## Methods

# Mathematical Models: Applied to Cable Theory

Additional Reference:
http://www.scholarpedia.org/article/Cable_theory

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# What we will do today

Understand cable theory equations from top to bottom, as a (very useful) example of how to use basic physics and mathematical tools in theoretical neuroscience

# Cable Theory

The voltage *V(x,t)* along a neural process is:

$$\tau \frac{\partial V(x,t)}{\partial t} = \lambda^2 \frac{\partial^2 V(x,t)}{\partial x^2} - V(x,t)$$ Passive (cable)

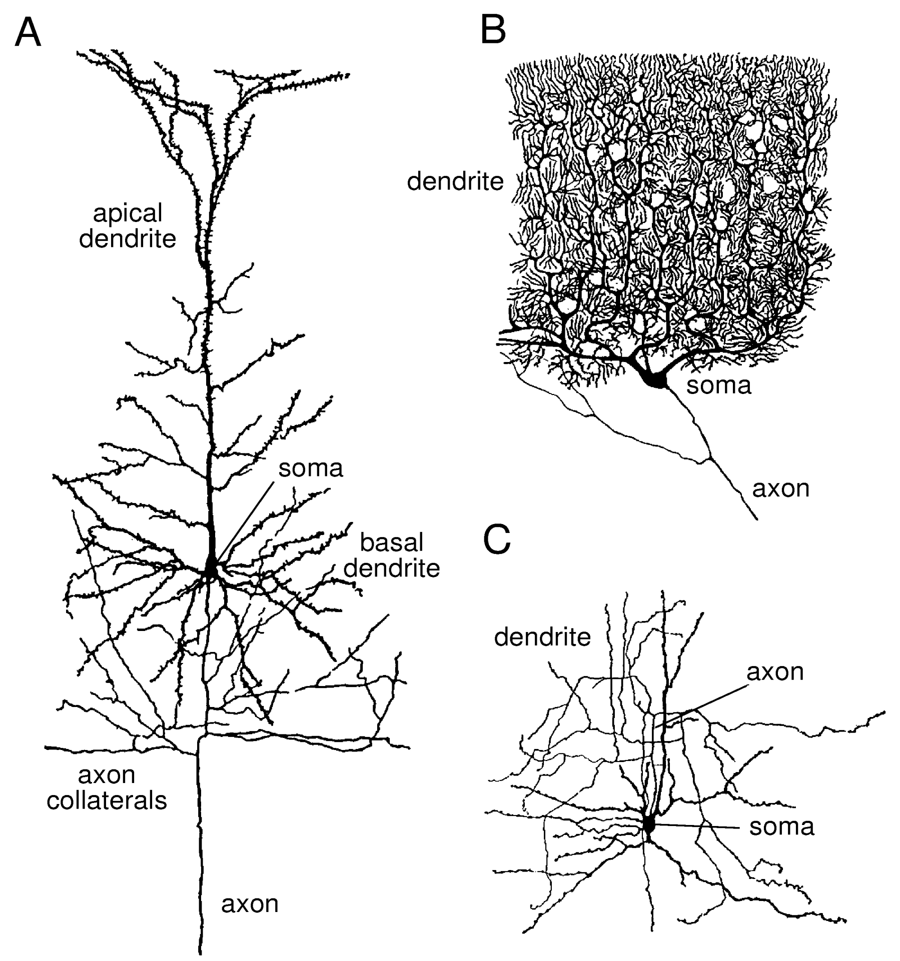
$$+\sum_k G_k(V,t)[V_{act,k} - V(x,t)]$$ Active currents

$$+\sum_i G_i(x,V,t)[V_{syn,i} - V(x,t)]$$ Chem. synapses

$$+\sum_j G_j(x)[V_j(x,t) - V(x,t)]$$ Electr. synapses

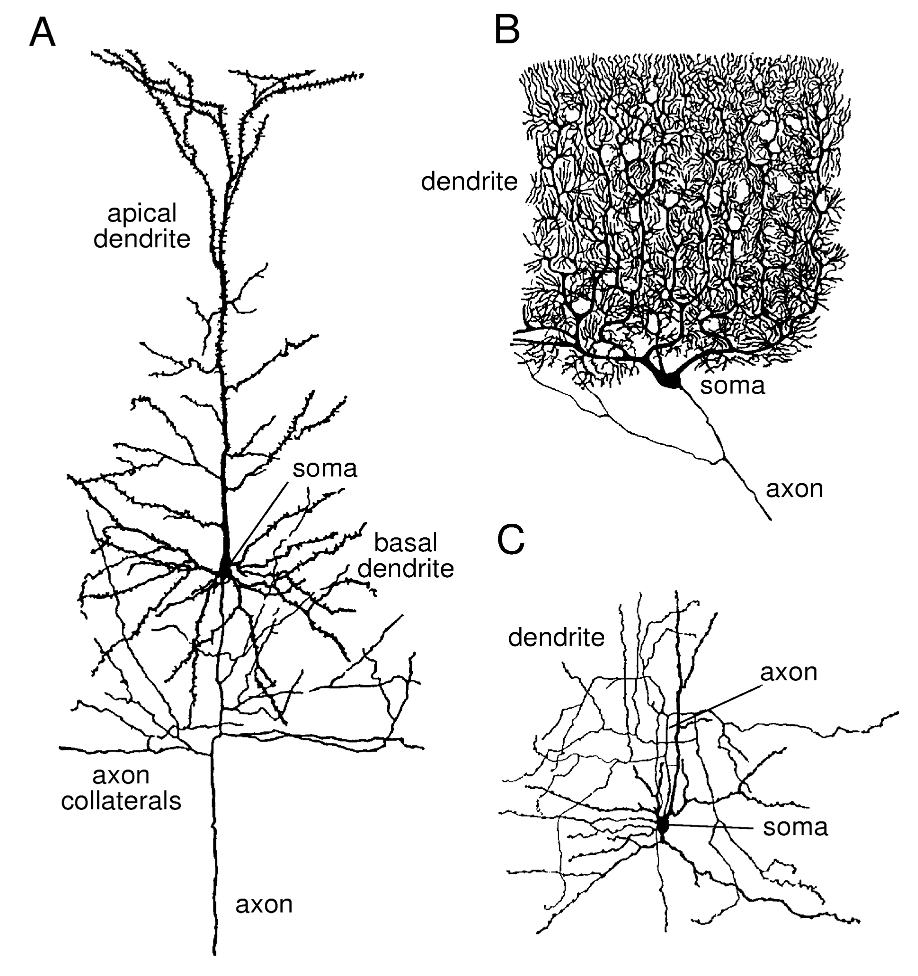
# The Problem: How to understand electrical signals in complex neuronal geometries

