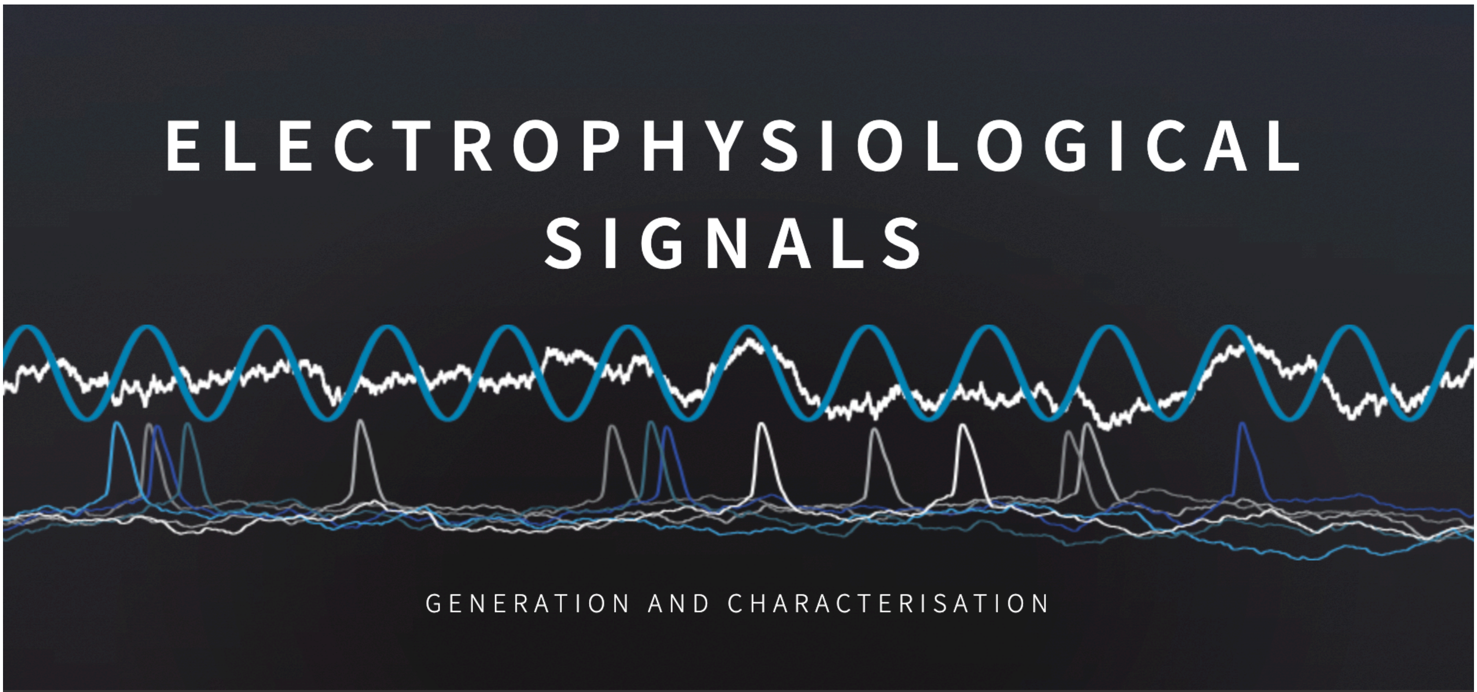



Michele GIUGLIANO

# Origin of Extracellular Signals

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

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

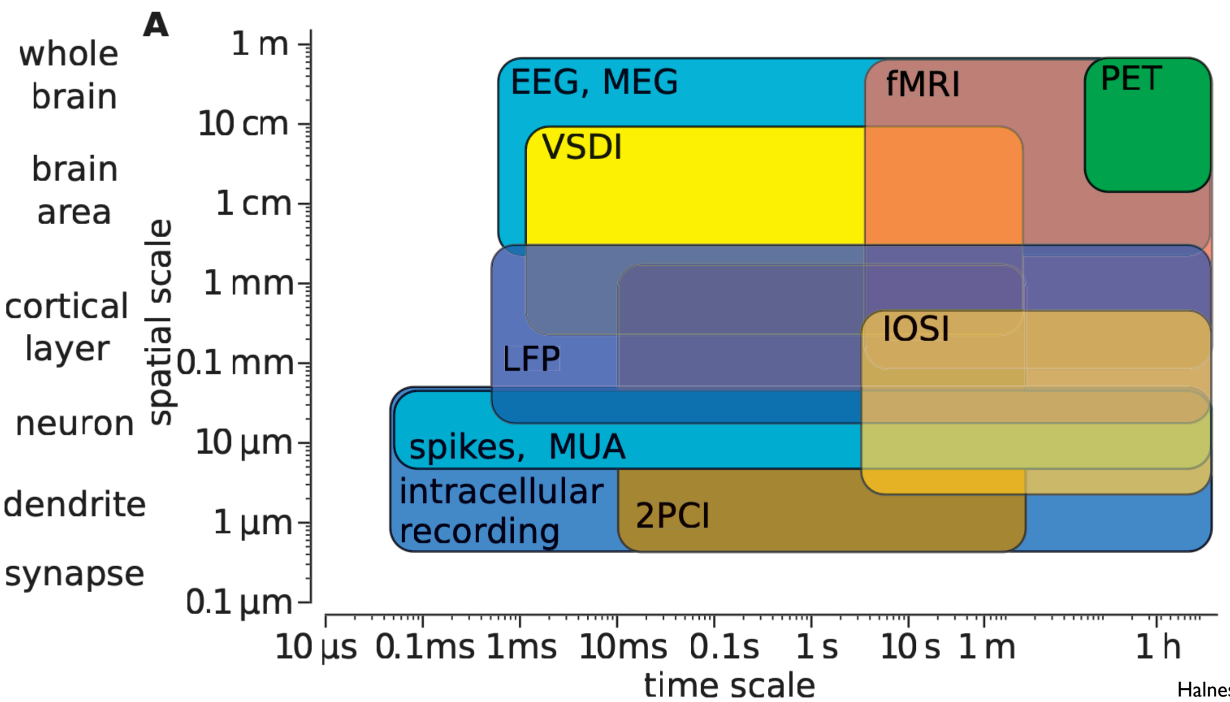
# References

**supporting your study and understanding**

Chapters from

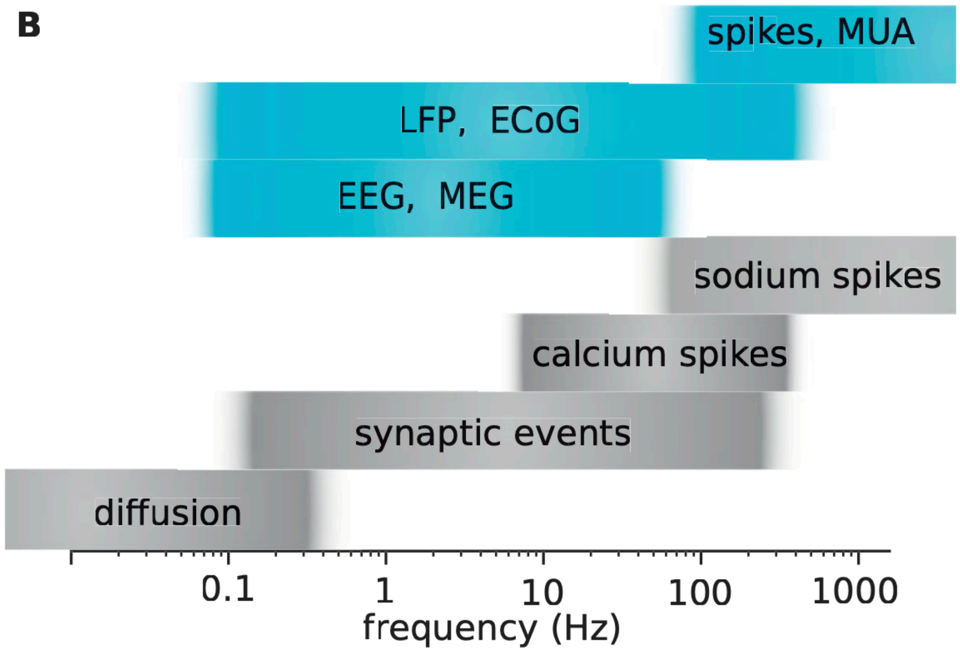
- Halnes et al., (2024) “*Electric Brain Signals*”
- Johnston & Wu (1994) *“Foundations of Cellular Neurophysiology"*
- Sterratt et al. (2011) “*Principles of Computational Modelling…*”
- Abbott LF, Dayan P (2001) “*Theoretical Neuroscience*”

