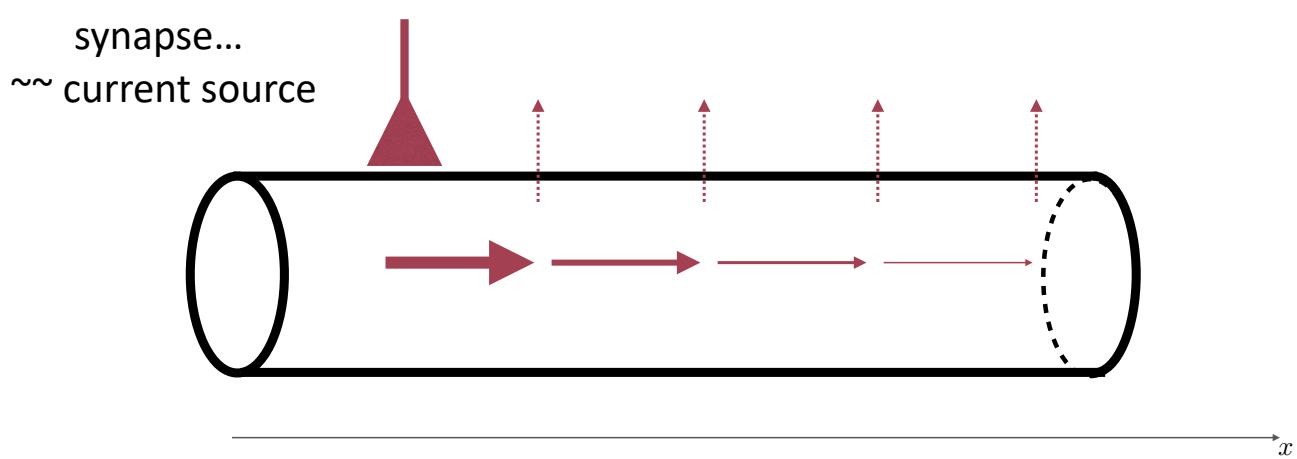
1959 Rall's Cable Theory for Neurites: motivations

- 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”.



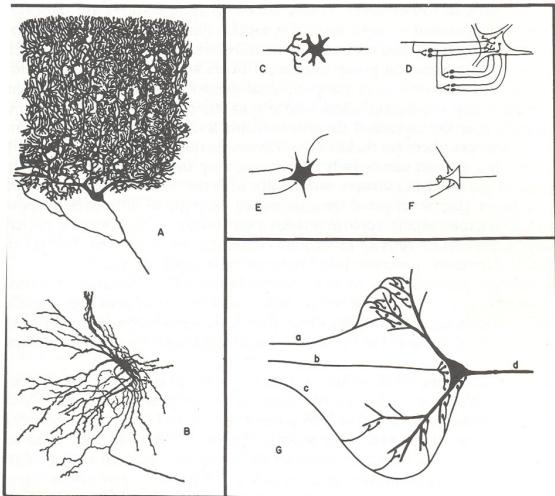
Wilfried Rall

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.



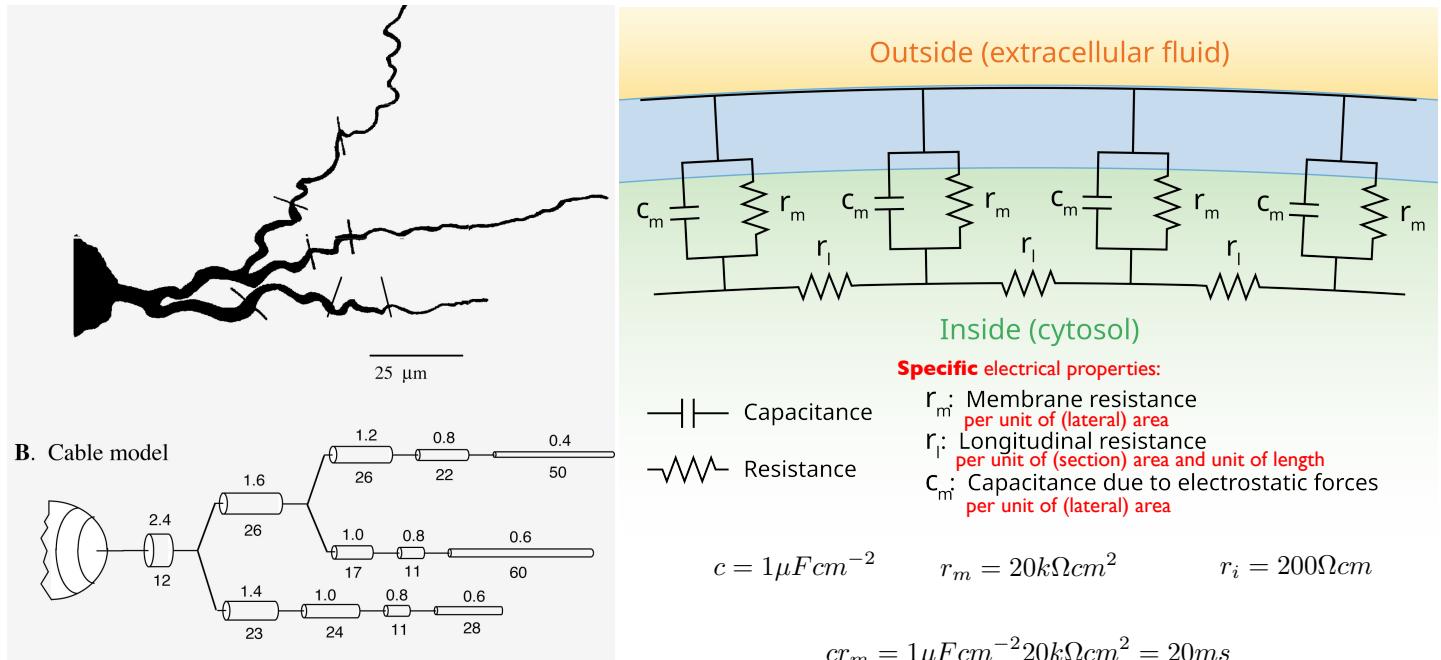
RESULTS:

- 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 O1BNO**
(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...

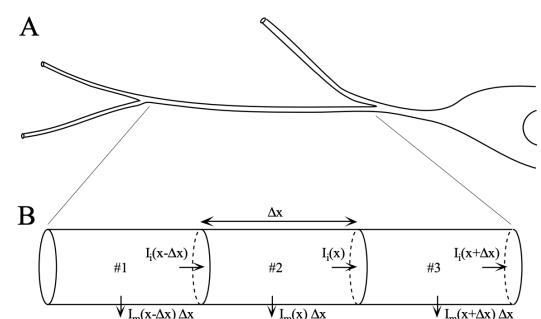
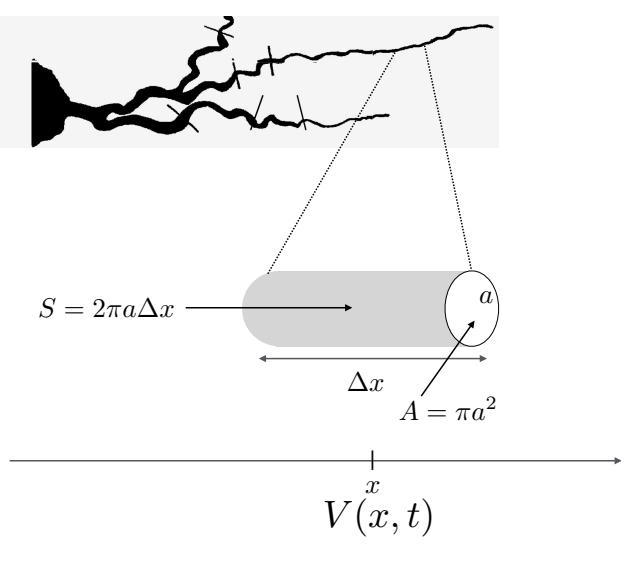
$$V(x, t)$$

Total electrical properties:

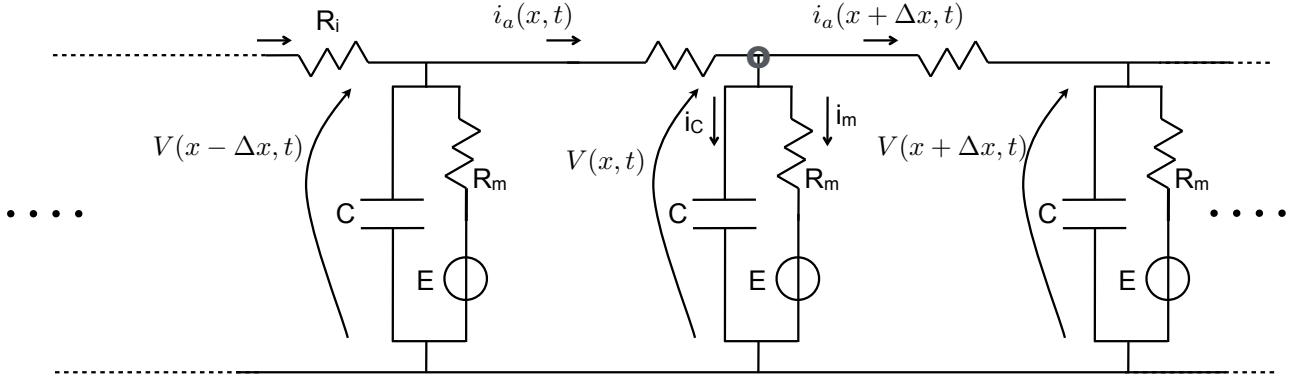
$$R_m = r_m/S = r_m/(2\pi a \Delta x) \quad r_m = 20 k\Omega cm^2$$

$$C = cS = c(2\pi a \Delta x) \quad c = 1 \mu F cm^{-2}$$

$$R_i = r_i \Delta x / (a^2 \pi) \quad r_i = 200 \Omega cm$$



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)

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

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

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

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

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

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

...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!

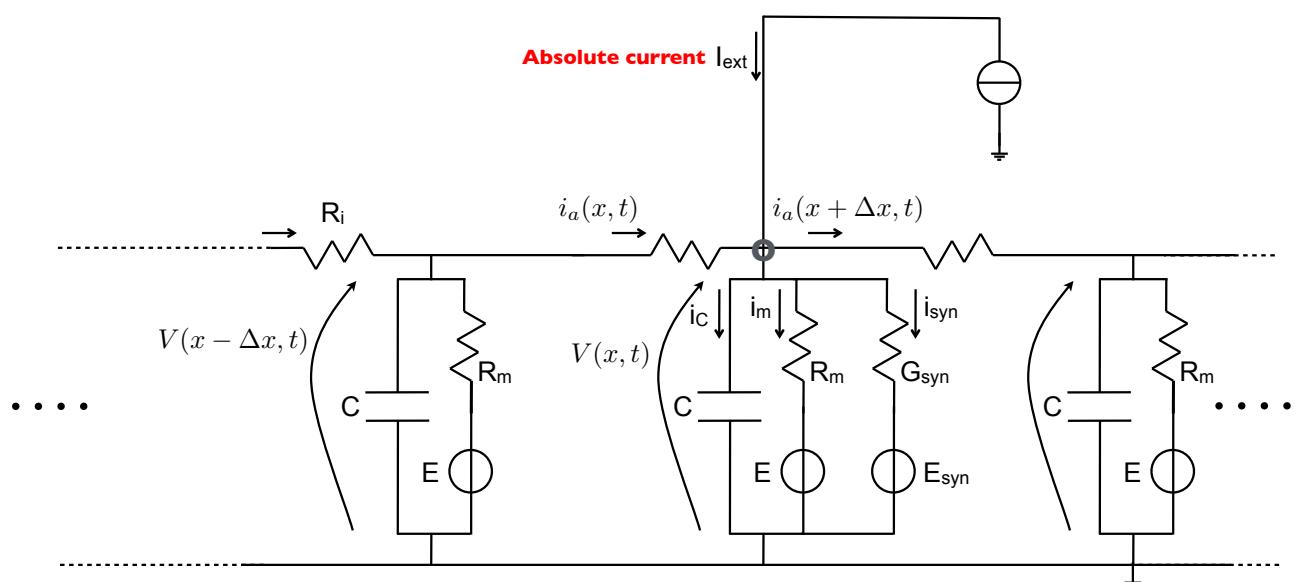
$$R_m = r_m/S = r_m/(2\pi a \Delta x)$$

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

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

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

...with synaptic and external current densities.



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

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

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

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

$$\tau_m = r_m c$$

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

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

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

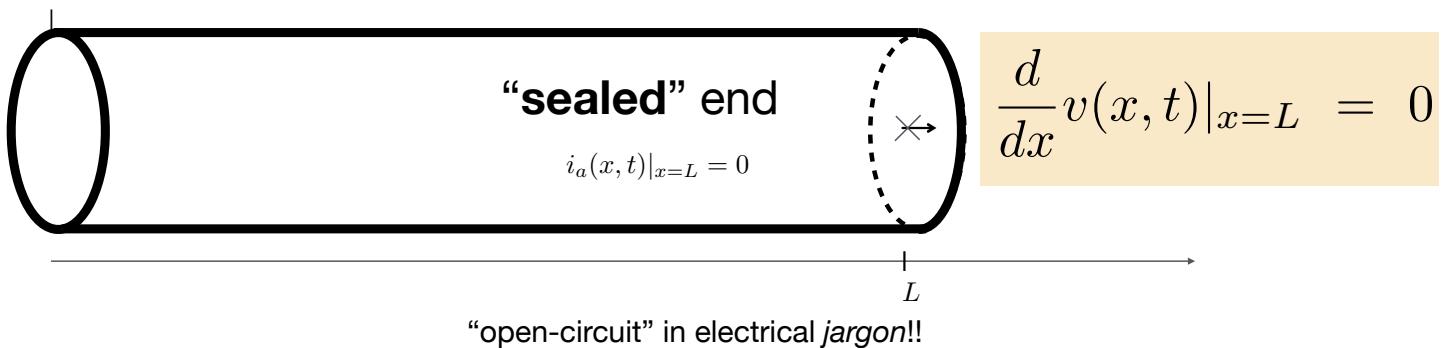
2 x Boundary conditions
1 x Initial condition
needed

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

Boundary conditions: 1

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

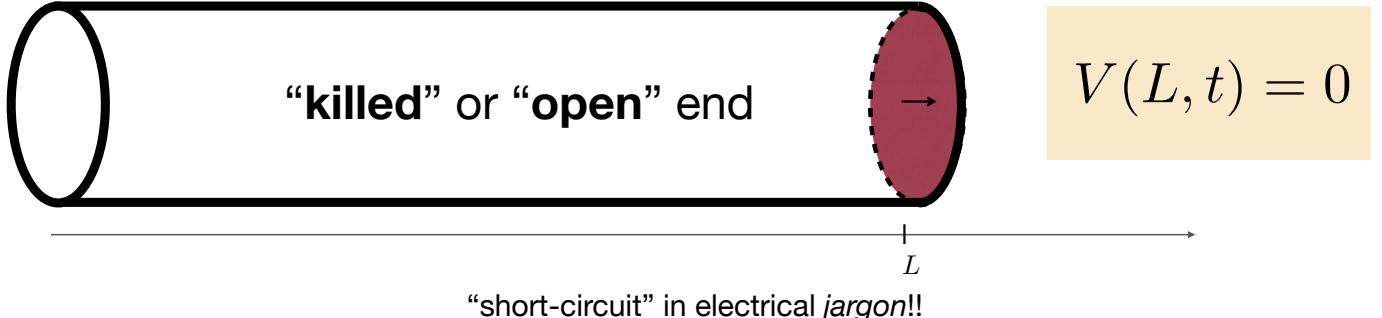
$$i_a(x, t)|_{x=L} = \frac{a^2 \pi}{r_i} \frac{v(x, t) - v(x + \Delta x, t)}{\Delta x}|_{x=L} = -\frac{a^2 \pi}{r_i} \frac{d}{dx} v(x, t)|_{x=L}$$



"open-circuit" in electrical jargon!!

