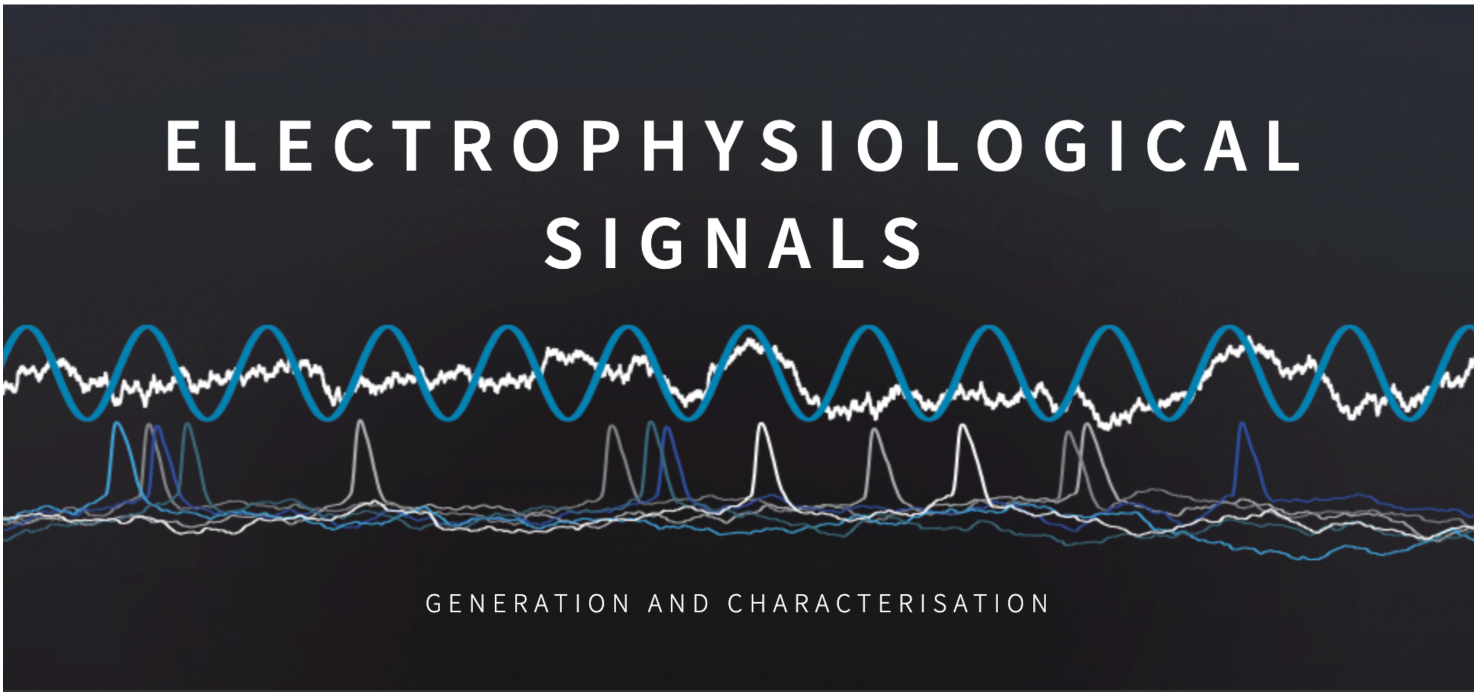


Michele GIUGLIANO

Origin of Extracellular Signals

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

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

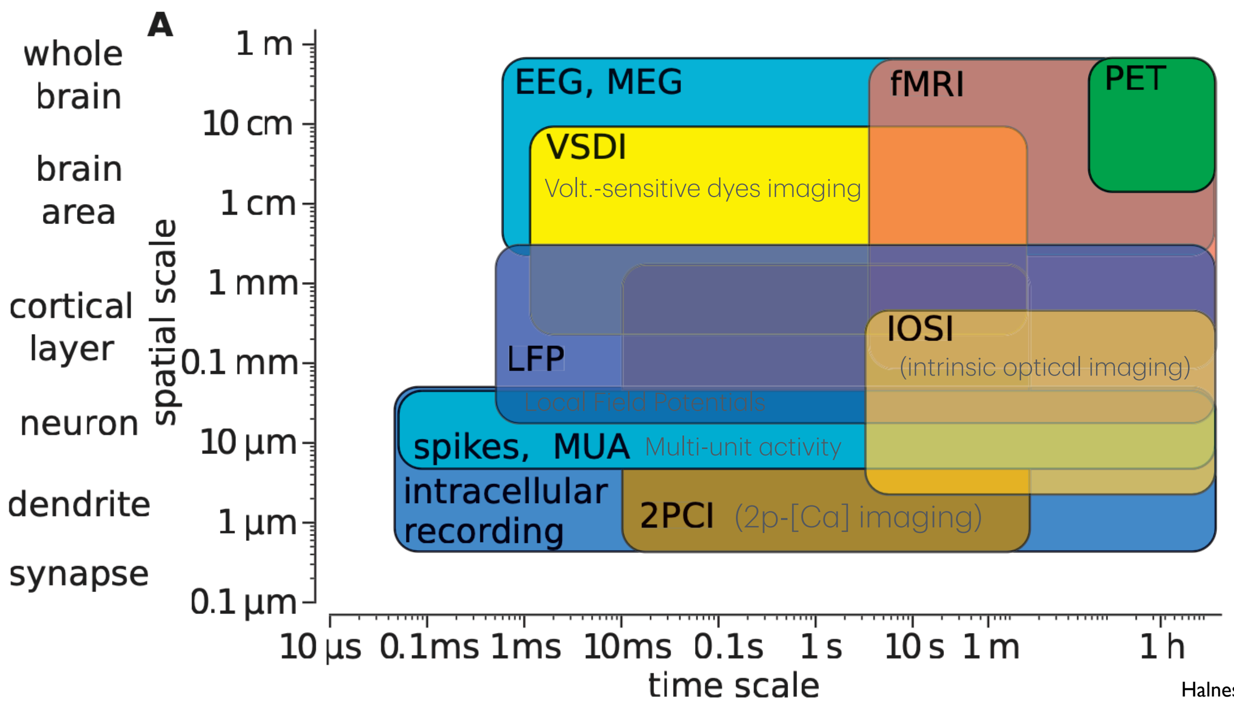
References

supporting your study and understanding

Chapters from

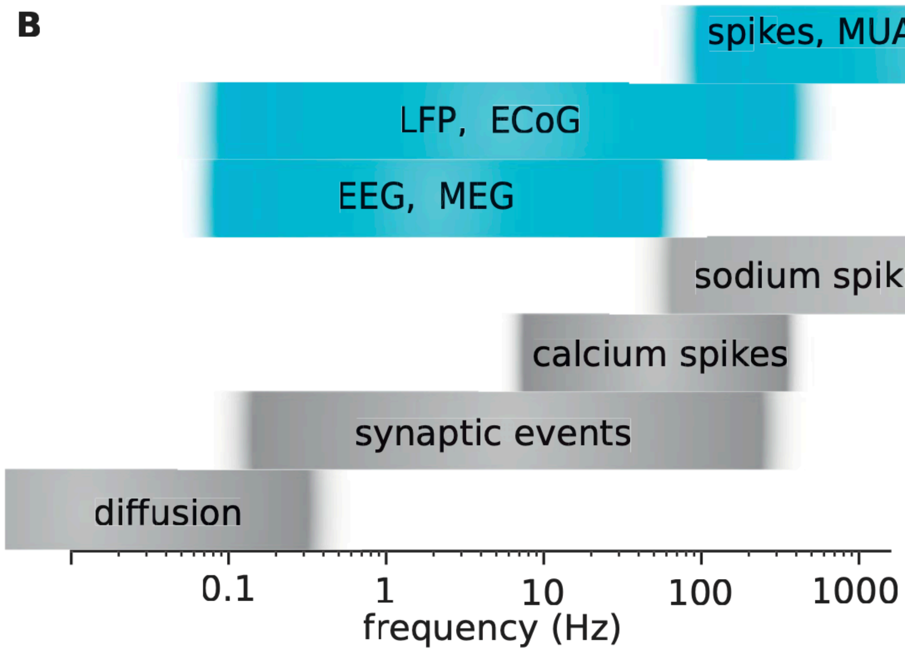
- Halnes et al., (2024) *“Electric Brain Signals”*
- Johnston & Wu (1994) *“Foundations of Cellular Neurophysiology"*
- Sterratt et al. (2011) *“Principles of Computational Modelling…”*
- Abbott LF, Dayan P (2001) *“Theoretical Neuroscience”*

Range of Techniques and Methods: not all the same!



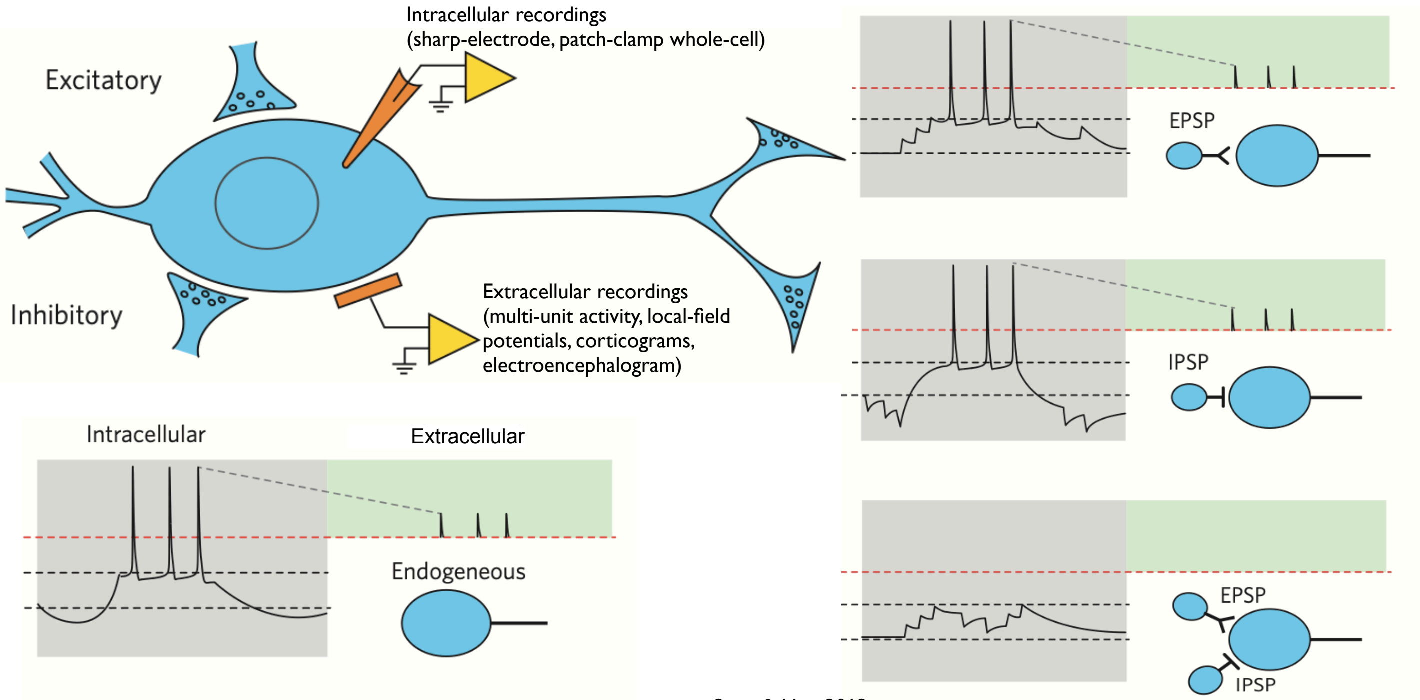
Halnes *et al.*, 2024

Heterogeneous (and multiple) time-scales



Halnes *et al.*, 2024

*<u>Extra</u>*cellular signals: only the *"fast/strong part"*?



Spira & Hai, 2013

*Extra*cellular signals: not so elementary!

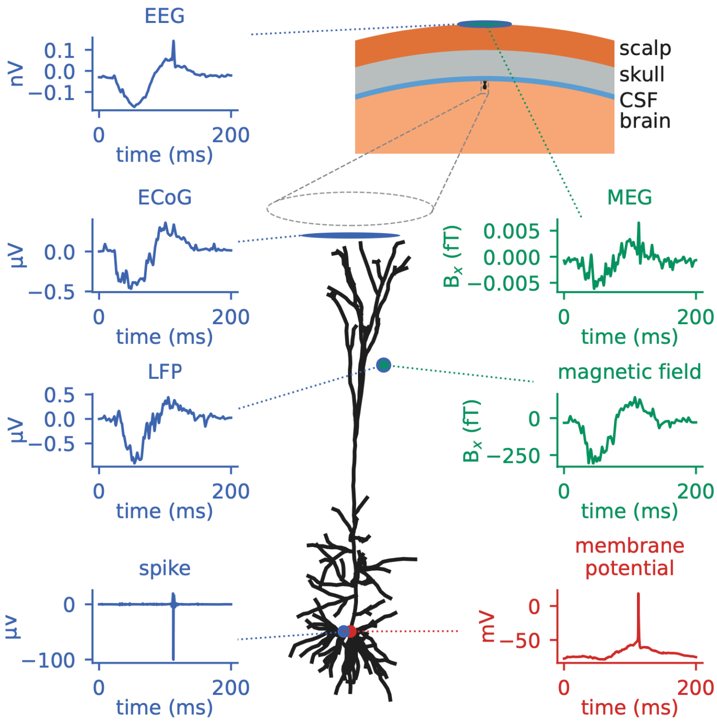
1) **Where** are you recording?

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?



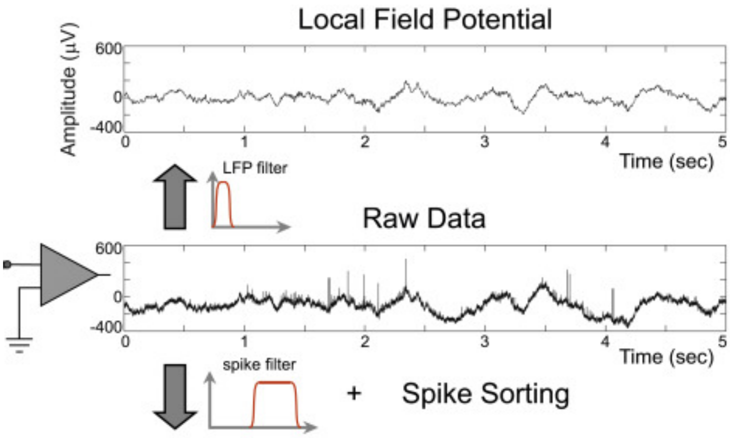
Halnes *et al.*, 2024

Low **F**requency **P**ar**ts**/components

I - 100 cycle/s

LFP

Local
Field
Potential



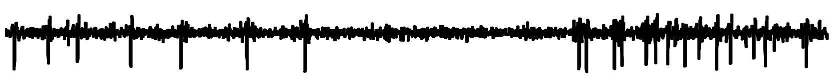
Raw recording

High-freq. components

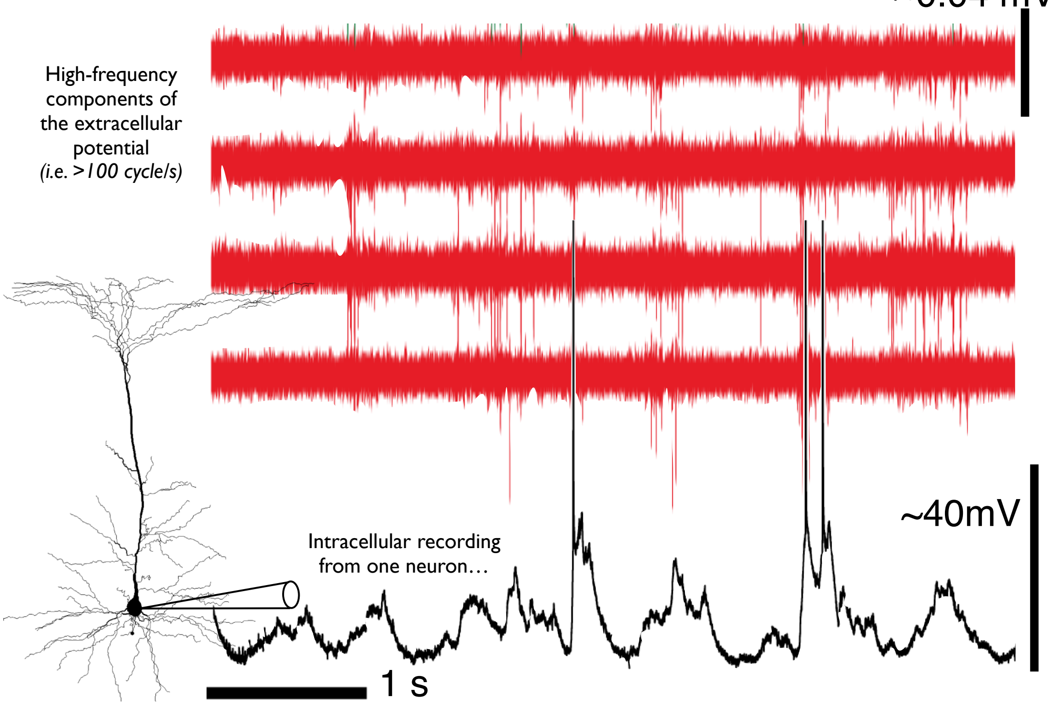
100 - 5000 cycle/s

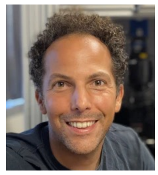
MUA
Multi-unit

SUA
Single-unit
Activity

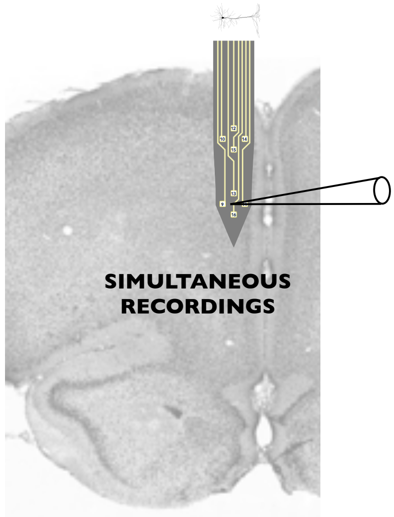


*Extra*cellular signals: APs, near the soma?



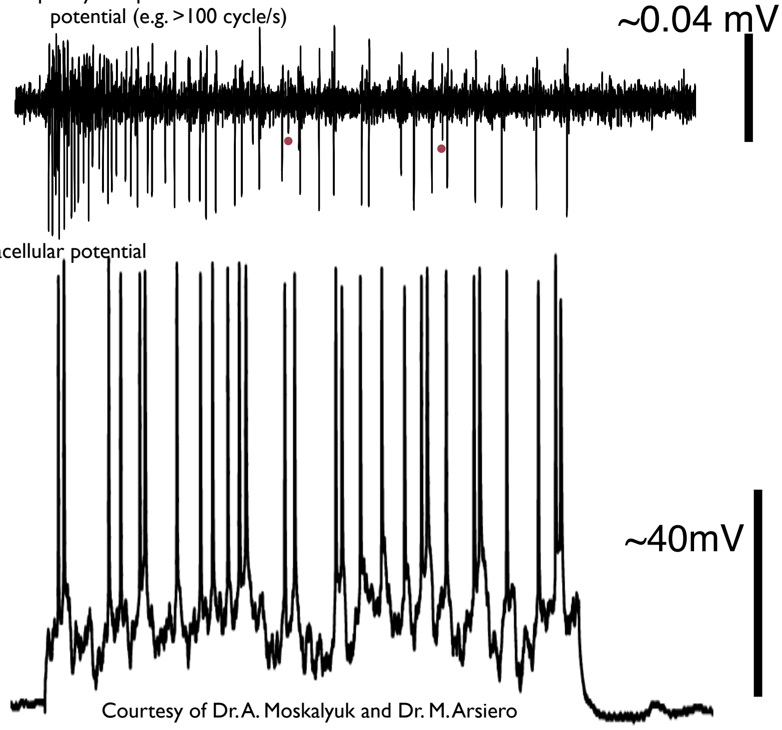


João COUTO

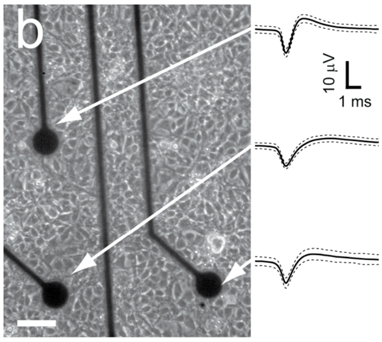


Courtesy of Dr. J. Couto

Extracellular signals: APs, near the soma?