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



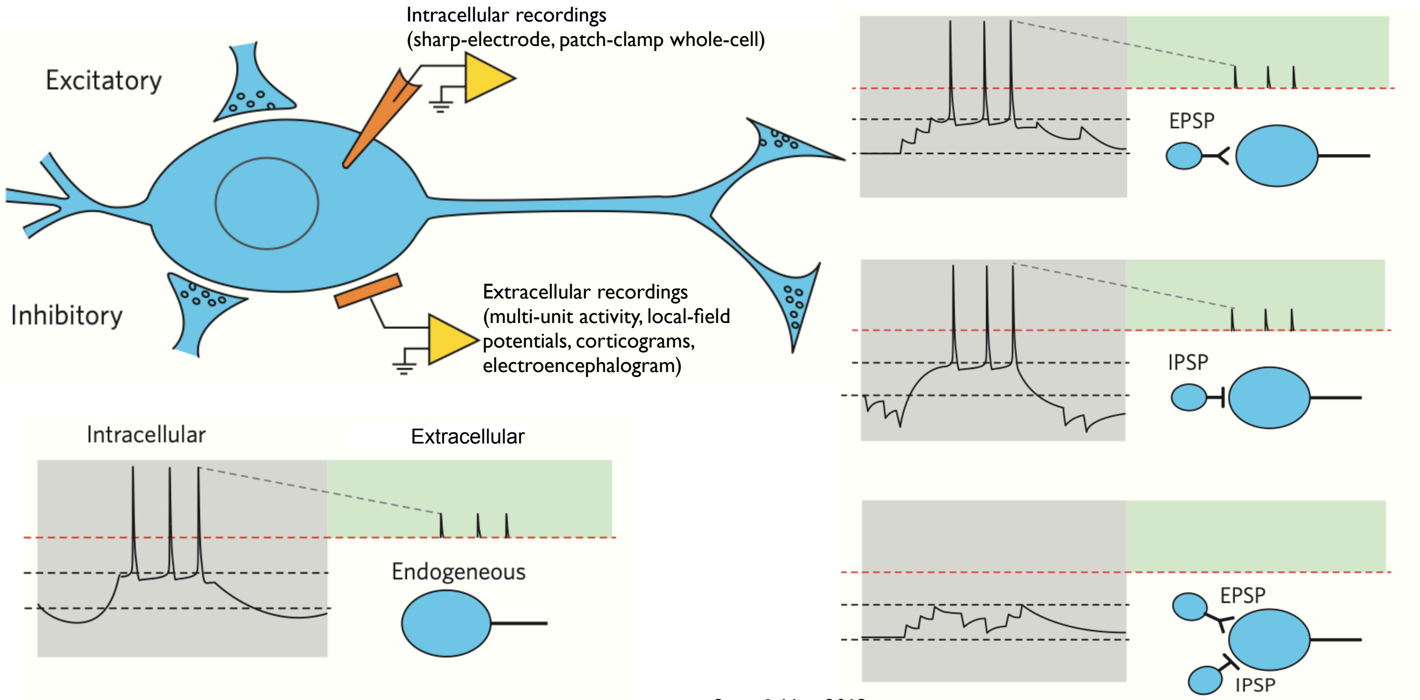

Halnes *et al.*, 2024

# Heterogeneous (and multiple) time-scales




Halnes *et al.*, 2024

# *__Extra__*cellular signals: only the *"fast/strong part"*?




Spira & Hai, 2013

# *Extra*cellular signals: not so elementary!

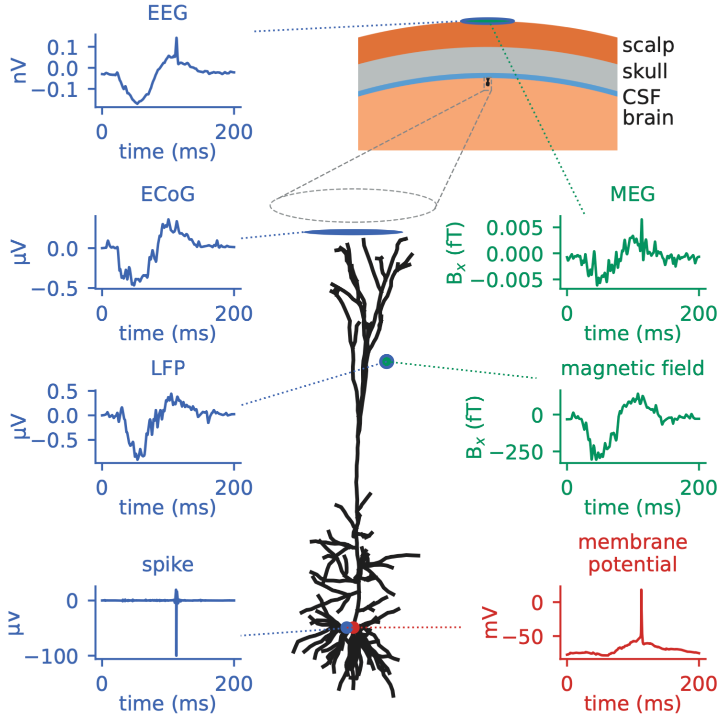
1) **Where** are you recording?

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?