Anatomy

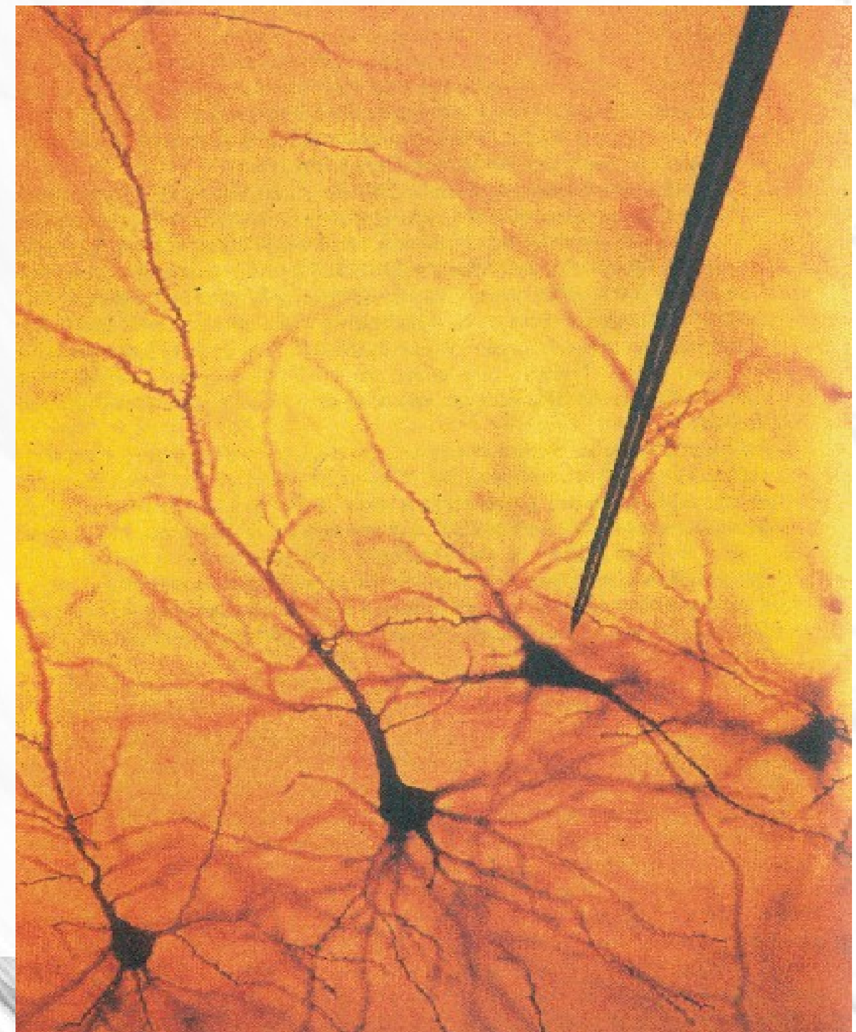


# The Problem:
# How to understand electrical signals in complex neuronal geometries

Anatomy

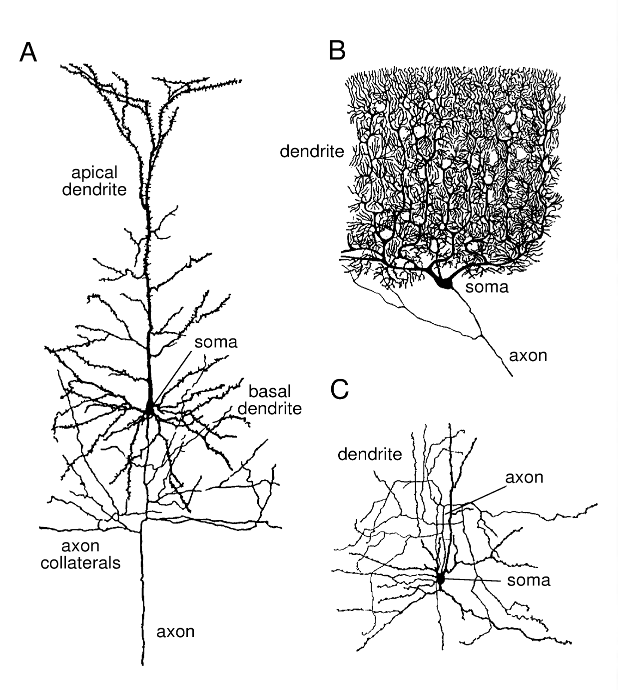



Physiology

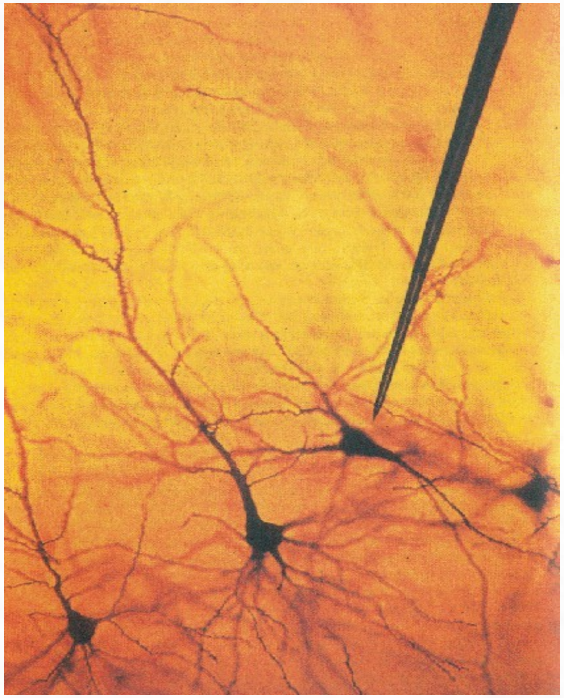


# The Problem:
# How to understand electrical signals in complex neuronal geometries

**Anatomy**




**Physiology**



Neither is sufficient to understand the electrical signalling within the cell.
Physics and Modeling to the rescue!

# Currents in Dendrites

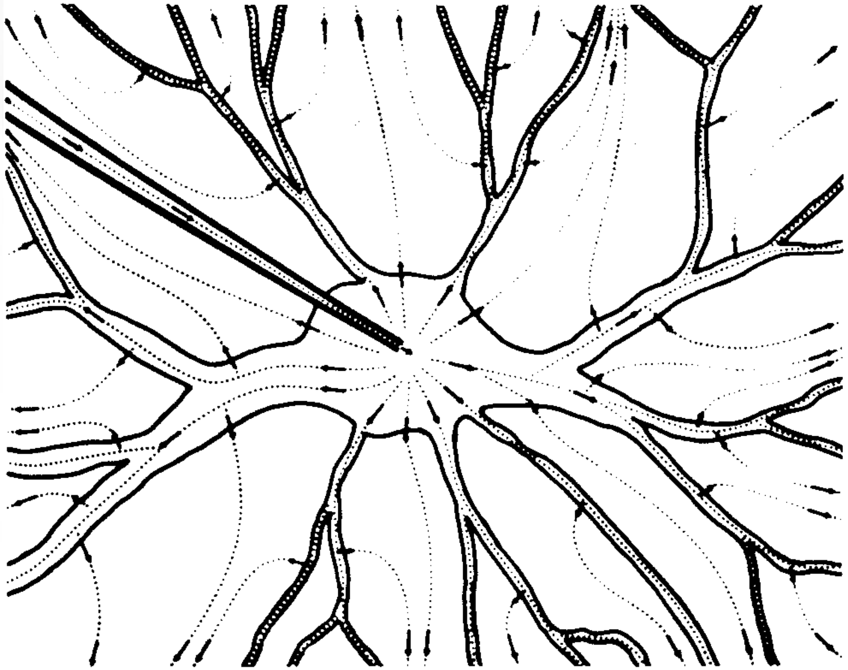


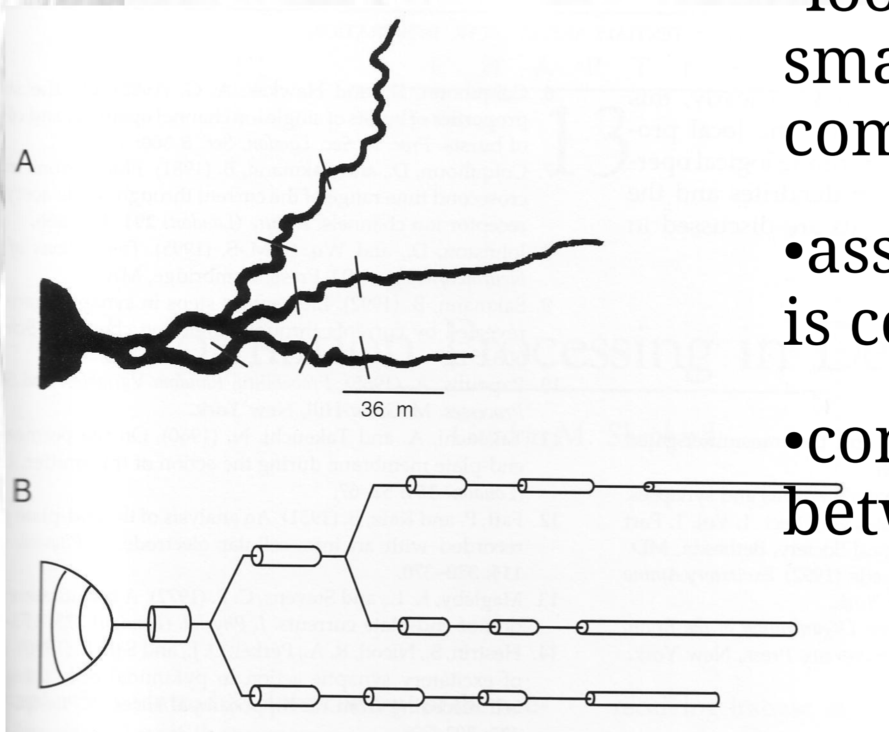
FIG. 2. Flow of electric current from a microelectrode whose tip penetrates the cell body (soma) of a neuron. Full extent of dendrites is not shown. External electrode to which the current flows is at a distance far beyond the limits of this diagram. [From Rall (139).]