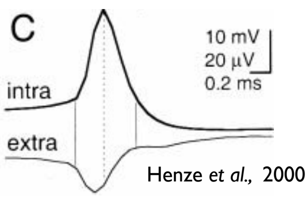


Courtesy of Dr. A. Moskalyuk and Dr. M. Arsiero



Dr. A. Moskalyuk

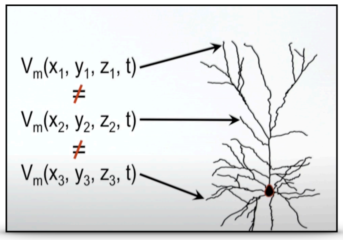
Dr. Eng. M. Arsiero

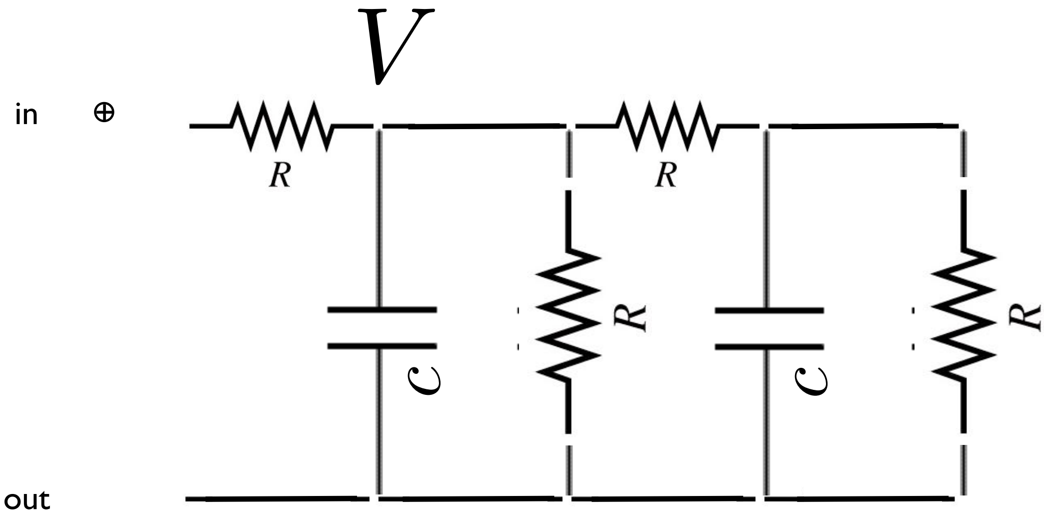


Henze *et al.*, 2000

How to make sense of this?

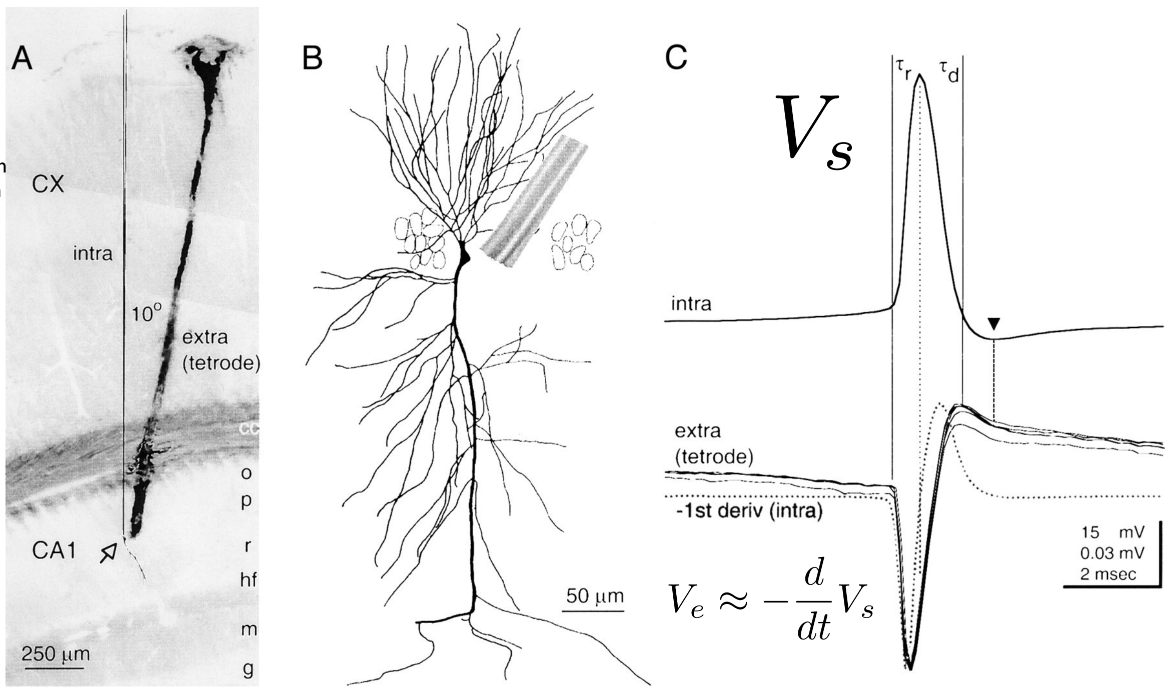
*Dendrites are **non**-isopotential portions of the neuron!*





Extracellular signals: APs, near the soma

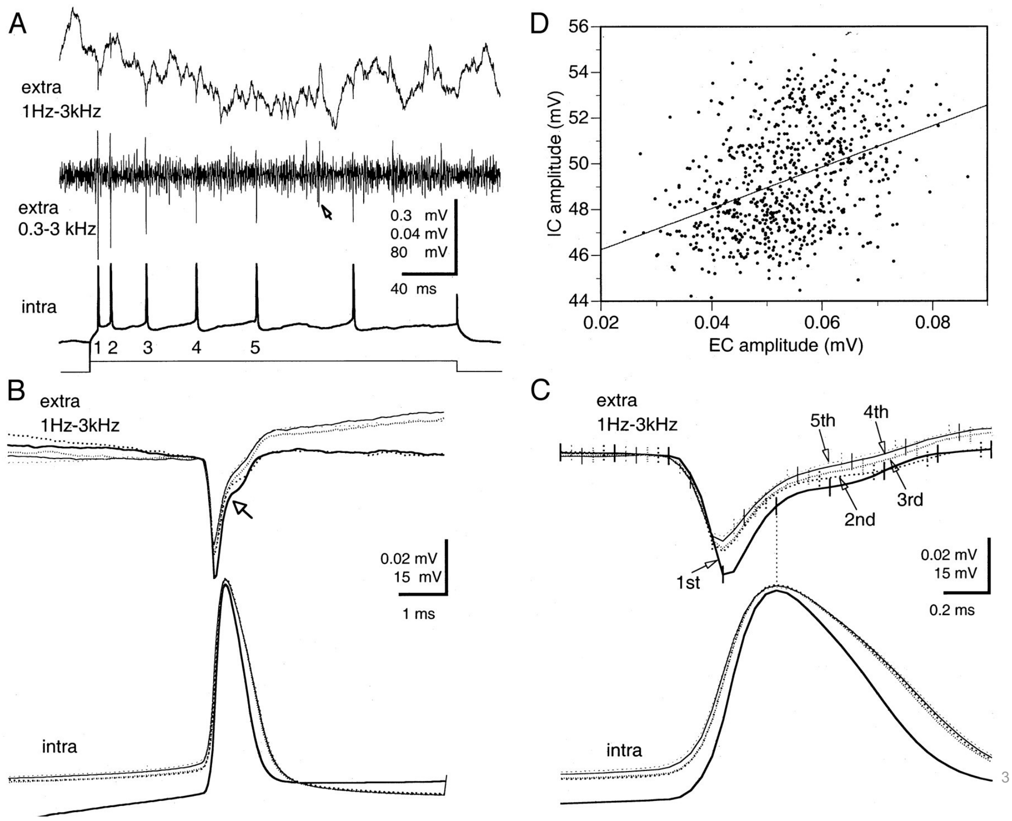
In vivo recordings from rat hippocampus, with <u>both</u> tungsten wire(s) and sharp electrodes.



György Buzsáki

CA1, hippocampal pyramidal cell

Henze *et al.,* 2000

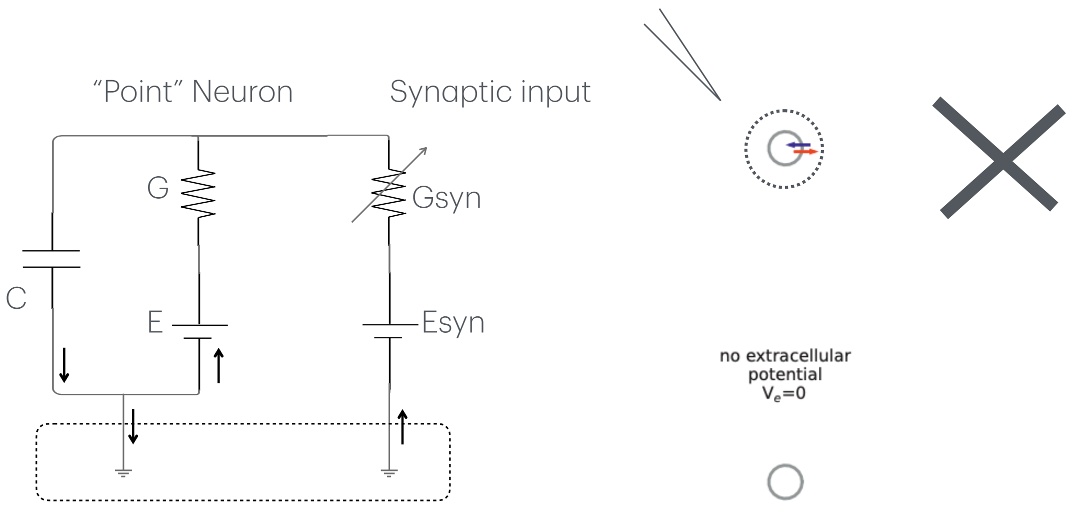


$$V_e \approx -\frac{d}{dt}V_s$$

V_e ~proportional to both **peak** AP amplitude **and slope**… V_s

Henze *et al.*, 2000

Extracellular signals: APs, near the soma?



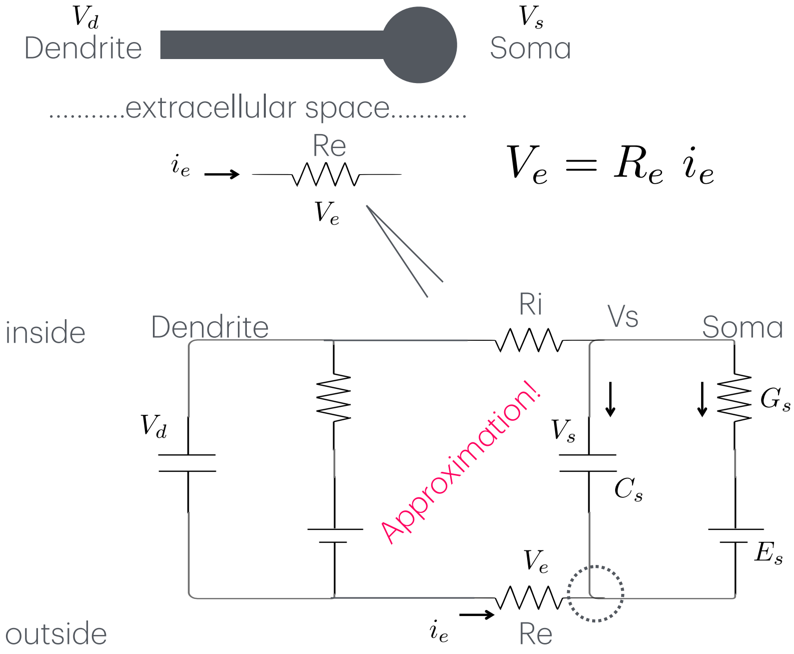
Currents, flowing in and out, **cancel** (<u>at the same point in space</u>).

No extracellular (difference of) potential(s) is generated.

Extracellular signals: APs, near the soma?

We must take the spatial extension of neurons into account!

$V_d \neq V_s$



$$V_e = R_e \; i_e$$

$$i_e + i_c + i_m = 0$$

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

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

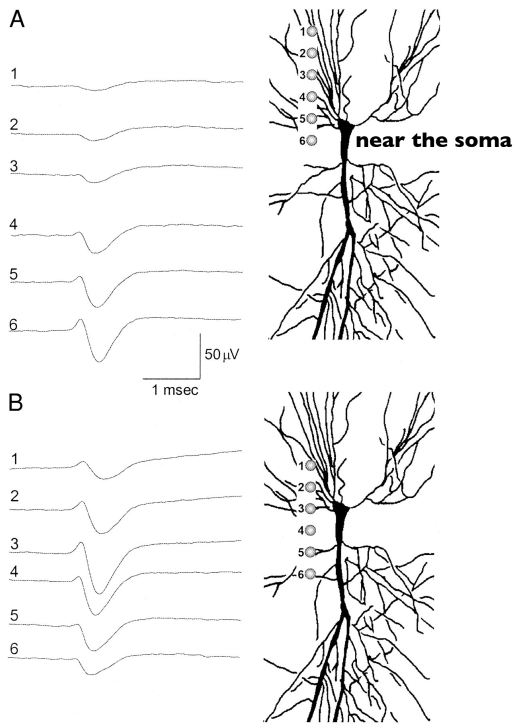
$$C_s \frac{d}{dt} V_s >> G_s (E_s - V_s)$$

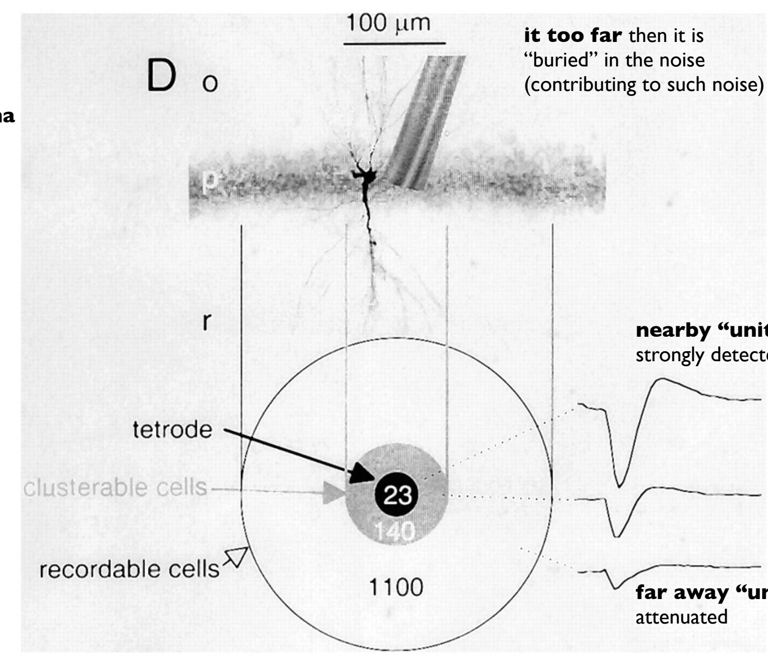
$$V_e \approx -\frac{d}{dt} V_s$$

Extracellular signals: position and distance

where are you recording?

how far are you recording?





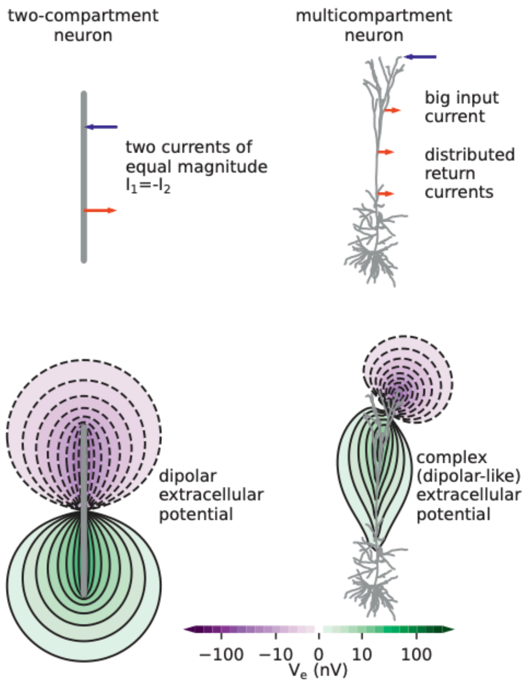
it too far then it is "buried" in the noise (contributing to such noise)

nearby "units" strongly detected

far away "units" attenuated

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**)

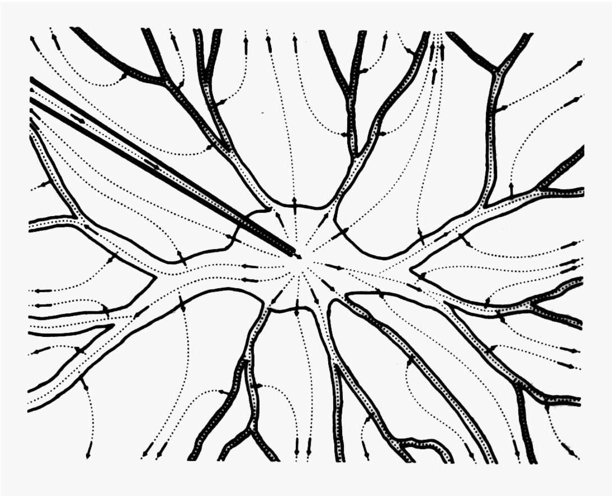
$$V_e(\mathbf{r}) = \sum_{\mathbf{n}} \frac{\mathbf{i_n}}{4\pi\sigma_{\mathbf{t}}|\mathbf{r}-\mathbf{r_n}|}$$

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)

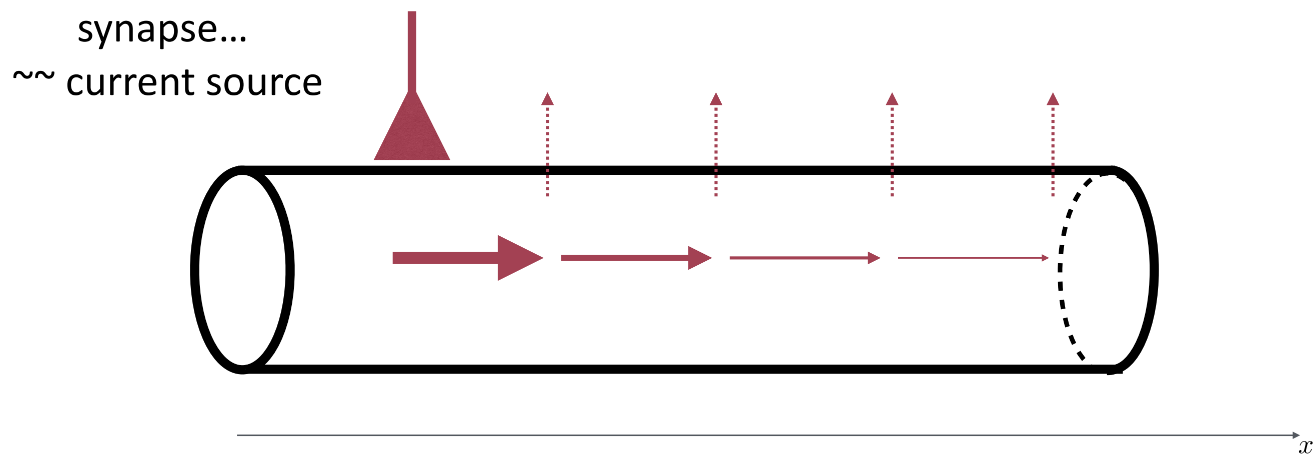
1959 Rall's Cable Theory for Neurites: motivations

- Most of the input current flows into the dendrites (not directly into soma)!
- Anyway, current have <u>to flow outside</u> the cell for"closing the circuit".