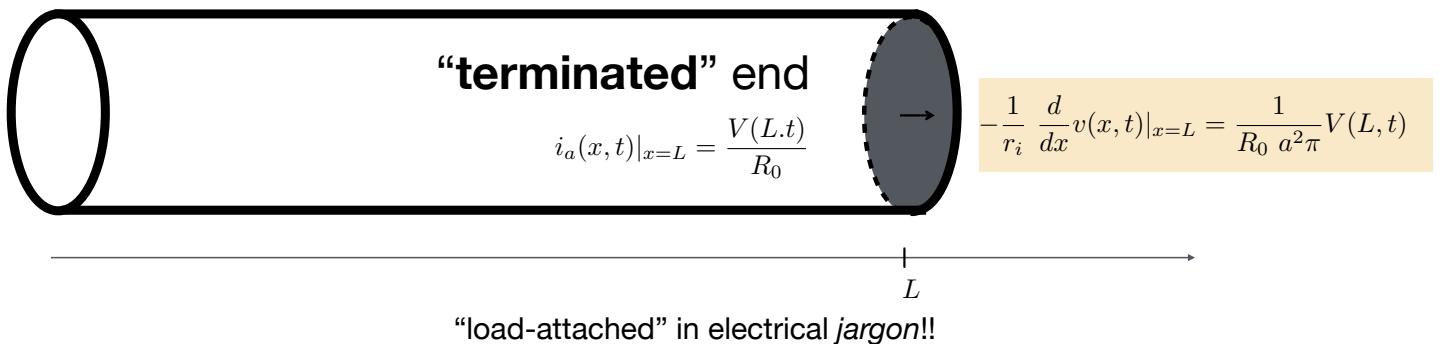
Boundary conditions: 2

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

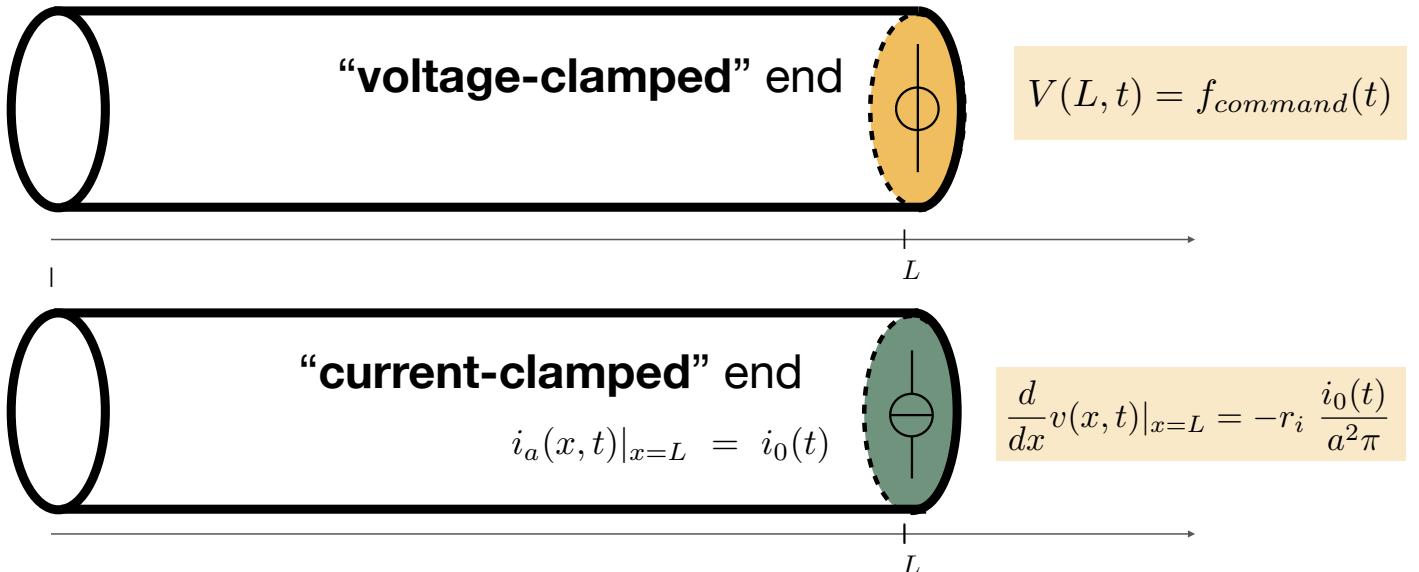


Boundary conditions: 3

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



Boundary conditions 4



Let's solve that *PDE!*

- *steady-state regimes*
- *transient regimes*

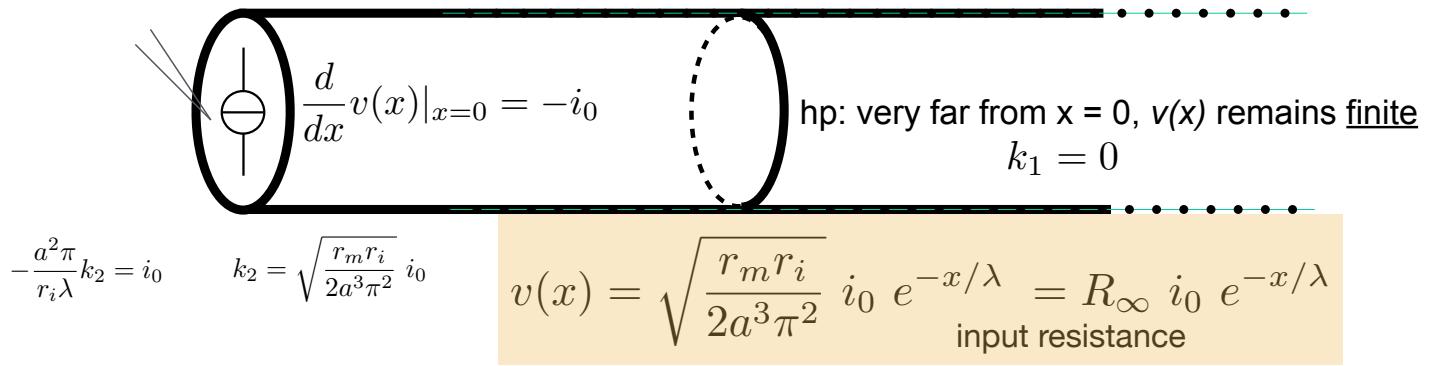
**Steady-state (w.r.t. time) - DC regime
semi-infinite cable...**

$$\frac{\partial v(x, t)}{\partial t} = 0$$

$$v(x, t) \rightarrow v(x)$$

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

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

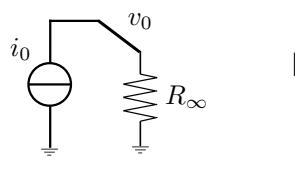
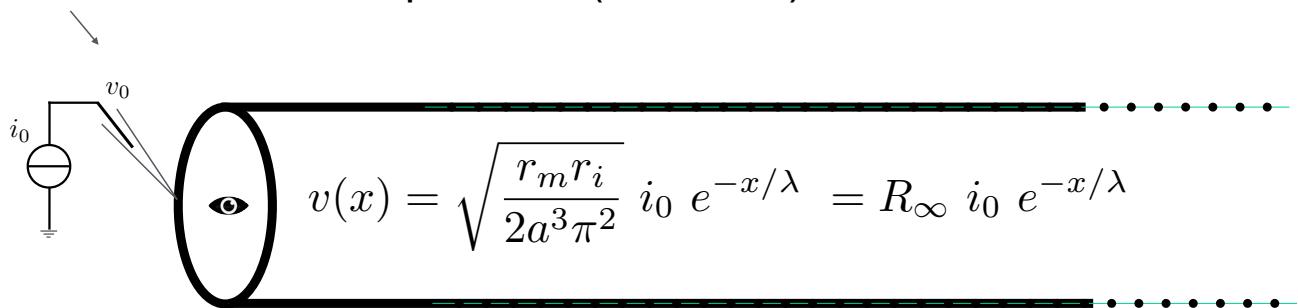


$$-\frac{a^2 \pi}{r_i \lambda} k_2 = i_0 \quad k_2 = \sqrt{\frac{r_m r_i}{2a^3 \pi^2}} i_0$$

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

input resistance

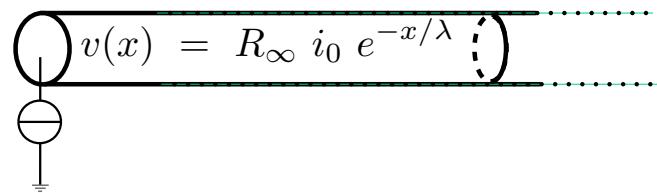
**Steady-state (w.r.t. time) - DC regime
equivalent (Thevenin) circuit**



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

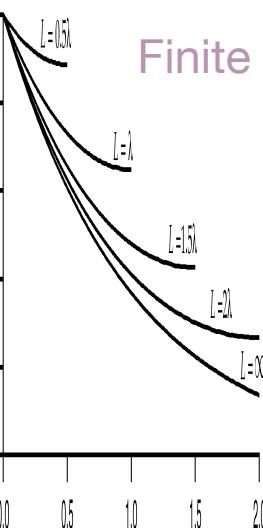
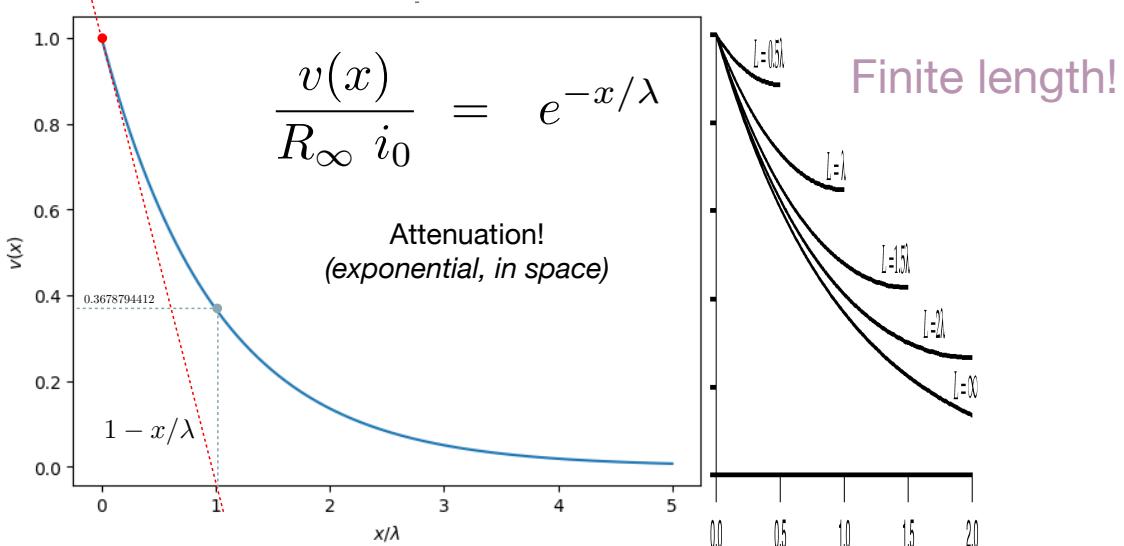
$$v_0 = R_\infty i_0$$

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



$$a = 4\mu m$$

$$\lambda = 500\mu m$$



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

$$\frac{d}{dx}v(x, t)|_{x=0} = -r_i \frac{i_0(t)}{a^2\pi} \quad \begin{array}{c} \text{Diagram of a finite cable} \\ \text{with boundary conditions at } x=0 \text{ and } x=L \end{array} \quad \frac{d}{dx}v(x, t)|_{x=L} = 0$$

$$v(x) = k_1 e^{x/\lambda} + k_2 e^{-x/\lambda} \quad v(x) = \frac{\hat{a} + \hat{b}}{2} e^{x/\lambda} + \frac{\hat{a} - \hat{b}}{2} e^{-x/\lambda}$$

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

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

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

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

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

$$\frac{d}{dx}v(x, t)|_{x=0} = -r_i \frac{i_0(t)}{a^2\pi} \quad \begin{array}{c} \text{Diagram of a finite cable} \\ \text{with boundary conditions at } x=0 \text{ and } x=L \end{array} \quad \frac{d}{dx}v(x, t)|_{x=L} = 0$$

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

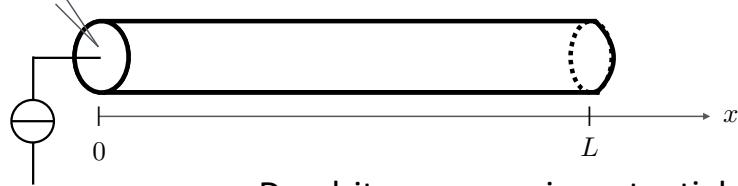
$$\frac{d}{dx}v(x) = \frac{\hat{a}}{\lambda} \sinh(x/\lambda) + \frac{\hat{b}}{\lambda} \cosh(x/\lambda)$$

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

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

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

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

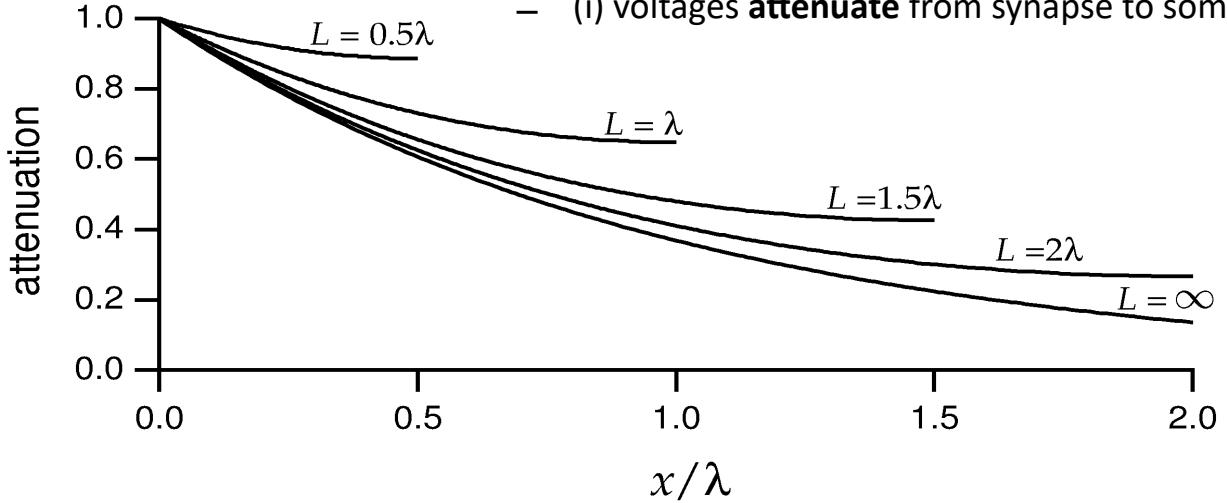


$$d = 4\mu m$$

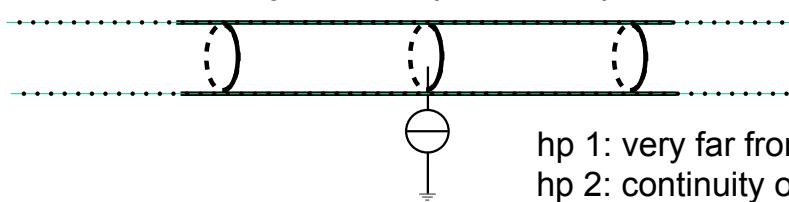
$$\lambda = 500\mu m$$

- Dendrites are non-isopotential portions of a neuron!