- 3-dimensional complex current flow

# One Law, One Fact, and One Approximation that we will use

- Conservation of charge: atoms/ions and electrons can be moved but not created or destroyed
- Cell membrane (a phospho-lipid bilayer) is a relatively poor conductor (but not an insulator!) compared to cytoplasm and extracellular medium
- Neglect voltage differences *across* dendrite (or axon)

# Compartmentalization




**Dendritic Tree**

•look at one piece at a time (remember small current flow across membrane compared to along dendrite!)

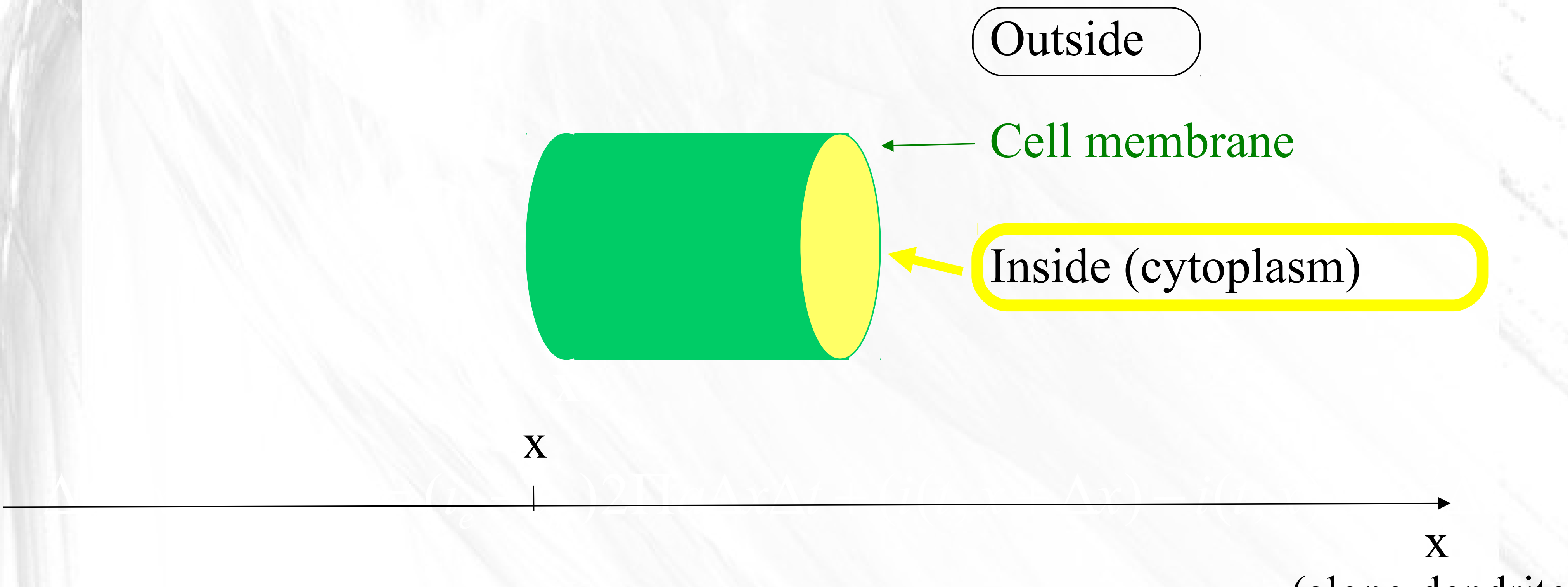
•assume voltage *within* each piece is constant

•compute currents in each piece and between neighboring pieces

NB: Subdividing the dendrite into finite-length segments is the basis for 'compartmental modeling' (solving ODEs numerically). In the following, we derive PDEs by subdividing the dendrite into pieces of length $\Delta x$ and consider the limit $\Delta x \rightarrow 0$

# The fundamental element

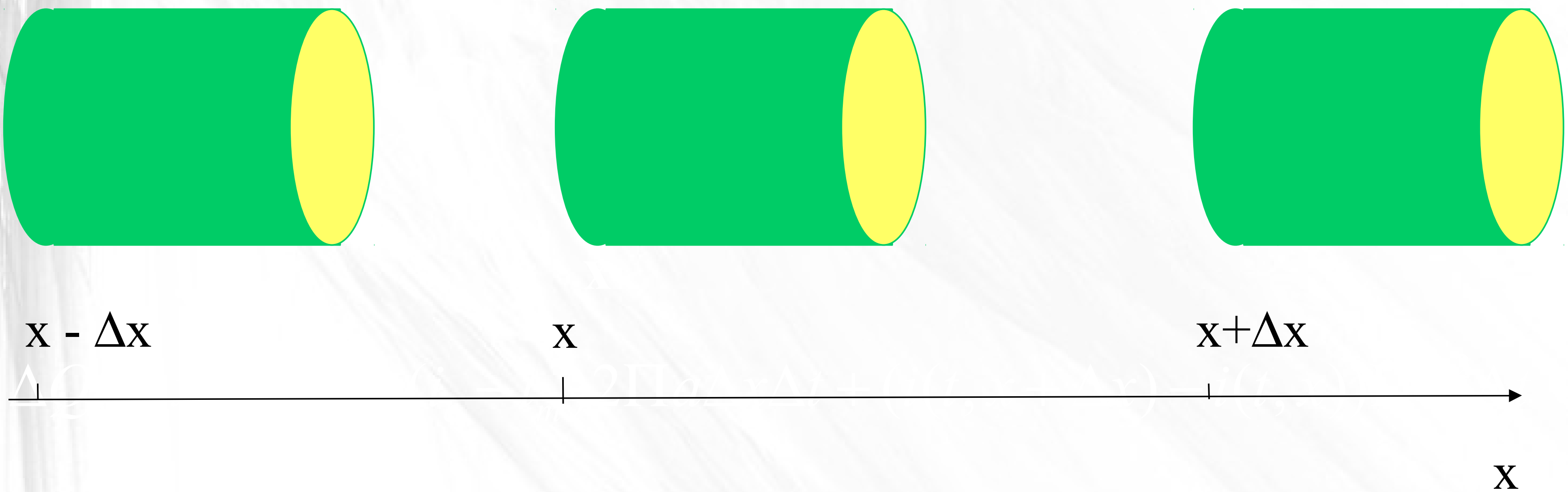
## A piece of dendrite at distance x from soma




Important:
Voltage is about the same everywhere in this element:
- Across the dendrite: this is our approximation!
- Along the dendrite: true if we make the element short enough!

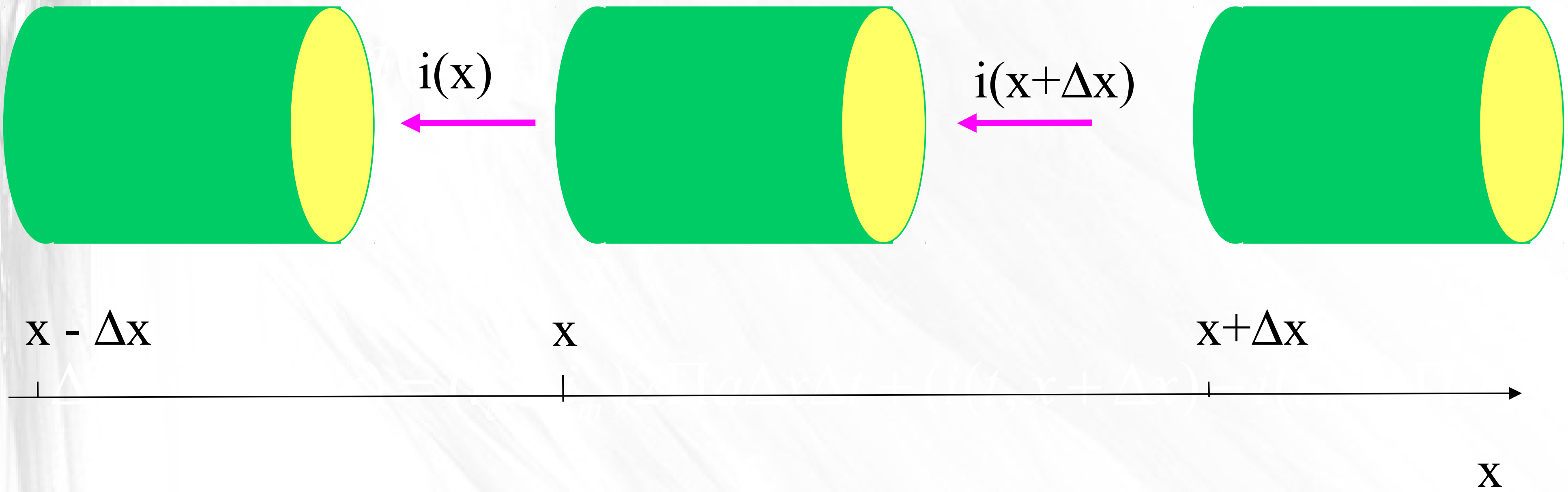
# The fundamental element

... and its two neighbors, at (x - Δx) and at (x + Δx):