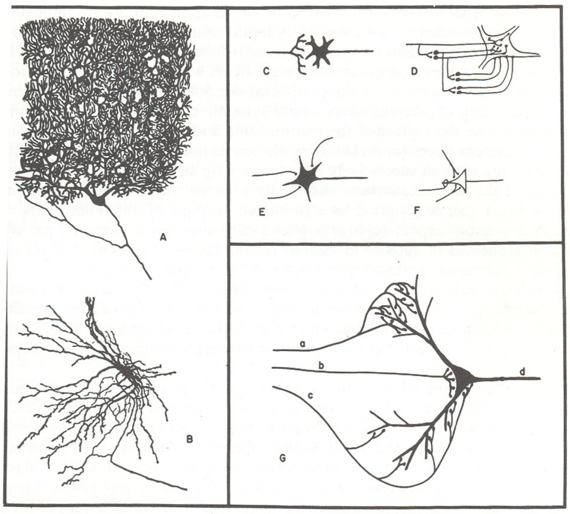
Wilfried Rall

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.



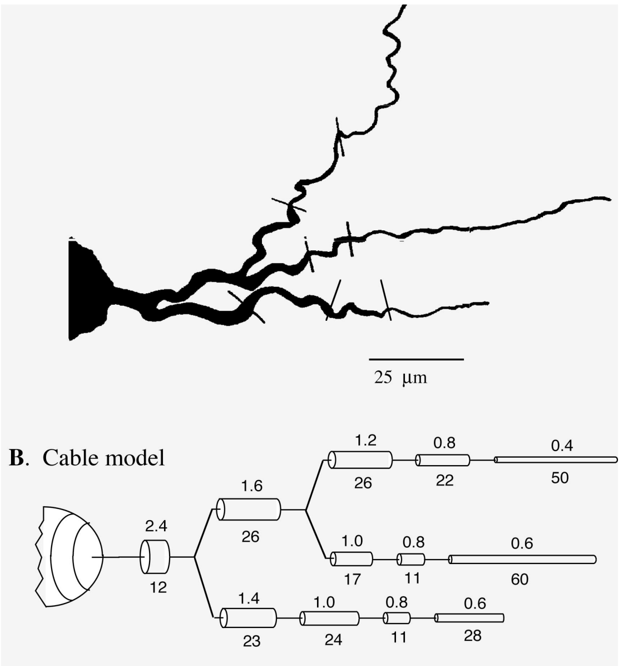
RESULTS:

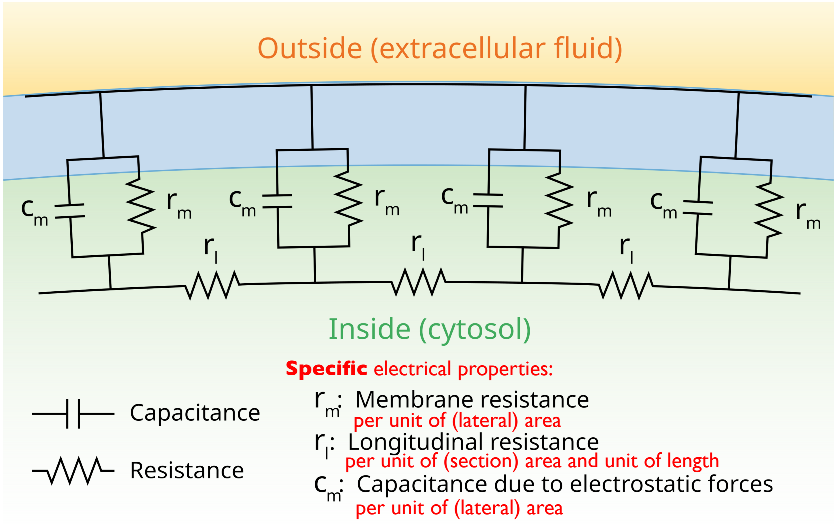
- Dendrites are non-isopotential portions of a neuron!
  – (i) voltages **attenuate** from synapse to soma!
  – (ii) it takes **time** for distal PSPs to reach the soma
  – (iii) the **shape** of EPSP/IPSP detected at the soma, **changes with** synaptic **distance**.

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!





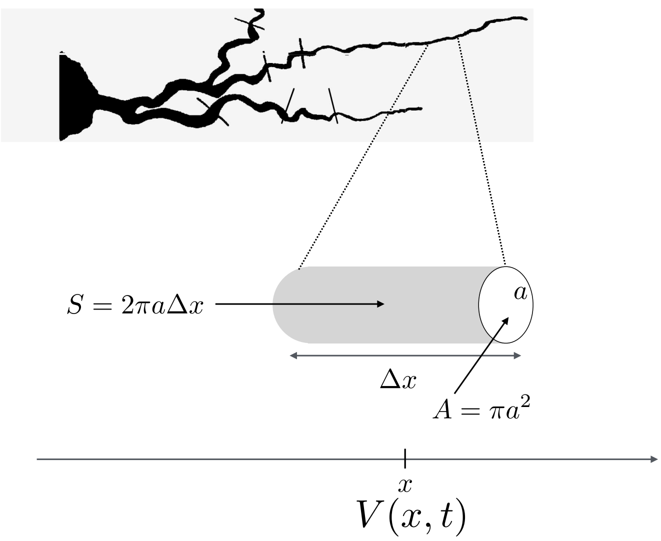
$$c = 1\mu F cm^{-2} \qquad r_m = 20k\Omega cm^2 \qquad r_i = 200\Omega cm$$

$$cr_m = 1\mu F cm^{-2} 20k\Omega cm^2 = 20ms$$

Cable Theory for Dendrites (and Axons)

Let's take an infinitesimal section…

$$V(x,t)$$

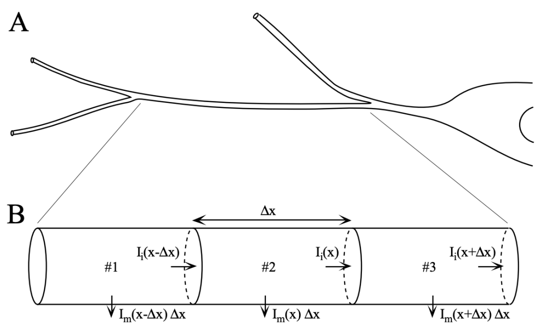


Total electrical properties:

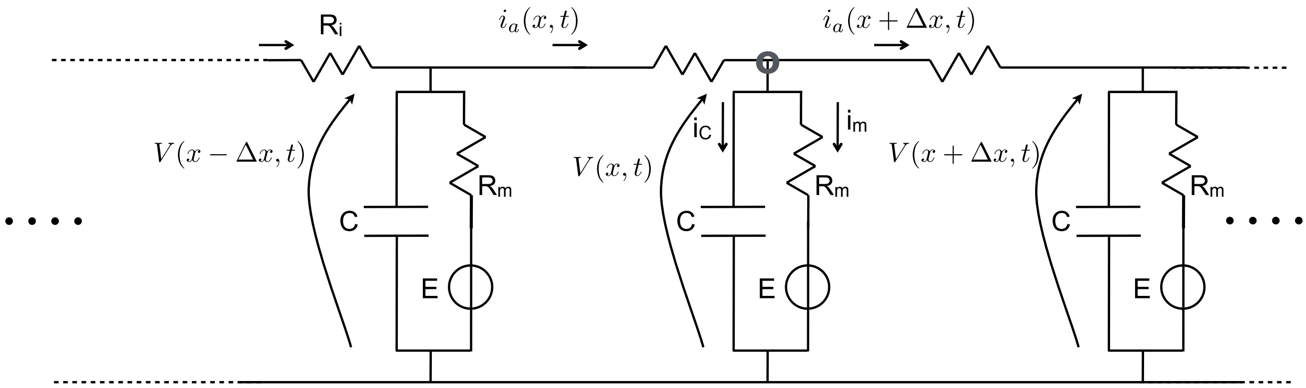
$$R_m = r_m/S = r_m/(2\pi a \Delta x) \qquad r_m = 20k\Omega cm^2$$

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

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



Cable Theory for Dendrites (and Axons)



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

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

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

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

$$i_C(x,t) = C\frac{dV(x,t)}{dt}$$

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

Cable Theory for Dendrites (and Axons)

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

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

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

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

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

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

…Invoking Taylor's…

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

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

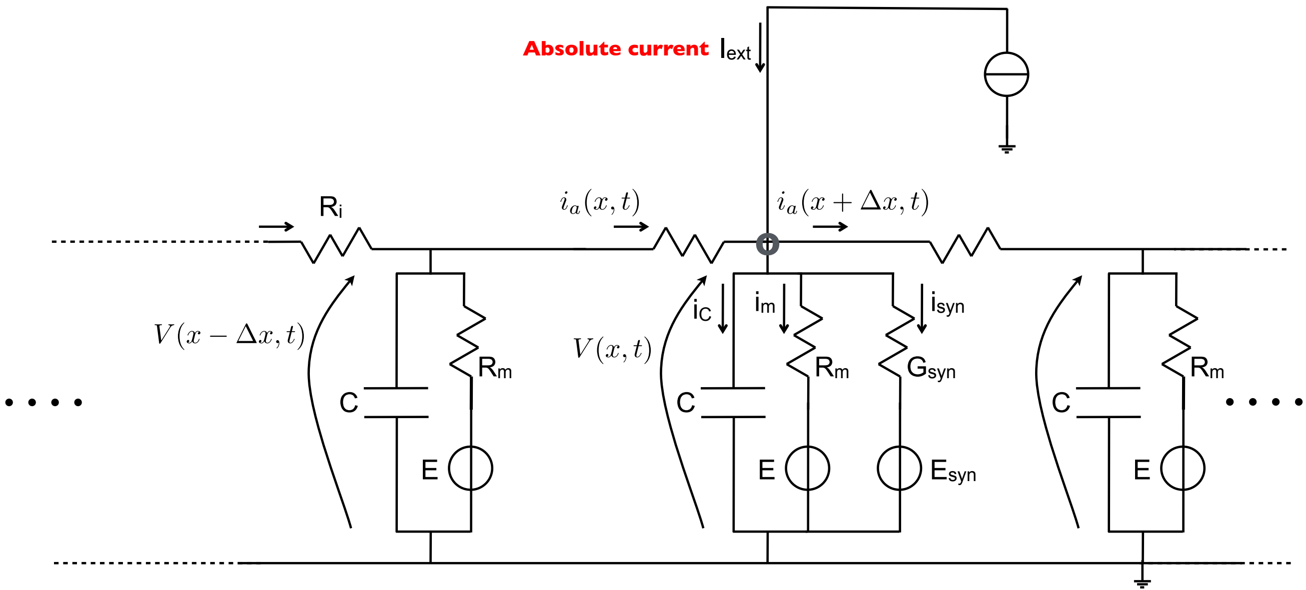
$$\frac{R_m}{R_i}\left(\Delta x^2 \frac{d^2v(x,t)}{dx^2}\right) = R_m C\frac{dv(x,t)}{dt} + v(x,t)$$

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***.



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

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

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

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

$$\tau_m = r_m c$$

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

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

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

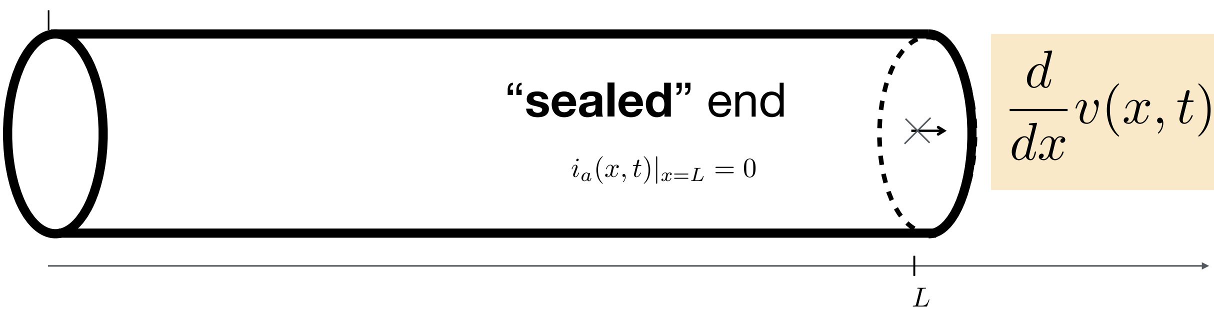
2 x Boundary conditions
1 x Initial condition
needed

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

Boundary conditions: 1

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

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

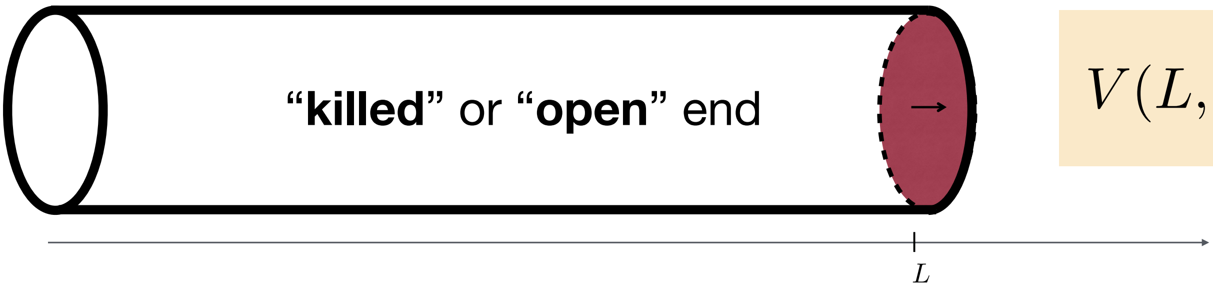


$$\frac{d}{dx}v(x,t)|_{x=L} = 0$$

“open-circuit” in electrical *jargon*!!

Boundary conditions: 2

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

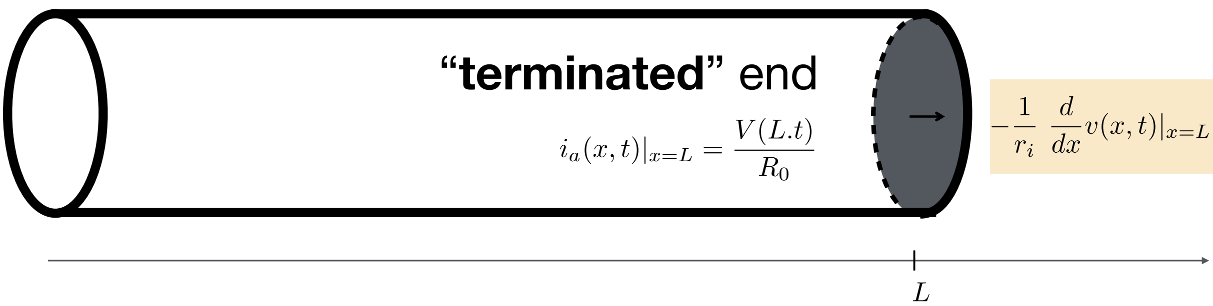


$$\boxed{V(L,t) = 0}$$

“short-circuit” in electrical *jargon*!!

Boundary conditions: 3

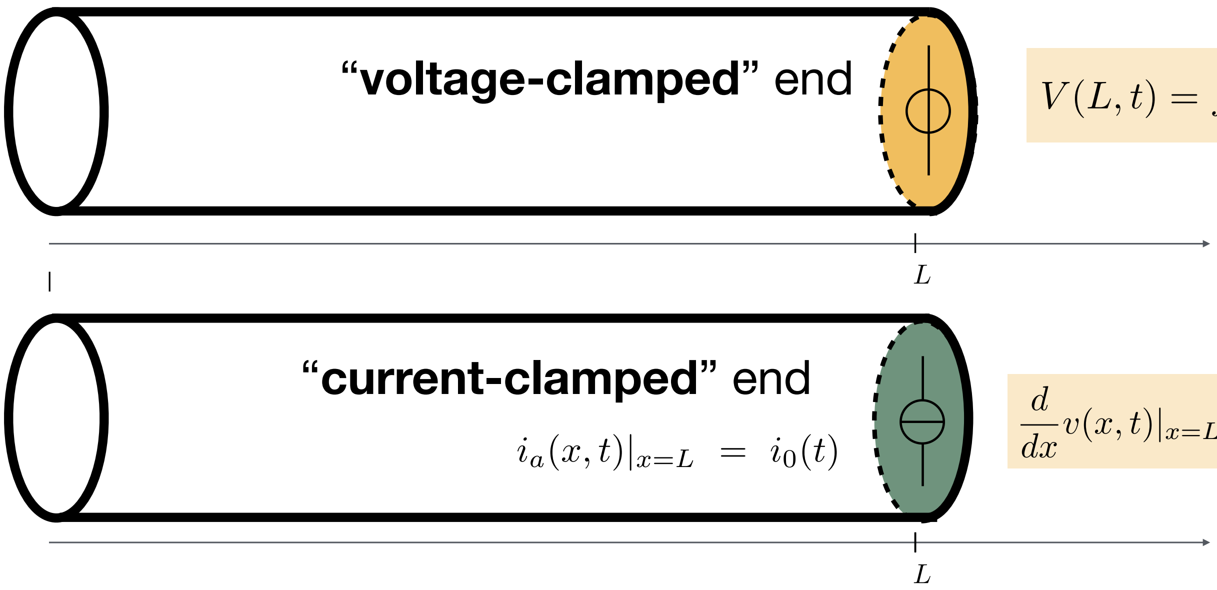
$$i_a(x,t) = \frac{v(x-\Delta x,t) - v(x,t)}{R_i} \qquad i_a(x+\Delta x,t) = \frac{v(x,t) - v(x+\Delta x,t)}{R_i}$$



$$\boxed{-\frac{1}{r_i}\,\frac{d}{dx}v(x,t)|_{x=L} = \frac{1}{R_0\ a^2\pi}V(L,t)}$$

“load-attached” in electrical *jargon*!!