– (i) voltages **attenuate** from synapse to soma!



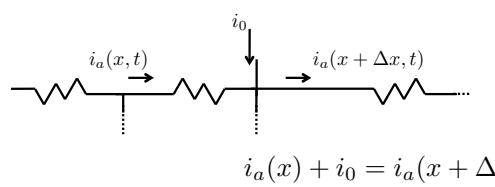
Steady-state (i.e. time) - infinite cable



$$d = 4\mu m$$

$$\lambda = 500\mu m$$

- hp 1: very far from $x = 0$, $v(x)$ remains finite
 hp 2: continuity of $v(x)$ for $x = 0$
 hp 3: slightly different boundary condition



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

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

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

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

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

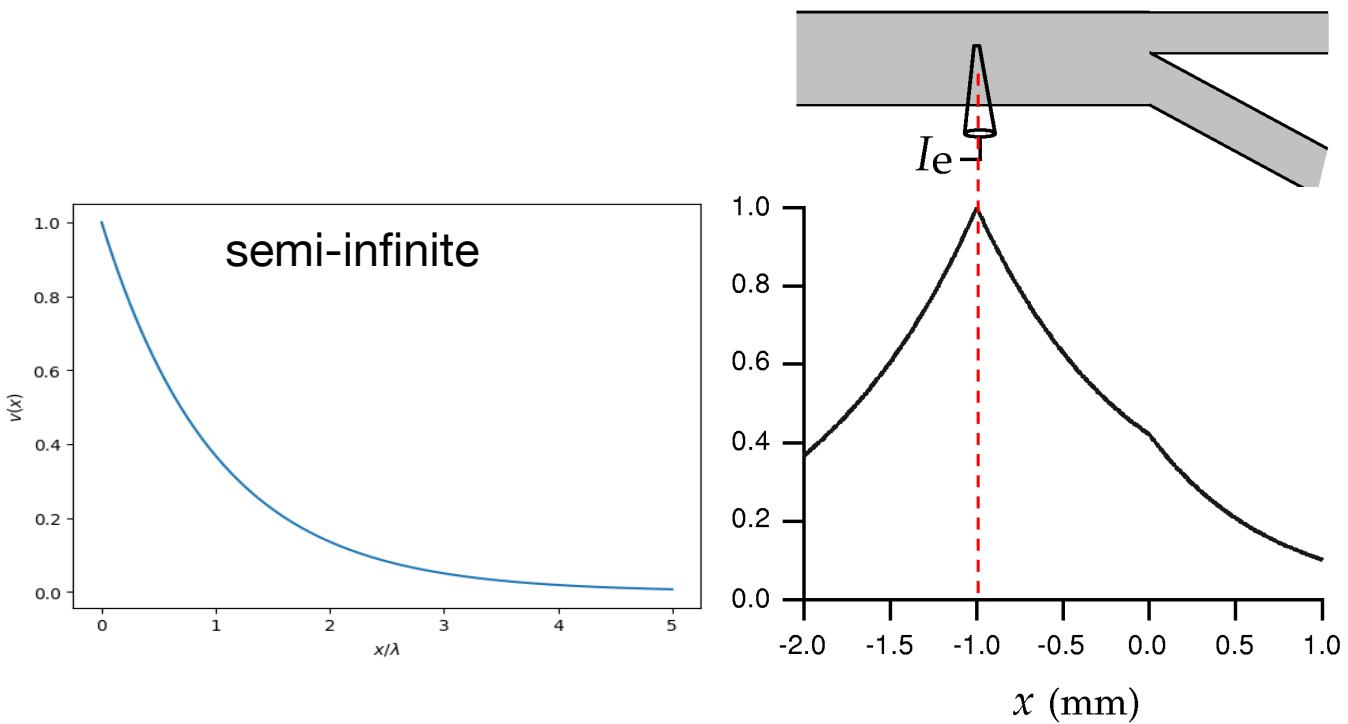
$$i_a(x, t) = \frac{V(x - \Delta x, t) - V(x, t)}{R_i}$$

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

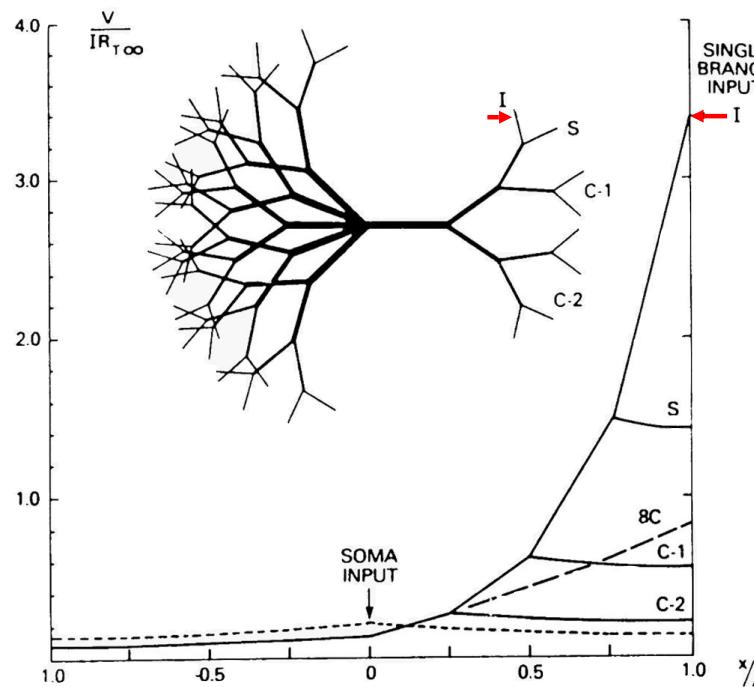
$$v(x - \Delta x, t) + v(x + \Delta x, t) \approx 2v(x, t) + \Delta x^2 \frac{d^2 v(x, t)}{dx^2}$$

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

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

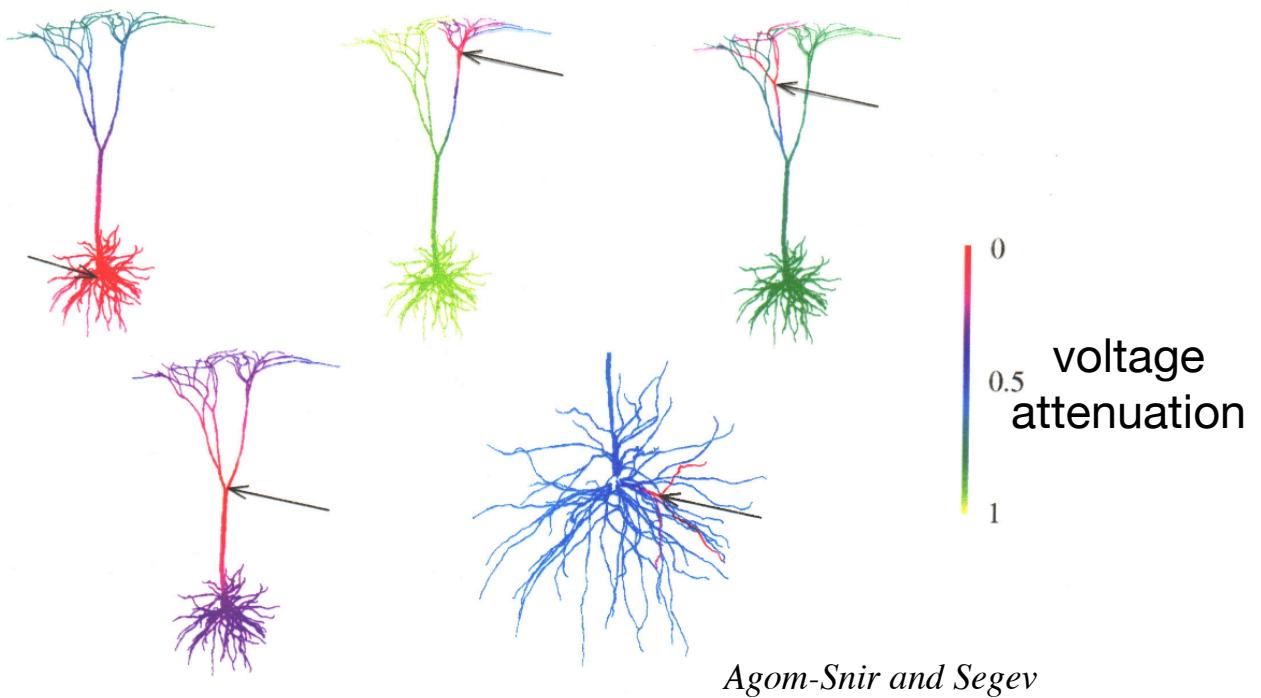


What do we learn? 1) Steep & asymmetrical voltage attenuation (from dendrites to the soma); 2) existence of synaptic *territories*



Rall & Rinzel, 1973

Dendritic “functional subunits” (“synaptic territory”)



Agom-Snir and Segev

What about...
transients?

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

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

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

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

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

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

e^{-x/λ^*} Before that... I do have a Frequency-dependent and
complex space-constant

$$\frac{1}{\lambda^*} = \frac{\sqrt{1 + \tau_m j \omega}}{\lambda} = A e^{j \phi} \quad A = \frac{\sqrt[4]{1 + \tau_m^2 \omega^2}}{\lambda} \quad \phi = \frac{1}{2} \arctan \tau_m \omega$$

$$e^{j \phi} = \cos(\phi) + j \sin(\phi) \quad \begin{matrix} \text{Euler's formula} \\ \text{the most beautiful} \\ \text{equation in mathematics} \end{matrix}$$

$$e^{-x/\lambda^*} = e^{-x} A \cos(\phi) - j x A \sin(\phi)$$

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

$$\sin(\arctan k) = \frac{k}{\sqrt{1+k^2}} \quad \sin(\alpha/2) = \pm \sqrt{\frac{1-\cos(\alpha)}{2}}$$

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

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

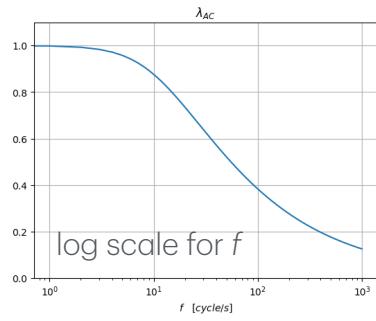
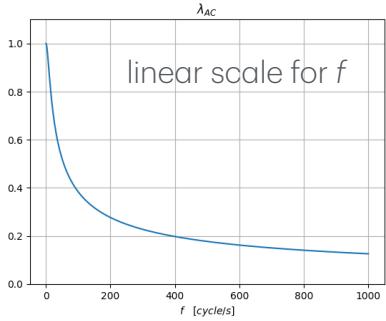
$$A = \frac{\sqrt[4]{1 + \tau_m^2 \omega^2}}{\lambda} \quad \phi = \frac{1}{2} \arctan \tau_m \omega \quad e^{j\phi} = \cos(\phi) + j \sin(\phi)$$

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

DC

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

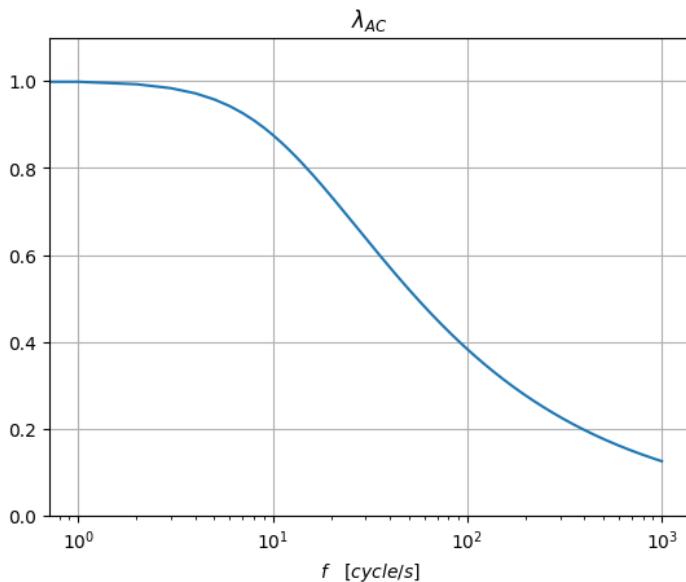
$$e^{-x/\lambda_{AC}} \quad \lambda_{AC} = \frac{1}{A \cos(\phi)} = \lambda \sqrt{\frac{2}{1 + \sqrt{1 + (2\pi f)^2 \tau_m^2}}}$$



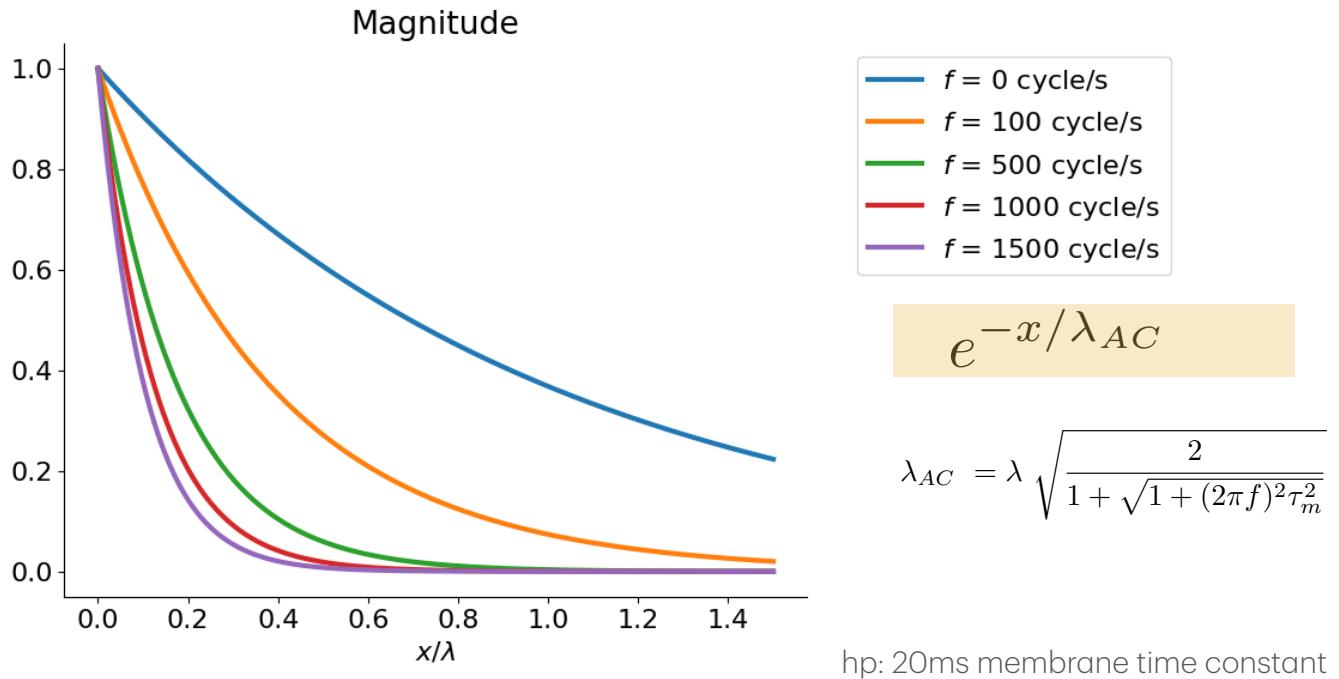
hp: 20ms membrane time constant

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

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

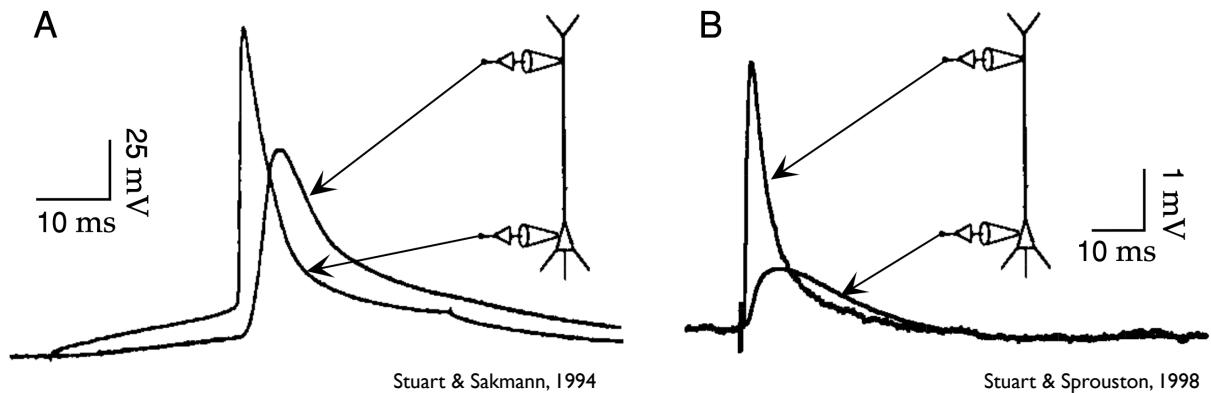


Sinusoidal Regime - AC - attenuation (semi-infinite cable...)