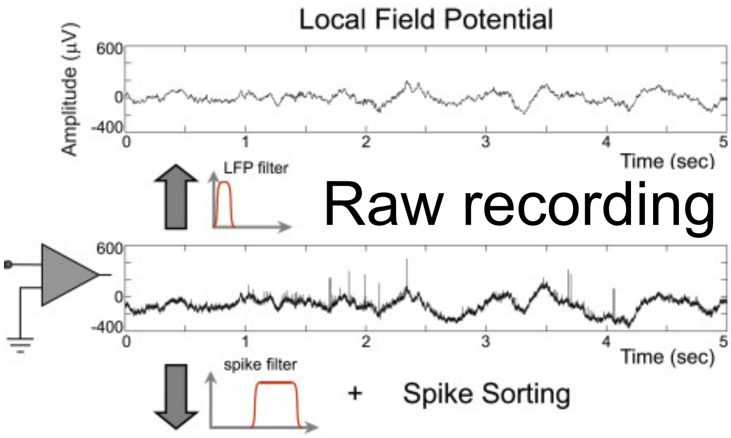

Halnes *et al.,* 2024

# Low **F**requency **P**art**s**/components

1 - 100 cycle/s

## LFP

Local
Field
Potential

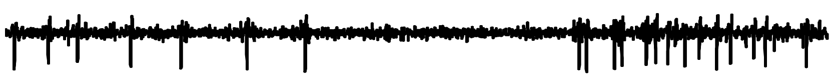



# High-freq. components

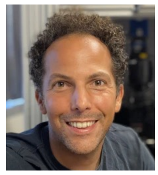
100 - 5000 cycle/s

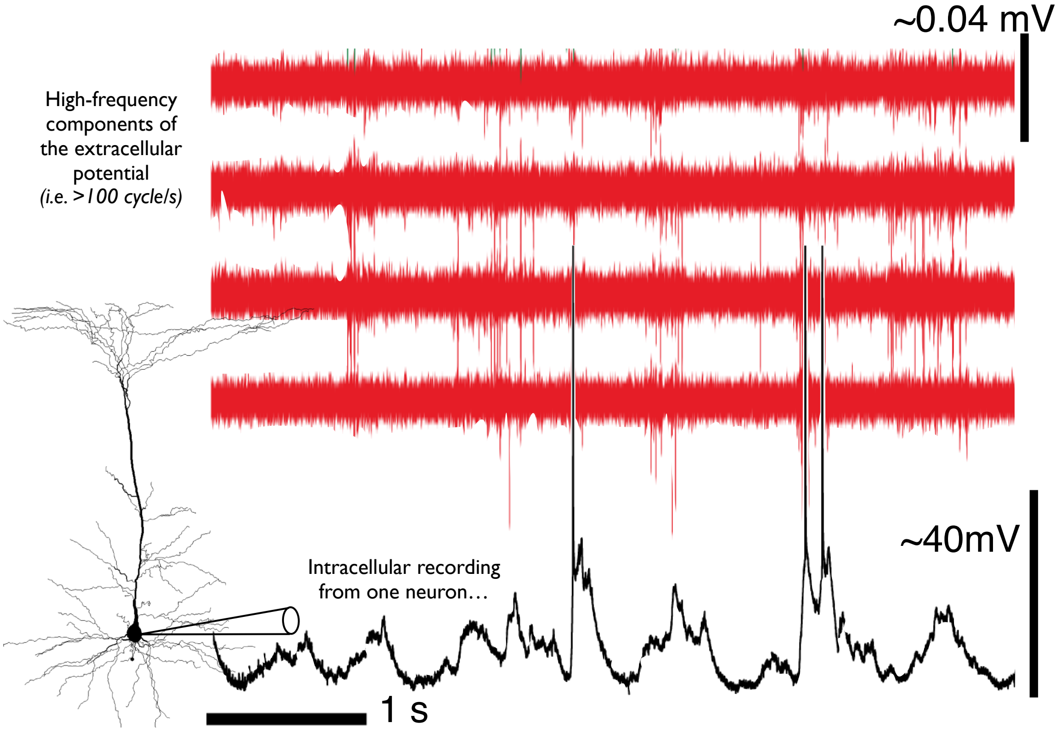
## MUA
## SUA

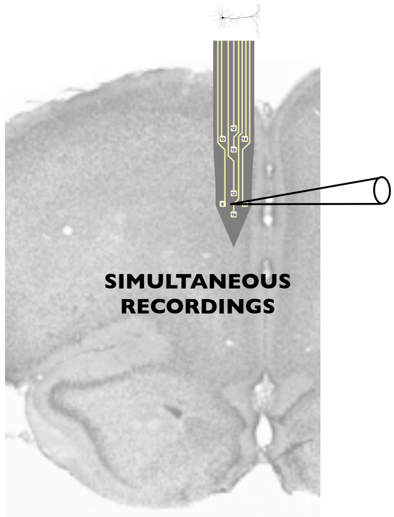
Multi-unit
Single-unit
Activity



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

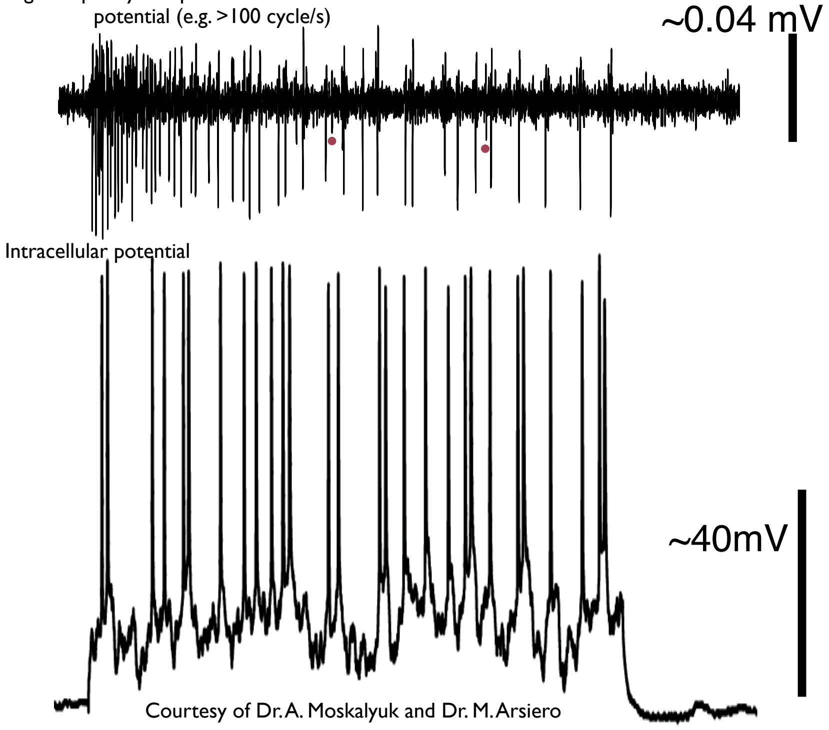


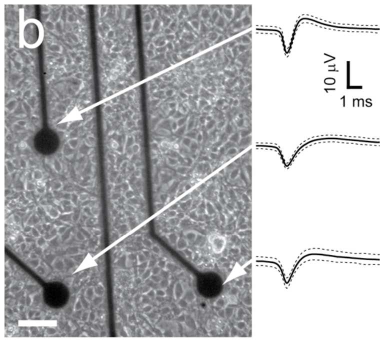




Courtesy of Dr. J. Couto

# Extracellular signals: APs, near the soma?

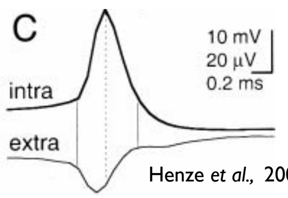



Courtesy of Dr. A. Moskalyuk and Dr. M. Arsiero




Dr. A. Moskalyuk

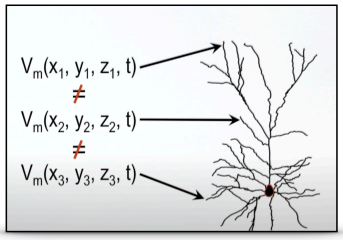
Dr. Eng. M. Arsiero

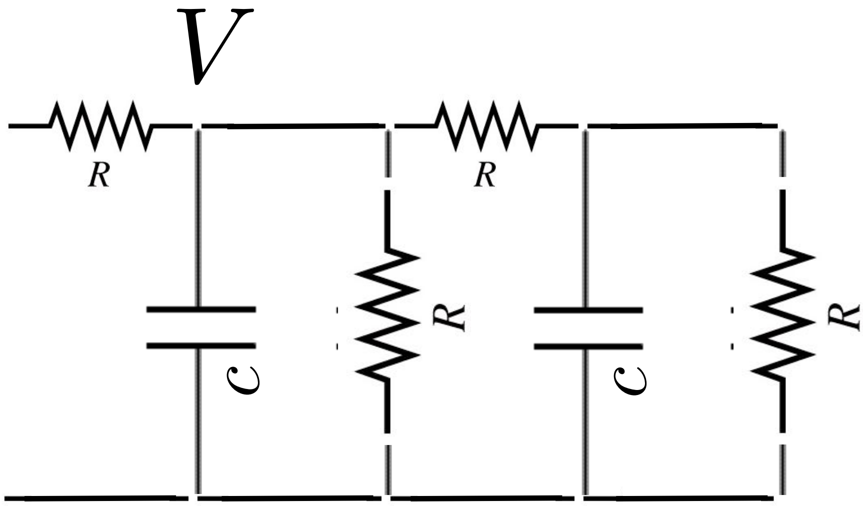



Henze *et al.*, 2000

## How to make sense of this?

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

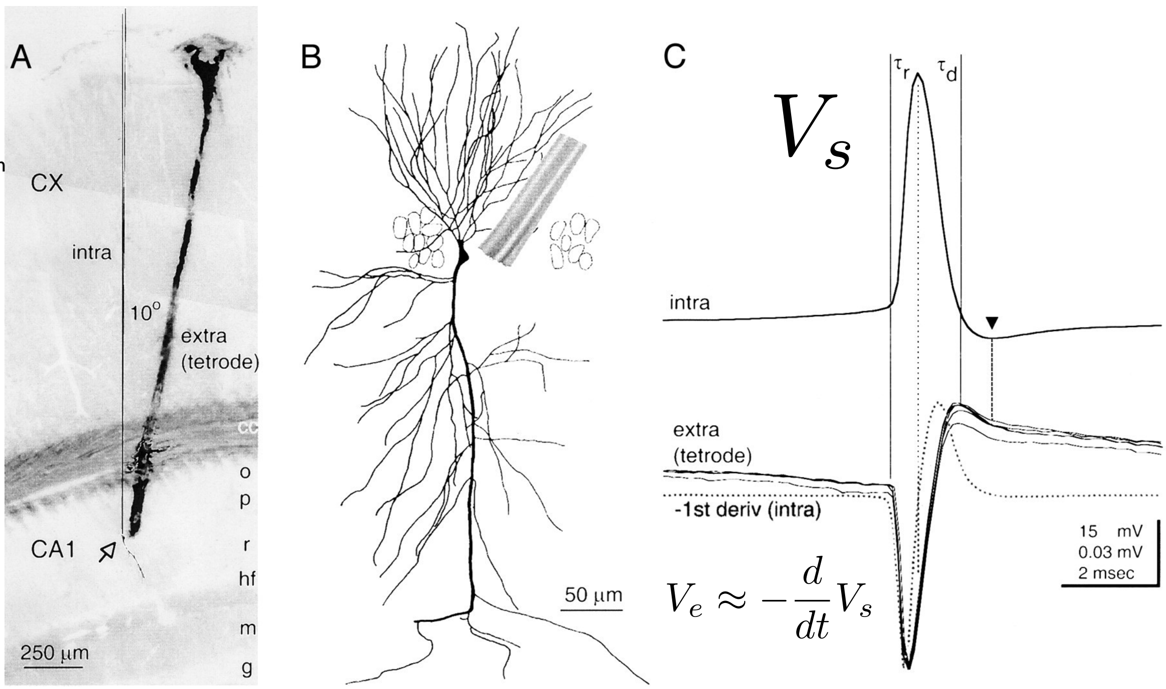



## Extracellular signals: APs, near the soma

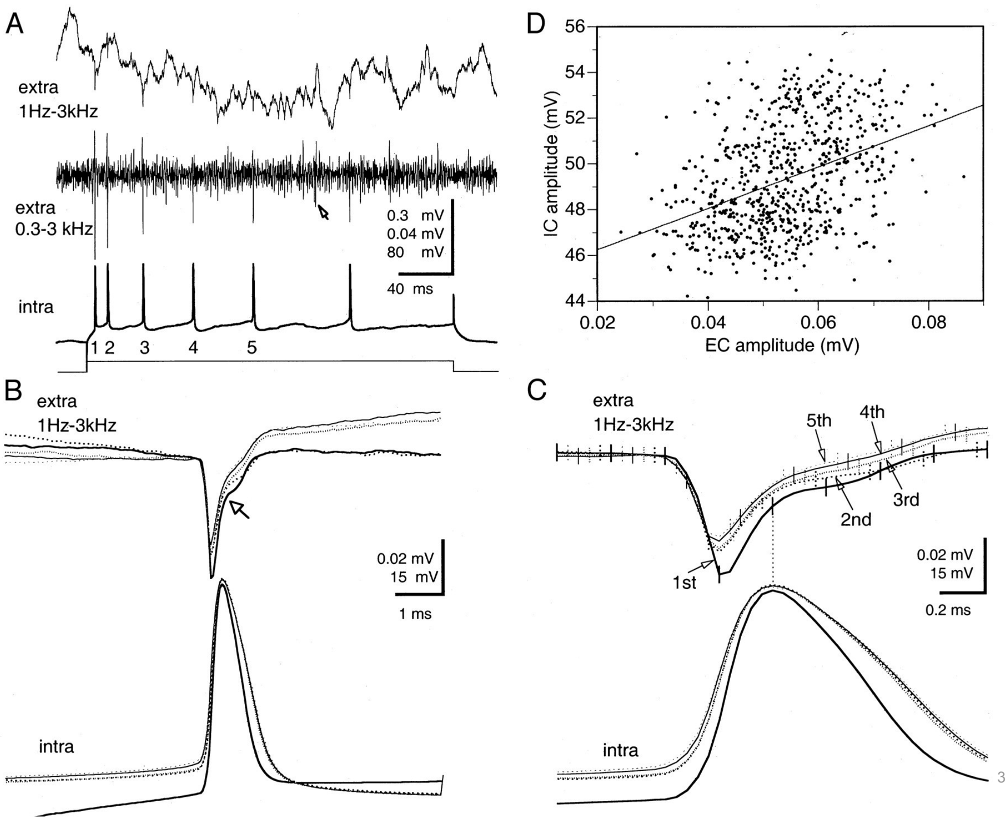
*In vivo* recordings from rat hippocampus, with both tungsten wire(s) and sharp electrodes.

György Buzsáki




CA1, hippocampal pyramidal cell

Henze *et al.,* 2000

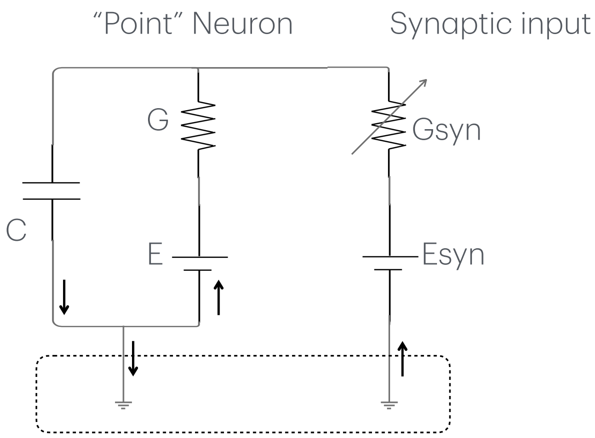


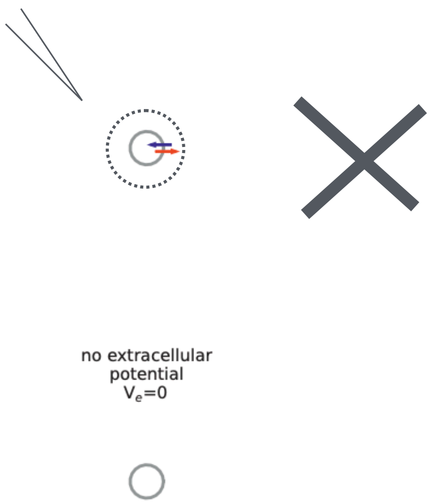

$$V_e \approx -\frac{d}{dt}V_s$$

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

Henze *et al.*, 2000

# Extracellular signals: APs, near the soma?



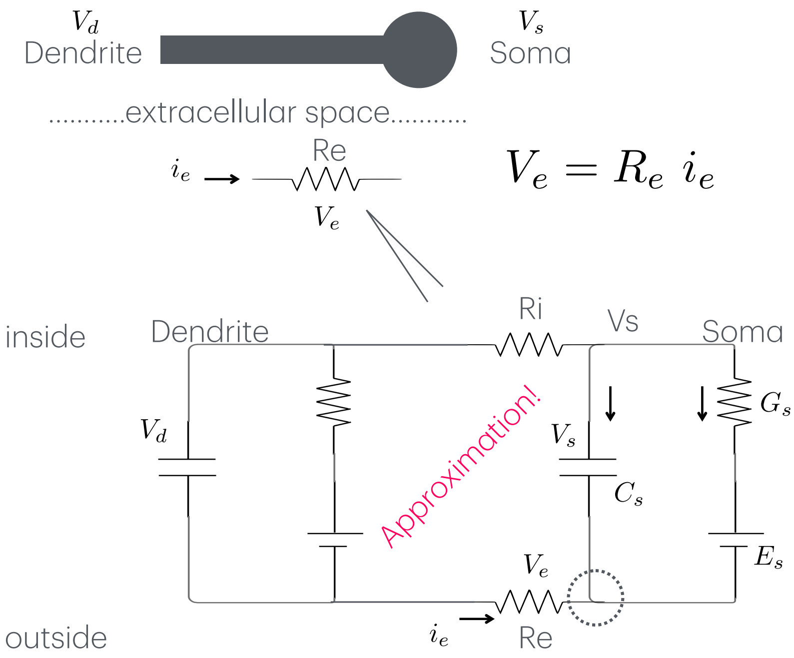

Currents, flowing in and out, **cancel** (<u>at the same point in space</u>).

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

# Extracellular signals: APs, near the soma?

We must take the spatial extension of neurons into account!