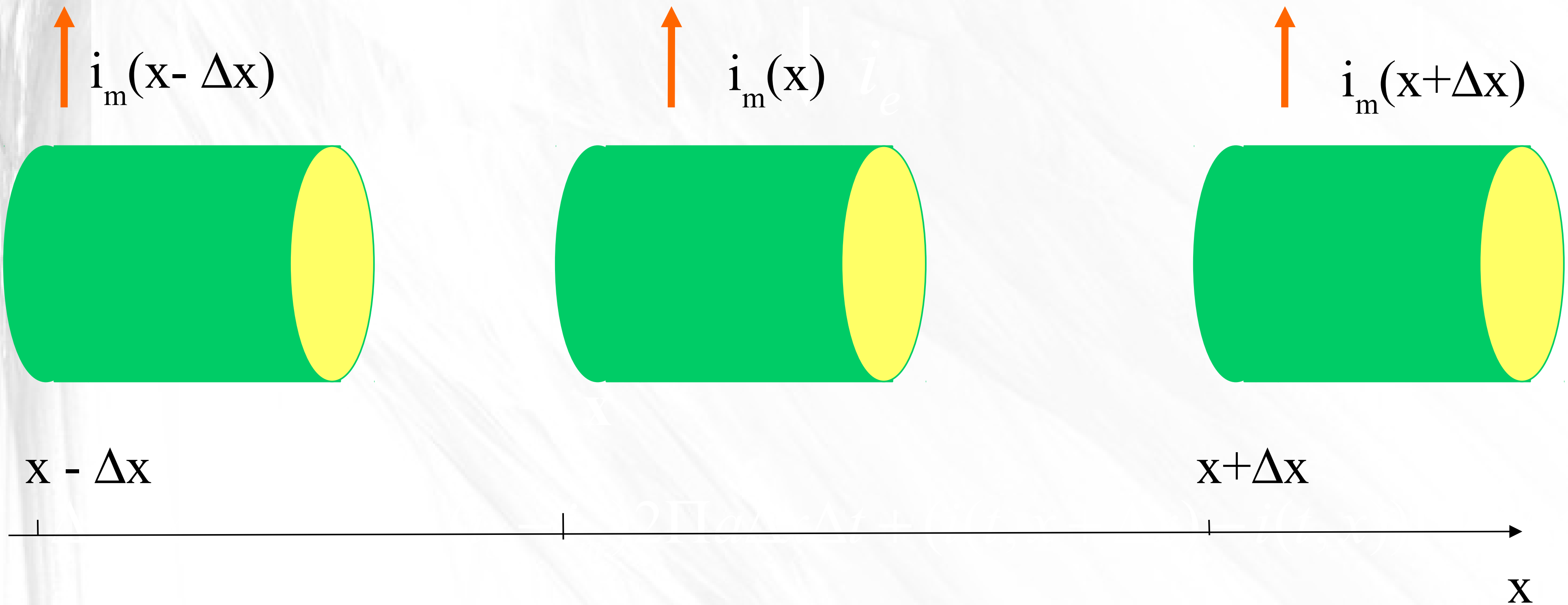
# The fundamental element

There are currents flowing from both neighbors into the center element (in general, these currents are not the same). The current flow *densities* are:

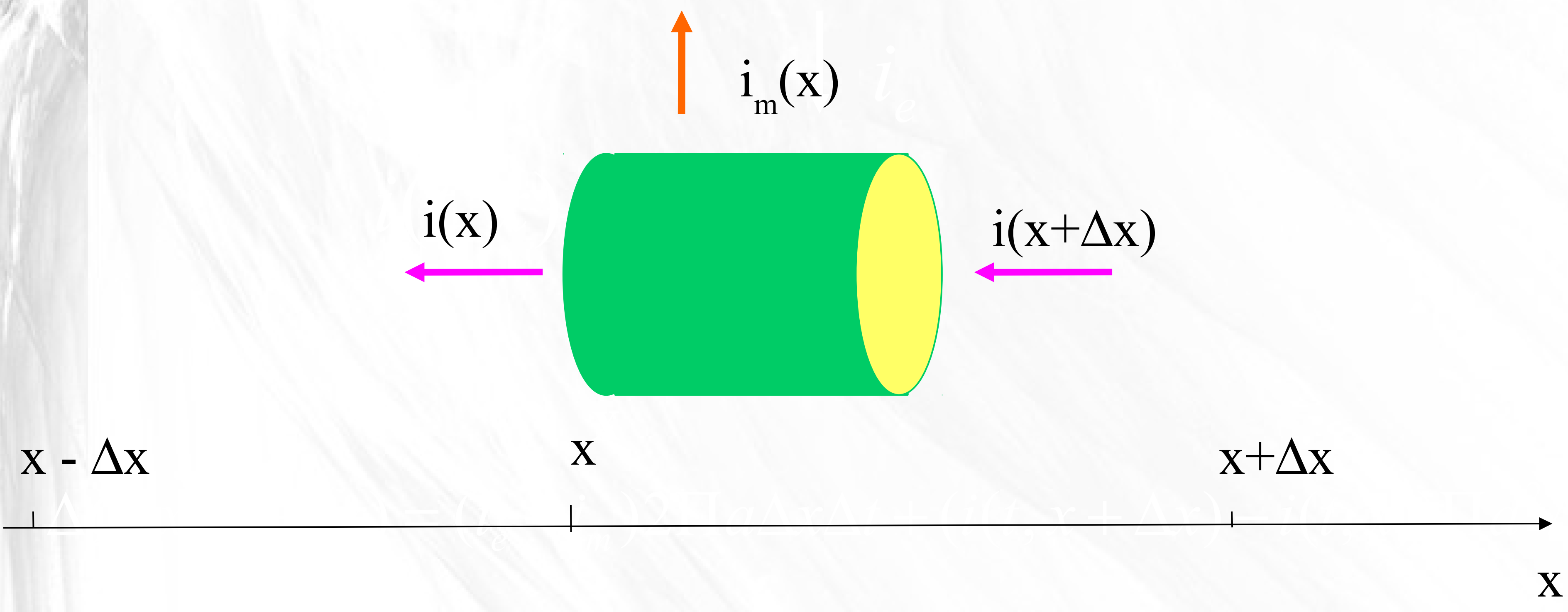


# The fundamental element

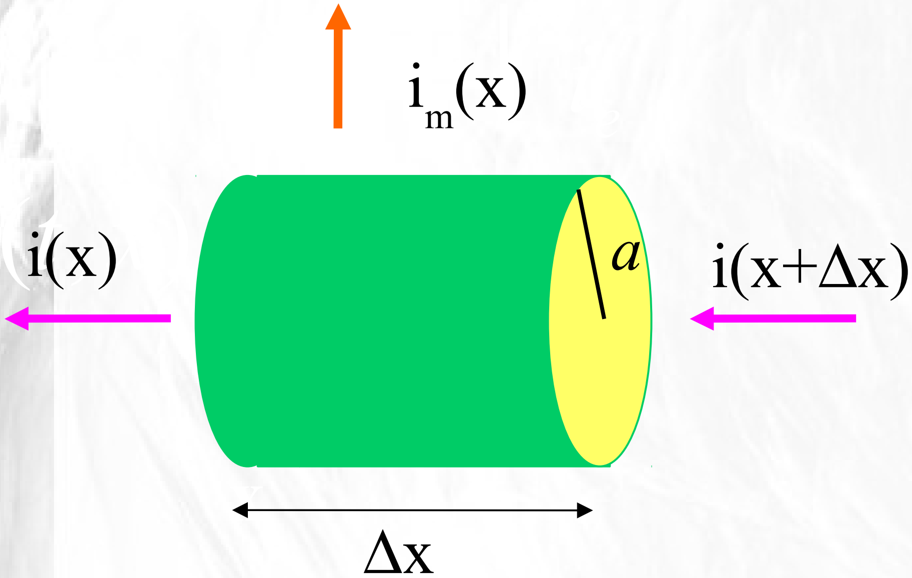
A current flows across the membrane of each element
(again, usually these current densities may be different for each element):



# The fundamental element: All current densities



# Compute all currents from their current densities




**Geometry**

- Radius of cylinder $a$
- Length of cylinder $\Delta x$
- Cross section surface $\pi a^2$
- Exterior surface $2\pi a \Delta x$

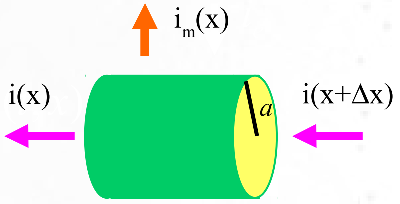
**Currents**

*(Convention: All incoming currents are counted positive)*

- From $x+\Delta x$ $\pi a^2 i(x+\Delta x,t)$
- From $x - \Delta x$ $-\pi a^2 i(x,t)$ (sign!)
- Across membrane $-2\pi a \Delta x\, i_m(V,x,t)$ (sign!)