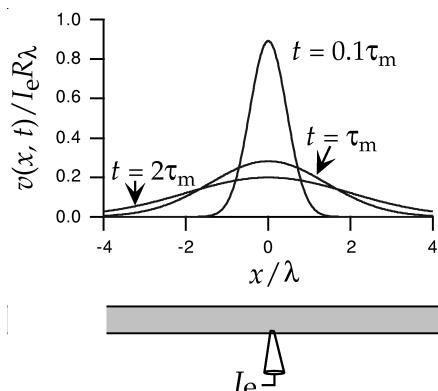


Of cables: synapses,
dendrites, and somata
(and back)

Back-propagating AP and (forward propagating) EPSPs



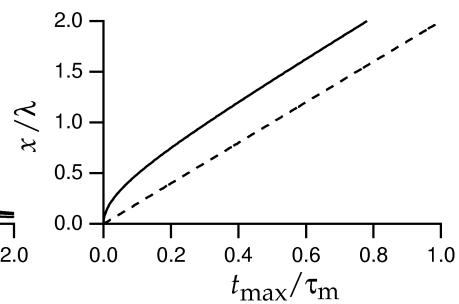
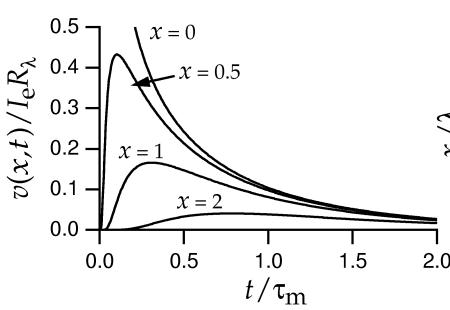
Transient solution (attenuation, shape change, delay)



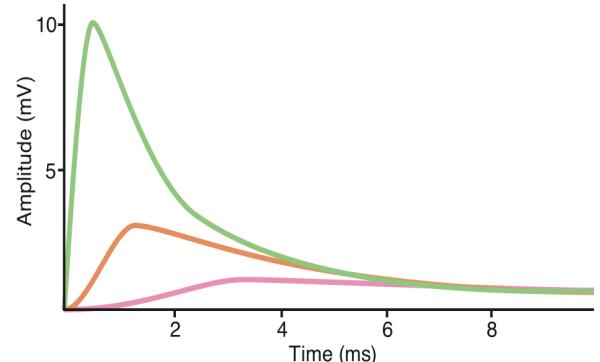
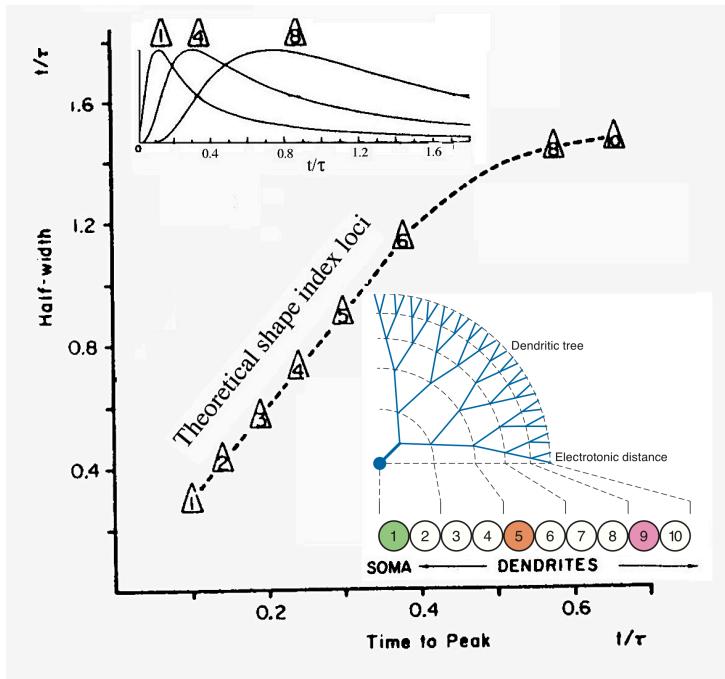
$$V(x,t) = \frac{I_e R_\lambda}{\sqrt{4\pi \lambda_m^2 t/\tau_m}} \exp\left(-\frac{\tau_m x^2}{4\lambda_m^2 t}\right) \exp\left(-\frac{t}{\tau_m}\right)$$

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

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

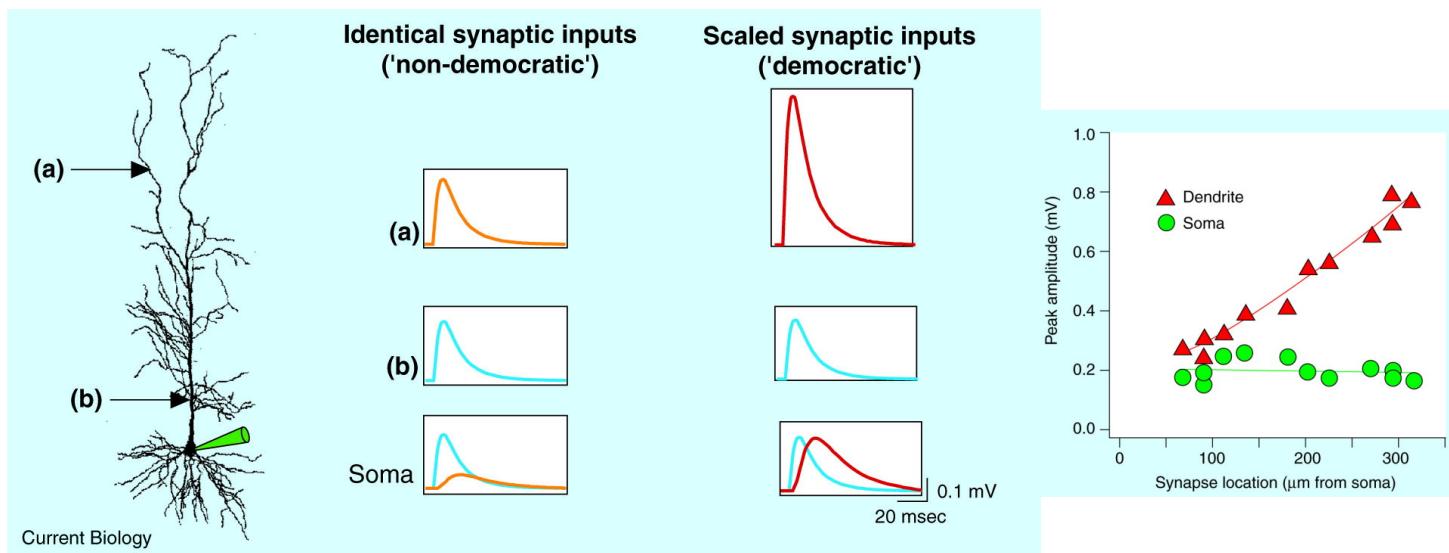


Experimental Predictions distal synapses are “broader” and “delayed”



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

Dendritic “democracy” (in CA1 pyramidal neurons)



CA1 pyramidal neuron

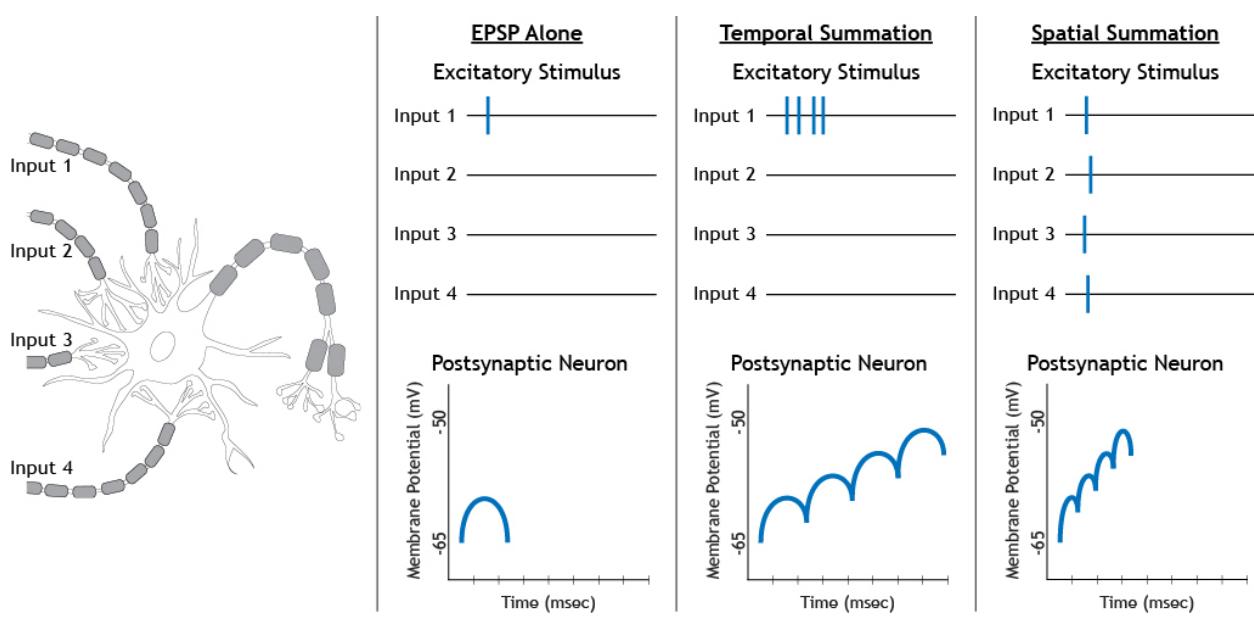
Häusser, 2001

ATTENDANCE TRACKING - **code ???**

(for statistical purposes only)

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

Temporal and Spatial summation

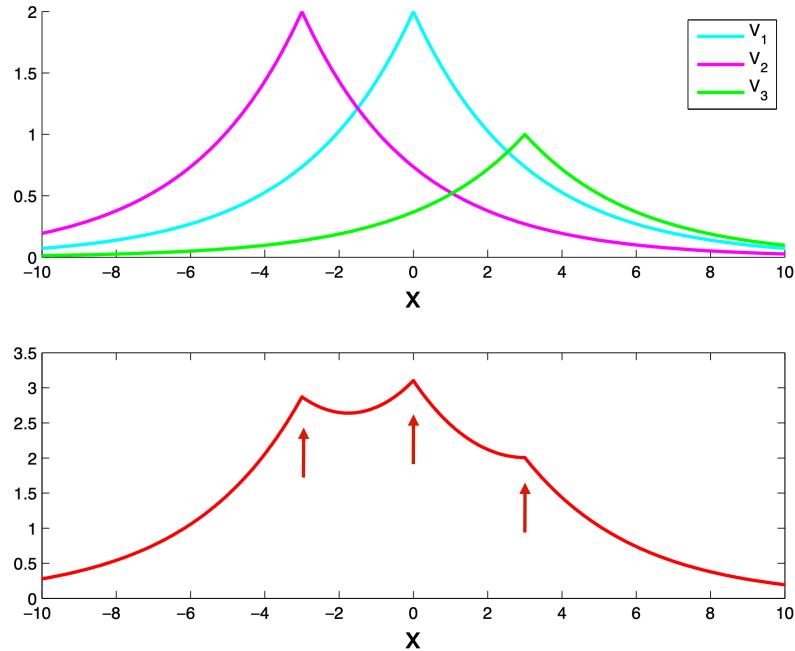


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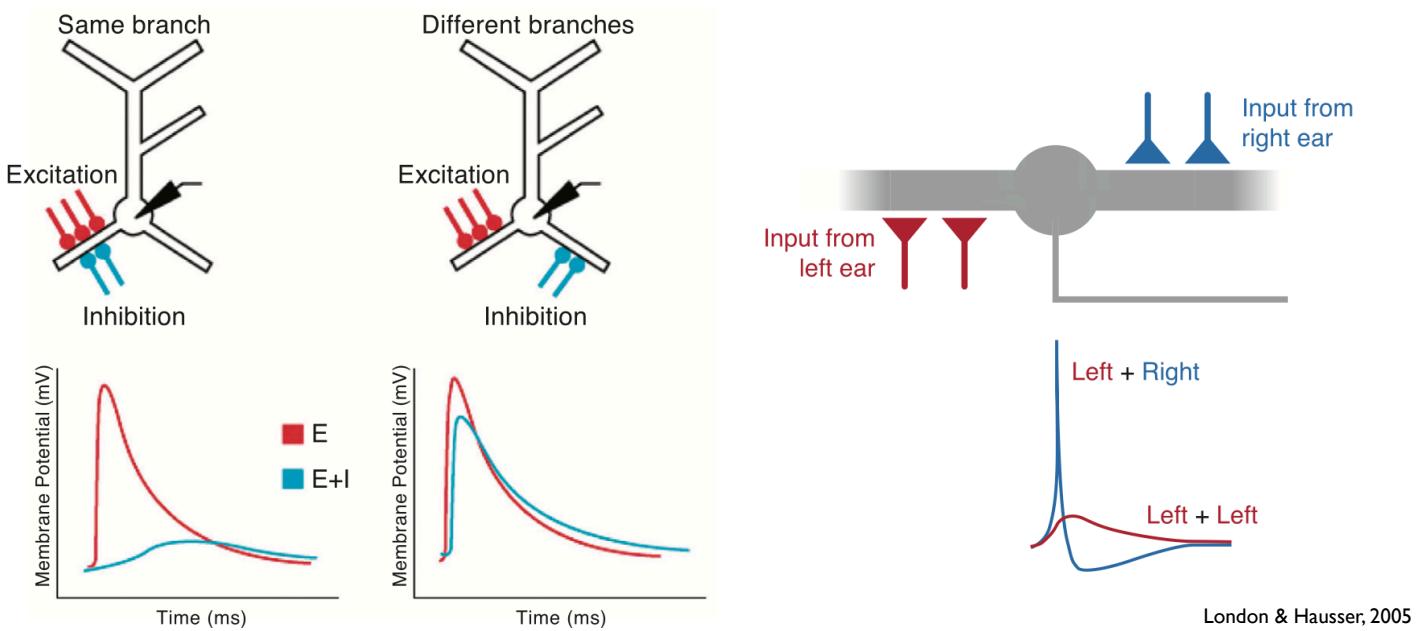
Temporal and (linear) Spatial summation