Boundary conditions 4



$$V(L,t) = f_{command}(t)$$

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

Let’s solve that *PDE!*

- steady-state regimes

- transient regimes

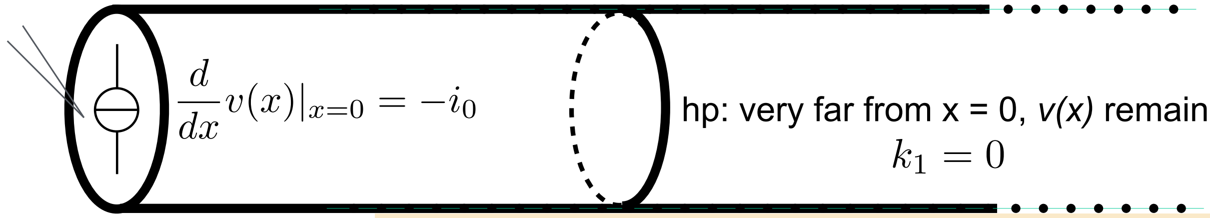
Steady-state (w.r.t. time) - DC regime
semi-**infinite** cable…

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

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

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

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



$$\frac{d}{dx} v(x)|_{x=0} = -i_0$$

hp: very far from x = 0, *v(x)* remains <u>finite</u>

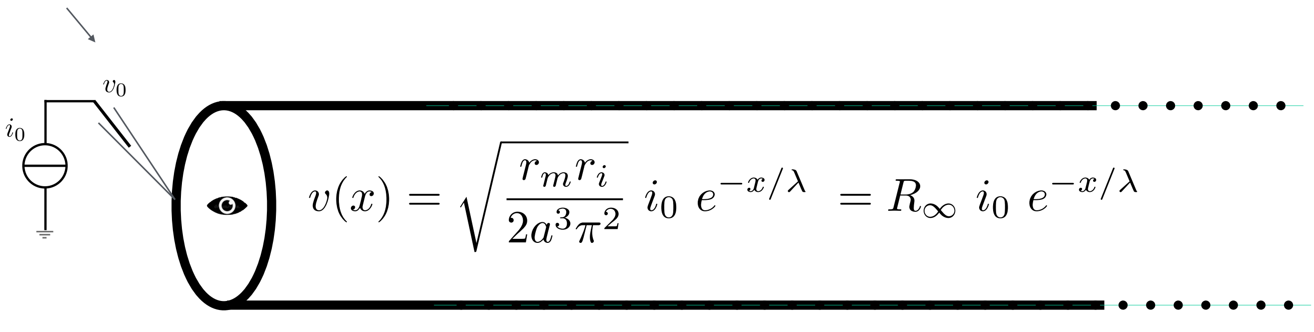
$$k_1 = 0$$

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

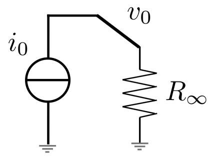
$$v(x) = \sqrt{\frac{r_m r_i}{2a^3\pi^2}}\ i_0\ e^{-x/\lambda} = R_\infty\ i_0\ e^{-x/\lambda}$$

input resistance

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



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

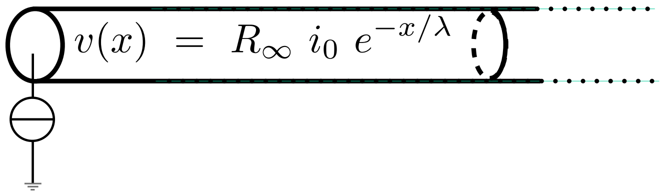


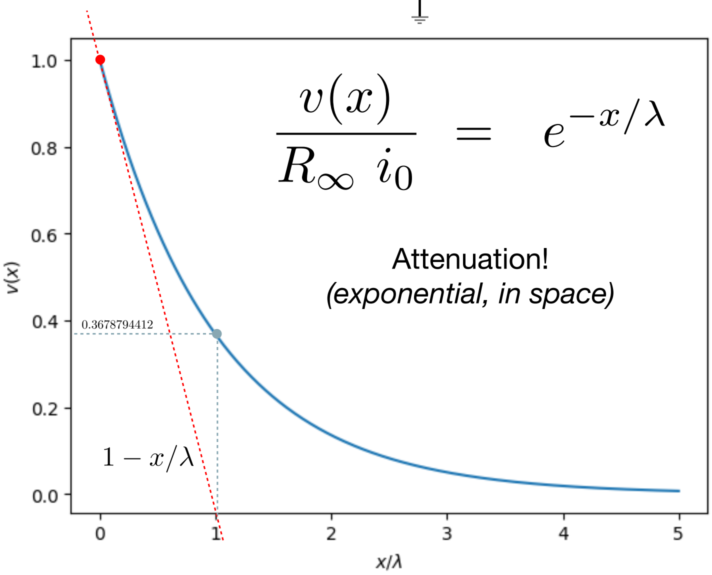
I *see* just an <u>equivalent</u> resistor/conductance from this point of the “circuit”…

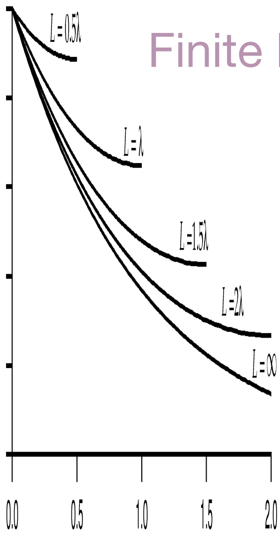
$$v_0 = R_\infty\ i_0$$

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

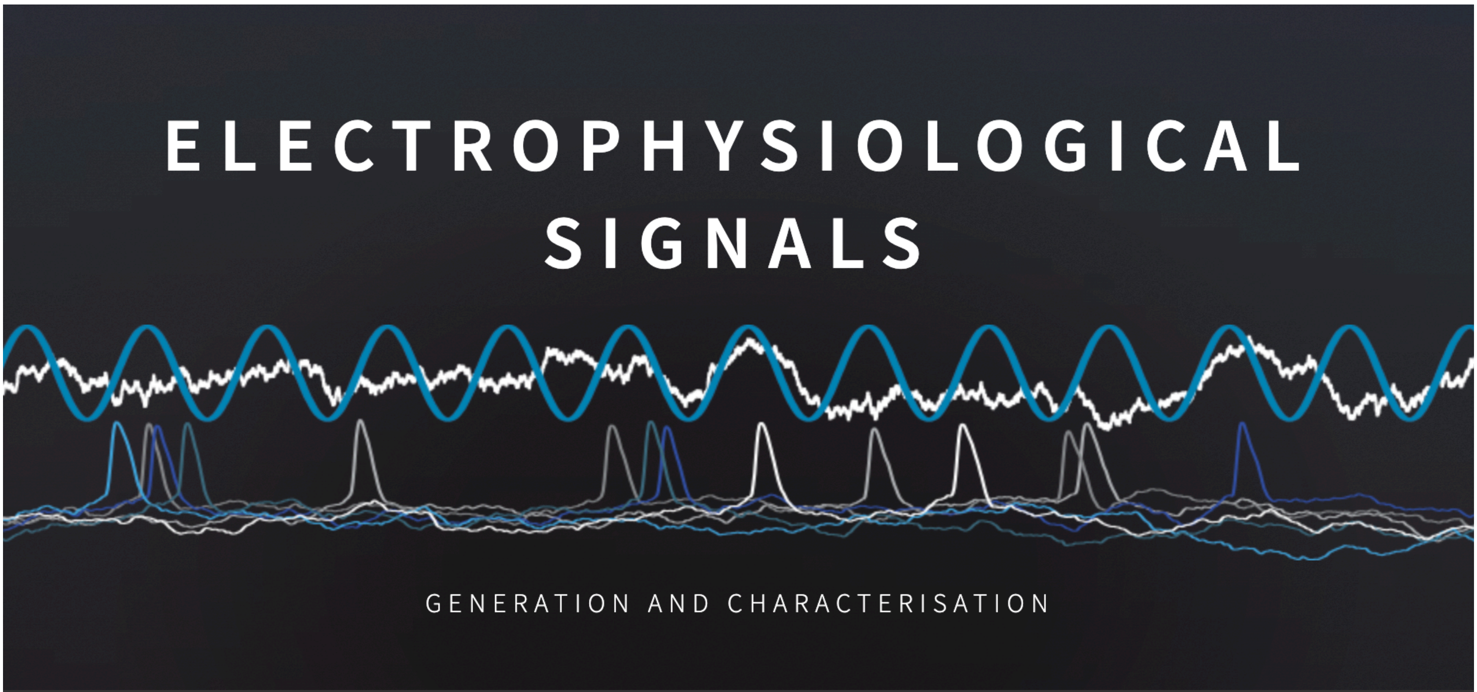
$$a \;= 4\mu m$$
$$\lambda = 500\mu m$$







Finite length!



Michele GIUGLIANO

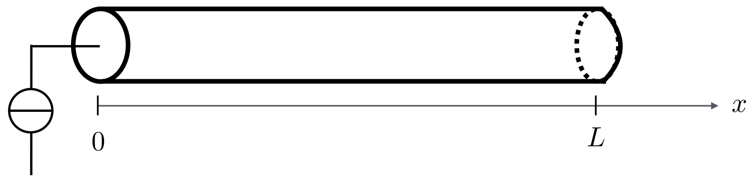
Origin of Extracellular Signals

ATTENDANCE TRACKING - **code T3LXY**
(for statistical purposes only)

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

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

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



$$\frac{d}{dx}v(x,t)|_{x=L} \;=\; 0$$

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

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

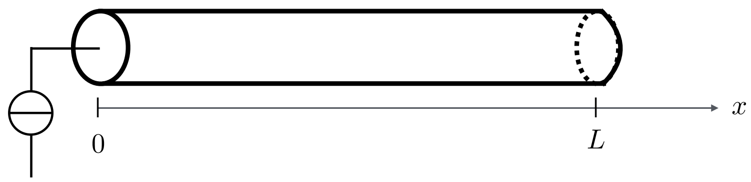
$$sinh(x) = \frac{e^x - e^{-x}}{2} \qquad cosh(x) = \frac{e^x + e^{-x}}{2} \qquad \frac{d}{dx}\cosh(x) \;= \sinh(x) \qquad \frac{d}{dx}\sinh(x) \;= \cosh(x)$$

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

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

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

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



$$\frac{d}{dx}v(x,t)|_{x=L} \;=\; 0$$

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

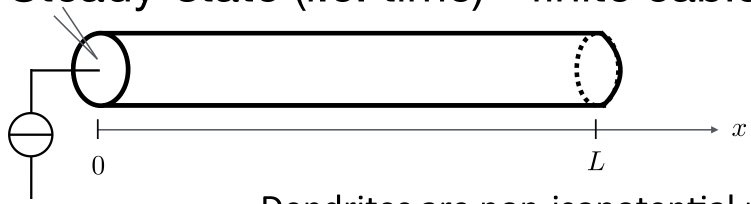
$$\frac{d}{dx}v(x) \;=\; \frac{\hat{a}}{\lambda}\sinh(x/\lambda) \;+\; \frac{\hat{b}}{\lambda}\cosh(x/\lambda)$$

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

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

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

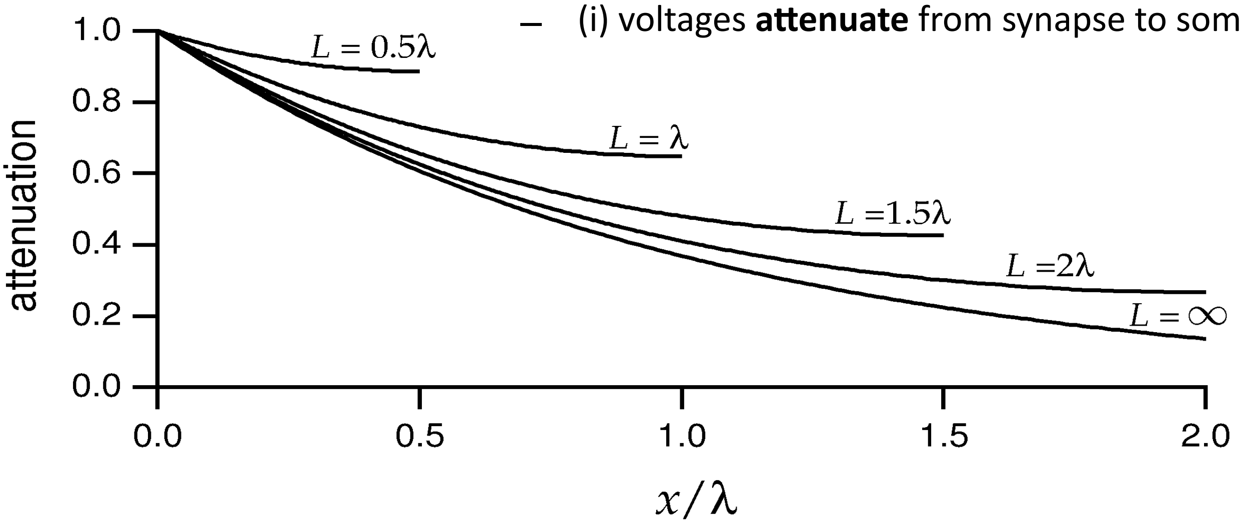
Steady-state (i.e. time) - finite cable



$d = 4\mu m$

$\lambda = 500\mu m$

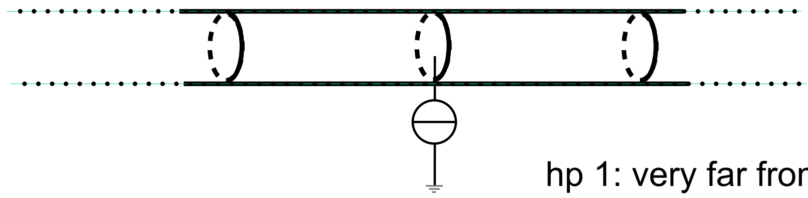
- Dendrites are non-isopotential portions of a neuron!
  - (i) voltages **attenuate** from synapse to soma!



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 <u>finite</u>
hp 2: continuity of *v(x)* for x = 0
hp 3: slightly different boundary condition

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

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

$$k \;=\; \frac{1}{2}\sqrt{\frac{r_m\; r_i}{2\pi^2 a^3}}\; I_0$$

$$\boxed{v(x) = \frac{1}{2} R_\infty e^{-|x|/\lambda}}$$

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

$$I_{ext}(x,t) \;=\; I_0 \;\Delta x \;\delta(x) \qquad\qquad i_{ext} = \frac{I_{ext}(x,t)}{2\pi a \Delta x} \qquad \lambda = \sqrt{\frac{a}{2}\frac{r_m}{r_i}}$$

$$\lambda^2 \frac{\partial^2 V(x)}{\partial x^2} = 0 + (V(x,t) - E) \;-\; r_m \;\frac{I_0}{2\pi a}\delta(x)$$

$$\int_{0^-}^{0^+} \lambda^2 \frac{\partial^2 V(x)}{\partial x^2} dx = \int_{0^-}^{0^+} (V(x,t) - E)dx \;-\; r_m \;\frac{I_0}{2\pi a} \int_{0^-}^{0^+} \delta(x) dx$$

$$\lambda^2 \frac{dV(x)}{dx}\Big|_{0^-}^{0^+} = 0 - \;r_m \;\frac{I_0}{2\pi a}$$

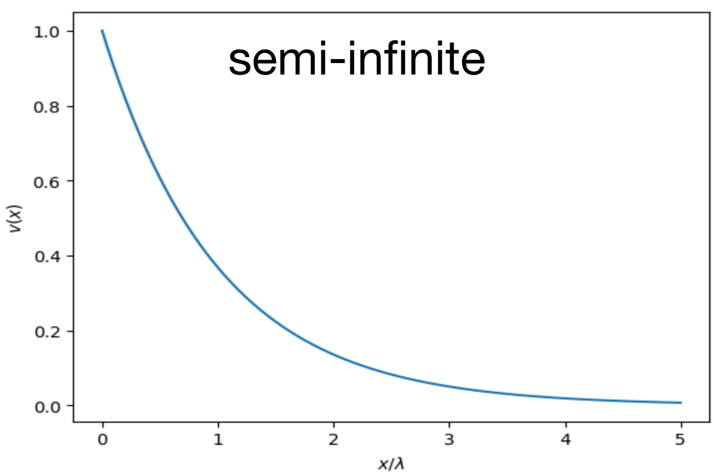
$$V(x) = E + k\; e^{-|x|/\lambda}$$

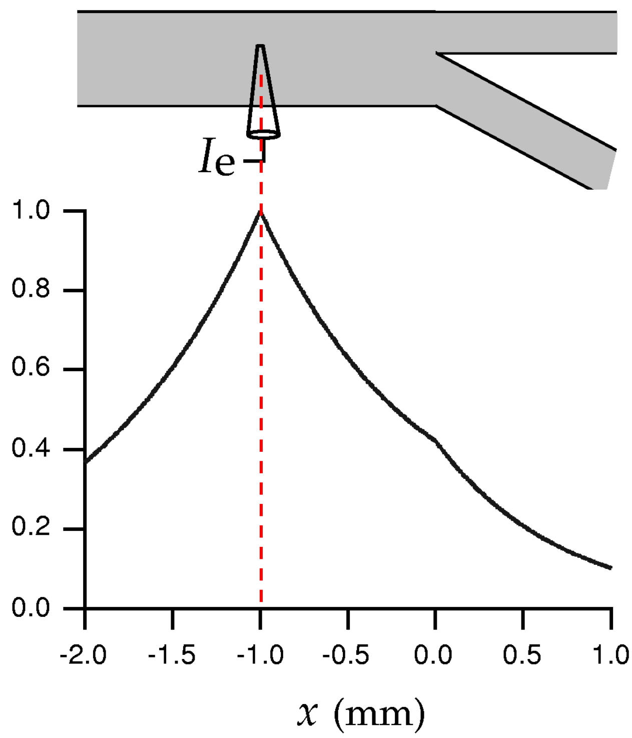
$$\frac{dV(x)}{dx}\Big|_{0^-}^{0^+} = -\frac{k}{\lambda} \;-\; (+\frac{k}{\lambda})$$

$$k \;=\; \frac{r_m}{2\lambda\; 2\pi a}\; I_0$$

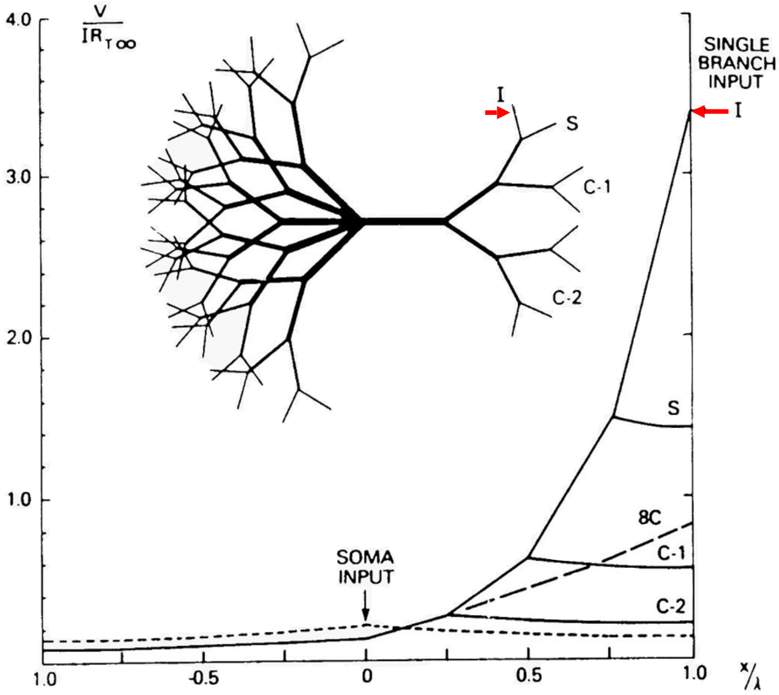
$$k \;=\; \frac{1}{2}\sqrt{\frac{r_m\; r_i}{2\pi^2 a^3}}\; I_0 \qquad V(x) = E + \frac{1}{2}\sqrt{\frac{r_m\; r_i}{2\pi^2 a^3}}\; I_0\; e^{-|x|/\lambda} \;=\; E + \frac{1}{2}R_\infty e^{-|x|/\lambda}$$

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



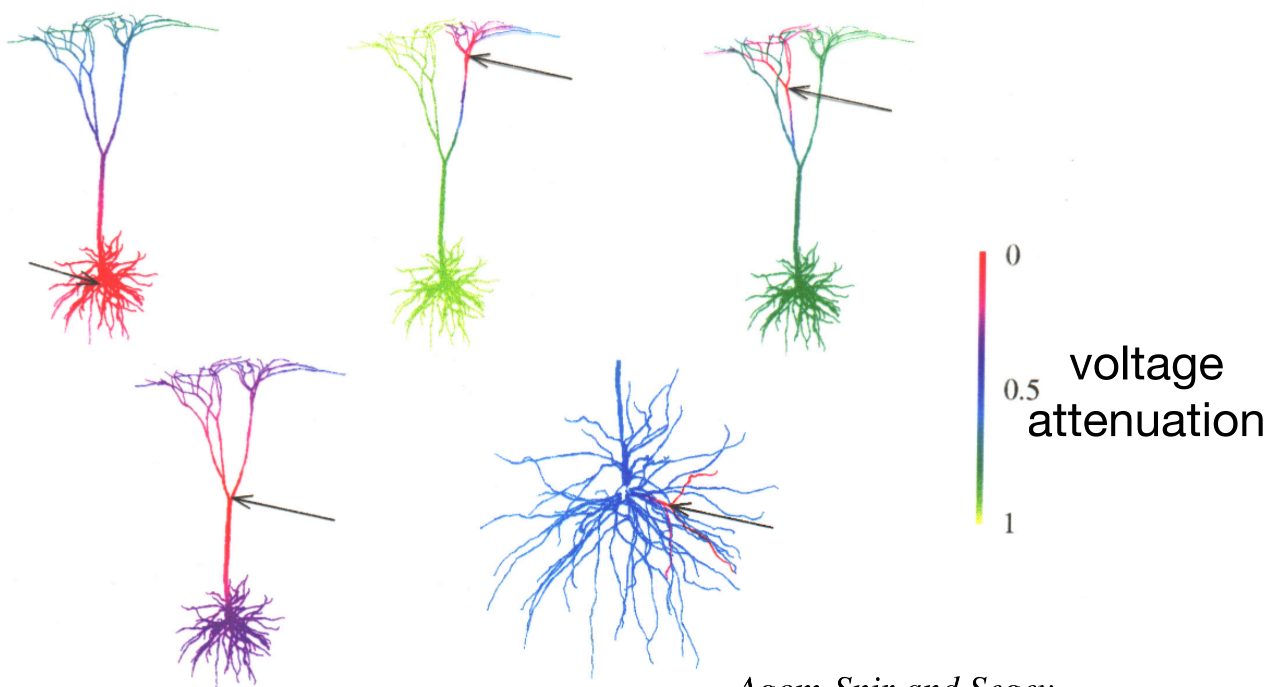


What do we learn? 1) Steep & asymmetrical voltage attenuation (from dendrites to the soma); 2) existence of synaptic *territories*



Rall & Rinzel, 1973

Dendritic “functional subunits” (“synaptic territory”)



Agom-Snir and Segev

What about…
transients?