- Total current: $I(x,t)=-2\pi a \Delta x\, i_m(V,x,t)+\pi a^2\{i(x+\Delta x,t)- i(x,t)\}$

# Conservation of Charge




Change in charge over time period $\Delta t$ is the sum of all currents times $\Delta t$:

$$\Delta Q(x,x+\Delta x,t)=I(x,t)\ \Delta t$$

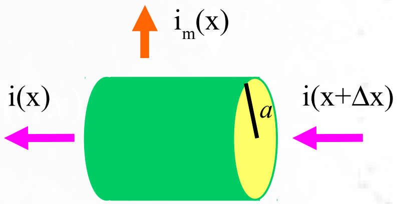
Divide by $\Delta t$:

$$\Delta Q(x,x+\Delta x,t)/\Delta t = I(x,t)$$

Change in charge leads to proportional change in voltage:

$\Delta V$ prop. to $\Delta Q$: $\Delta Q = C_m\ \Delta V$ with $C_m$ =“Capacitance”

# Conservation of Charge




Copying equation from previous page:

$\Delta Q(x,x+\Delta x,t)/\Delta t = C_m \, \Delta V(x,t)/\Delta t = I(x,t)$

$= -2\pi \, a \, \Delta x \, i_m(V,x,t) + \pi \, a^2\{i(x+\Delta x,t) - i(x,t)\}$

In the limit when Δt goes to zero:

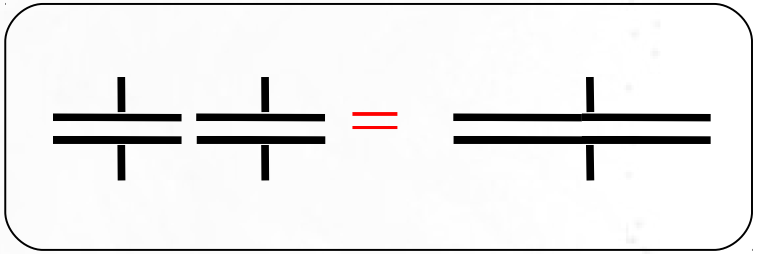
$$C_m \frac{\partial V(x,t)}{\partial t} = \mathbf{I(V,x,t)} =$$

"*Partial* derivative with respect to t"

$$-2\pi a \Delta x i_m(V,x,t) + \pi a^2[i(x+\Delta x,t) - i(x,t)]$$

# Capacitance

Capacitance is proportional to area:



$C_m = 2\pi\, a\, \Delta x\, c_m$

$c_m$ = capacitance per area

Use to replace $C_m$:

$$2\pi a \Delta x\, c_m \frac{\partial V(x,t)}{\partial t} = \mathbf{I(V,x,t)} =$$

$$-2\pi a \Delta x\, i_m(V,x,t) + \pi a^2 [i(x+\Delta x,t) - i(x,t)]$$

# Spatial Derivative

Divide both sides by (2π a Δx):

$$c_m \frac{\partial V(x,t)}{\partial t} = -i_m(V,x,t) + \frac{a[i(x+\Delta x,t) - i(x,t)]}{2\Delta x}$$

Pull out a/2 on right hand side:

$$c_m \frac{\partial V(x,t)}{\partial t} = -i_m(V,x,t) + \frac{a}{2}\frac{i(x+\Delta x,t) - i(x,t)}{\Delta x}$$

RHS becomes spatial derivative for Δx towards zero:

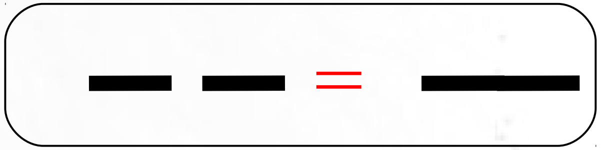
$$c_m \frac{\partial V(x,t)}{\partial t} = -i_m(V,x,t) + \frac{a}{2}\frac{\partial i(x)}{\partial x}$$

“*Partial* derivative
with respect to space”

# Current Along Dendrite

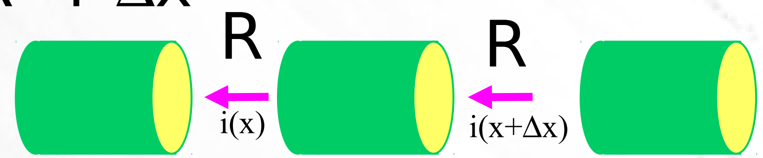
Ohm's law: Current is proportional to voltage difference:

V=R I



R=resistance, proportional to length,

with material-dependent constant r: R=r Δx




Since I=V/R, we get

i(x,t)=

$$\frac{V(x,t)-V(x-\Delta x,t)}{R}=\frac{V(x,t)-V(x-\Delta x,t)}{r\,\Delta x}=\frac{1}{r}\,\frac{V(x,t)-V(x-\Delta x,t)}{\Delta x}$$

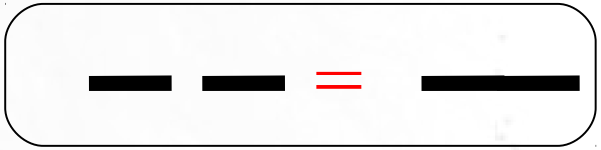
Again, in the limit Δx towards zero,

$$i(V,x,t)=\frac{1}{r}\,\frac{\partial V(x,t)}{\partial x}$$

# Current Along Dendrite

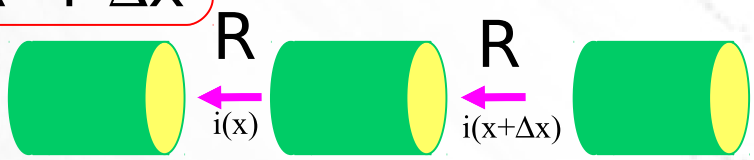
Ohm's law: Current is proportional to voltage difference:

U=R I



R=resistance, proportional to length,

with material-dependent constant r: $\boxed{R = r\,\Delta x}$




Since I=U/R, we get

i(x,t)=

$$\frac{V(x+\Delta x,t)-V(x,t)}{R}=\frac{V(x+\Delta x,t)-V(x,t)}{r\,\Delta x}=\frac{1}{r}\,\frac{V(x+\Delta x,t)-V(x,t)}{\Delta x}$$

Again, in the limit Δx towards zero,

$$i(V,x,t)=\frac{1}{r}\,\frac{\partial V(x,t)}{\partial x}$$

Recall:

# Final Result

$$c_m \frac{\partial V(x,t)}{\partial t} = -i_m(V,x,t) + \frac{a}{2}\frac{\partial i(V,x,t)}{\partial x}$$

Use formula for i(x,t) from previous slide:

$$i(V,x,t) = \frac{1}{r}\frac{\partial V(x,t)}{\partial x}$$

to get:

$$\boxed{c_m \frac{\partial V(x,t)}{\partial t} = -i_m(V,x,t) + \frac{a}{2r}\frac{\partial^2 V(x,t)}{\partial x^2}}$$

“Partial differential equation for V(x,t)”

Only depends on membrane currents $i_m$

# Linear Cable Theory

Assume (!) that transmembrane current is linear:

$i_m(V,x,t) = V(x,t)/r_m$

with $r_m$ constant (i.e., constant "leakage resistance").