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

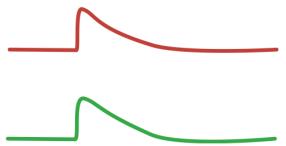
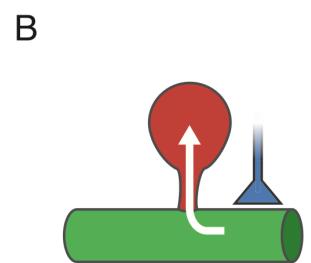
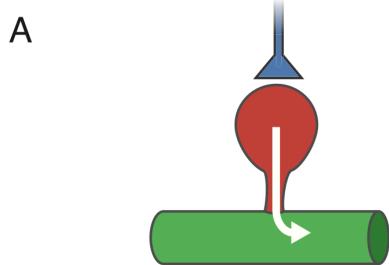
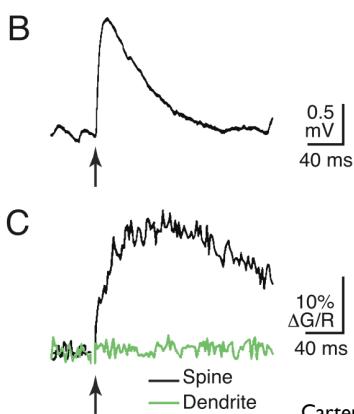
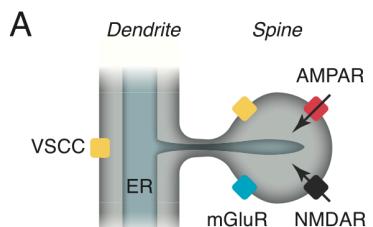
$$V_{sum} = V_1(x) + V_2(x) + V_3(x)$$



(sub)linear Spatial Summation

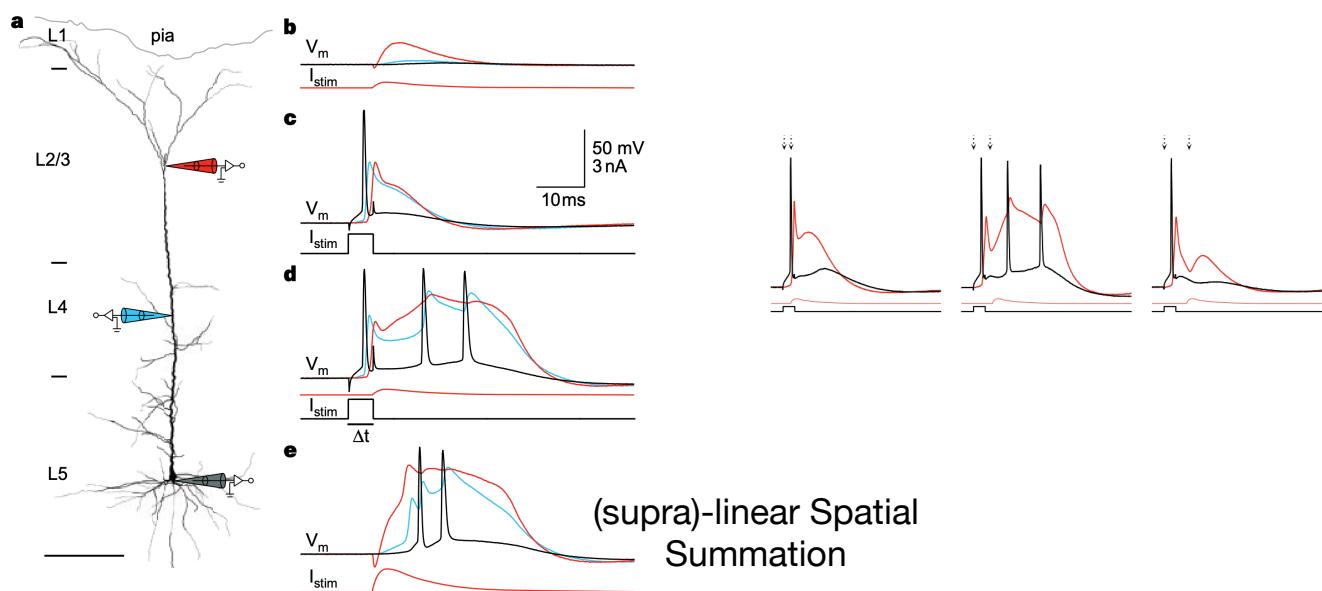


Dendritic spines, depolarization, and Ca⁺⁺ influx



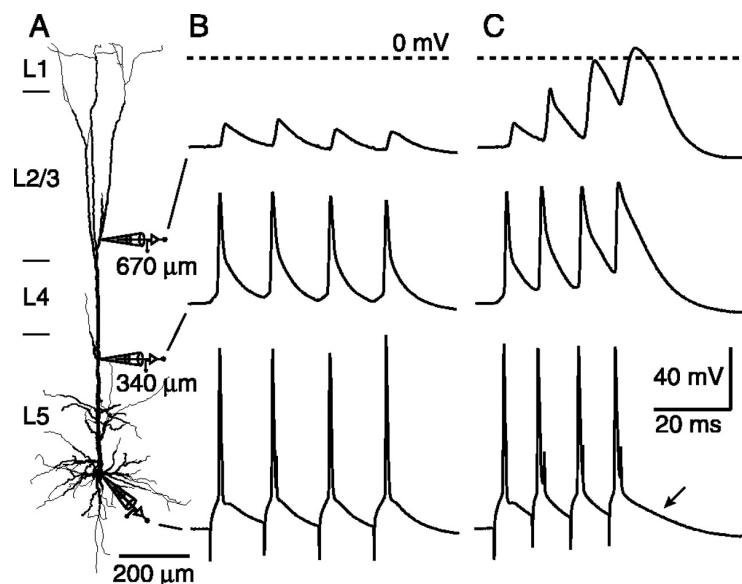
Spruston, 2008

This **back-propagating AP activated Ca²⁺ spike firing (BAC)** is a coincidence detection mechanism (distal inputs & AP firing)



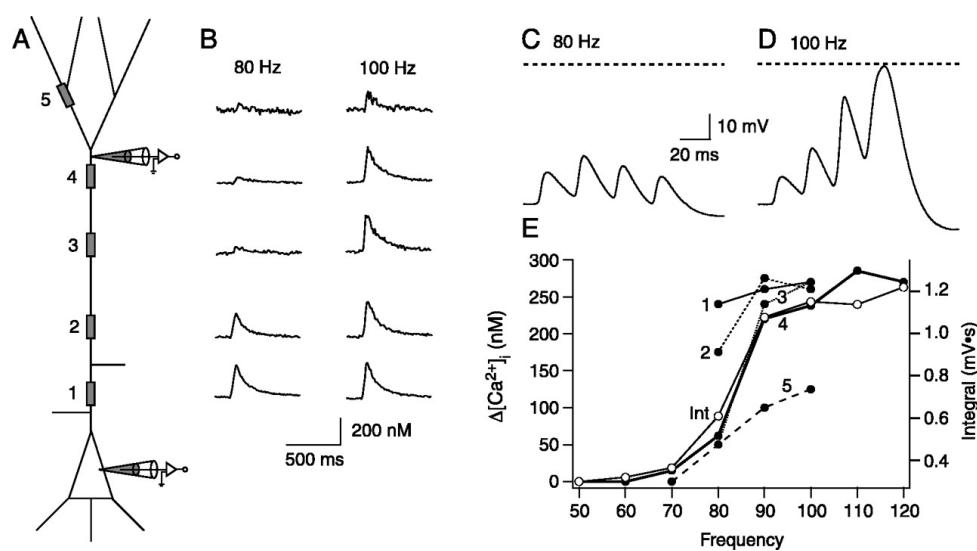
Larkum, Zhu, & Sakmann, 1999

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



Larkum et al. 1999

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



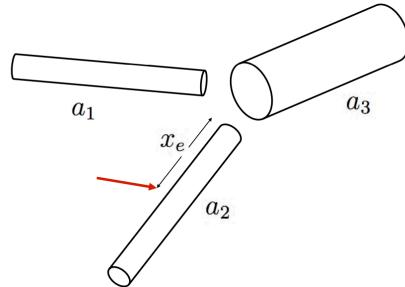
Larkum et al. 1999

Branching points

$$v_1(x) = I_e R_{\lambda_1} p_1 \exp\left(-\frac{x}{\lambda_1} - \frac{x_e}{\lambda_2}\right)$$

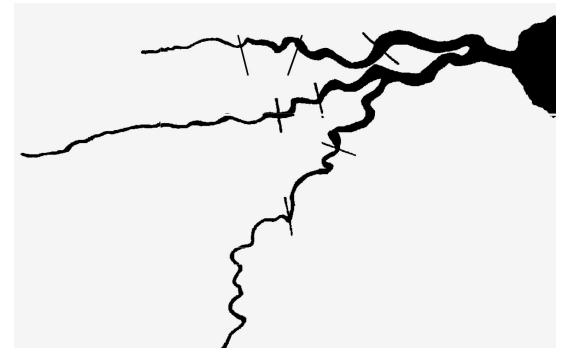
$$v_2(x) = I_e R_{\lambda_2} \left[(p_2 - 1) \exp\left(-\frac{x}{\lambda_2} - \frac{x_e}{\lambda_2}\right) + \exp\left(-\frac{|x_e - x|}{\lambda_2}\right) \right]$$

$$v_3(x) = I_e R_{\lambda_3} p_3 \exp\left(-\frac{x}{\lambda_3} - \frac{x_e}{\lambda_2}\right)$$



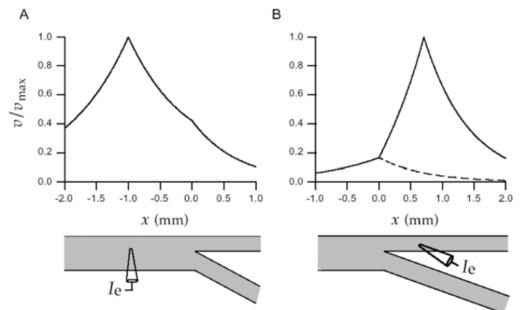
$$p_i = \frac{a_i^{3/2}}{a_1^{3/2} + a_2^{3/2} + a_3^{3/2}}$$

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

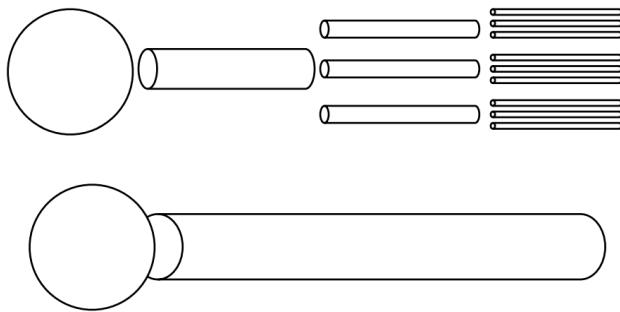


thick → thin

thin → thick



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/λ is set equal to total electrotonic length of tree segments $\sum_i \frac{L_i}{\lambda_i}$

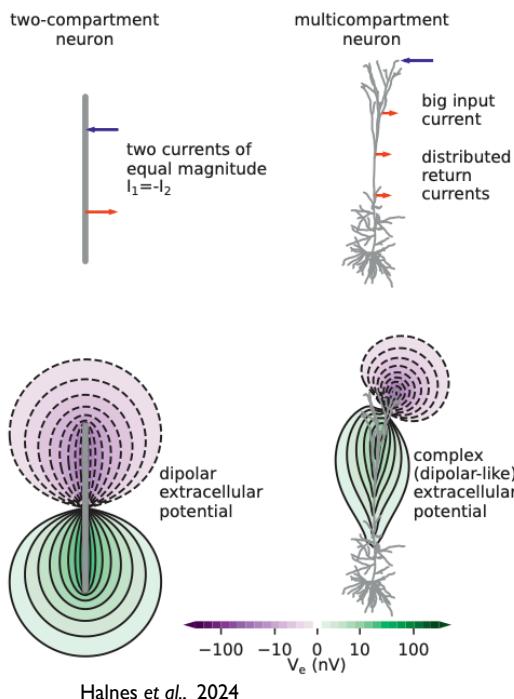
The Rall model is exact when

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

Let's discuss extracellular signals and volume-conductor theory

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

Extracellular signals: more in general, how to?

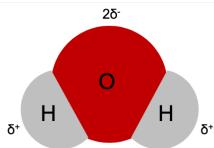


- Describing, across space, ionic currents changes.
(cable theory)

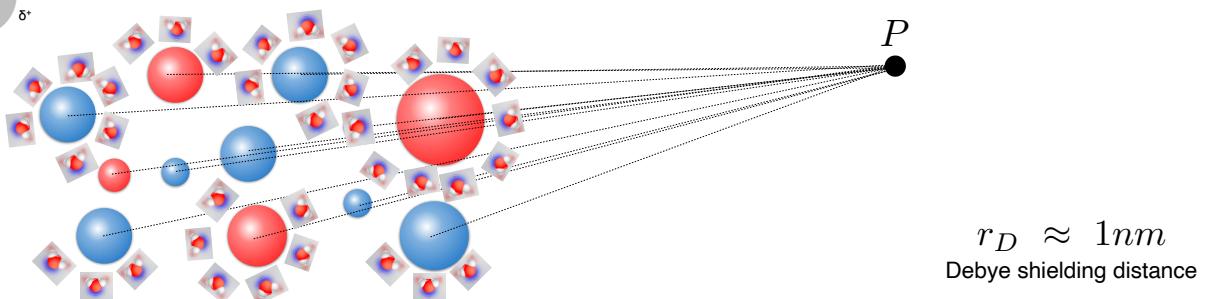
$$\lambda^2 \frac{\partial^2 v(x, t)}{\partial x^2} = \tau_m \frac{\partial v(x, t)}{\partial t} + v(x, t)$$

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

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



Extracellular potential V_e



$$V_{total}(P) = \frac{1}{4\pi\epsilon_r\epsilon_0} \left(\frac{Q_1 e^{-r_1/r_D}}{r_{P-Q_1}} + \frac{Q_2 e^{-r_2/r_D}}{r_{P-Q_2}} + \dots + \frac{Q_M e^{-r_M/r_D}}{r_{P-Q_M}} \right)$$

Very hard to use for macroscopic distances, where
shielding in space and ultrafast *relaxation* times must be considered.
(Across the plasma membrane was ok to use it!)

Extracellular potential V_e

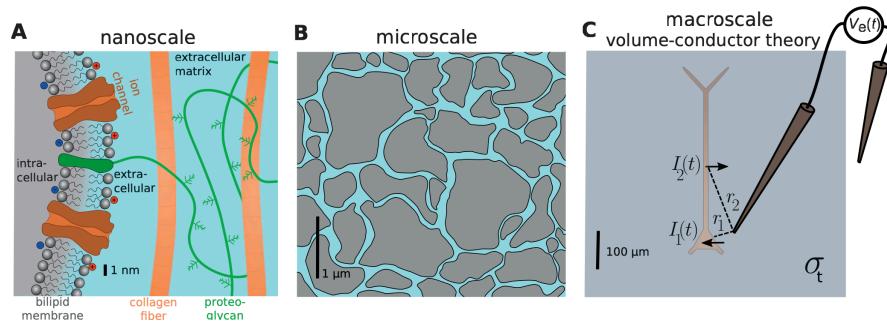
⇒ Particles move with a velocity proportional (by μ - *mobility*) to the external force field

$$F_{ext} + F_{friction} = m \frac{dv(t)}{dt} \quad F_{friction} = -\lambda v(t)$$

$$v(t) = k e^{-\frac{\lambda}{m}t} + \frac{F_{ext}}{\lambda}$$

$$\frac{\lambda}{m} \gg 1$$

$$\frac{m}{\lambda} \approx 1\text{ns} \quad \text{relaxation time, for ions movement in solution}$$



(single) ion channels,
capacitive properties
individual ions...