Sinusoidal Regime - AC regime
semi-infinite cable…

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

$$W(x,\omega) \;=\; \frac{1}{2\pi} \int_{-\infty}^{\infty} v(x,t) e^{-j\omega t} dt$$

Fourier transform: *time* “disappears”…

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

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

$$W(x,\omega) \;=\; R_\infty \; I_0(\omega) \; e^{-x/\lambda^*}$$

$$\lambda^* \;=\; \frac{\lambda}{\sqrt{1 + \tau_m j \omega}}$$

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

$$M \;=\; M(x,\omega) \;= ?$$

e^{-x/λ^*} Before that… I do have a Frequency-dependent <u>and</u> 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

$$e^{-x/\lambda^*} = e^{-x\ \ Acos(\phi)\ -j\ \ xAsin(\phi)}$$

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

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

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

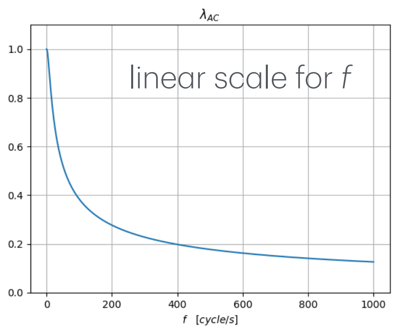
$$W(x,\omega) = R_\infty\ I_0(\omega)\ M\ e^{j\Phi} \qquad M = M(x,\omega) = ?$$

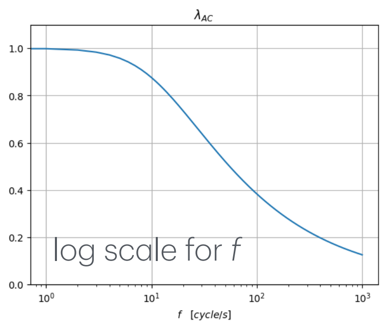
$$A = \frac{\sqrt[4]{1+\tau_m^2\omega^2}}{\lambda} \qquad \phi = \frac{1}{2}\arctan\tau_m\omega \qquad e^{j\ \phi} = cos(\phi)\ +\ j\ sin(\phi)$$

$$W(x,\omega) = R_\infty\ I_0(\omega)\ e^{-xAcos(\phi)}\ e^{-jxAsin(\phi)}$$

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

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

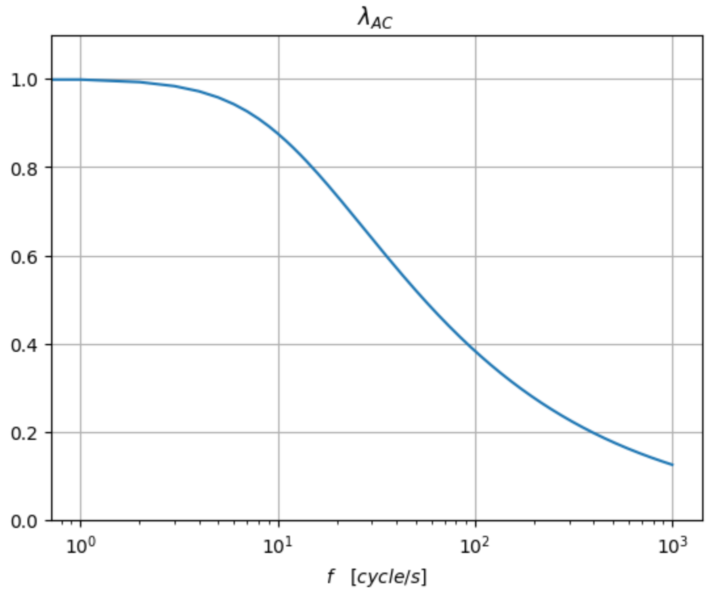




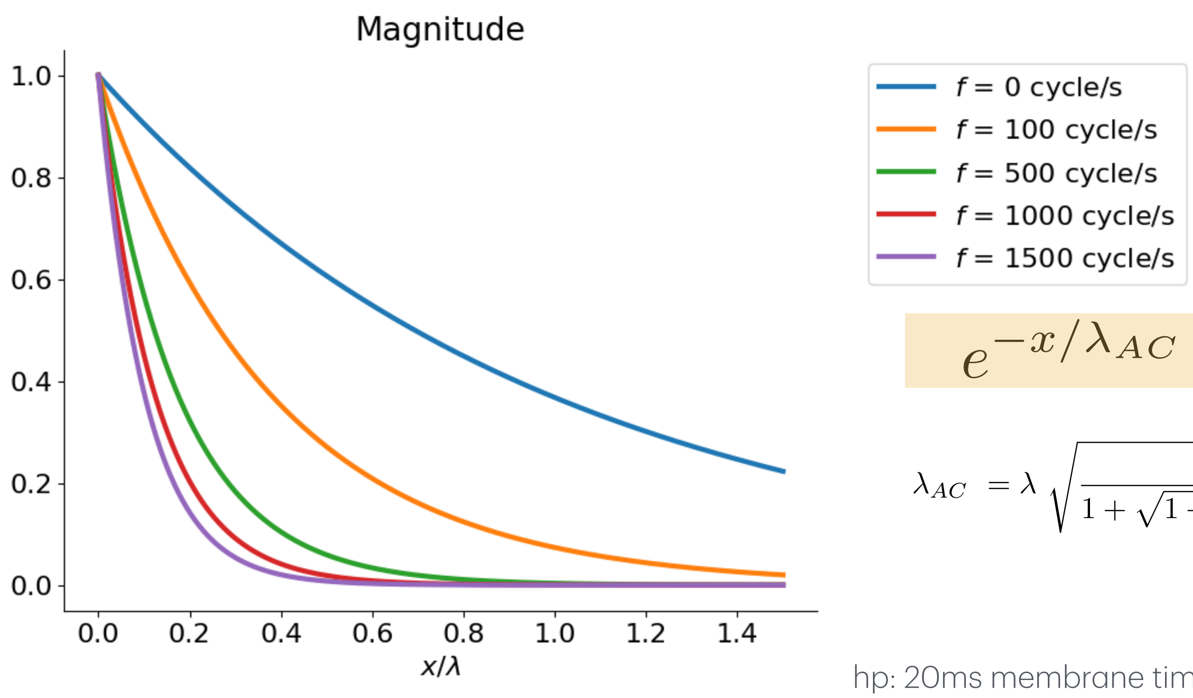
hp: 20ms membrane time constant

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…)



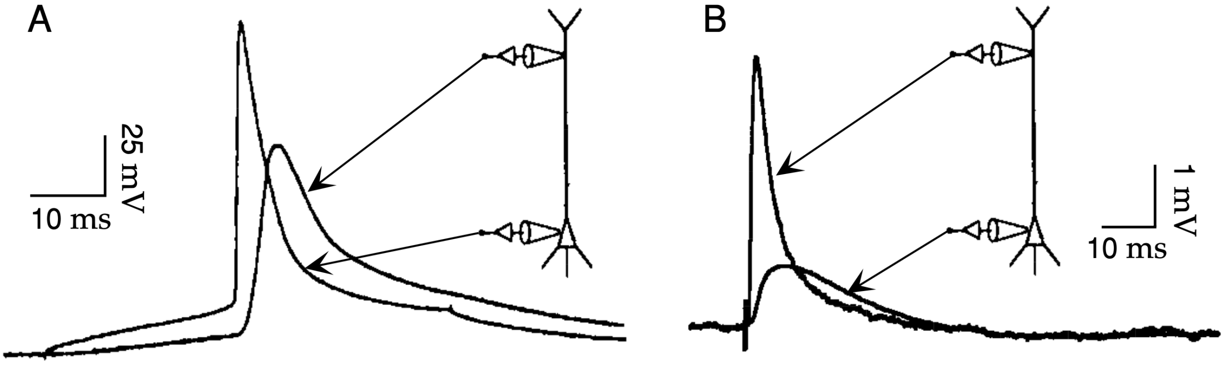
$$e^{-x/\lambda_{AC}}$$

$$\lambda_{AC} = \lambda \sqrt{\frac{2}{1 + \sqrt{1 + (2\pi f)^2 \tau_m^2}}}$$

hp: 20ms membrane time constant

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

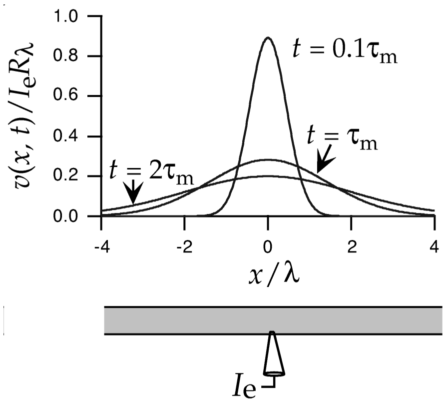
Back-propagating AP and (forward propagating) EPSPs



Stuart & Sakmann, 1994

Stuart & Sprouston, 1998

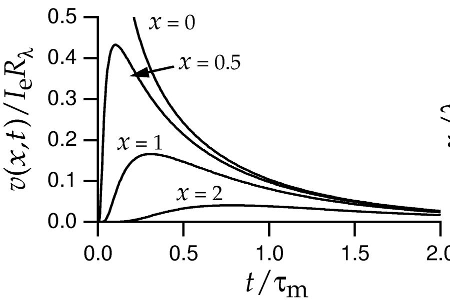
Transient solution (attenuation, shape change, delay)

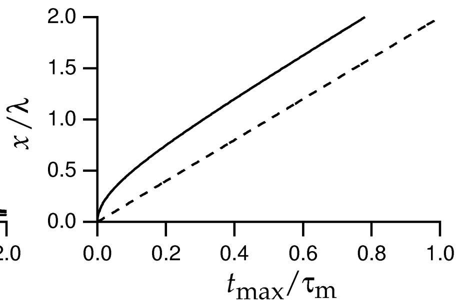


$$V(x,t) = \frac{I_e R_\lambda}{\sqrt{4\pi\,\lambda_m^2\, t/\tau_m}} \exp\left(-\frac{\tau_m\, x^2}{4\lambda_m^2\, t}\right) \exp\left(-\frac{t}{\tau_m}\right)$$

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

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

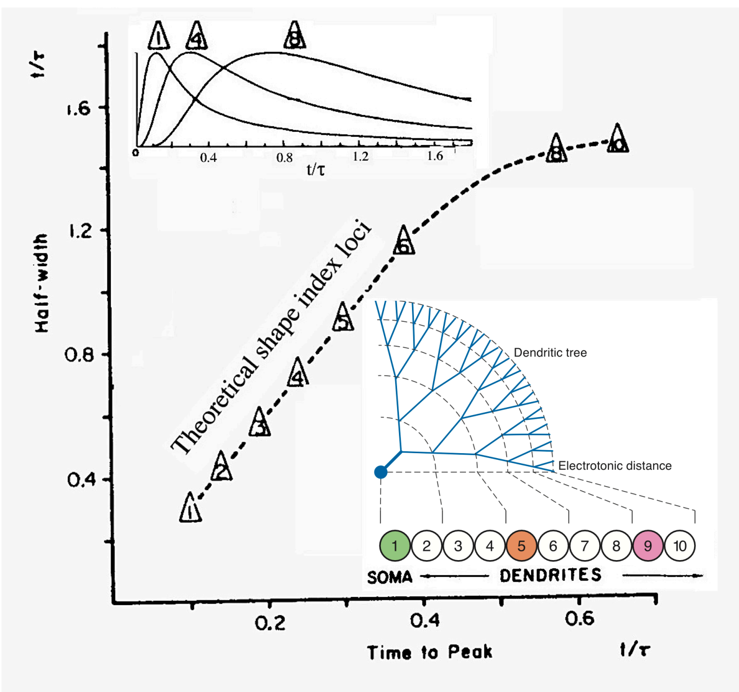


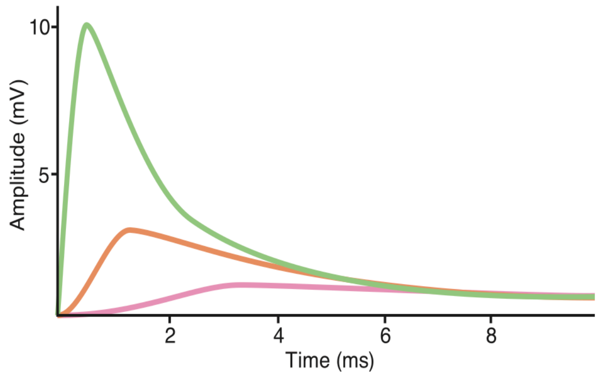


$$t_{max} \approx \frac{x\,\tau_m}{2\,\lambda_m} \qquad \Rightarrow$$

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

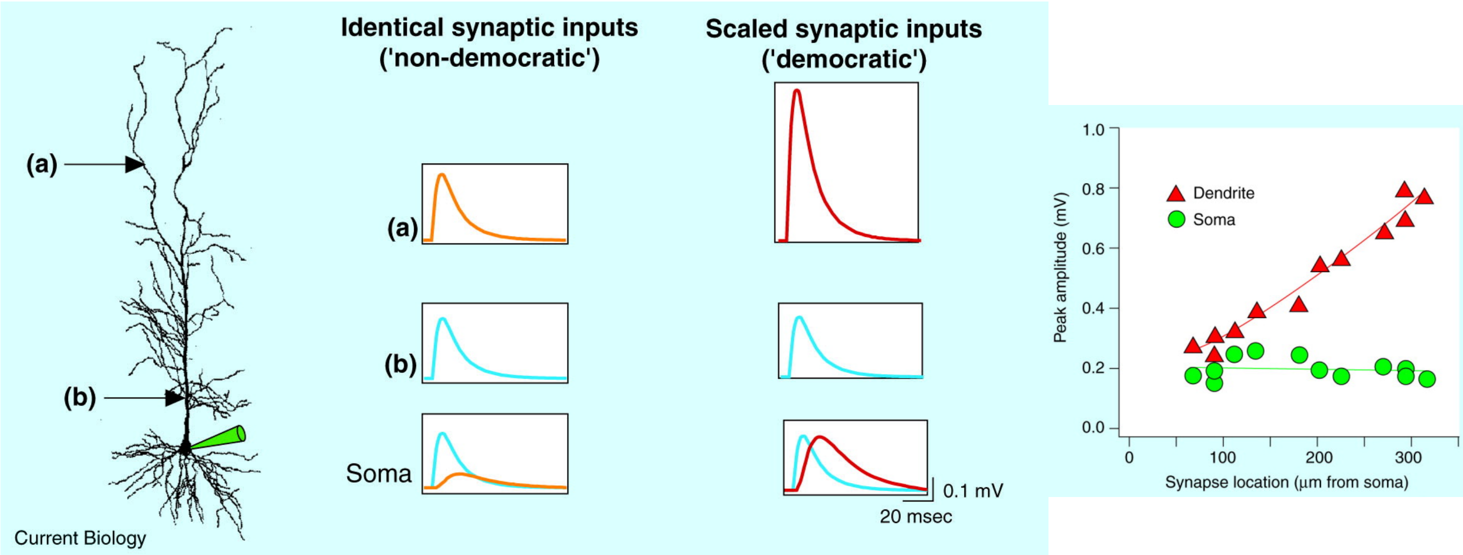
Experimental Predictions
distal synapses are “broader” and “delayed”





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

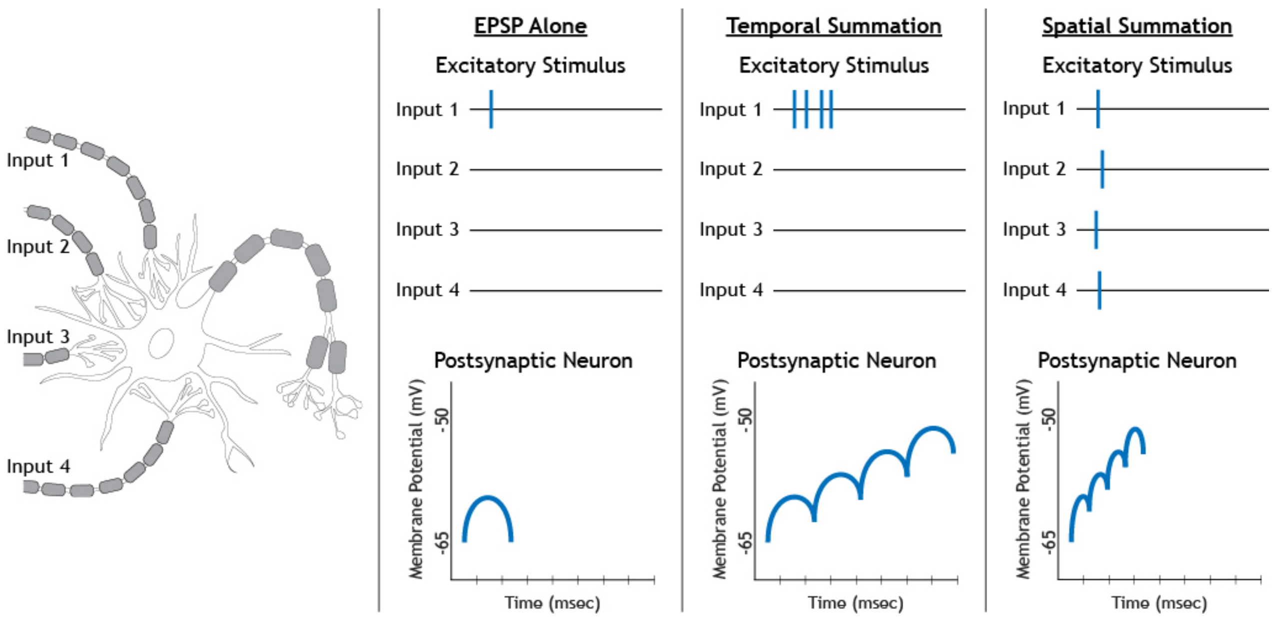
Dendritic “democracy” (in CA1 pyramidal neurons)