$V_d \neq V_s$




$$V_e = R_e\, i_e$$

$$i_e + i_c + i_m = 0$$

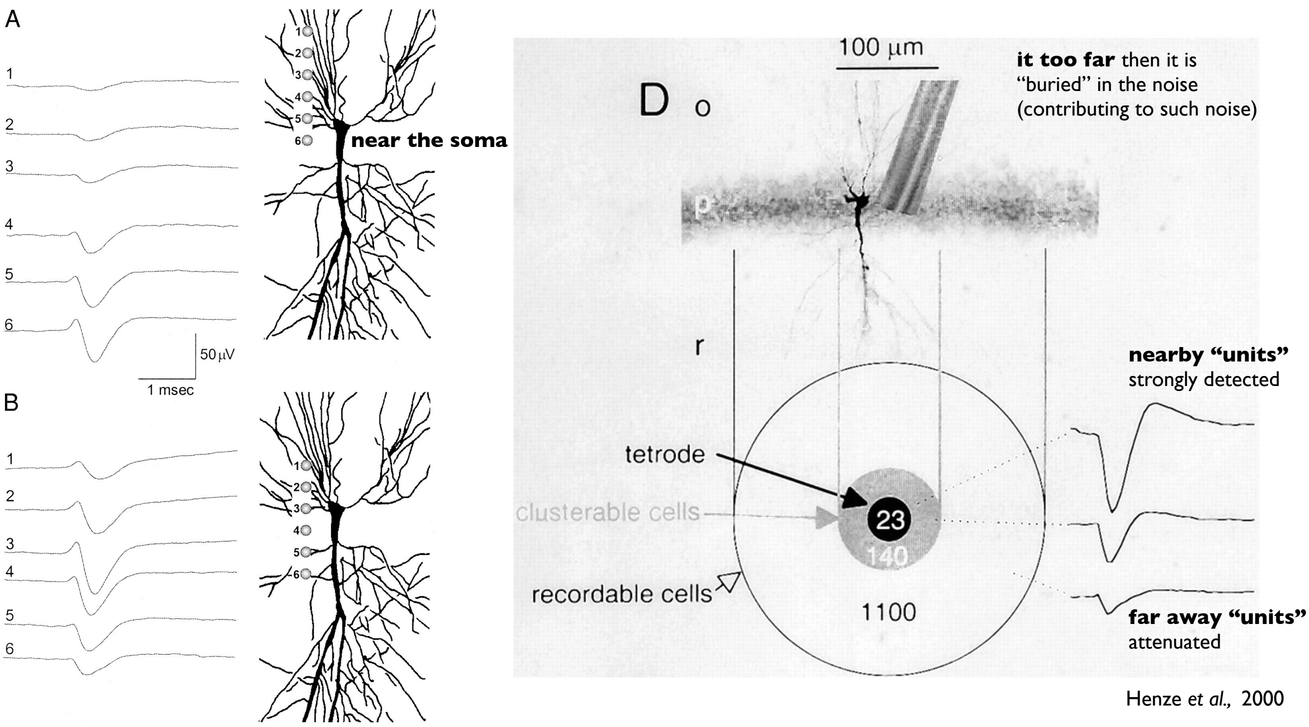
$$i_e + C_s \frac{d}{dt} V_s + G_s(V_s - E_s) = 0$$

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

$$C_s \frac{d}{dt} V_s >> G_s(E_s - V_s) \qquad \boxed{V_e \approx -\frac{d}{dt} V_s}$$

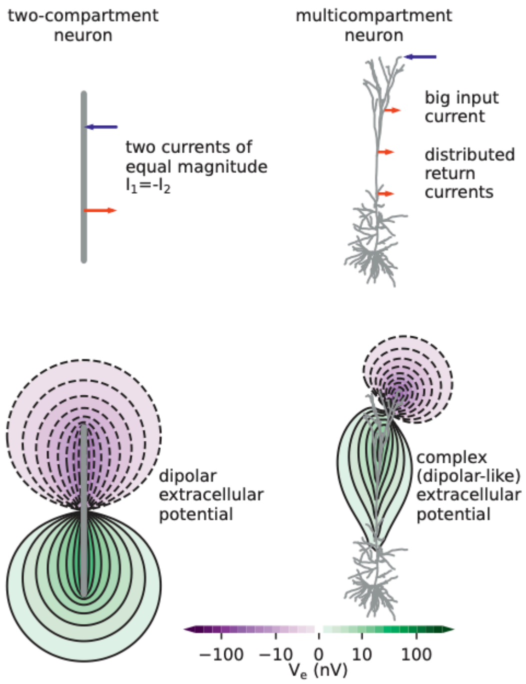
# Extracellular signals: position and distance

**where** are you recording? **how far** are you recording?




Henze *et al.*, 2000

# Extracellular signals: more in general, how to?



Haines 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**)

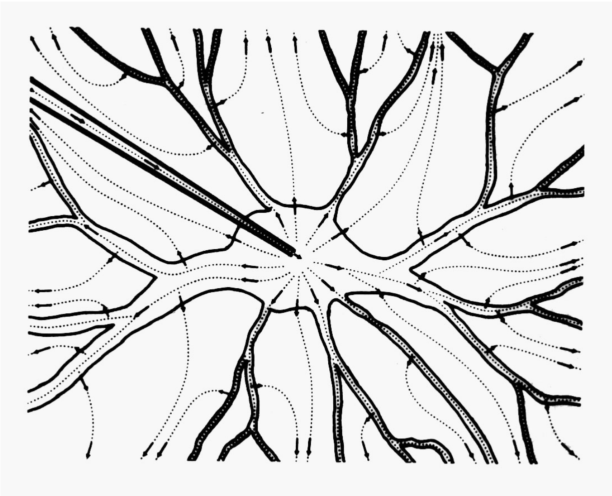
$$V_e(\mathbf{r}) = \sum_{\mathbf{n}} \frac{\mathbf{i_n}}{4\pi\sigma_{\mathbf{t}}|\mathbf{r}-\mathbf{r_n}|}$$

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)

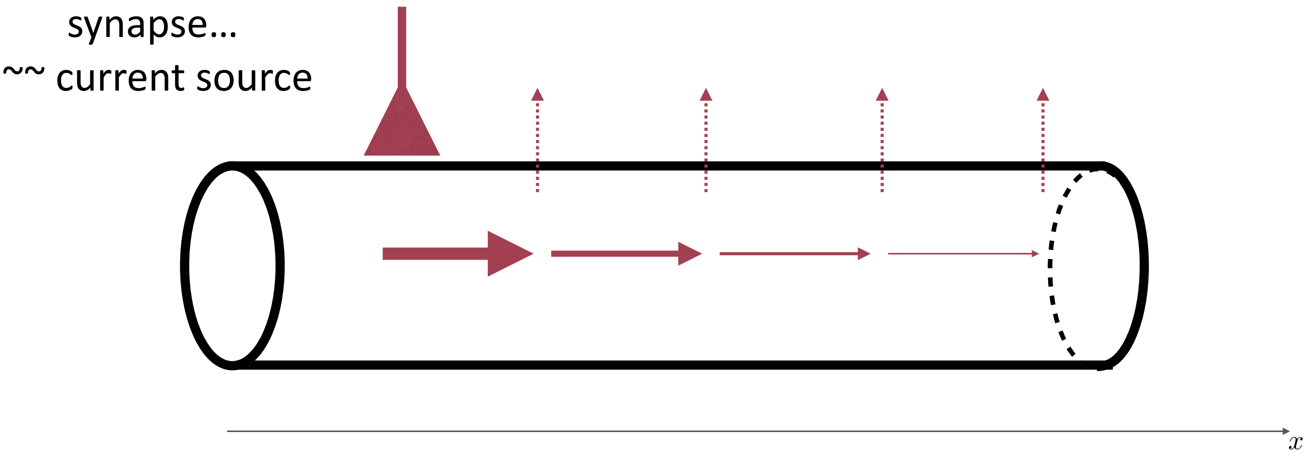
# 1959 Rall's Cable Theory for Neurites: motivations

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



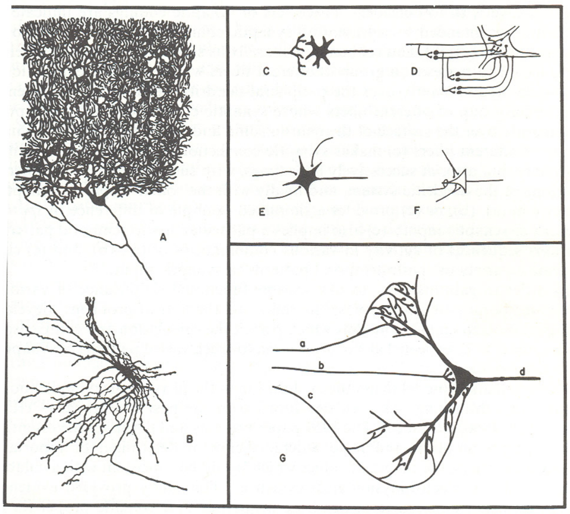

Wilfried Rall

# 1959 Rall's Cable Theory for Neurites: intuition



# 1959 Rall's Cable Theory for Neurites: motivations

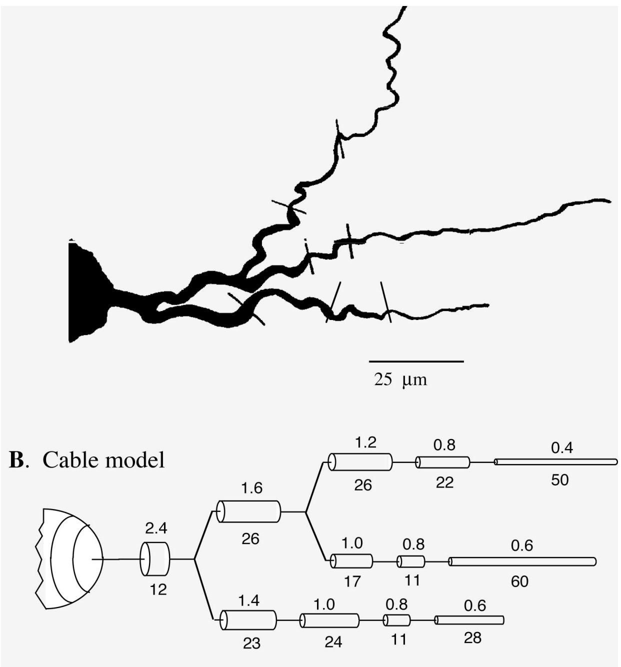
- Understanding the **impact** of (**remote**) **dendritic** synapses activation (i.e. inputs) on the membrane potential of the **soma/axon** (i.e. output) region.