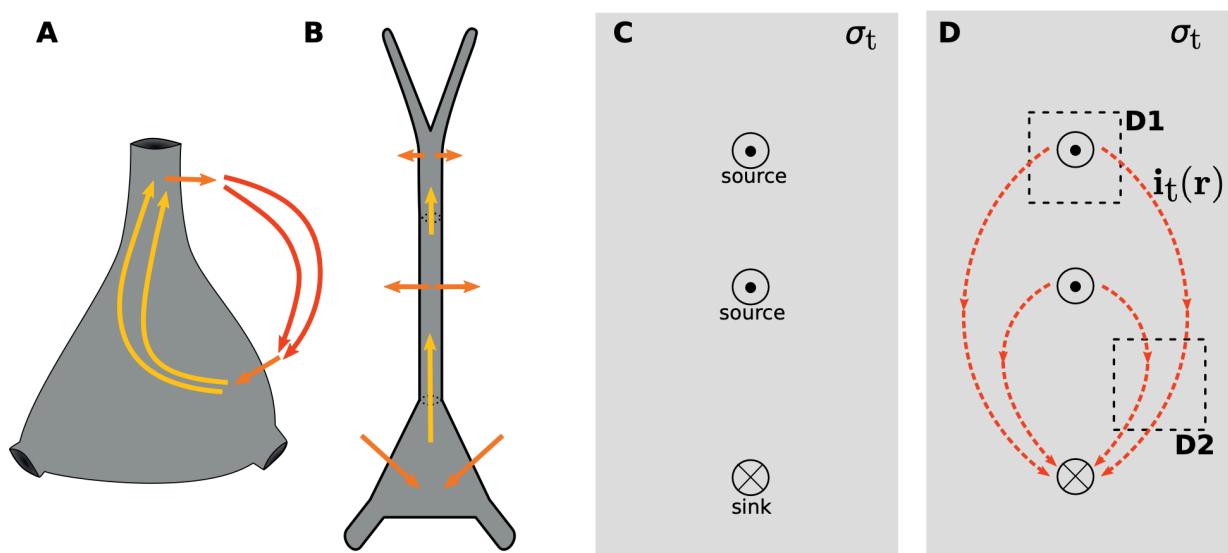
concentrations,
densities,...

bulk properties,
current flows

At **macroscale** (i.e. distances \gg Debye's and times \gg relaxation time)
intracell. and extracell. spaces are effectively **electroneutral** (thus **isopotential**)

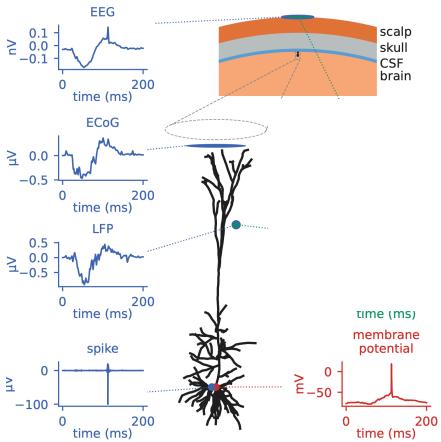
Extracellular potentials can be inferred (in much simpler terms than ionic charges distribution and movements) from the **conservation of charge**,
applied to currents: no accumulation of current exist (Kirchoff's).

Not “charges” but “*Current sources (and sinks)*”



Extracellular potential V_e

Volume Conductor Theory



Halnes et al., 2024

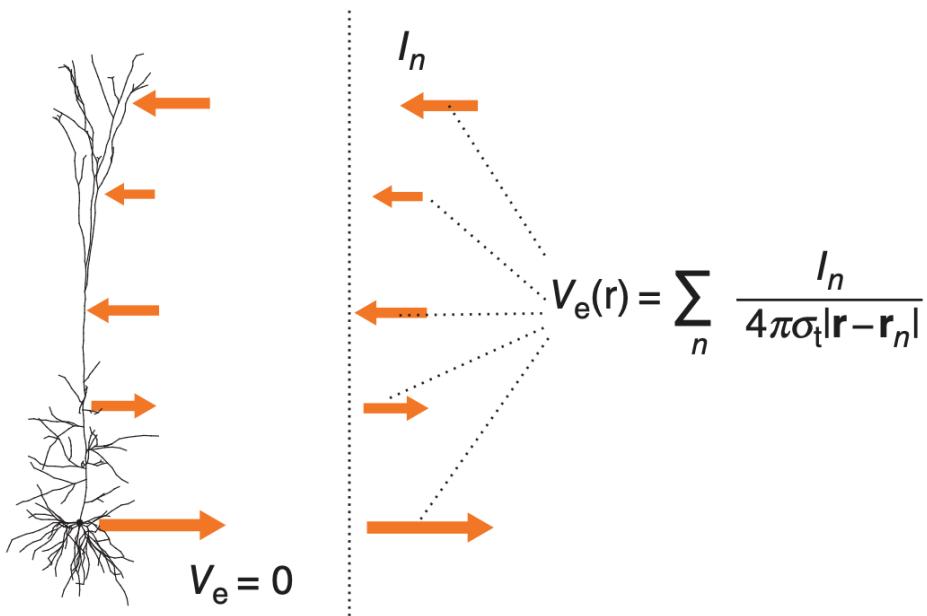
Assumptions of VCT:

- all intracellular $V(x,t)$ and $I(x,t)$ are known or measured;
 - (from cable theory, cell excitability, synapses location)
- V_e does NOT affect intracellular V and I (no “ephaptic” interactions)
- the brain tissue is a continuous medium (i.e. a “volume” conductor)
- the macroscopic tissue conductivity is uniform (in space), constant (in time), and isotropic (across space directions);
- at macro scale the tissue is Ohmic (in 3D)

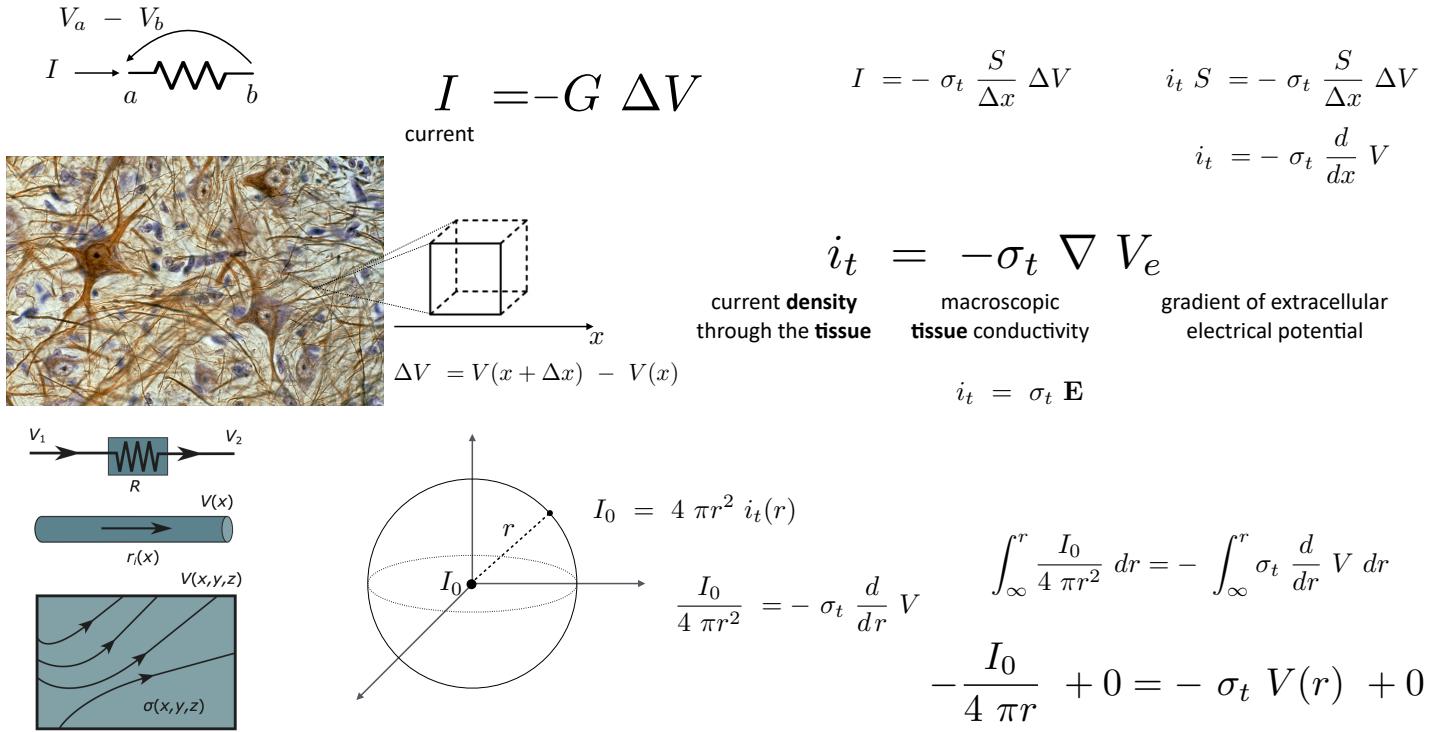
Starting point for “forward” description of the origin of extracellular spikes, LFPs, ECoGs, EEGs.

Extracellular potential V_e

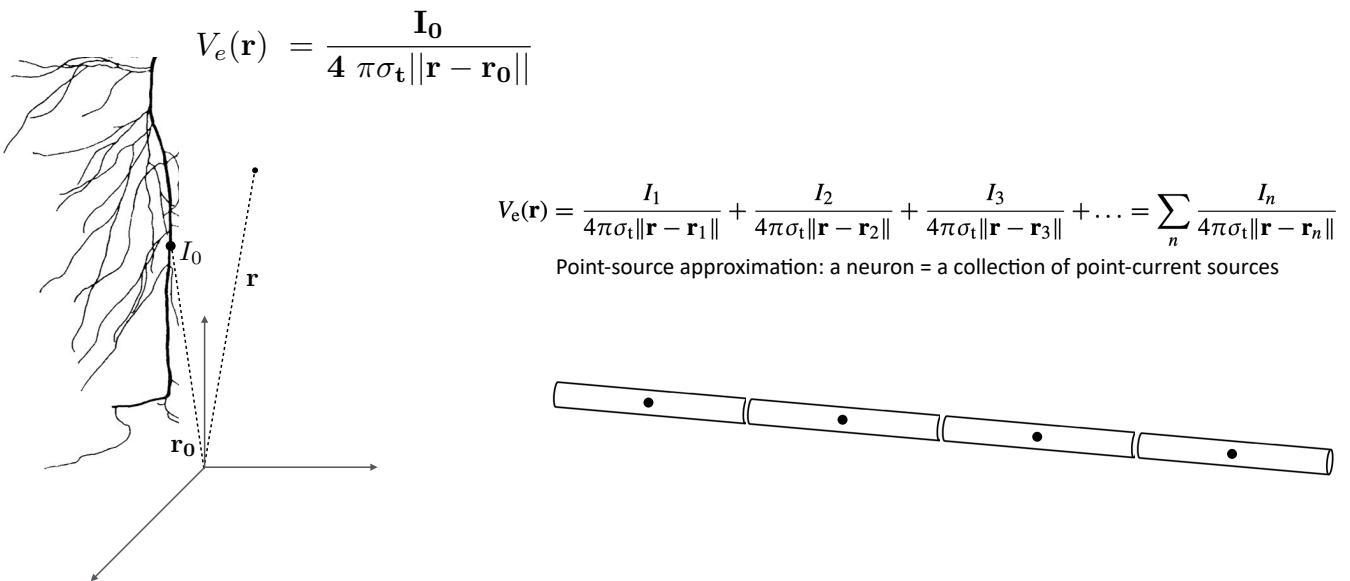
Volume Conductor Theory



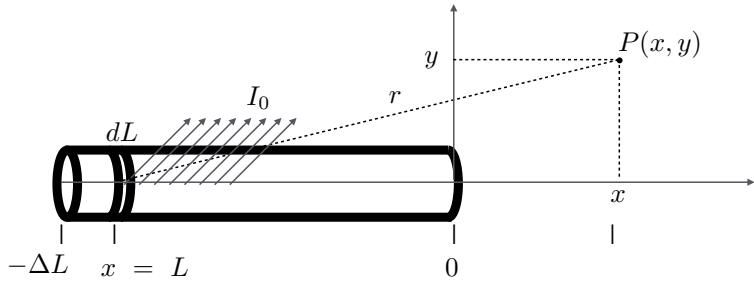
Ohm's law (for a volume c.) and *point* sources



(A set of) “Point current” source(s)



A better approximation: “line”-sources



$$r = \sqrt{(x - L)^2 + y^2}$$

$$V_e(\mathbf{r}) = \frac{\mathbf{I}_0}{4 \pi \sigma_t \|\mathbf{r} - \mathbf{r}_0\|}$$