(We also set resting potential to zero). Then,

$$c_m \frac{\partial V(x,t)}{\partial t} = -V(x,t)/r_m + \frac{a}{2r} \frac{\partial^2 V(x,t)}{\partial x^2}$$

Only depends on V! Multiply by $r_m$

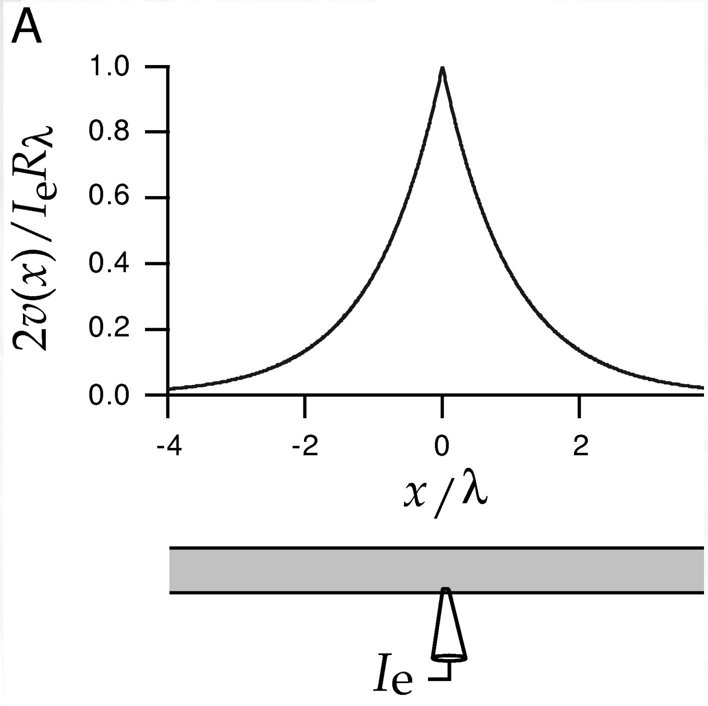
$$r_m c_m \frac{\partial V(x,t)}{\partial t} = -V(x,t) + \frac{a r_m}{2r} \frac{\partial^2 V(x,t)}{\partial x^2}$$

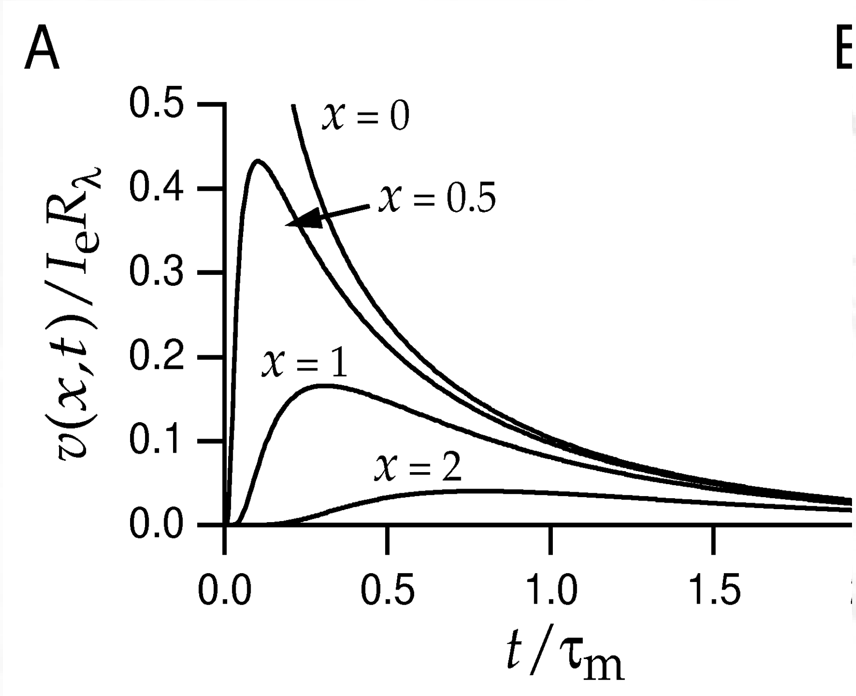
$$\boxed{\tau \frac{\partial V}{\partial t} = -V + \lambda^2 \frac{\partial^2 V}{\partial x^2}}$$

$\tau = r_m \; c_m$ Membrane time constant

$\lambda^2 = r_m a/(2r)$ Membrane space constant

# Physical Interpretation of Membrane Parameters




Inject constant current at point x=0, current decays as exp(-|x|/λ)

Inject charge at x=0, t =0: Current decays as exp(-t/τ)

# Cable Theory

Our result:

$$\tau \frac{\partial V}{\partial t} = -V + \lambda^2 \frac{\partial^2 V}{\partial x^2}$$

Compare with first line of:

$$\tau \frac{\partial V(x,t)}{\partial t} = \lambda^2 \frac{\partial^2 V(x,t)}{\partial x^2} - V(x,t)$$ Passive (cable)

$$+\sum_k G_k(V,t)[V_{act,k} - V(x,t)]$$ Active currents

$$+\sum_i G_i(x,V,t)[V_{syn,i} - V(x,t)]$$ Chem. synapses

$$+\sum_j G_j(x)[V_j(x,t) - V(x,t)]$$ Electr. synapses

# What about the other lines?

Go back to our 'Main Result" for general (non-linear) membrane currents:

$$c_m \frac{\partial V(x,t)}{\partial t} = -i_m(x,t) + \frac{a}{2r}\frac{\partial^2 V(x,t)}{\partial x^2}$$

Other terms: additional transmembrane currents (conductance times voltage difference ; note G=1/R), from currents NOT obeying Ohm's 'linear' law:

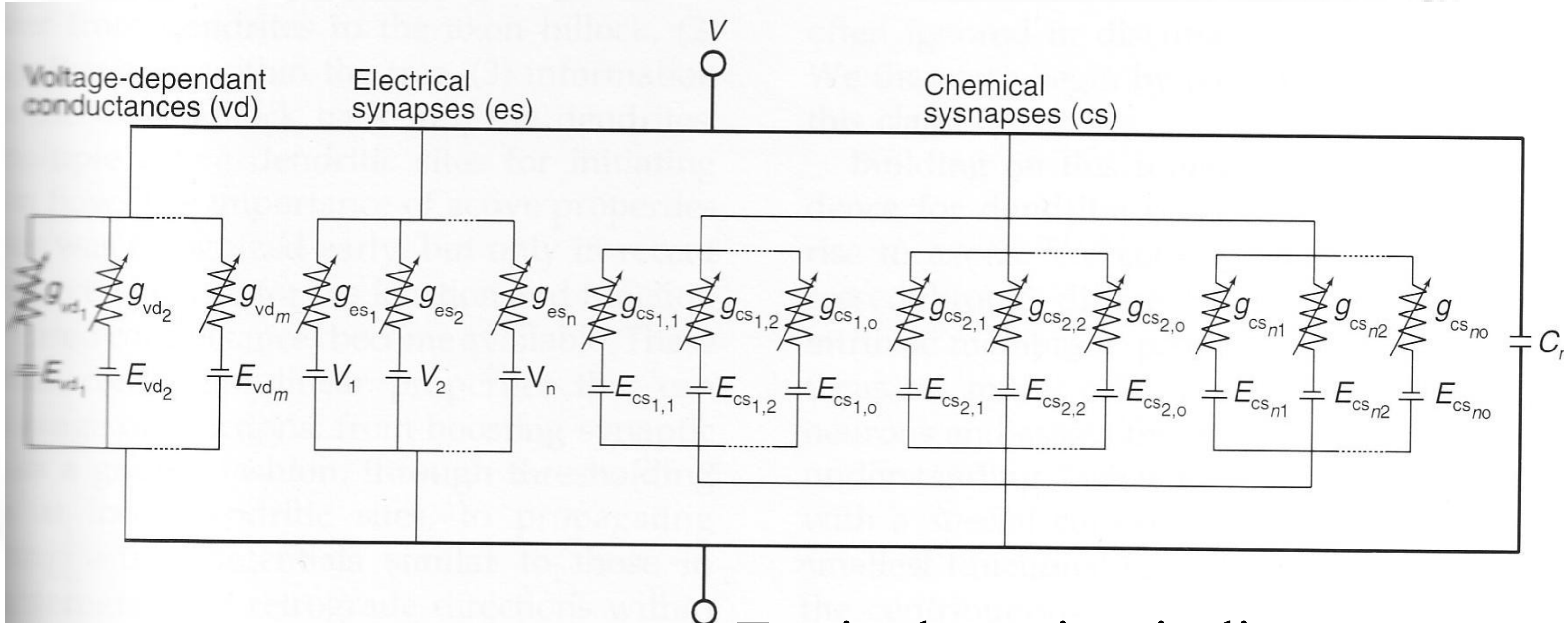
$$\tau \frac{\partial V(x,t)}{\partial t} = \lambda^2 \frac{\partial^2 V(x,t)}{\partial x^2} - V(x,t) \qquad \text{Passive (cable)}$$

$$+\sum_k G_k(V,x,t)[V_{act,k} - V(x,t)] \qquad \text{Active currents (HH, ...)}$$

$$+\sum_i G_i(x,V,t)[V_{syn,i} - V(x,t)] \qquad \text{Chem. synapses}$$

$$+\sum_j G_j(x)[V_j(x,t) - V(x,t)] \qquad \text{Electr. synapses}$$

# Membrane Patch Model with Synapses




Equivalent circuit diagram

NMDA...