CA1 pyramidal neuron

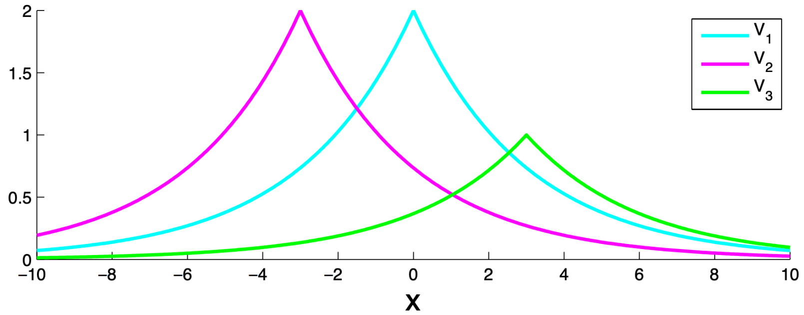
Häusser, 2001

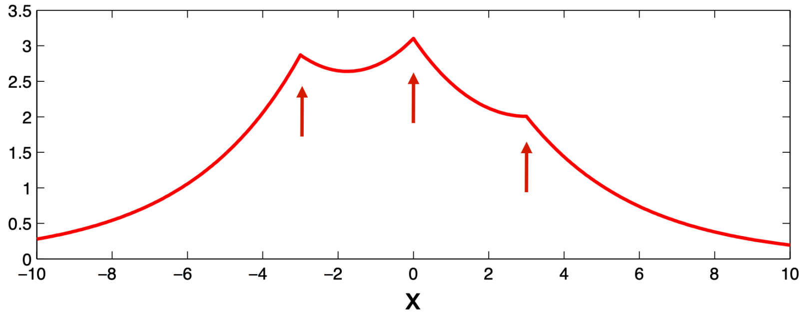
Temporal and Spatial summation



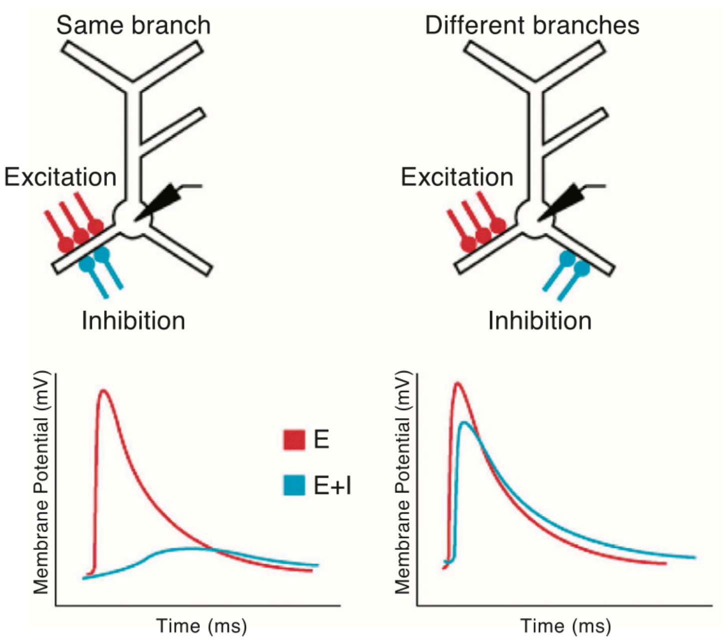
Temporal and (linear) Spatial summation

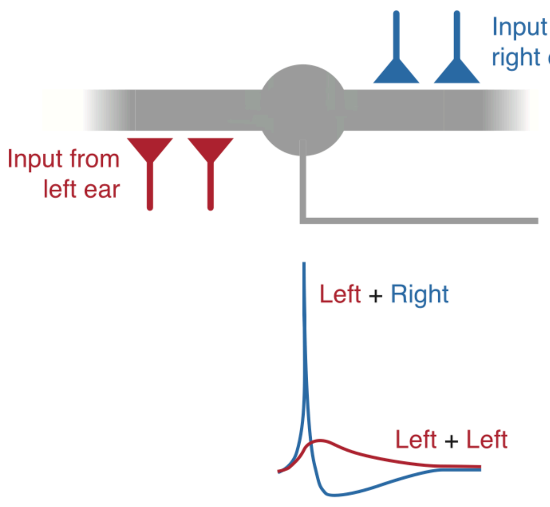
$$I_{sum}(x) = I_1(x) + I_2(x) + I_3(x) \qquad V_{sum} = V_1(x) + V_2(x) + V_3(x)$$





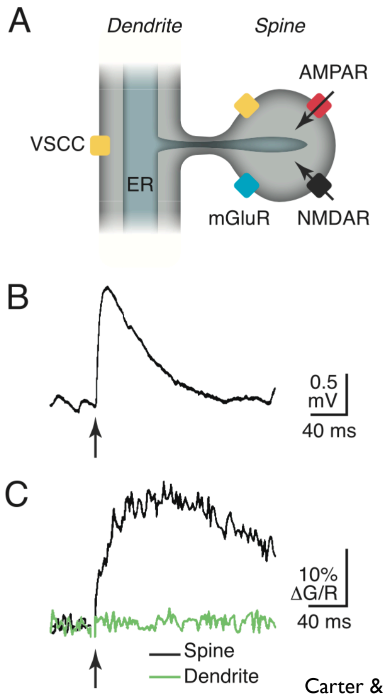
(sub)linear Spatial Summation



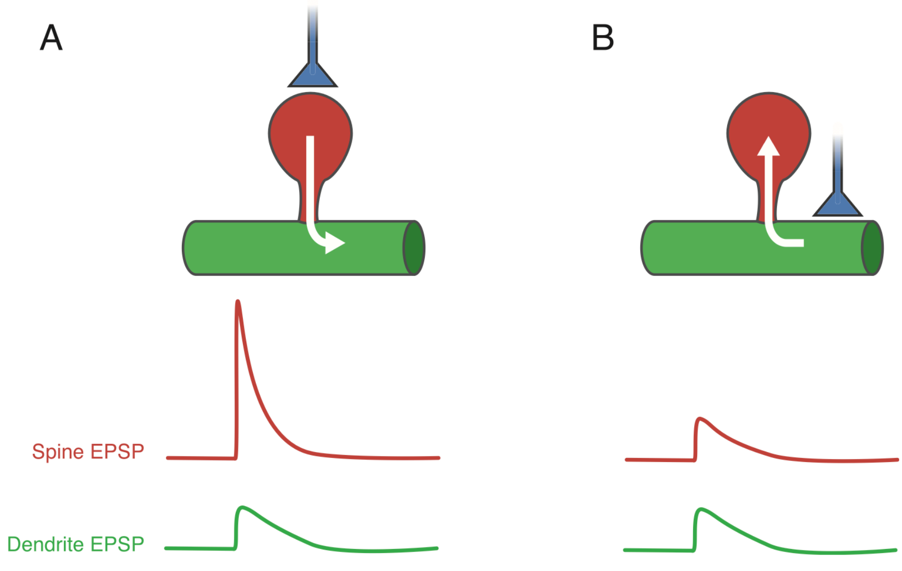


London & Hausser, 2005

Dendritic spines, depolarization, and Ca++ influx

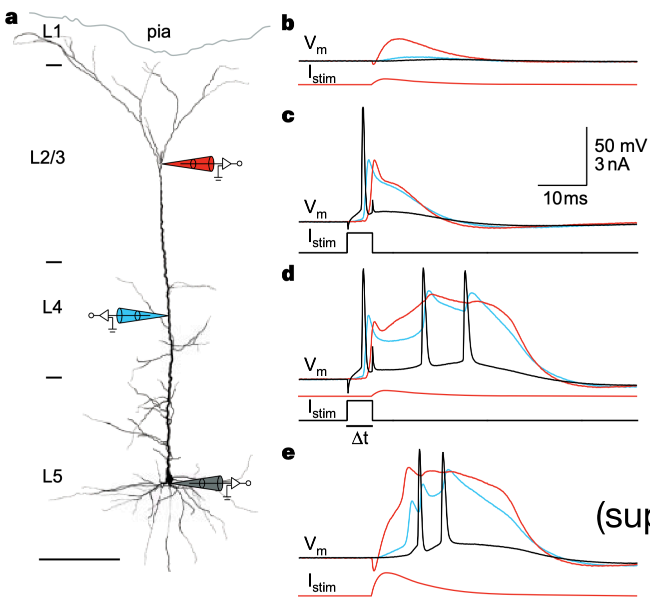


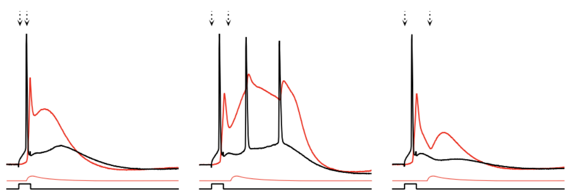
Carter & Sabatini, 2008



Sprouston, 2008

This **b**ack-propagating **A**P activated **C**a2+ spike firing (BAC) is a coincidence detection mechanism (distal inputs & AP firing)

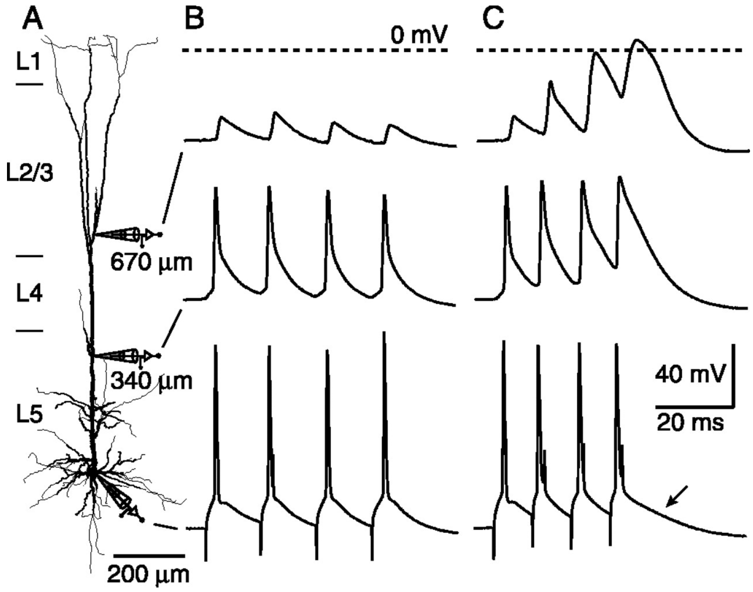




(supra)-linear Spatial Summation

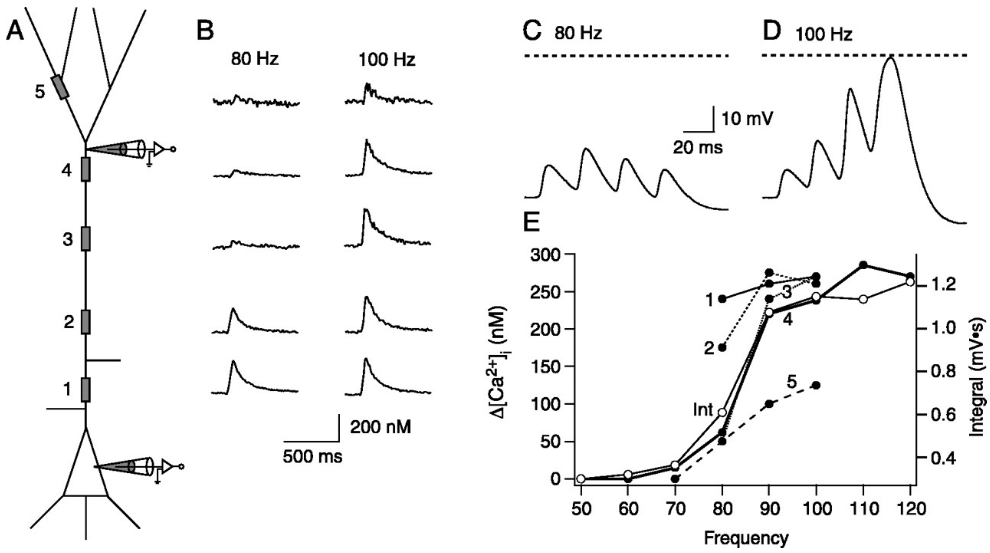
Larkum, Zhu, & Sakmann, 1999

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



Larkum et al. 1999

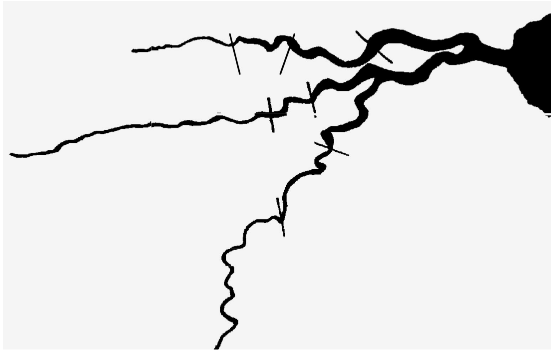
Ca++ *electrogenesis* in distal apical dendrites of L5 pyr. cells at a critical frequency of back-propagating AP

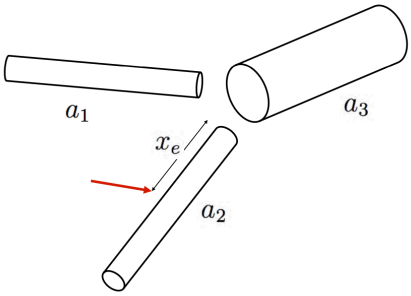


Larkum et al. 1999

Branching points

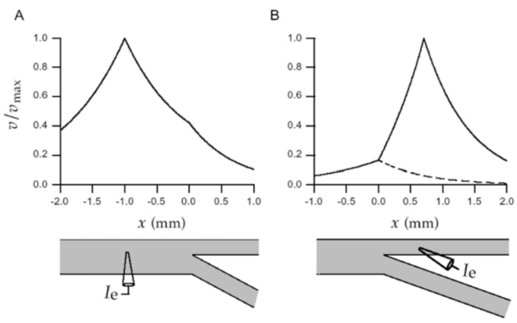
$$
\begin{aligned}
v_1(x) &= I_e\, R_{\lambda_1}\, p_1 \exp\left(-\frac{x}{\lambda_1} - \frac{x_e}{\lambda_2}\right) \\
v_2(x) &= I_e\, R_{\lambda_2} \left[(p_2 - 1) \exp\left(-\frac{x}{\lambda_2} - \frac{x_e}{\lambda_2}\right) + \exp\left(-\frac{|x_e - x|}{\lambda_2}\right)\right] \\
v_3(x) &= I_e\, R_{\lambda_3}\, p_3 \exp\left(-\frac{x}{\lambda_3} - \frac{x_e}{\lambda_2}\right)
\end{aligned}
$$





thick $\to$ thin

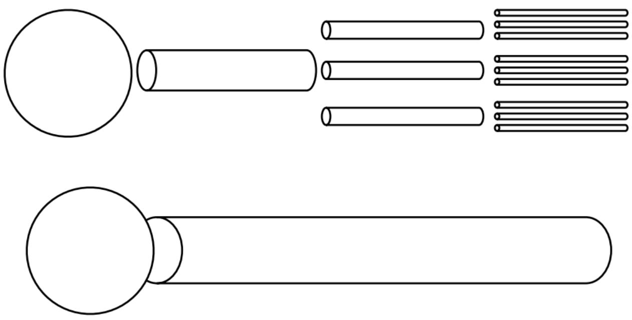
thin $\to$ thick



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

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

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

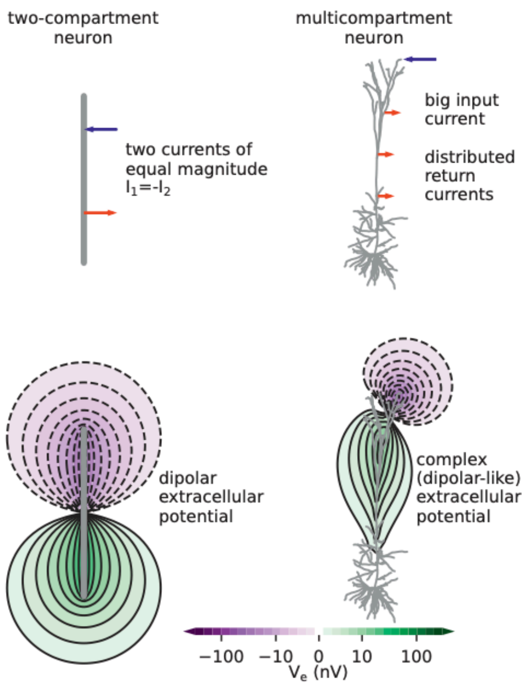
The Rall model is exact when

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

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?



Halnes *et al.*, 2024

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

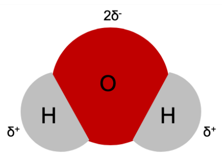
  (**cable theory**)

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

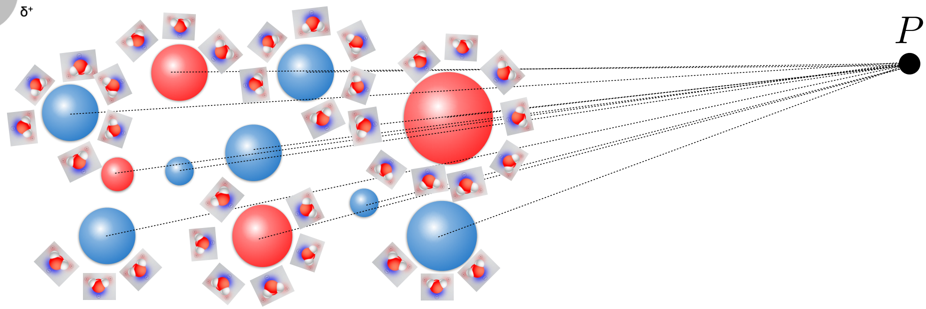
- Computing extracellular potentials, from the **spatial distribution of transmembrane currents**.

  (**volume-conductor theory**)

$$V_e(\mathbf{r}) = \sum_{\mathbf{n}} \frac{\mathbf{i_n}}{4\pi\sigma_{\mathbf{t}}|\mathbf{r}-\mathbf{r_n}|}$$



*Extra*cellular potential *Ve*



$$r_D \approx 1nm$$

Debye shielding distance

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

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!)

*Extra*cellular potential *Ve*

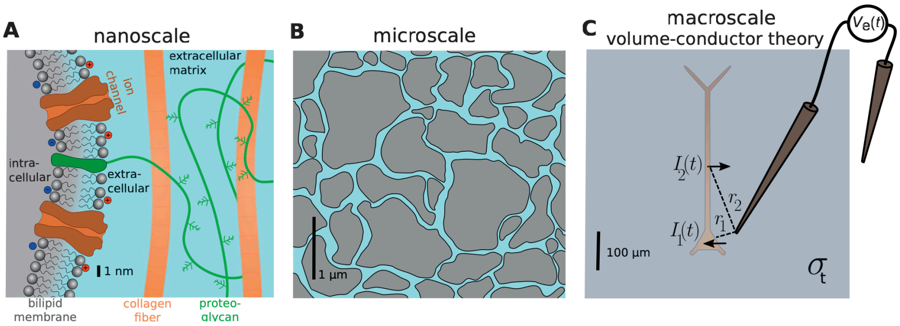
⇒ Particles move with a velocity proportional (by u - *mobility*) to the external force field

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

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

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

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



(single) ion channels, capacitive properties individual ions…

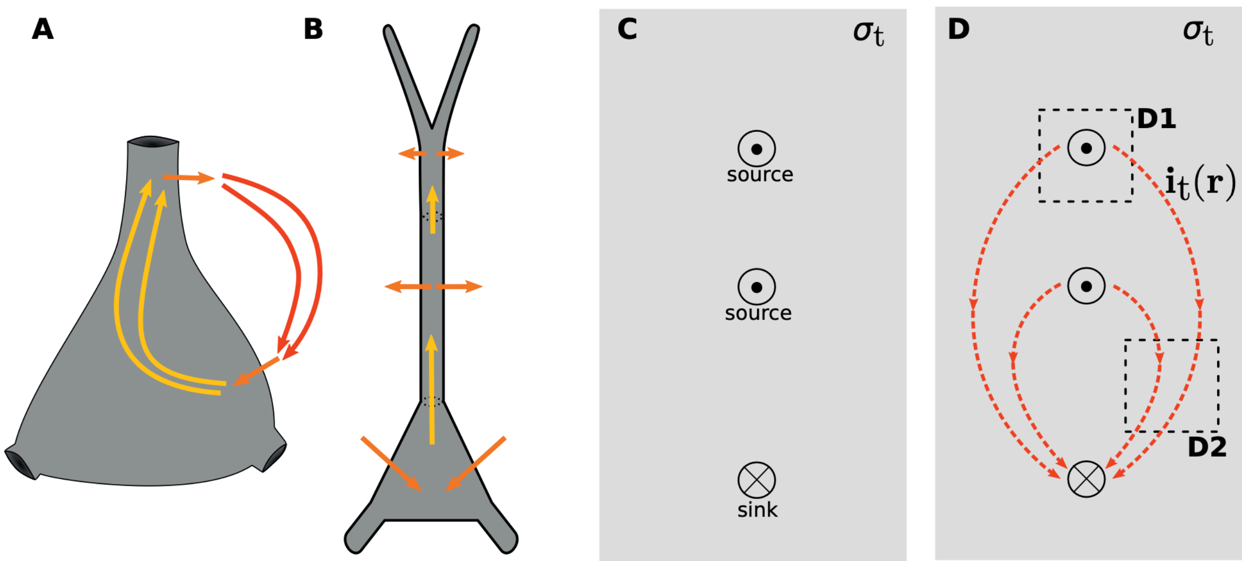
concentrations, densities,…

bulk properties, current flows

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

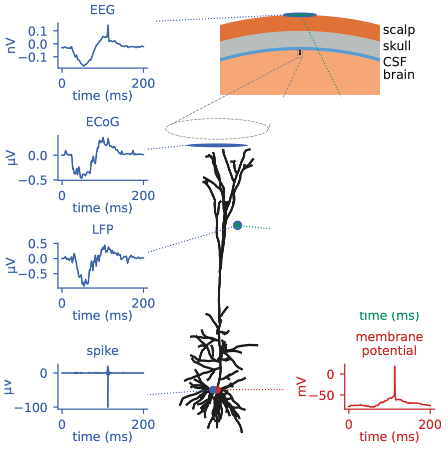
Extracellular potentials can be inferred (in much simpler terms than ionic charges distribution and movements) from the **conservation of charge**, **applied to currents**: *no accumulation of current exist (Kirchoff's).*

Not "charges" but "*Current sources (and sinks)*"



Halnes *et al.*, 2024

*<u>Extra</u>*cellular potential *Ve*
Volume Conductor Theory



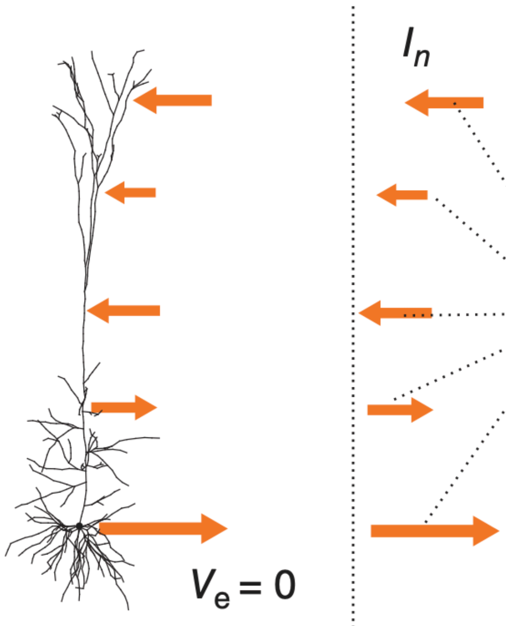
Halnes *et al.*, 2024

Assumptions of VCT:

- all intracellular *V(x,t)* and *I(x,t)* are known or measured;
    - *(from cable theory, cell excitability, synapses location)*
- *Ve* 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)

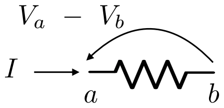
Starting point for "forward" description of
the origin of extracellular spikes, LFPs, ECoGs, EEGs.