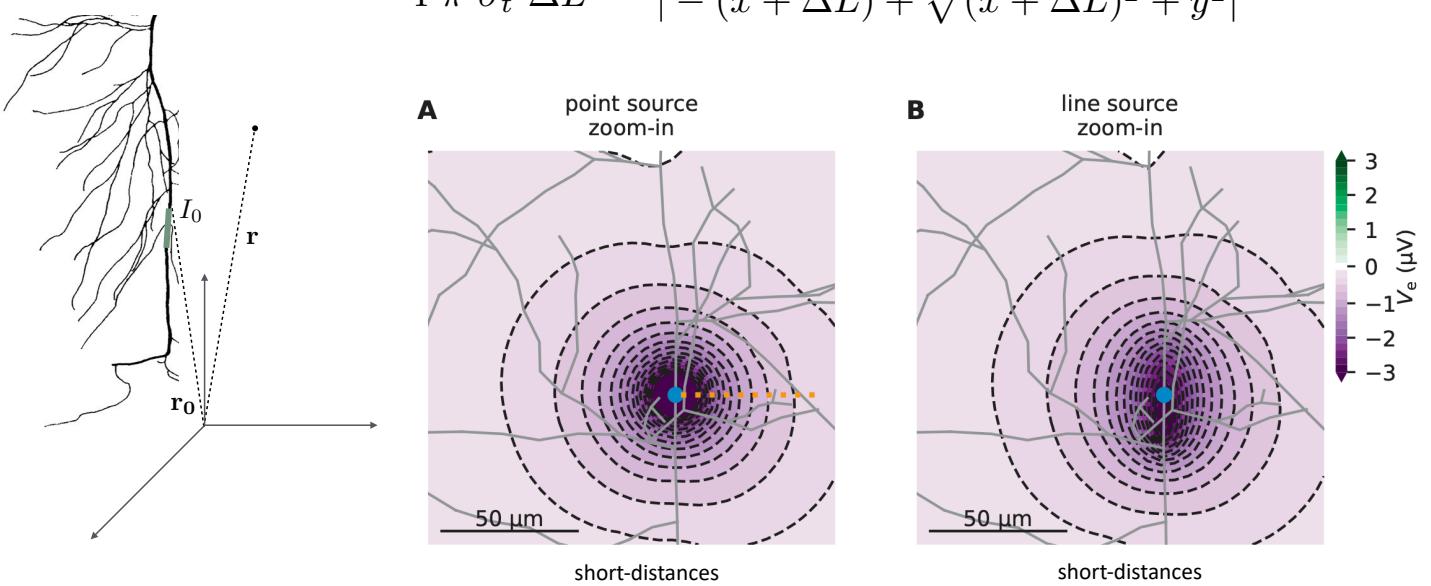
$$dI_0 = I_0 \frac{dL}{\Delta L} \quad V_e(\mathbf{r}) dL = \frac{I_0}{\Delta L} \frac{dL}{4 \pi \sigma_t \sqrt{(x - L)^2 + y^2}} \quad V_e(\mathbf{r}) = \int_{-\Delta L}^0 \frac{I_0}{\Delta L} \frac{dL}{4 \pi \sigma_t \sqrt{(x - L)^2 + y^2}}$$

$$\int \frac{dt}{\sqrt{t^2 + a^2}} = \ln |t + \sqrt{t^2 + a^2}| + K$$

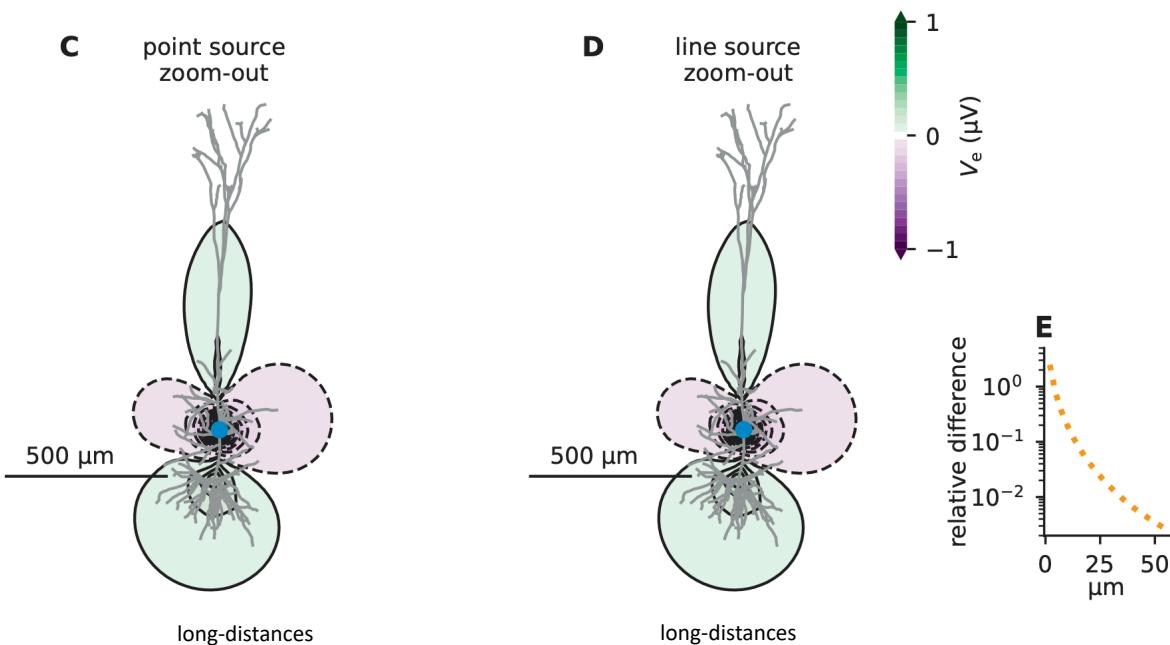
$$V_e(\mathbf{r}) = \frac{I_0}{4 \pi \sigma_t \Delta L} \ln \frac{|-x + \sqrt{x^2 + y^2}|}{|-(x + \Delta L) + \sqrt{(x + \Delta L)^2 + y^2}|}$$

“Point-source” vs “Line-source” approaches

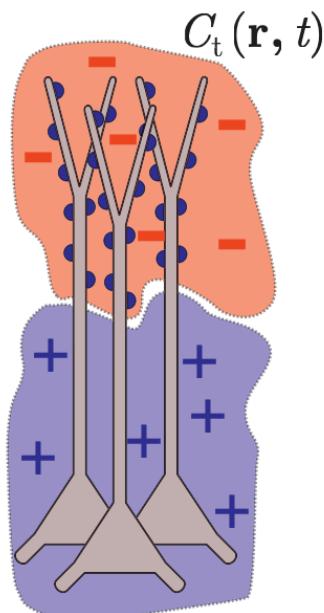
$$V_e(\mathbf{r}) = \frac{I_0}{4 \pi \sigma_t \Delta L} \ln \frac{|-x + \sqrt{x^2 + y^2}|}{|-(x + \Delta L) + \sqrt{(x + \Delta L)^2 + y^2}|}$$



“Point-source” vs “Line-source” approaches



More generally: CSD - current source *density*



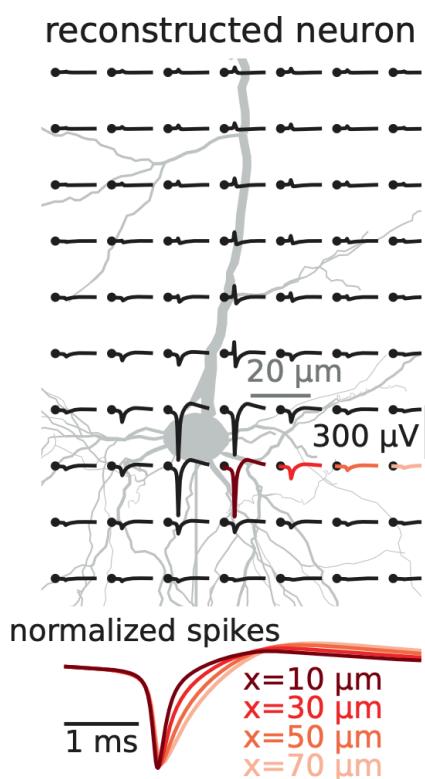
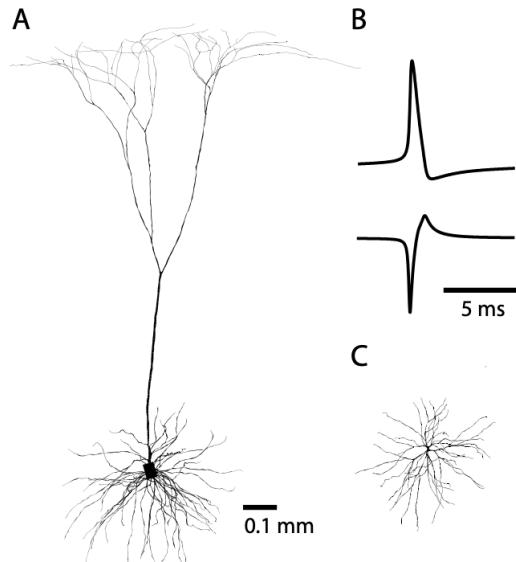
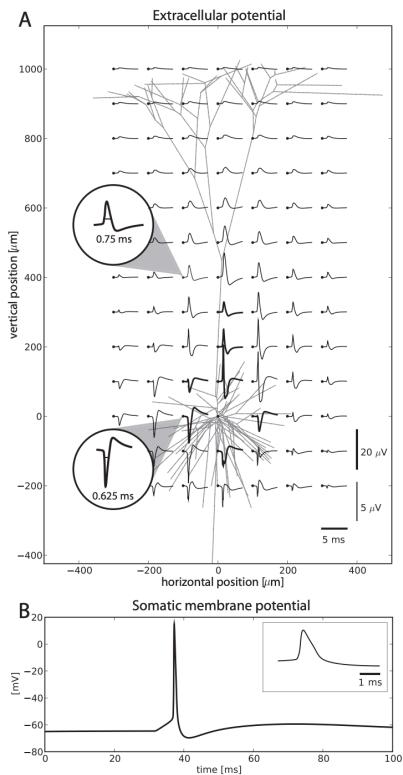
- current source density (in the tissue) C_t is
 - *a continuous function of time and position*
 - *usually estimated in the “inverse” problem (from measured V_e to C_t)*
 - *can be a collection of Dirac’s delta functions (in 3D), and then it reduces to the point-source approximation already discussed*

$$\nabla i_t = C_t$$

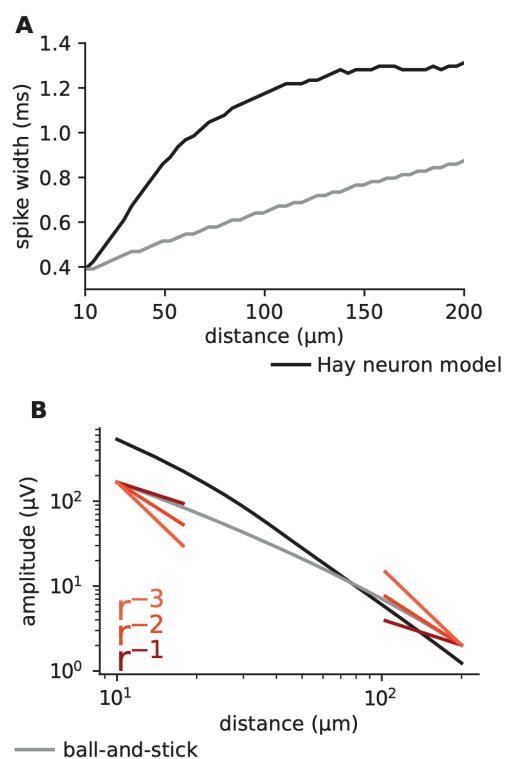
$$\sigma_t \nabla^2 V_e = -C_t$$

More complicated partial-derivatives differential equation...

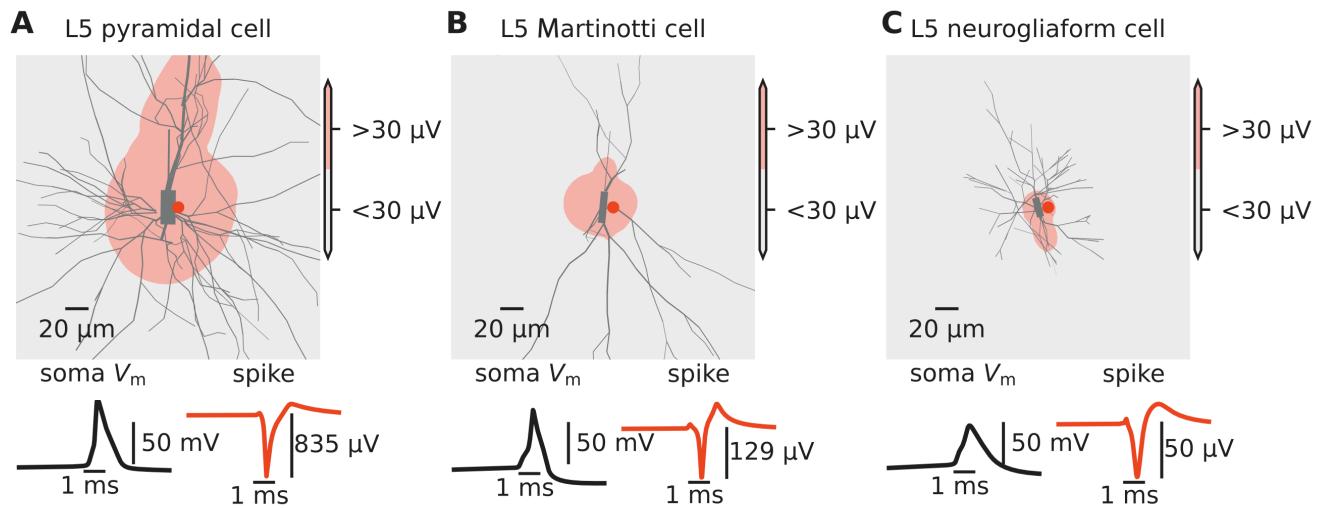
VCT - spikes



Spike shapes



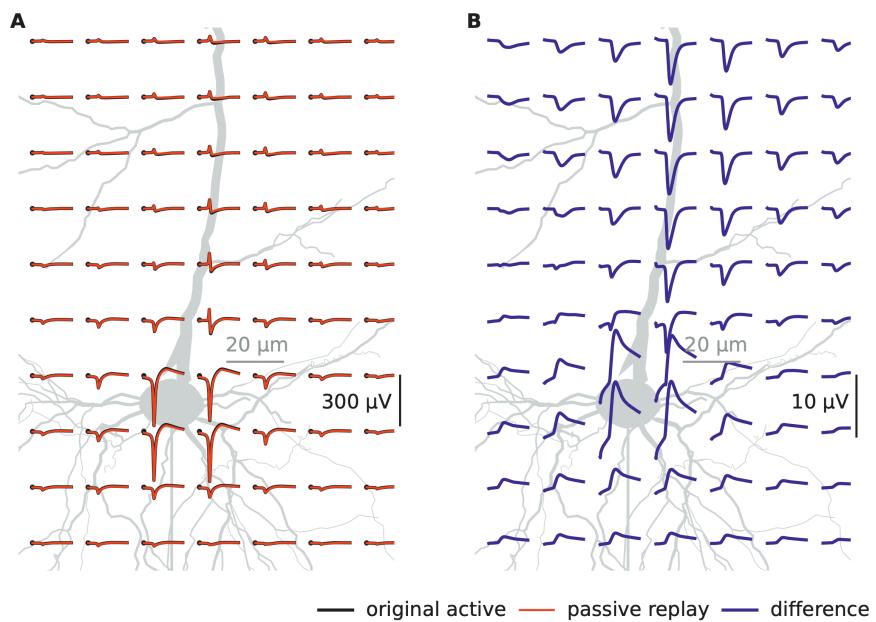
Spike detectability: depends on cell morphology



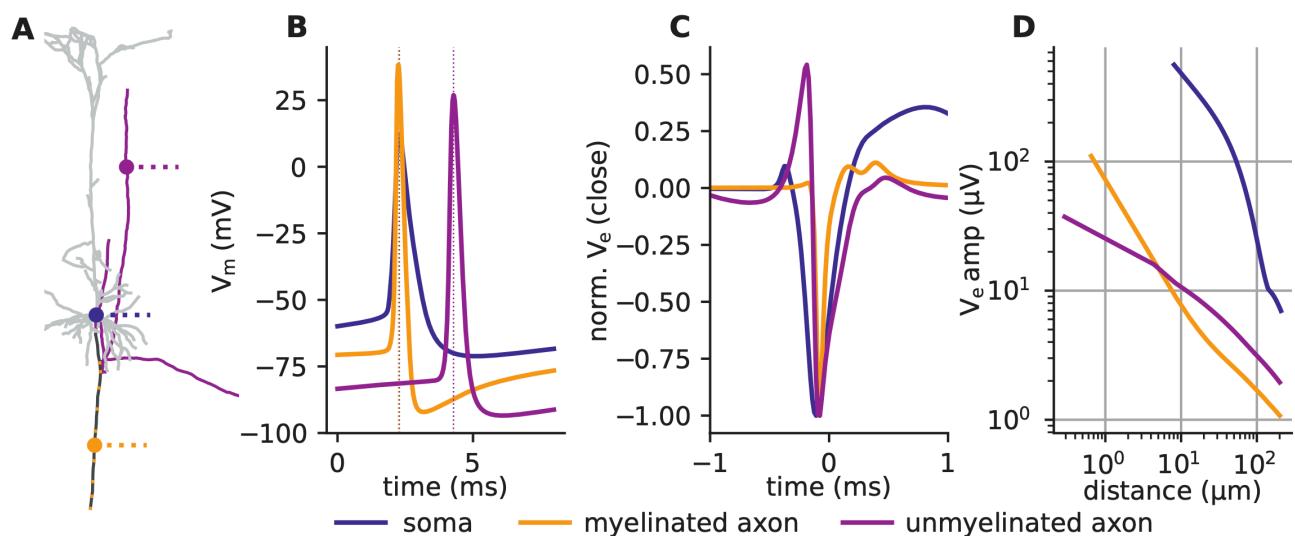
ATTENDANCE TRACKING - **code ???**
(for statistical purposes only)