$$\sum_i G_i(x,V,t)[V_{syn},i - V(x,t)]$$

$$\sum_j G_j(x)[V_j(x,t) - V(x,t)]$$

$G_i(x,V,t)$, $G_j(x)$: conductances of chem. and elect. synapses

$V_i$: reversal potential of chemical synapse

$V_j$: transmembrane potential of *other* neuron at electrical synapse

# Now add space: Currents in Dendrites

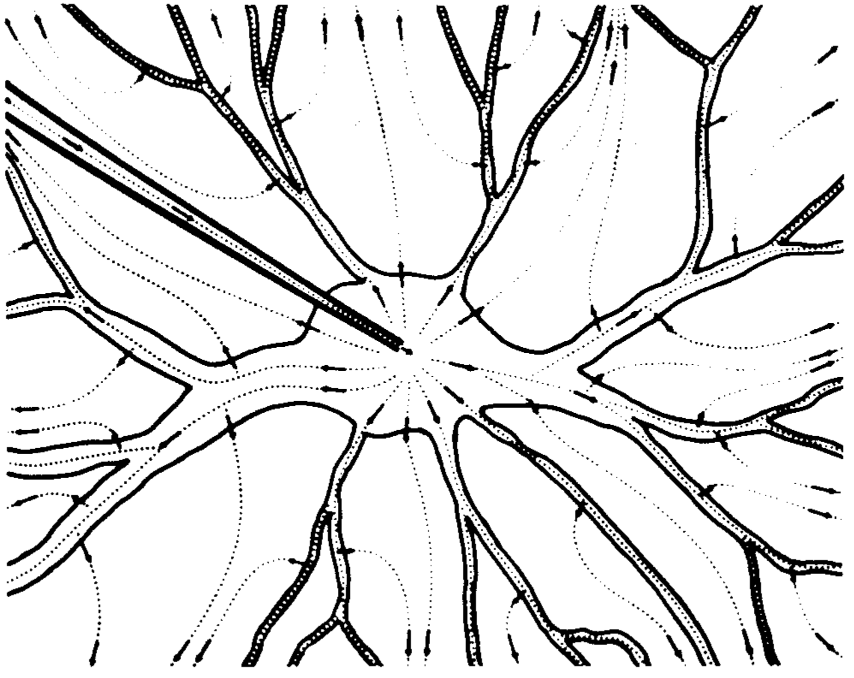
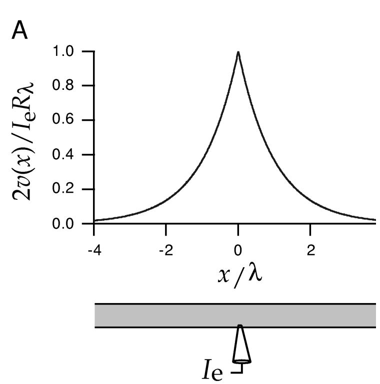


FIG. 2. Flow of electric current from a microelectrode whose tip penetrates the cell body (soma) of a neuron. Full extent of dendrites is not shown. External electrode to which the current flows is at a distance far beyond the limits of this diagram. [From Rall (139).]

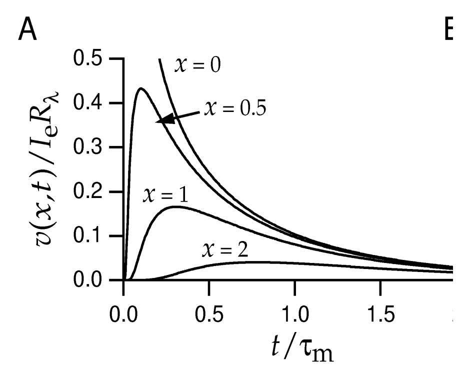
- 3-dimensional complex current flow

# Dendritic Integration

- Dendrites:
  Collect, Combine, Compute
- Divergence and convergence factors:
  - typically 1000s of synapses per neuron
  - Up to 200,000 (cerebellar Purkinje cells)
- How to understand this 'synaptic integration' process quantitatively in complex geometries?
- Combine the insights we have:




Time




Space

# Spatio-temporal summation in dendrites

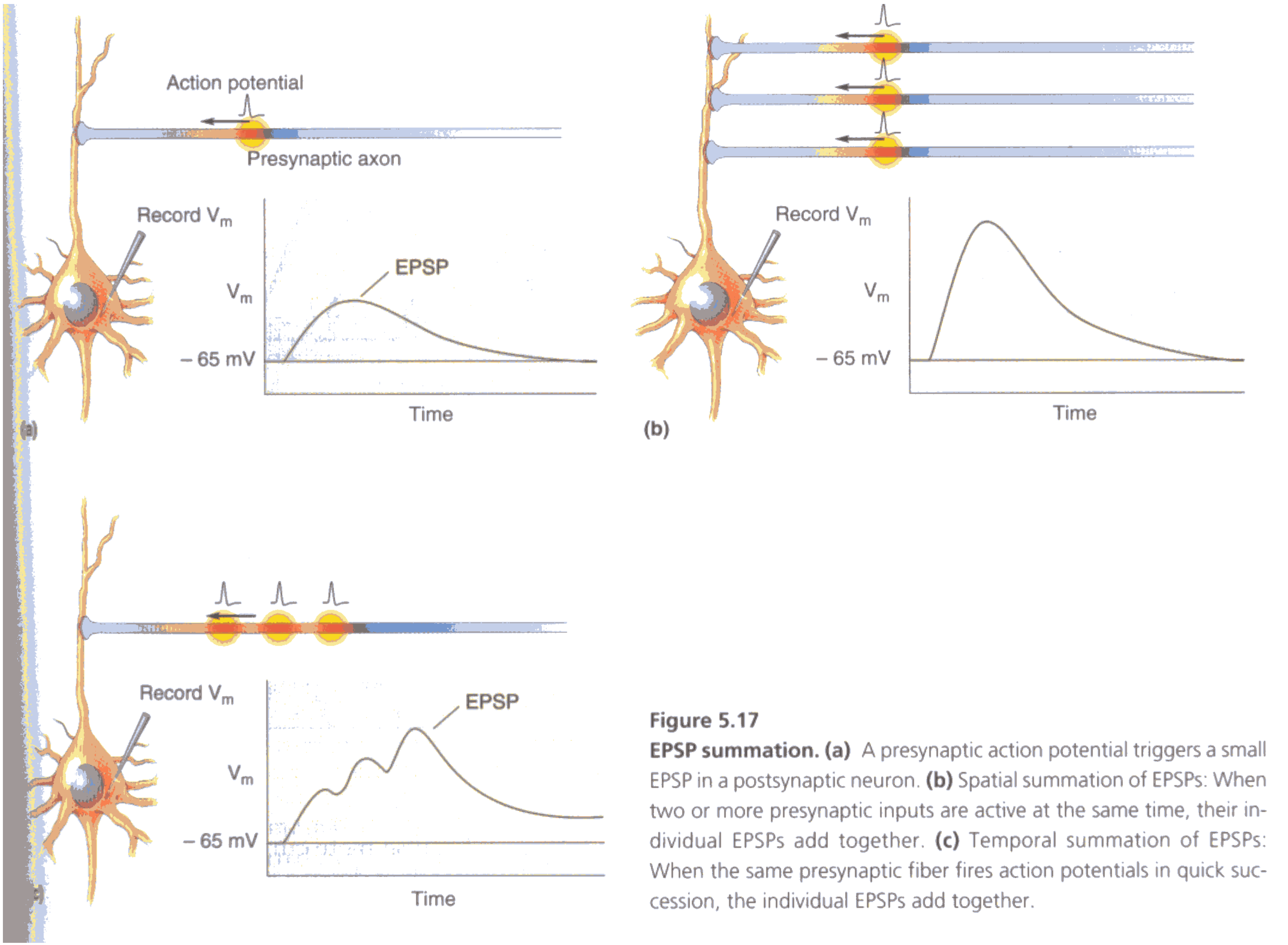
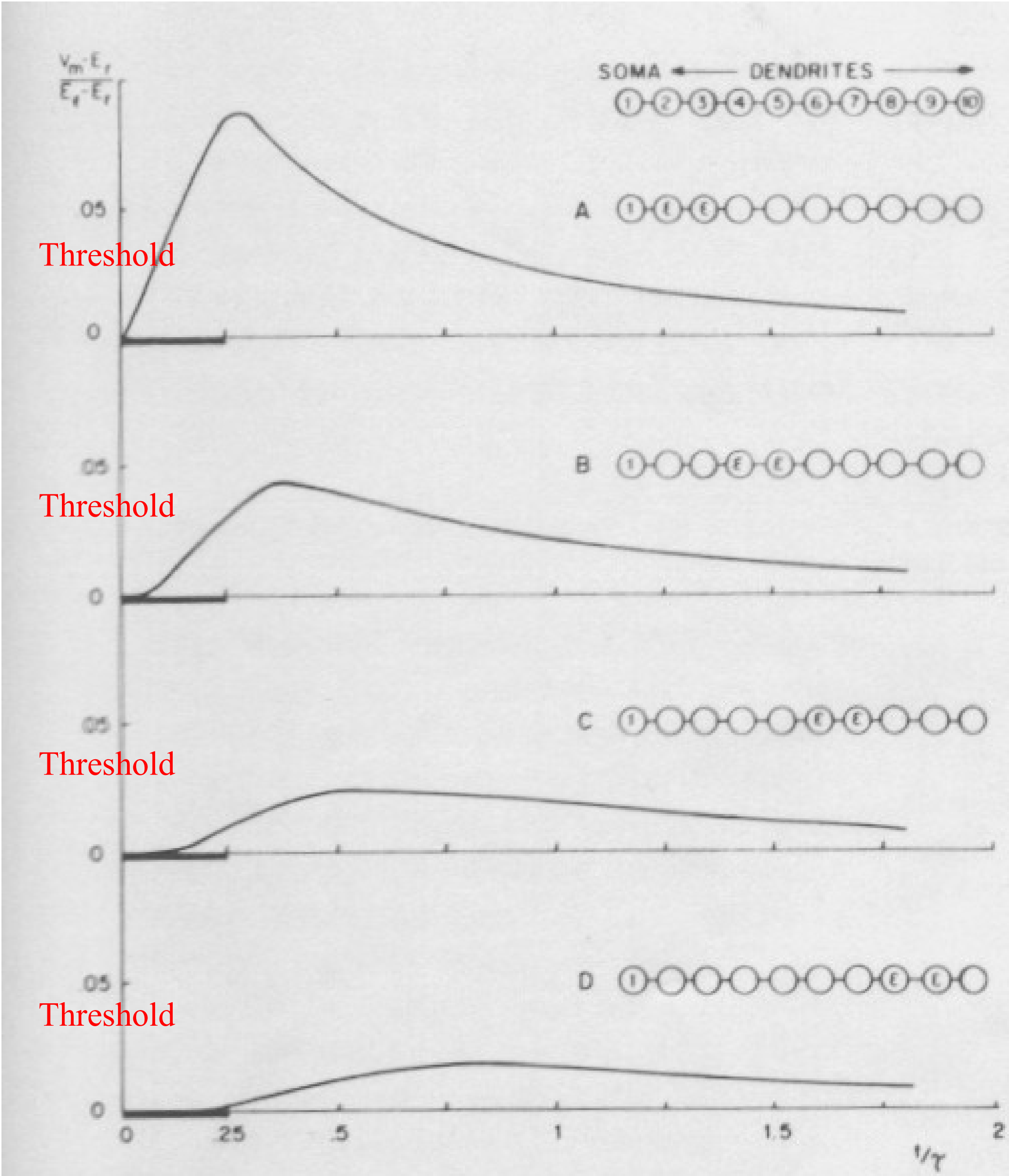