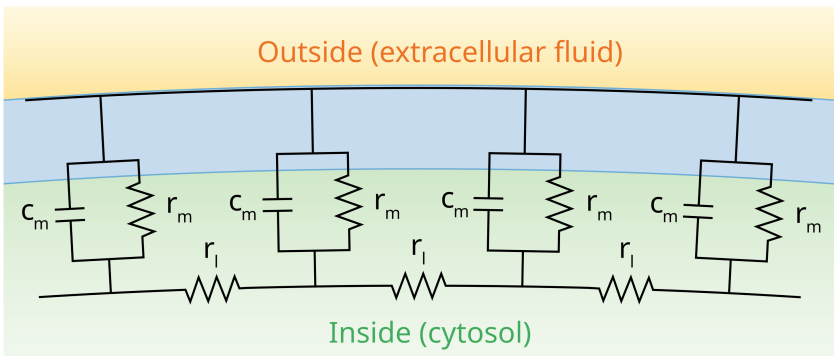


RESULTS:

- 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**.

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




**Specific** electrical properties:

Capacitance — $r_m$: Membrane resistance per unit of (lateral) area

Resistance — $r_l$: Longitudinal resistance per unit of (section) area and unit of length

$c_m$: Capacitance due to electrostatic forces per unit of (lateral) area

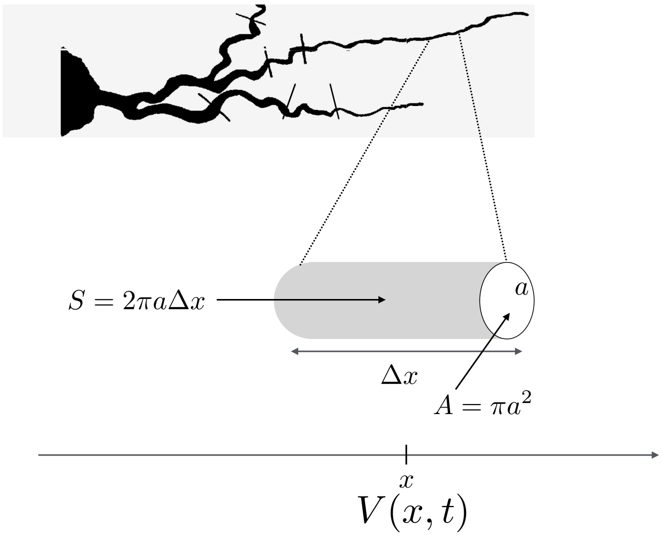
$c = 1\mu F cm^{-2}$ $\quad r_m = 20 k\Omega cm^2$ $\quad r_i = 200 \Omega cm$

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

# Cable Theory for Dendrites (and Axons)

Let's take an infinitesimal section…

$$V(x,t)$$

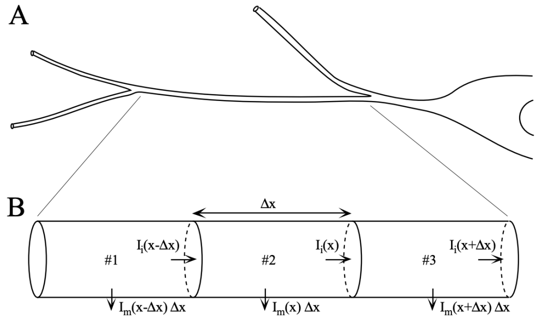



**Total** electrical properties:

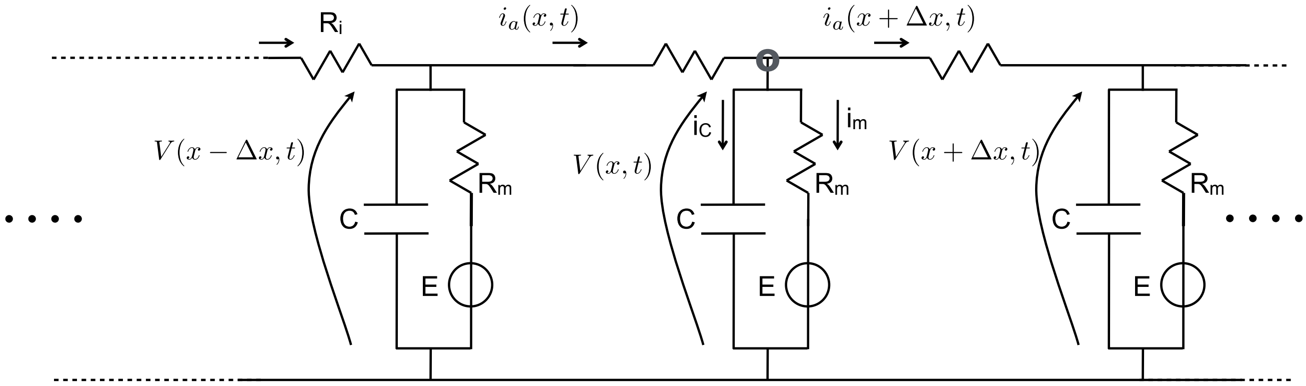
$R_m = r_m/S = r_m/(2\pi a \Delta x)$ $\qquad r_m = 20k\Omega cm^2$

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

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




# Cable Theory for Dendrites (and Axons)




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

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

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

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

# Cable Theory for Dendrites (and Axons)

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

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

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

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

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

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

---

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

…Invoking Taylor's…

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

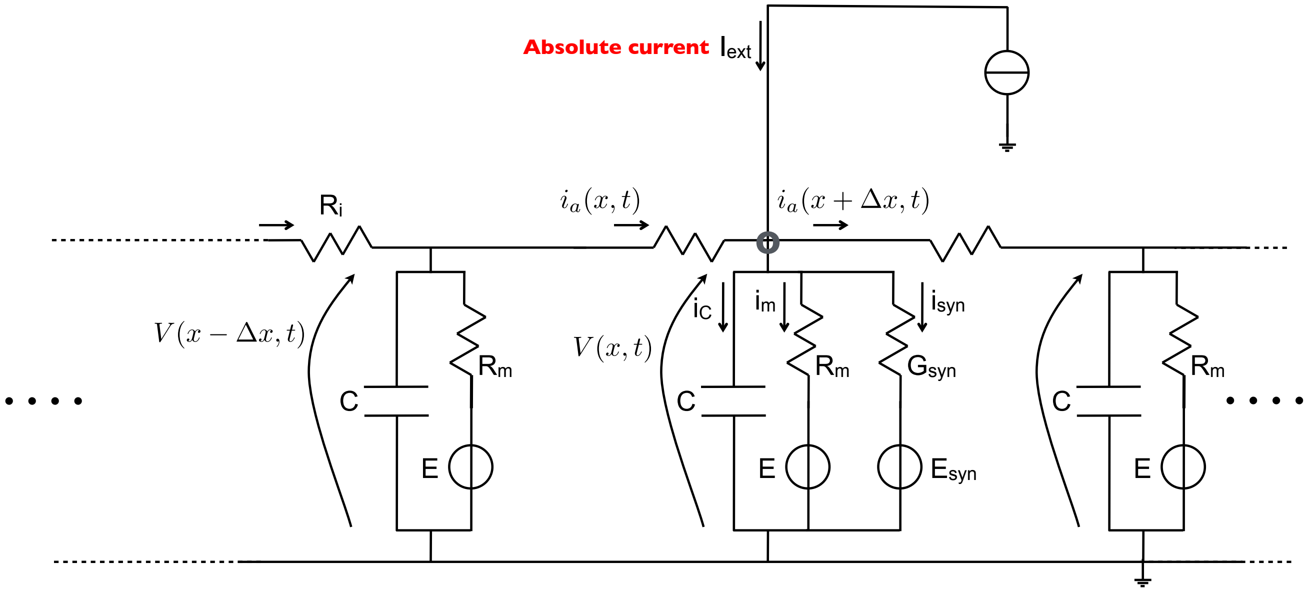
$$\frac{R_m}{R_i}\left(\Delta x^2\frac{d^2v(x,t)}{dx^2}\right) = R_m C\frac{dv(x,t)}{dt} + v(x,t)$$

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*.




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

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

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

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

$$\tau_m = r_m c$$

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

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

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

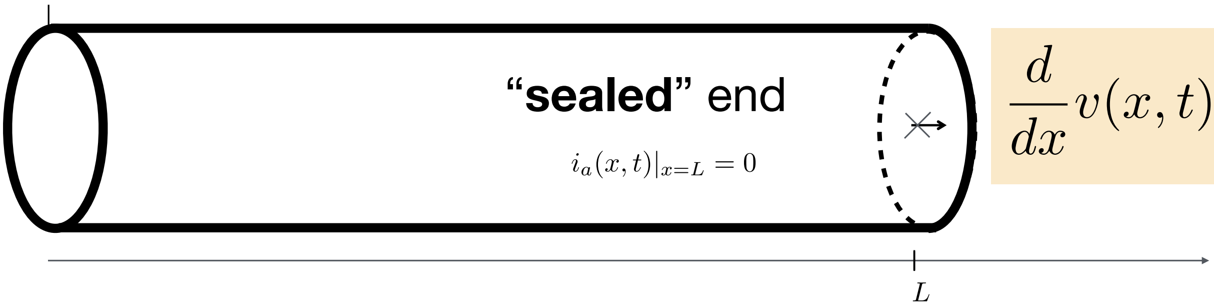
2 x Boundary conditions
1 x Initial condition
needed