*<u>Extra</u>*cellular potential *Ve*
Volume Conductor Theory



$$V_e(\mathrm{r}) = \sum_n \frac{I_n}{4\pi\sigma_t|\mathbf{r}-\mathbf{r}_n|}$$

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

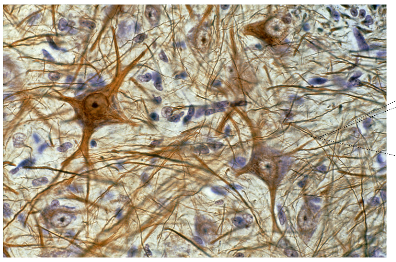


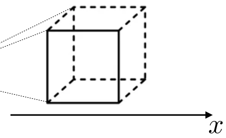
$$I = -G \, \Delta V$$

current

$$I = -\sigma_t \frac{S}{\Delta x} \Delta V \qquad i_t \, S = -\sigma_t \frac{S}{\Delta x} \Delta V$$

$$i_t = -\sigma_t \frac{d}{dx} V$$



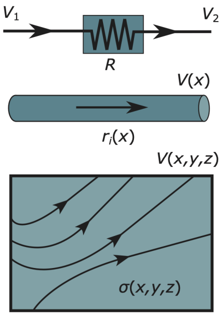


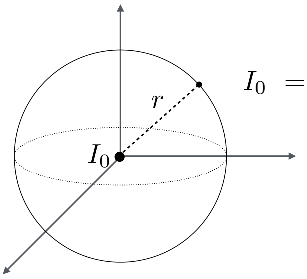
$$\Delta V = V(x + \Delta x) - V(x)$$

$$i_t = -\sigma_t \nabla V_e$$

current **density** through the **tissue** — macroscopic **tissue** conductivity — gradient of extracellular electrical potential

$$i_t = \sigma_t \mathbf{E}$$





$$I_0 = 4 \pi r^2 \, i_t(r)$$

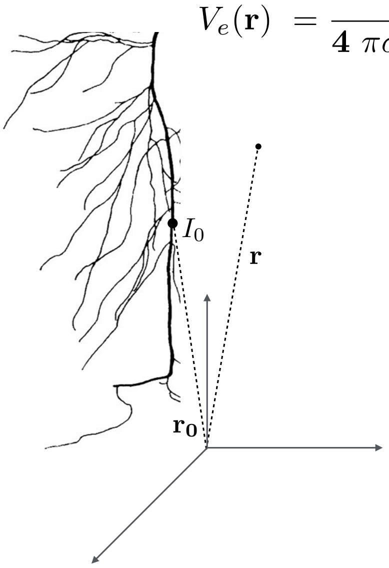
$$\frac{I_0}{4 \pi r^2} = -\sigma_t \frac{d}{dr} V$$

$$\int_{\infty}^{r} \frac{I_0}{4 \pi r^2} dr = -\int_{\infty}^{r} \sigma_t \frac{d}{dr} V \, dr$$

$$-\frac{I_0}{4 \pi r} + 0 = -\sigma_t V(r) + 0$$

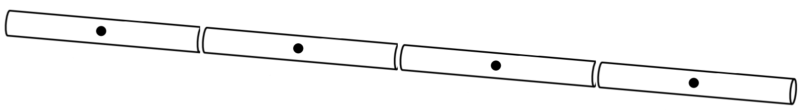
(A set of) "Point current" source(s)

$$V_e(\mathbf{r}) = \frac{\mathbf{I_0}}{\mathbf{4} \, \pi \sigma_\mathbf{t} ||\mathbf{r} - \mathbf{r_0}||}$$

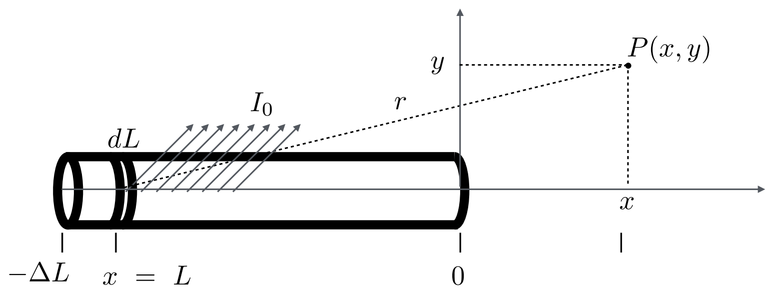


$$V_e(\mathbf{r}) = \frac{I_1}{4\pi\sigma_t\|\mathbf{r} - \mathbf{r}_1\|} + \frac{I_2}{4\pi\sigma_t\|\mathbf{r} - \mathbf{r}_2\|} + \frac{I_3}{4\pi\sigma_t\|\mathbf{r} - \mathbf{r}_3\|} + \ldots = \sum_n \frac{I_n}{4\pi\sigma_t\|\mathbf{r} - \mathbf{r}_n\|}$$

Point-source approximation: a neuron = a collection of point-current sources



A **better** approximation: “line”-sources



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

$$V_e(\mathbf{r}) = \frac{\mathbf{I_0}}{\mathbf{4}\ \pi \sigma_{\mathbf{t}} ||\mathbf{r} - \mathbf{r_0}||}$$

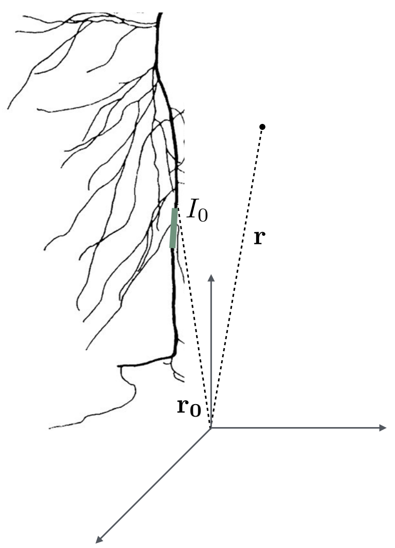
$$dI_0 = I_0 \frac{dL}{\Delta L} \qquad V_e(\mathbf{r})_{dL} = \frac{I_0}{\Delta L} \frac{dL}{4\ \pi\ \sigma_t\ \sqrt{(x-L)^2 + y^2}} \qquad V_e(\mathbf{r}) = \int_{-\Delta L}^{0} \frac{I_0}{\Delta L} \frac{dL}{4\ \pi\ \sigma_t\ \sqrt{(x-L)^2 + y^2}}$$

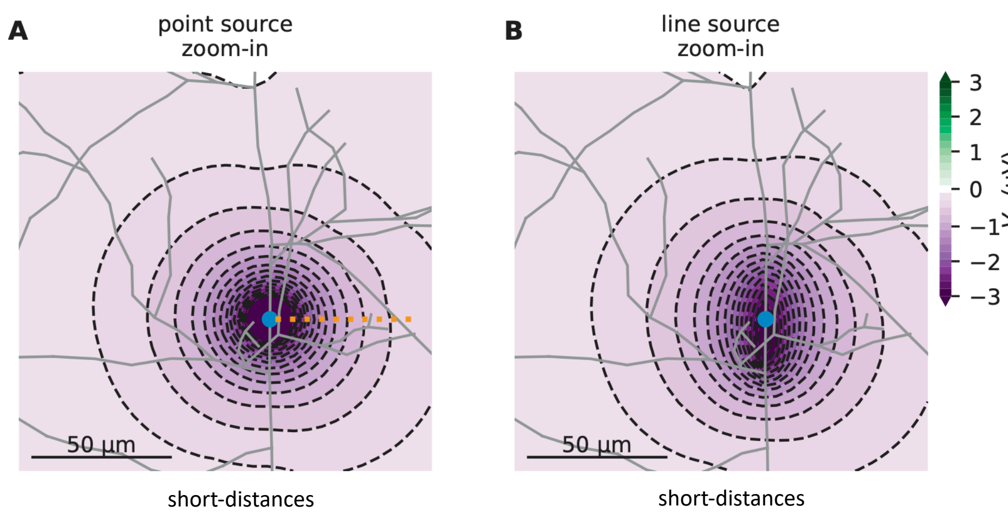
$$\int \frac{dt}{\sqrt{t^2 + a^2}} = \ln|t + \sqrt{t^2 + a^2}| + K$$

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

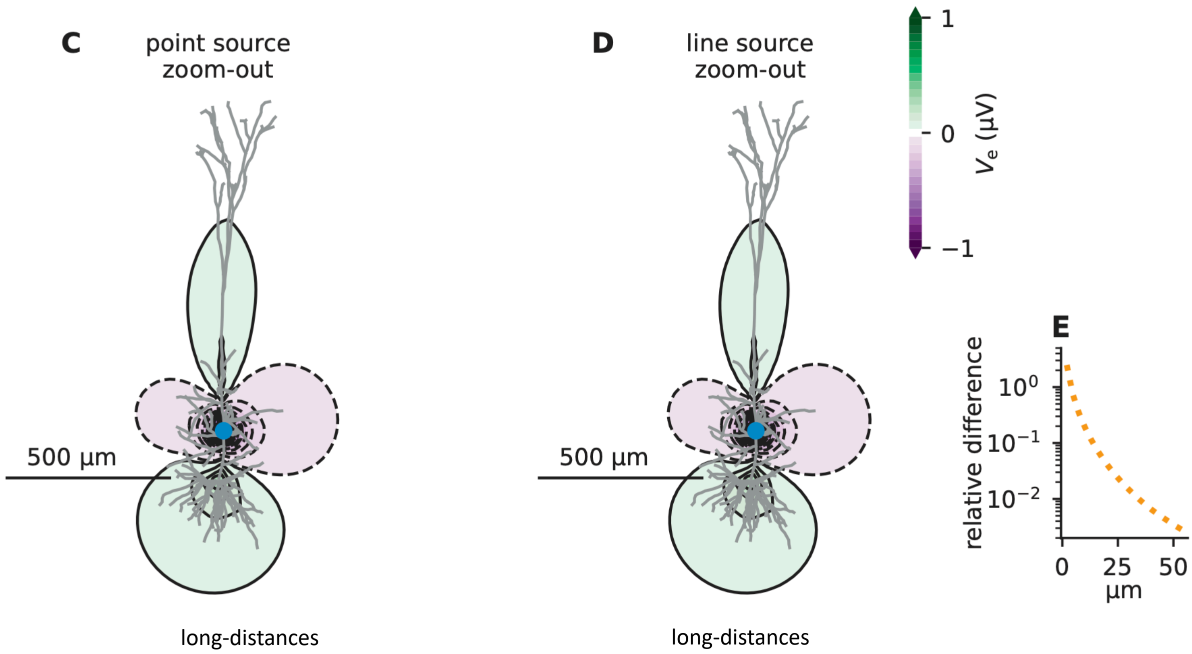
“Point-source” vs “Line-source” approaches

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

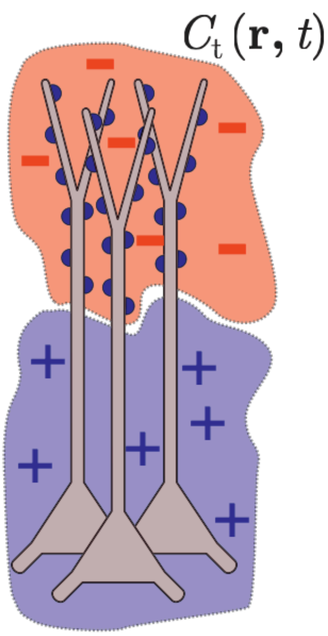




“Point-source” vs “Line-source” approaches



More generally: CSD - current source *density*



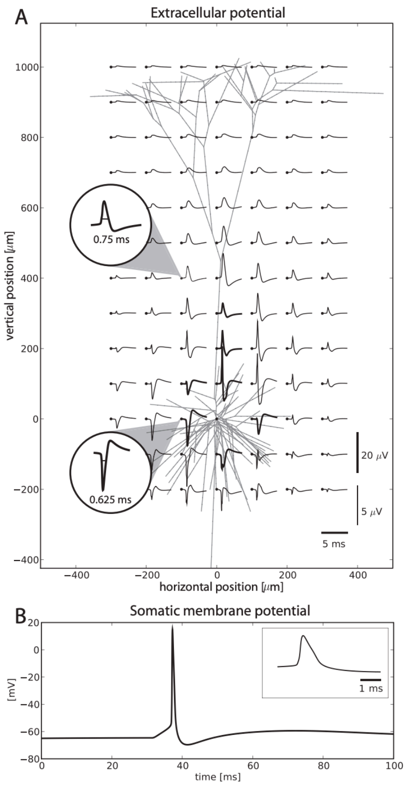
- current source density (in the tissue) Ct is
  - *a continuous function of time and position*
  - *usually estimated in the “inverse” problem (from measured Ve to Ct)*
  - *can be a collection of Dirac’s delta functions (in 3D), and then it reduces to the point-source approximation already discussed*

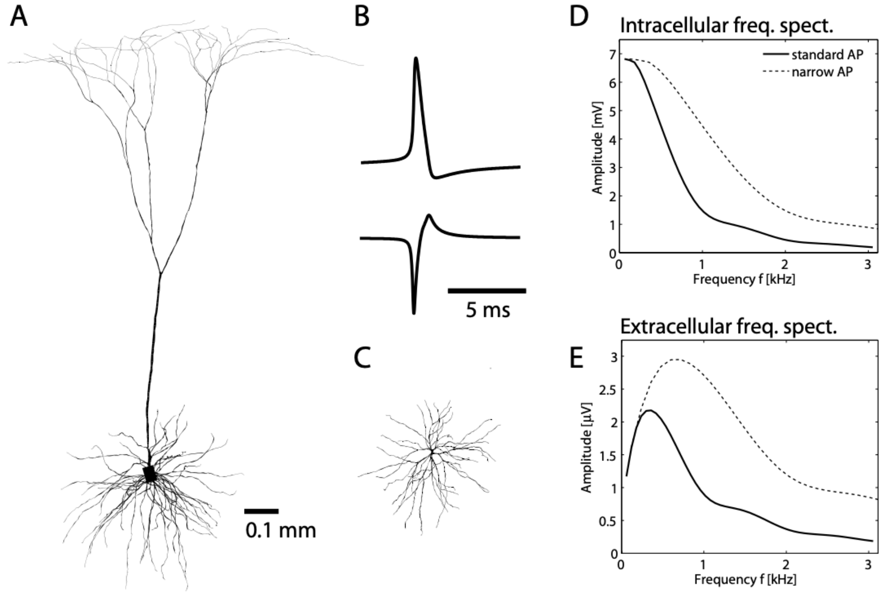
$$\nabla \; i_t \; = C_t$$

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

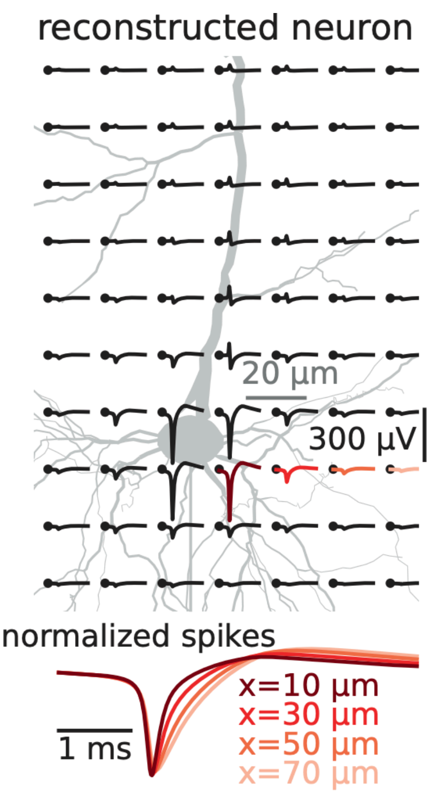
More complicated partial-derivatives differential equation…