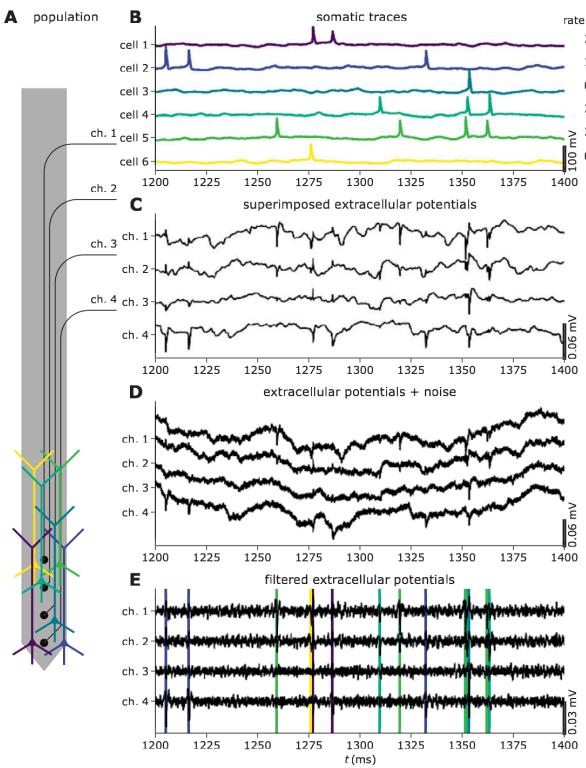
<https://www.unimore.it/it/servizi/unimore-app>

Spikes: weak impact of *active* dendrites



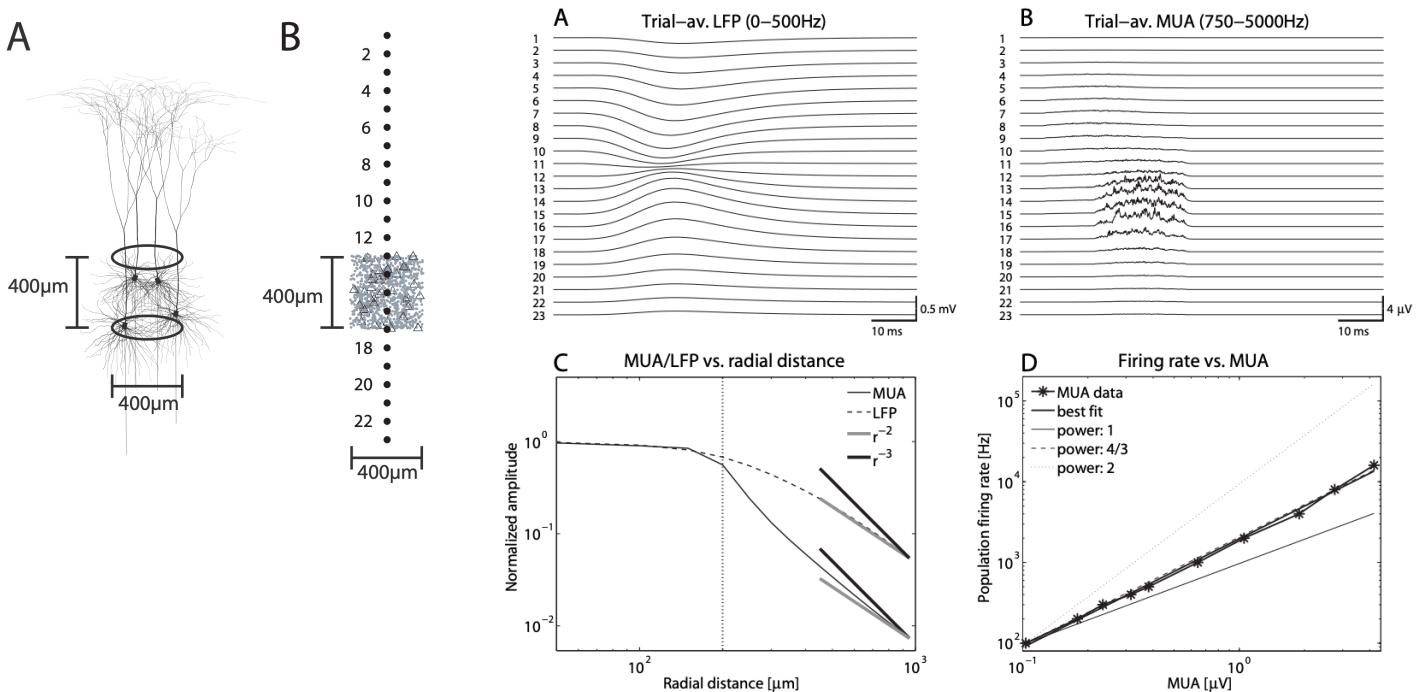
Axonal Spikes: impact of *myelinated* axon





Forward modeling of V_e may guide development/benchmark of *spike-sorting* algorithms.

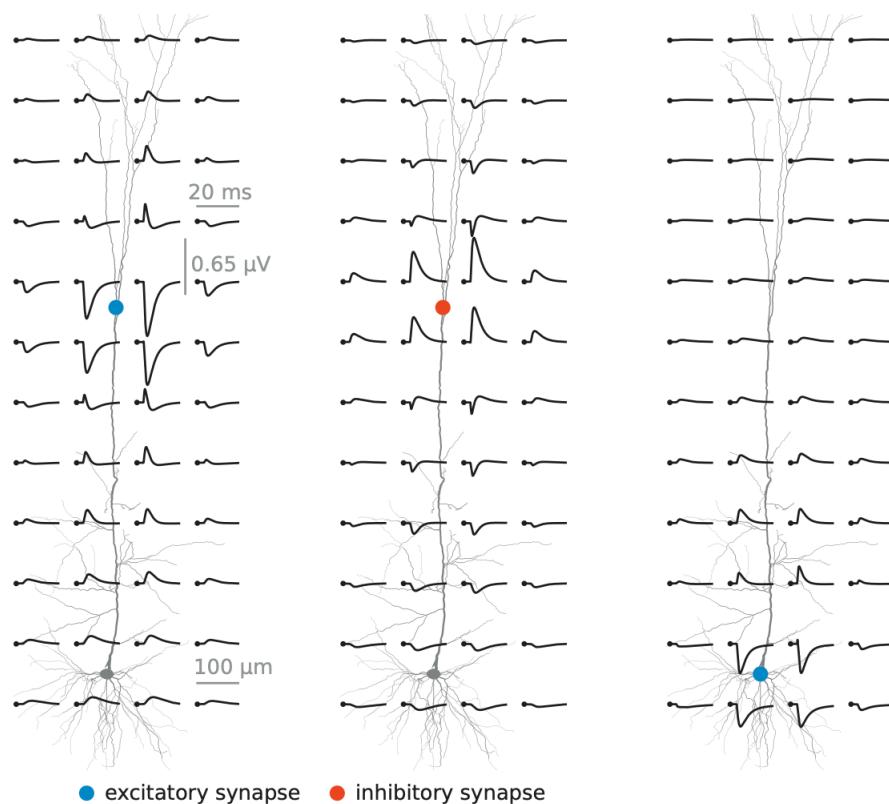
VCT - LFP and MUA - population of pyr. cells



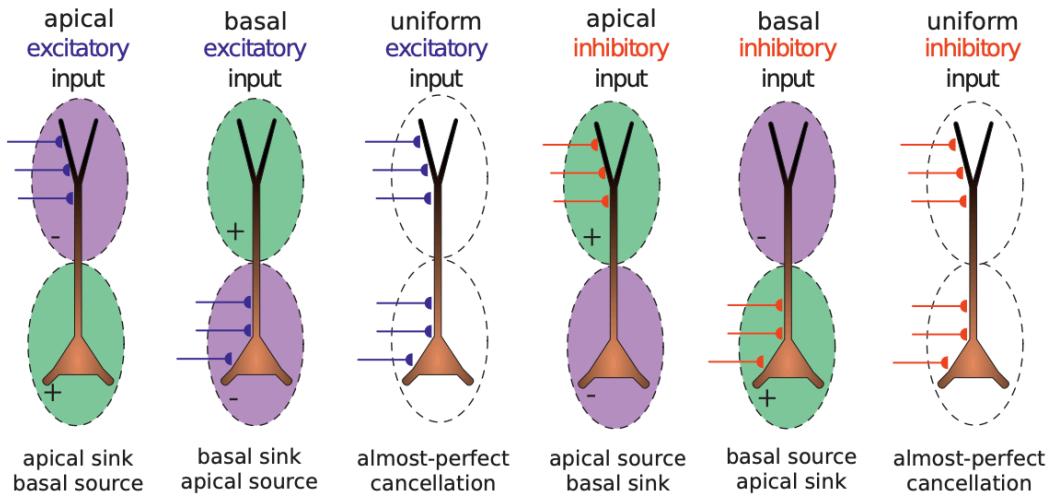
Local Field Potentials

Several processes contribute to LFP (the low-frequency part of the extracellular V)

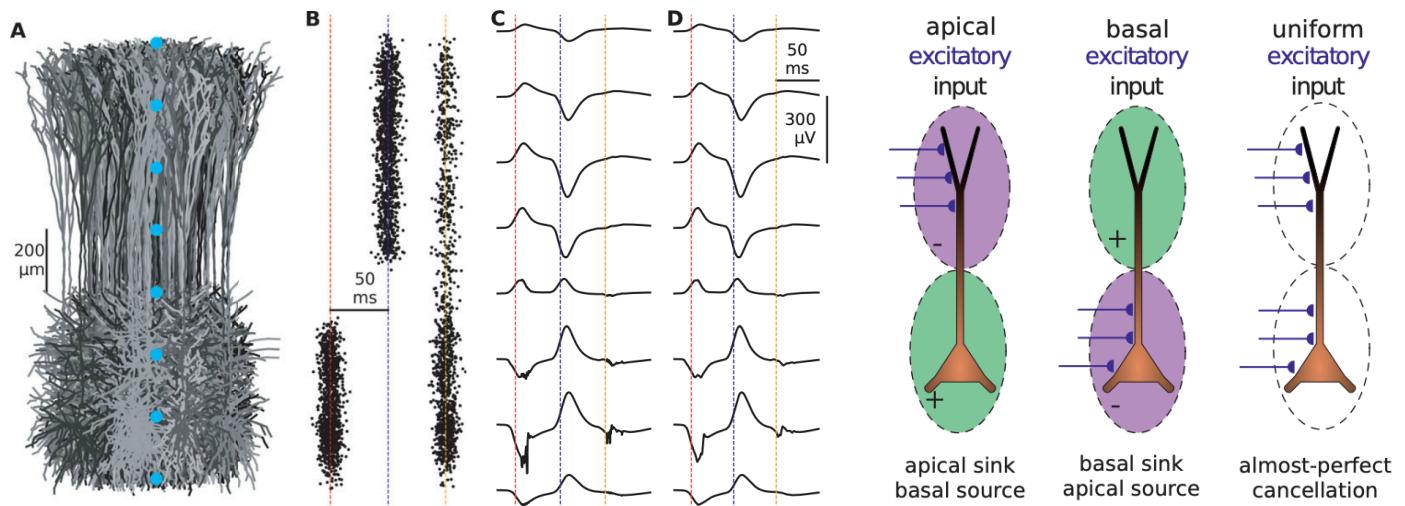
- **synaptic currents (and associated return currents) - MAIN CONTRIBUTOR**
- regular spikes, contributing to low-frequencies (e.g. sodium-mediated AP)
- slow intrinsic membrane currents, mediated by NMDAr or Ca-spikes, etc.
- membrane currents in glial cells
- current loops through neurons, glia and the extracellular space
- diffusion electrical potentials arising from concentration differences of ions in the extracellular space.



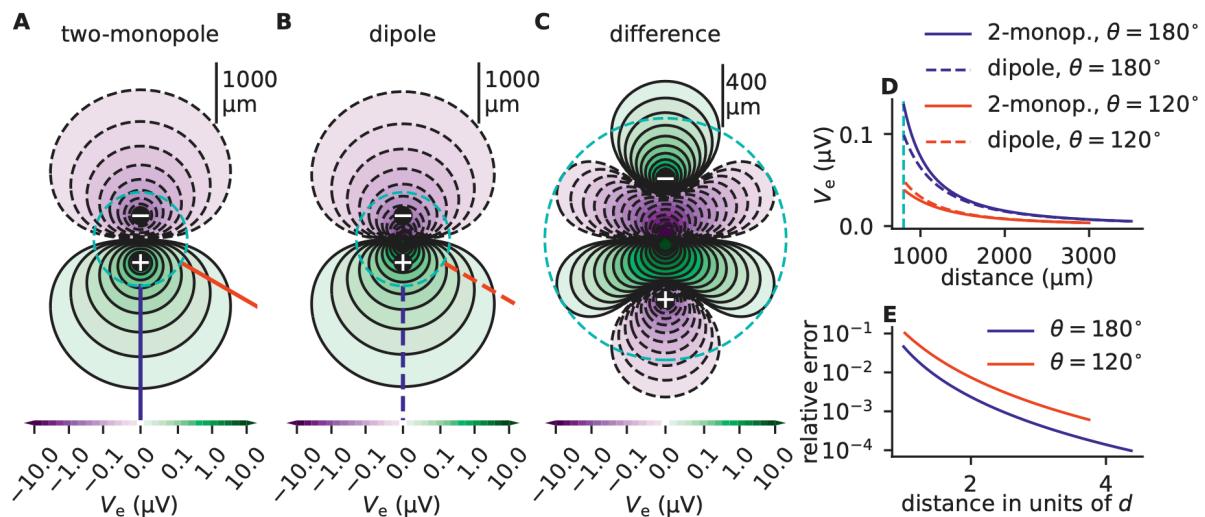
Typical “motifs” of configuration: sources an sinks’ arrangement is not “obvious”



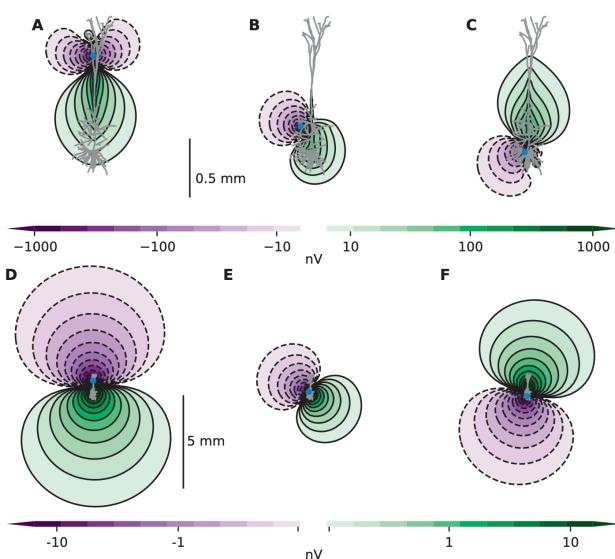
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At large distance extracellular potentials resembles those generated by a *dipole*



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$$V_e(r) \approx \frac{1}{4\pi\sigma_t} \frac{P \cos\theta}{R^2}$$

$$P = \sum_{n=1}^N I_n \mathbf{r}_n$$

$$P = -I \mathbf{r}_1 + I \mathbf{r}_2 = I \mathbf{d}$$