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

## Boundary conditions: 1

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

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

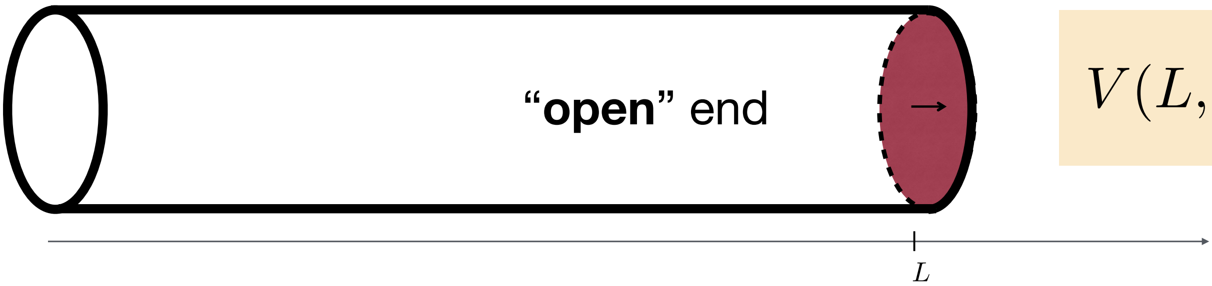



$$\frac{d}{dx}v(x,t)|_{x=L} \;=\; 0$$

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

## Boundary conditions: 2

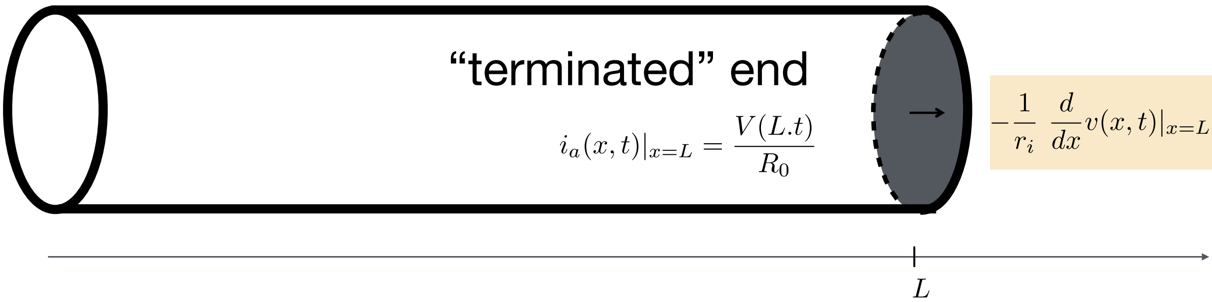
$$V_{in}(L,t) = V_{out} = 0$$




$$V(L,t) = 0$$

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

# Boundary conditions: 3

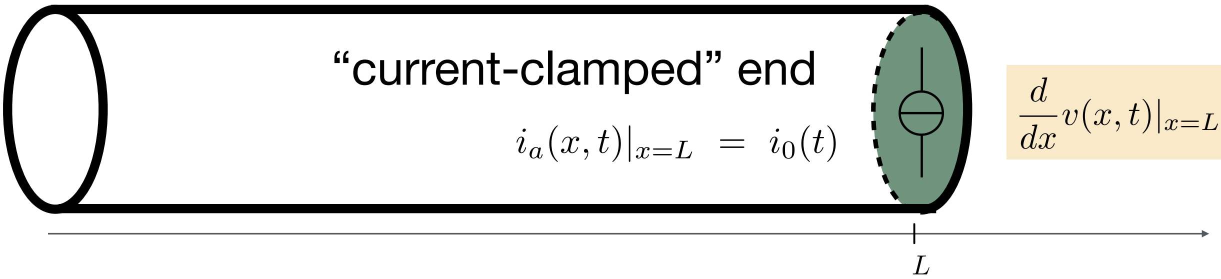



$$-\frac{1}{r_i}\ \frac{d}{dx}v(x,t)|_{x=L} = \frac{1}{R_0\ a^2\pi}V(L,t)$$

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

# Boundary conditions 4


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




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

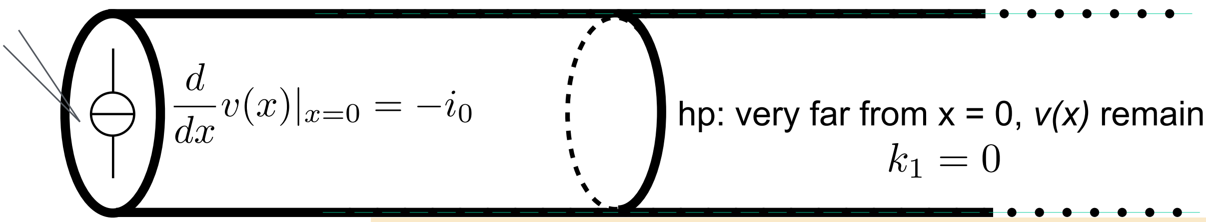
## **Steady-state** (w.r.t. time) - DC regime
## semi-**infinite** cable…

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

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

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

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




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

$$k_1 = 0$$

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

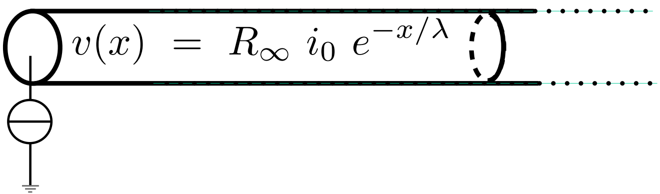
$$v(x) = \sqrt{\frac{r_m r_i}{2 a^3 \pi^2}}\; i_0\; e^{-x/\lambda} = R_\infty\; i_0\; e^{-x/\lambda}$$

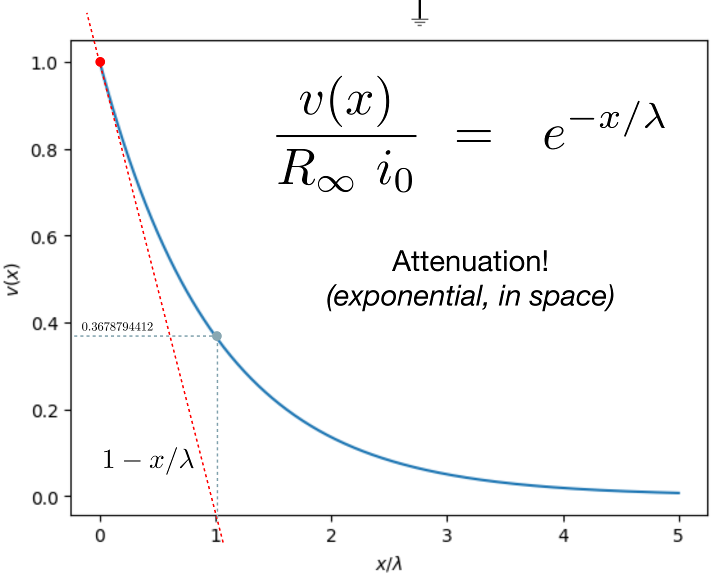
input resistance

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

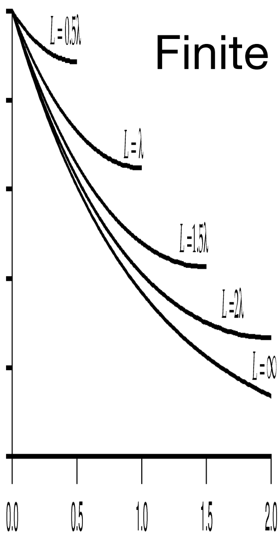
$d = 4 \mu m$

$\lambda = 500 \mu m$




Finite length

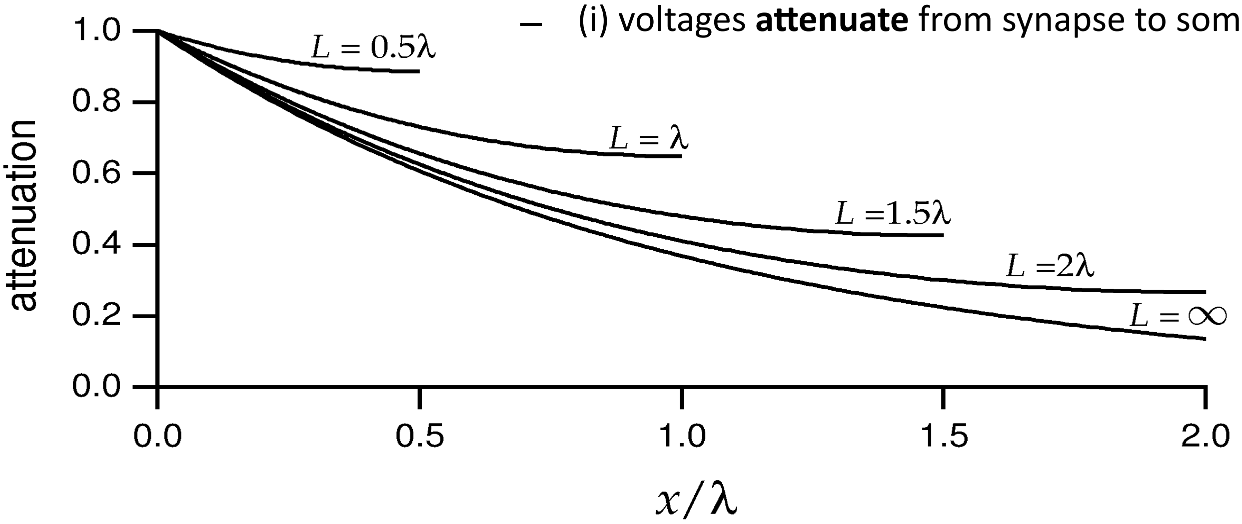


## Steady-state (i.e. time) - finite cable

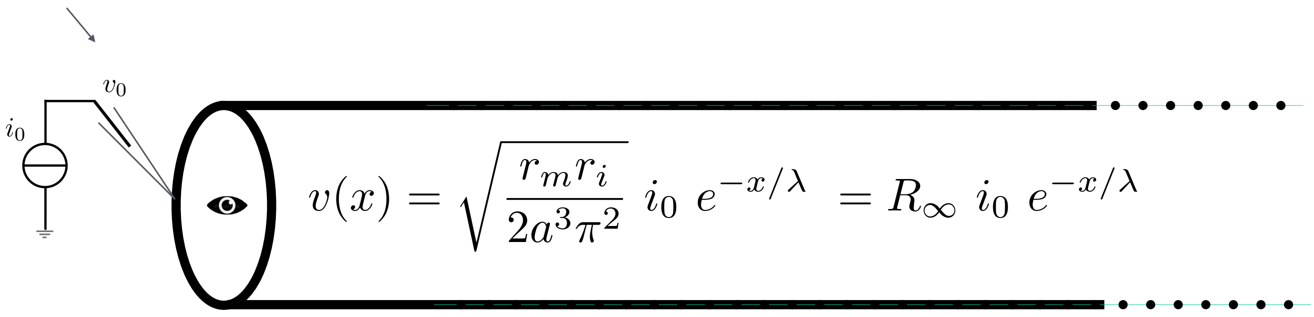

$d = 4\mu m$

$\lambda = 500\mu m$

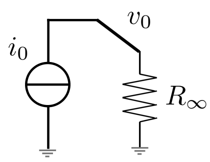
- Dendrites are non-isopotential portions of a neuron!
  - (i) voltages **attenuate** from synapse to soma!