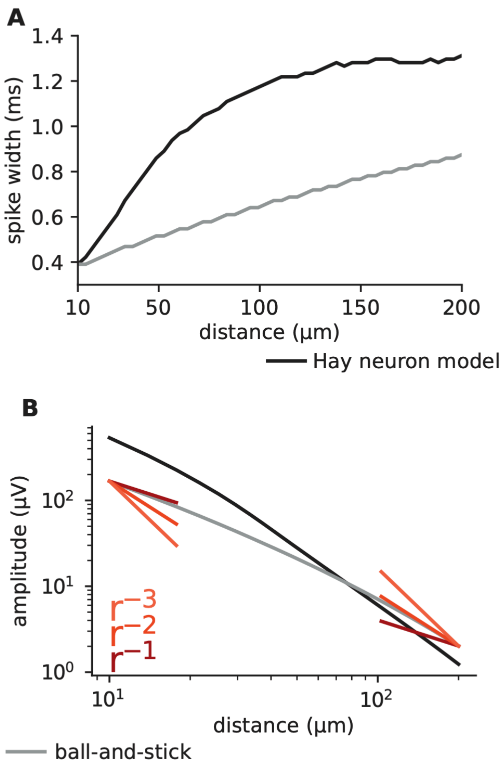
VCT - spikes



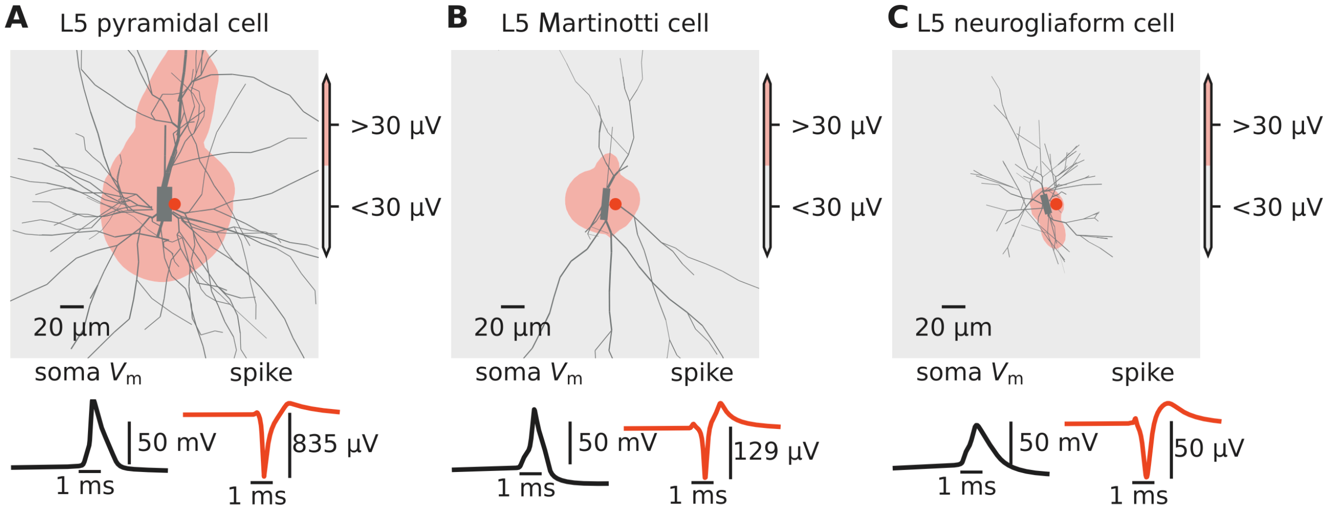


Spike shapes

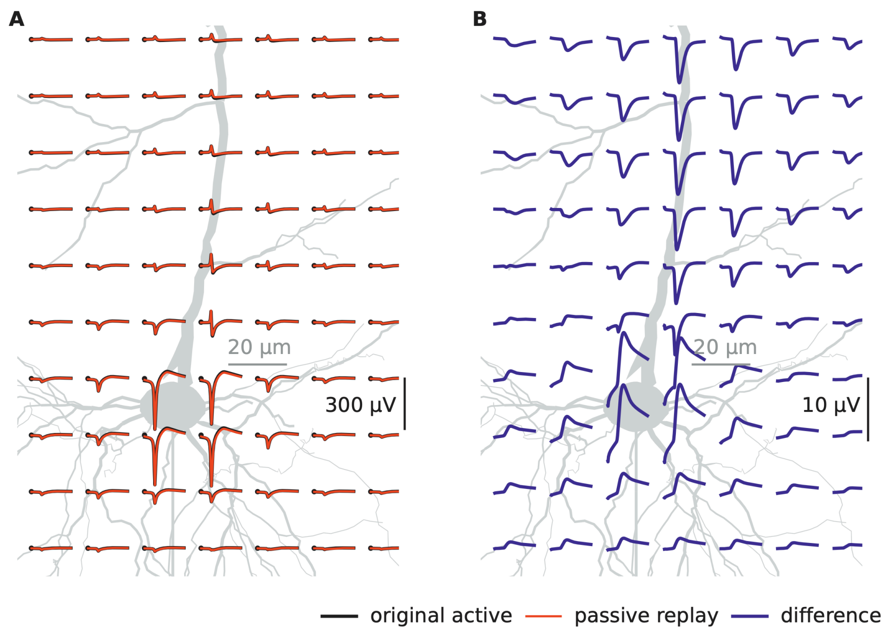




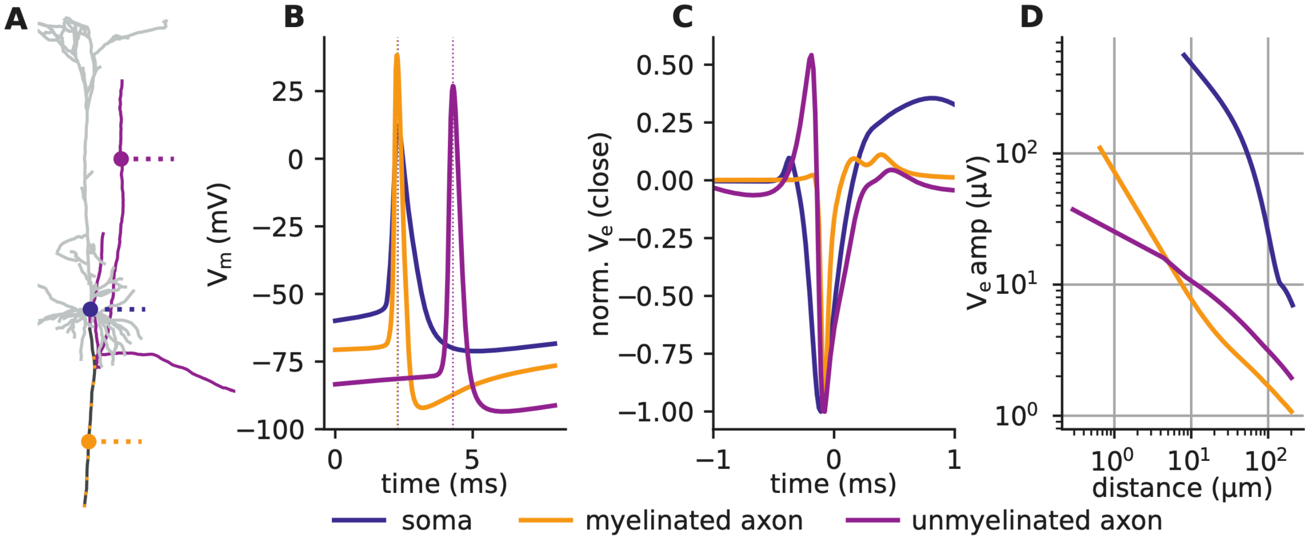
Spike detectability: depends on cell morphology

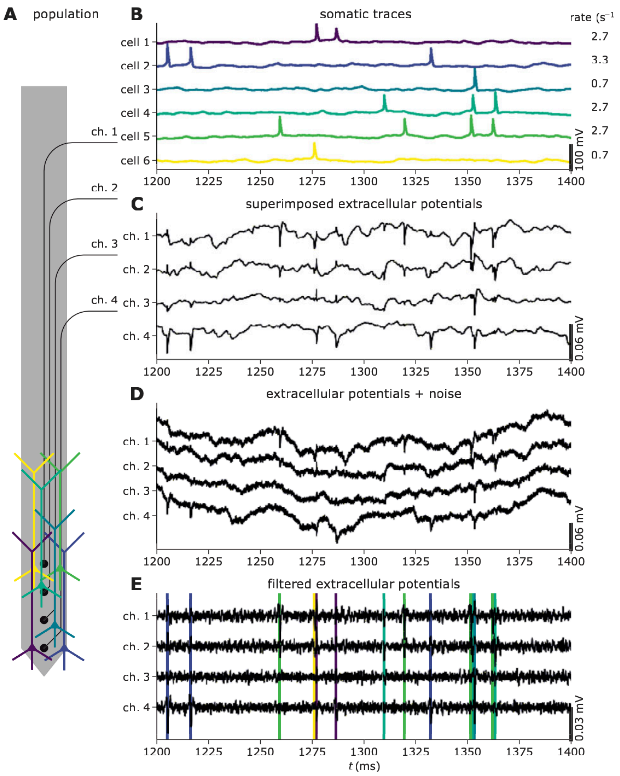


Spikes: weak impact of *active* dendrites



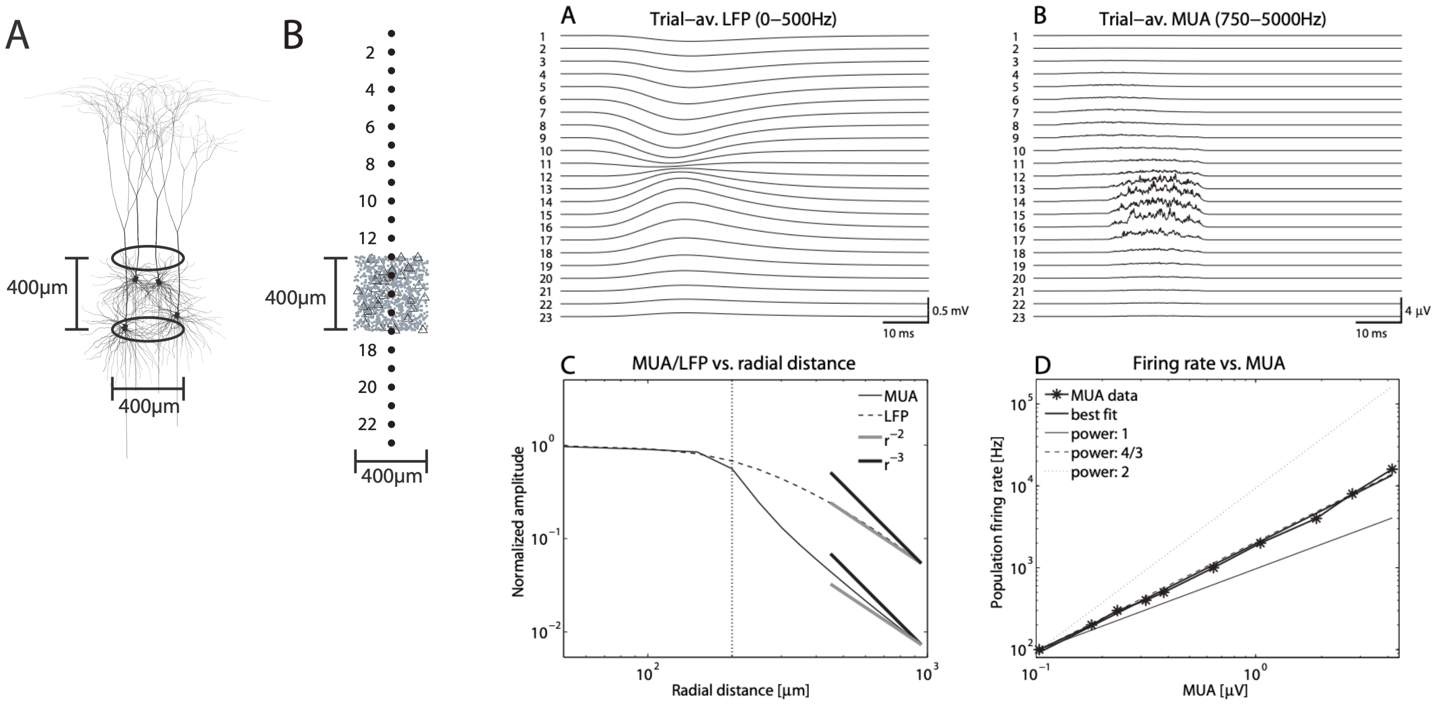
Axonal Spikes: impact of *myelinated* axon





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

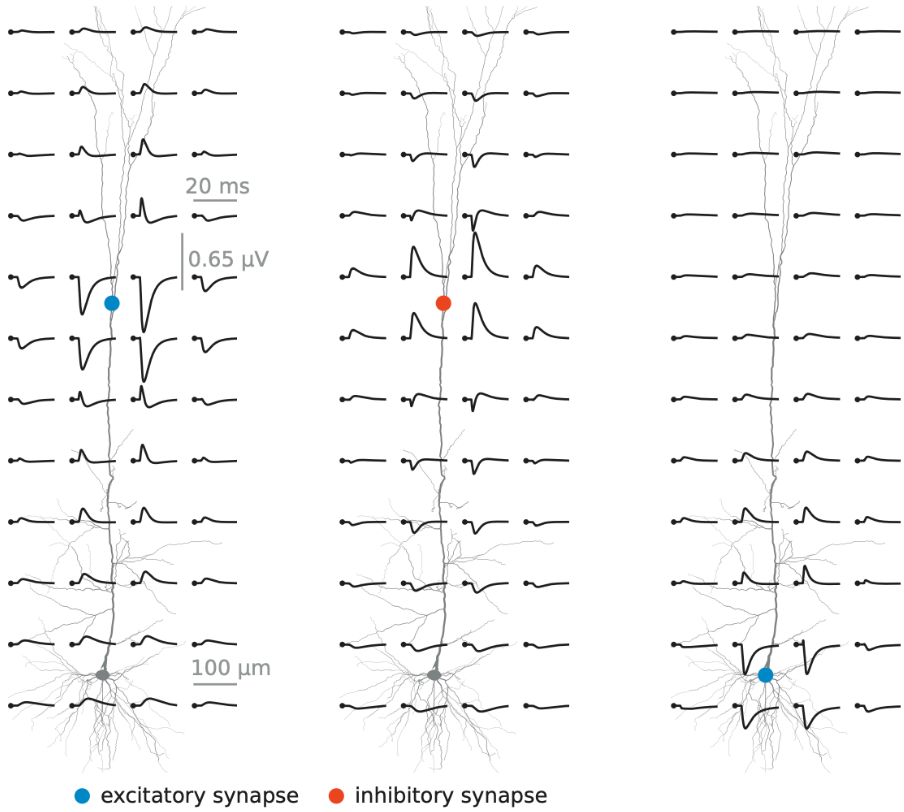
VCT - LFP and MUA - population of pyr. cells



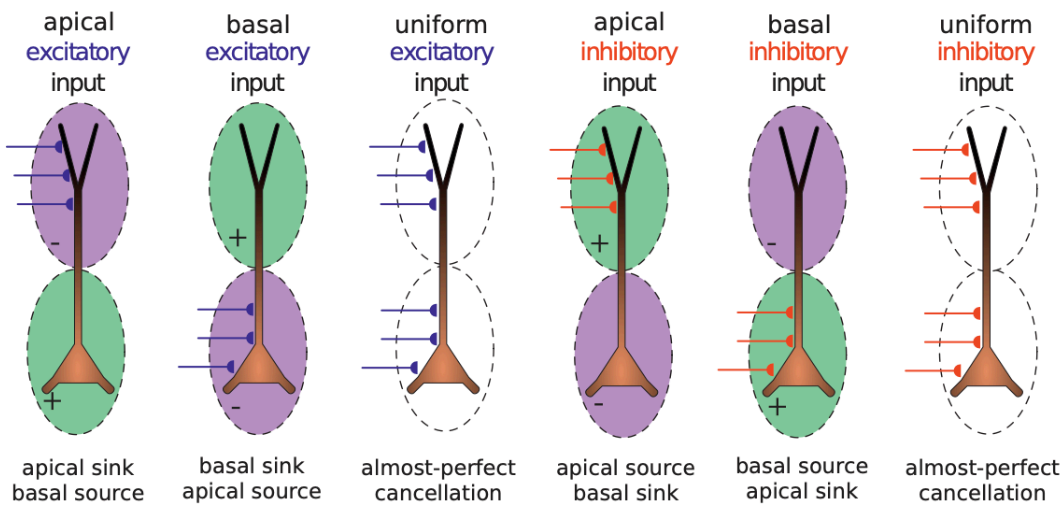
Local Field Potentials

Several processes contribute to LFP (the low-frequency part of the extracell.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.

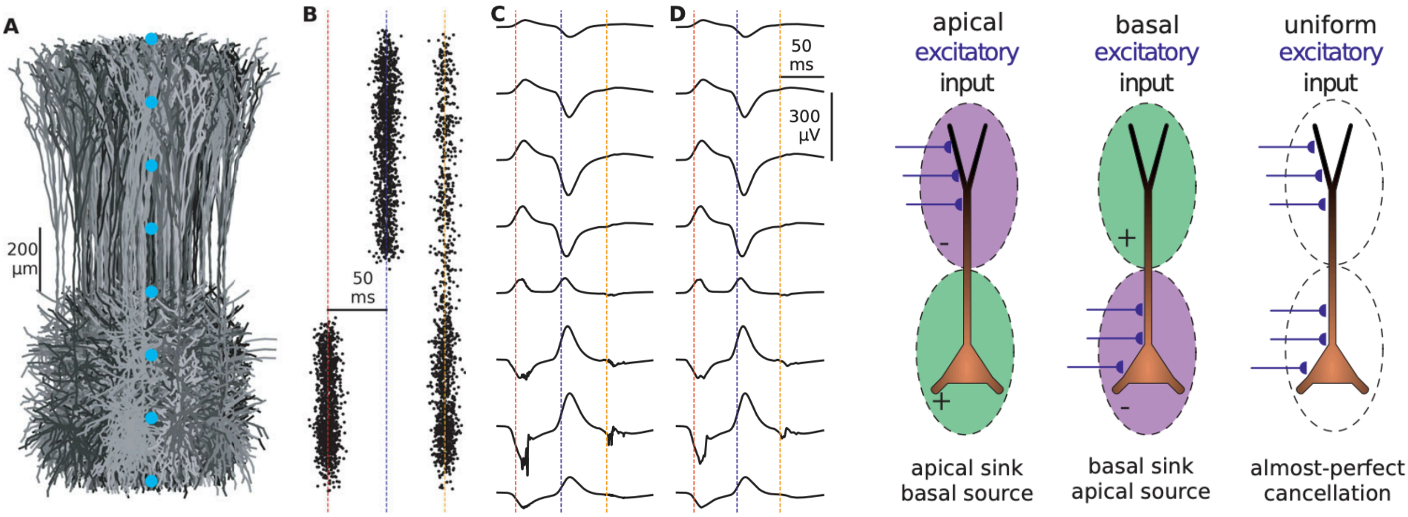


Typical "motifs" of configuration:
sources an sinks' arrangement is not "obvious"

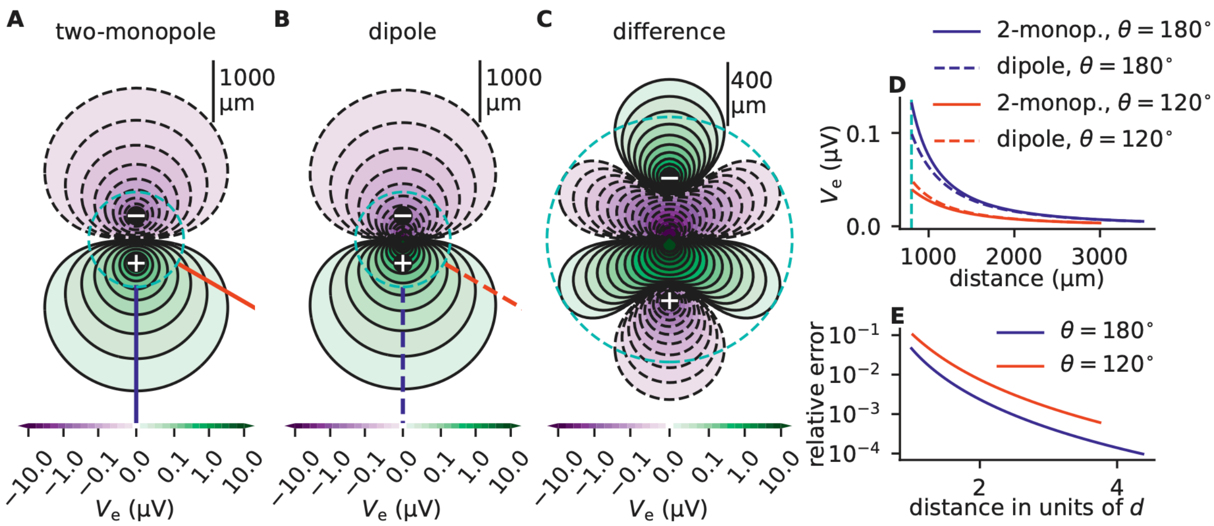


Typical “motifs” of configuration:

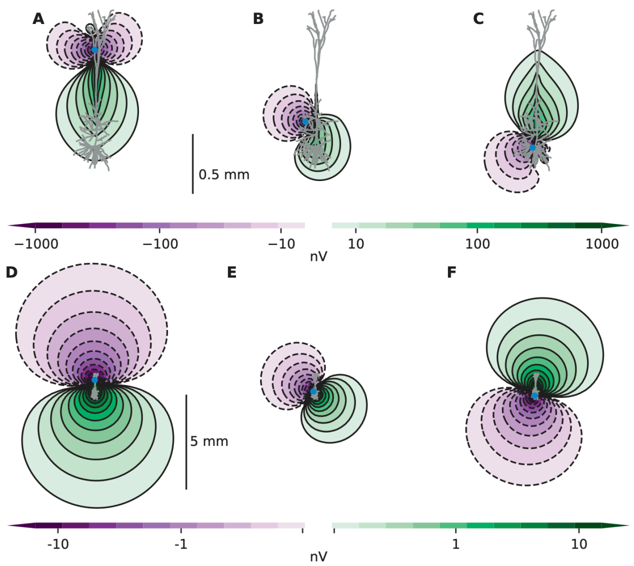
sources an sinks’ arrangement is not “obvious”



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



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



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

$$P \;=\; \sum_{n=1}^{N} I_n\ \mathbf{r_n}$$

$$P \;=\; -I\ \mathbf{r_1} \;+\; I\ \mathbf{r_2} \;=\; I\ \mathbf{d}$$