**Figure 5.17**

**EPSP summation. (a)** A presynaptic action potential triggers a small EPSP in a postsynaptic neuron. **(b)** Spatial summation of EPSPs: When two or more presynaptic inputs are active at the same time, their individual EPSPs add together. **(c)** Temporal summation of EPSPs: When the same presynaptic fiber fires action potentials in quick succession, the individual EPSPs add together.

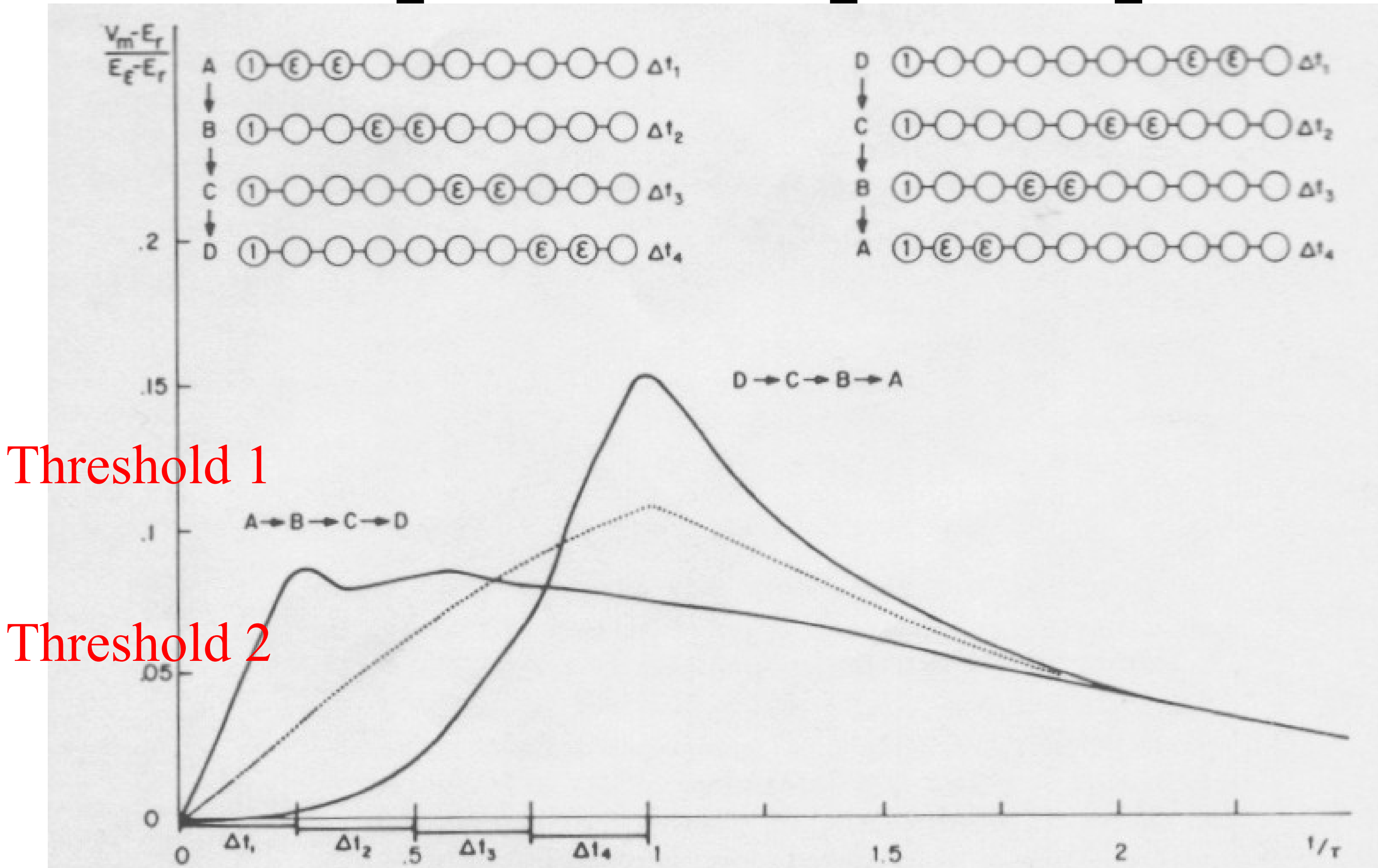
# Influence of synaptic location




Rall, 1963

- Proximal synapses: fast-rising, high, fast decaying V(t)
- Distal synapses: slowly-rising, low, prolonged V(t)
- Different response, depending on threshold
- Can be very different for active membrane!

# Spatiotemporal patterns




- Identical total synaptic input
- Different time course
- Different response dependent on threshold

# Conclusions

- Rigorous, quantitative approaches can be applied to neuroscience
- It *is* possible to understand the math!