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




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



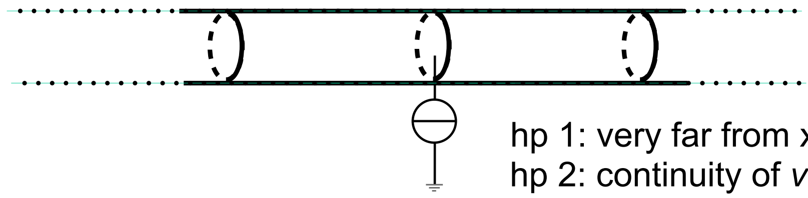

I *see* just an <u>equivalent</u> resistor/conductance from this point of the "circuit"…

$$v_0 \ = \ R_\infty\ i_0$$

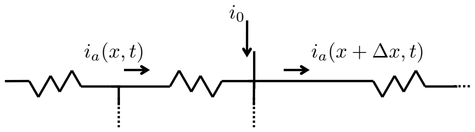
# Steady-state (i.e. time) - infinite cable

$d = 4\mu m$

$\lambda = 500\mu m$



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




$$i_a(x) + i_0 = i_a(x+\Delta x)$$

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

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

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

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

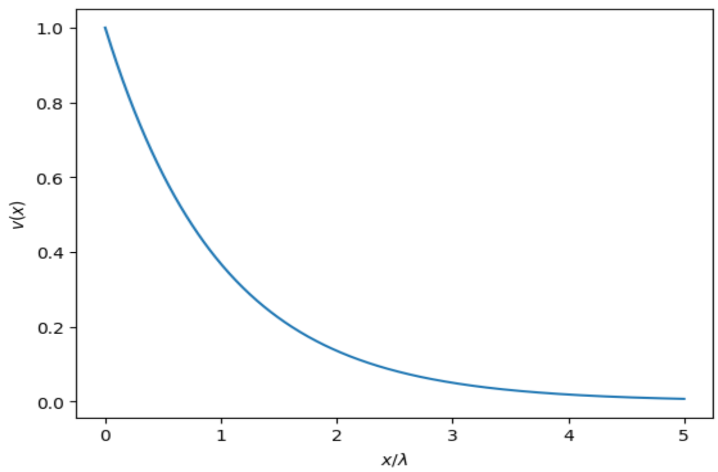
$$v(x-\Delta x,t) + v(x+\Delta x,t) \approx 2v(x,t) + \Delta x^2\ \frac{d^2 v(x,t)}{dx^2}$$

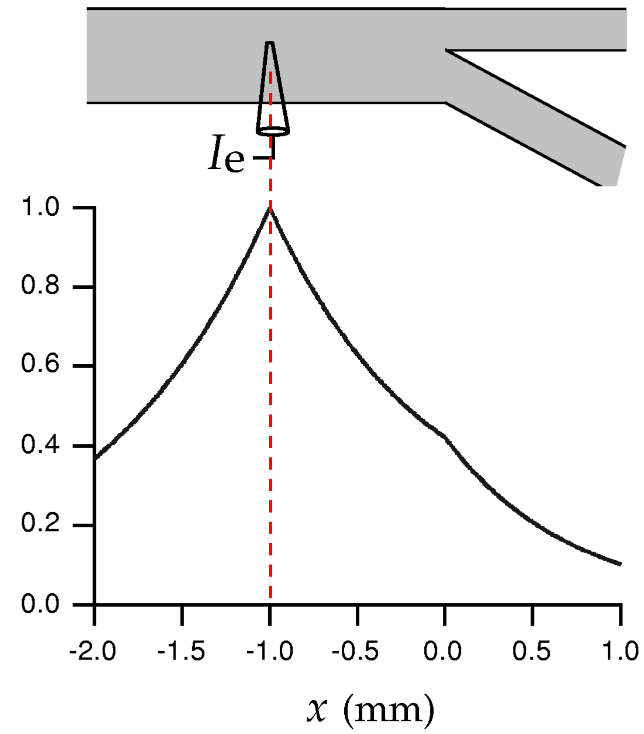
$$\frac{\Delta x^2}{R_i}\frac{d^2 v(x,t)}{dx^2}|_{x=0} \;=\; -i_0$$

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

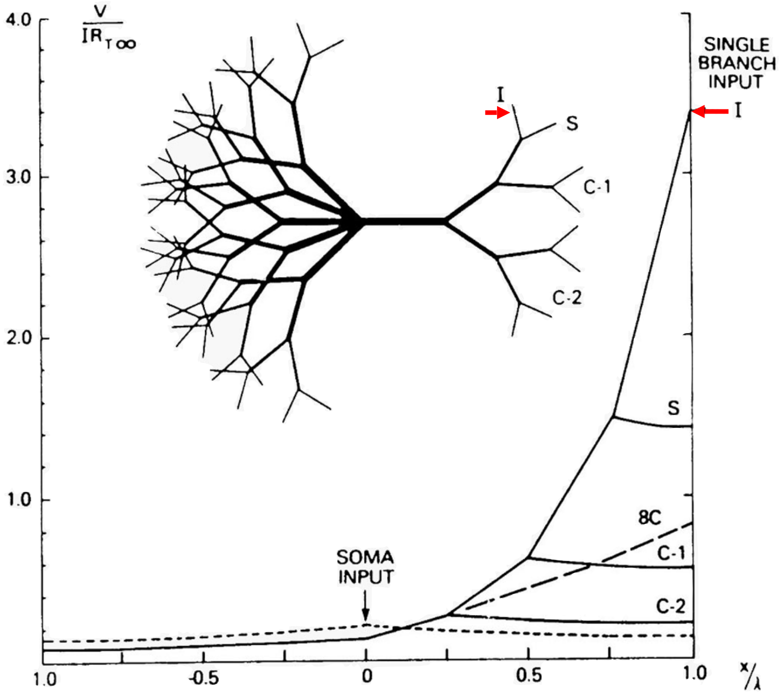
$$k \;=\; -\frac{r_m}{\Delta x}\ \frac{i_0}{2\pi a} \qquad k \;=\; -r_m I_0$$

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



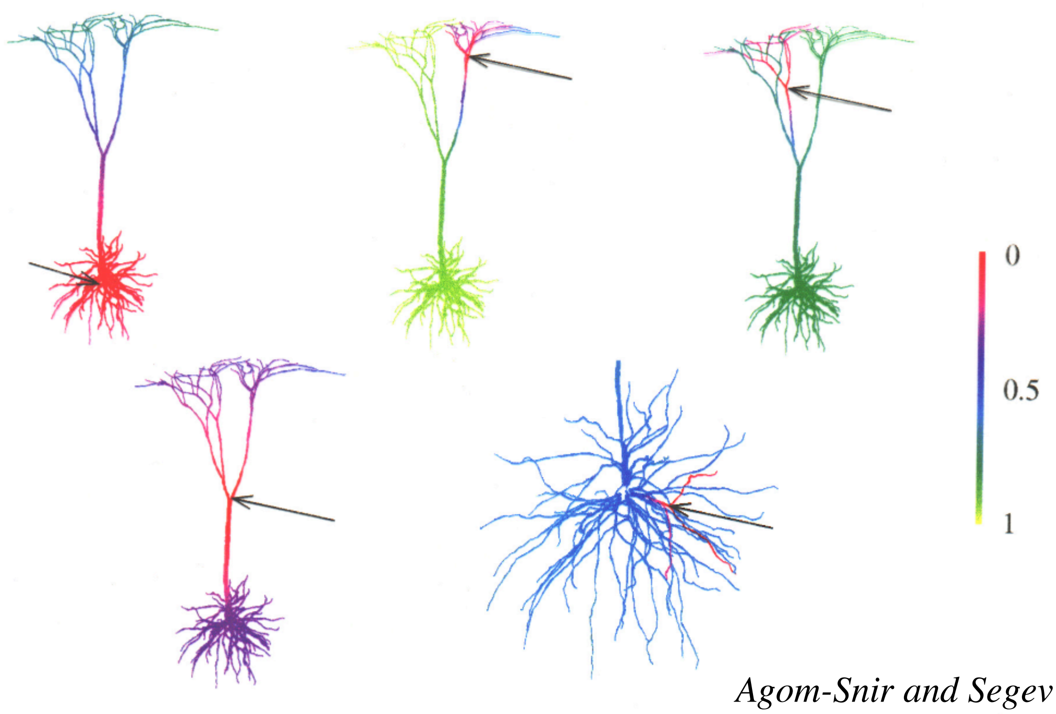



Steep and asymmetrical voltage attenuation
(from dendrites to the soma; synaptic *territories*




Rall & Rinzel, 1973

**Dendritic "functional subunits" ("synaptic territory")**




*Agom-Snir and Segev*

## Sinusoidal Regime - AC regime semi-infinite cable…

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

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

Fourier transform: *time* “disappears”…

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

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

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

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

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

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

## 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*

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

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

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

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

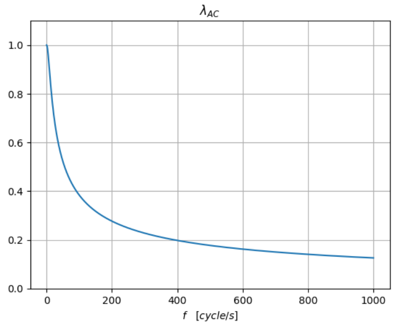
$$cos(0.5 \arctan k) = \pm \sqrt{\frac{1+\frac{1}{\sqrt{1+k^2}}}{2}}$$

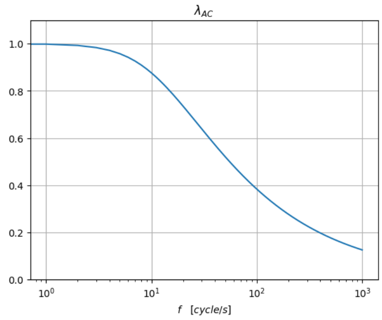
$$W(x,\omega) = R_\infty \; I_0(\omega) \; M \; e^{j\Phi} \qquad M = M(x,\omega) = ?$$

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

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

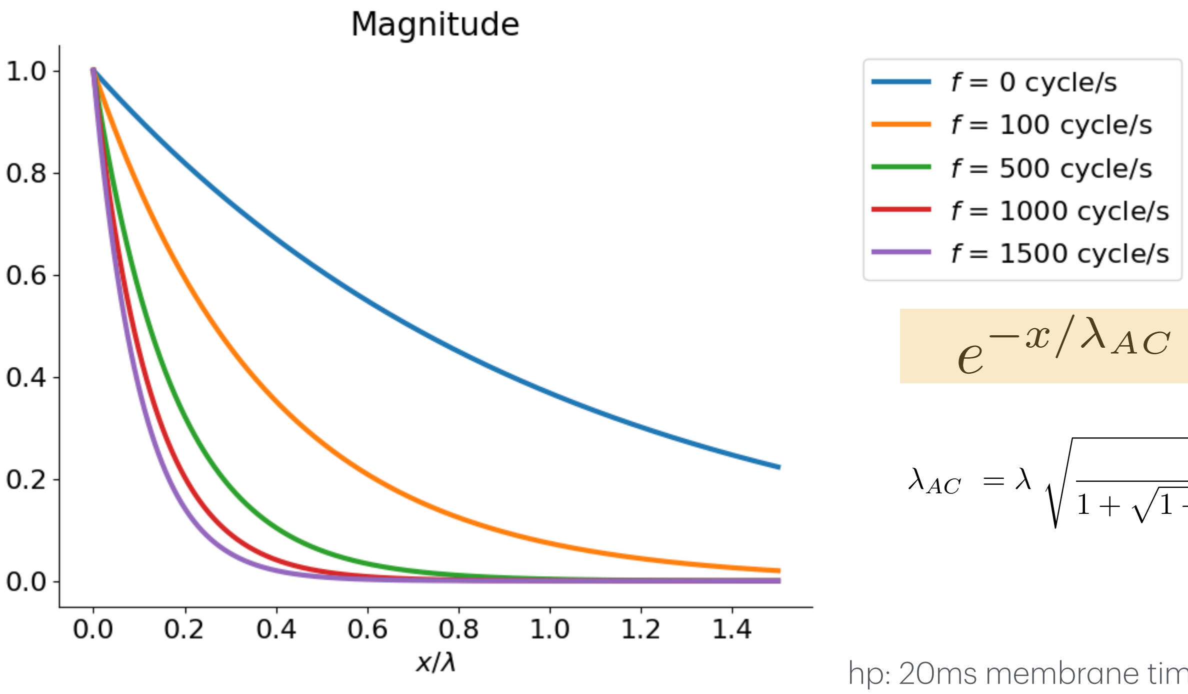
$$e^{-x/\lambda_{AC}} \qquad \lambda_{AC} = \frac{1}{Acos(\phi)} = \lambda\sqrt{\frac{2}{1+\sqrt{1+(2\pi f)^2\tau_m^2}}}$$




hp: 20ms membrane time constant

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



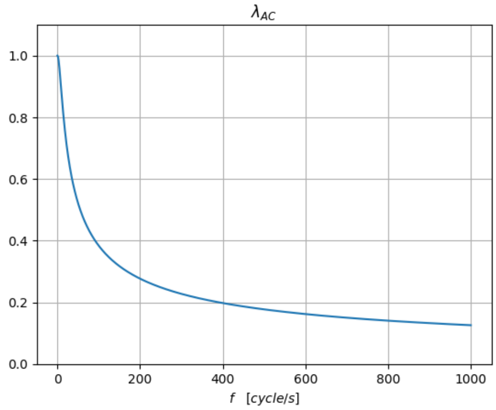

$$e^{-x/\lambda_{AC}}$$

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

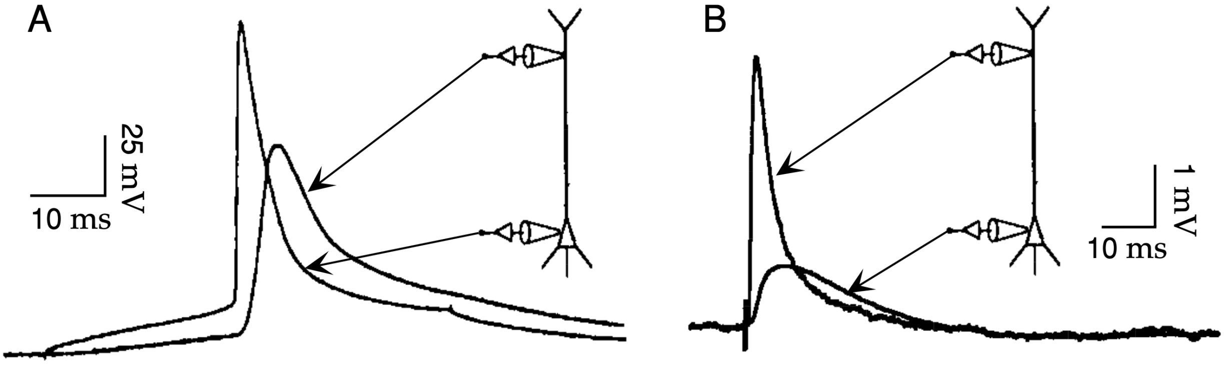
hp: 20ms membrane time constant

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

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




# Back-propagating AP
# Forward propagating EPSPs

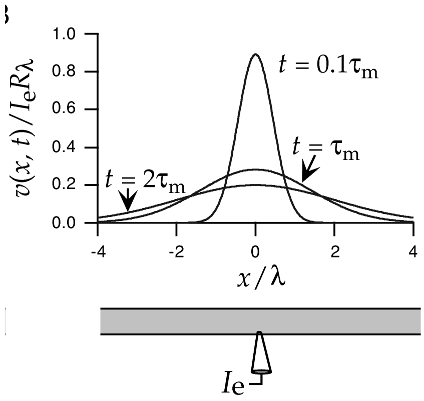



Stuart & Sakmann, 1994

Stuart & Sprouston, 1998

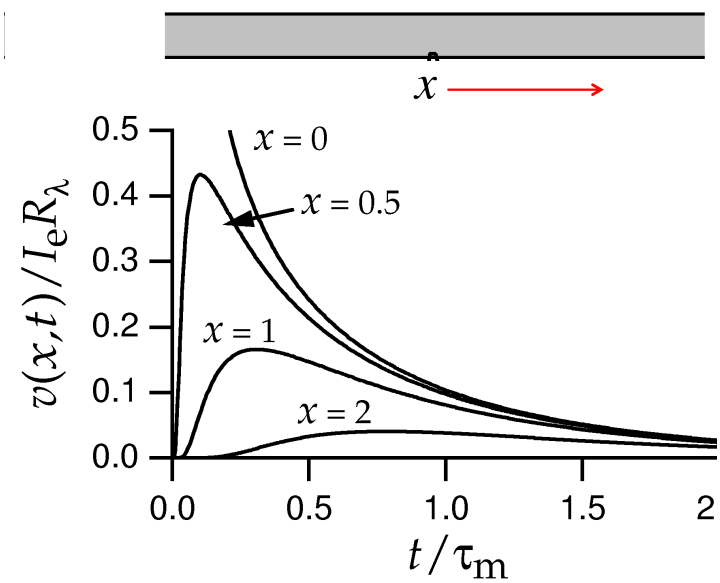
# Transient synapses

$$V(x,t) = \sum_{i=0}^{\infty} C_i e^{-t/\tau_i}$$



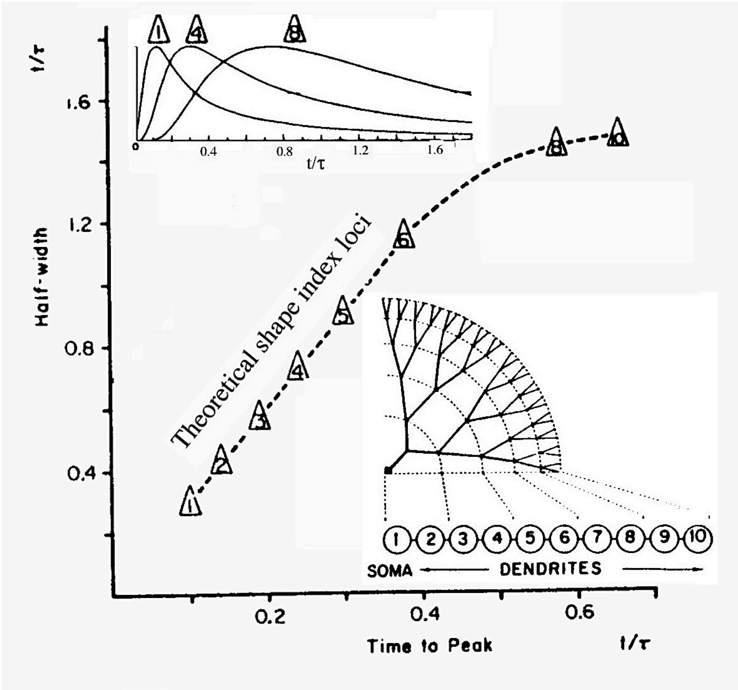

# Transient synapse

*(attenuation, shape change, delay)*

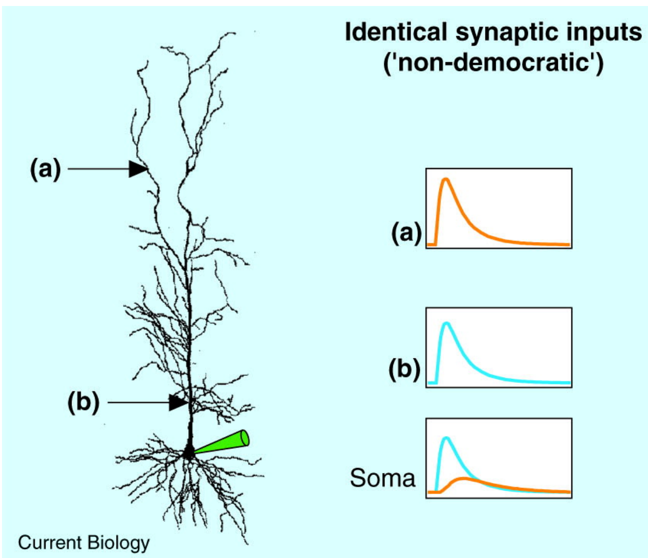


**Experimental predictions**

**distal synapses are broader and delayed**

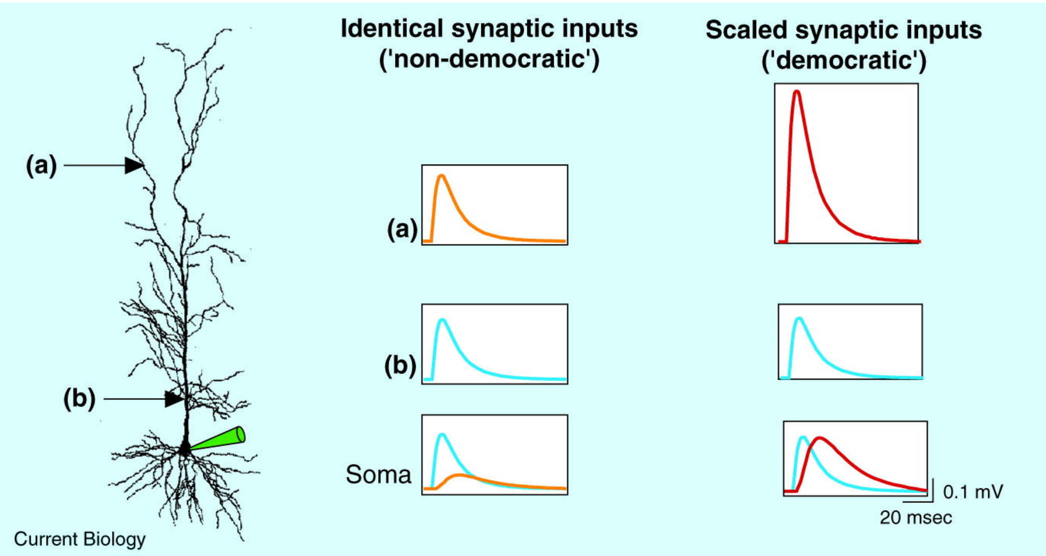


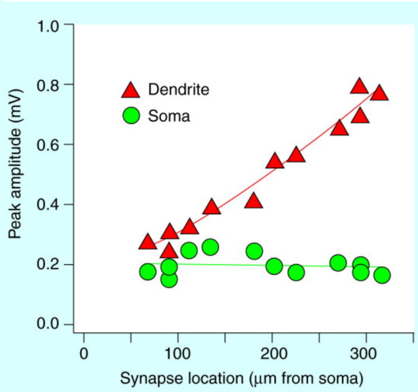

## Synaptic potentials attenuate from the origin towards other regions of the dendrites/neuron




Häusser, 2001

# Dendritic “democracy” (in CA1 pyramidal neurons)




CA1 pyramidal neuron

Häusser, 2001