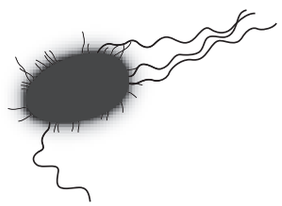
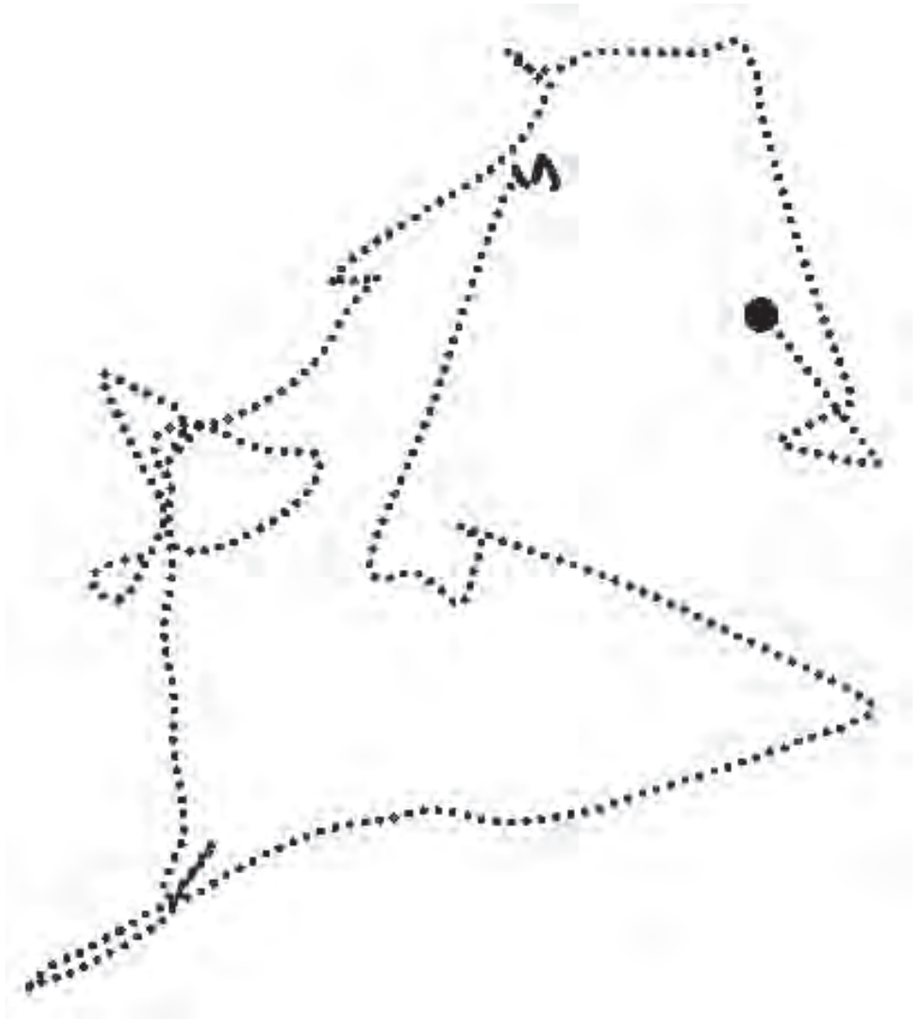
Connecting Neurons to Perform Computation

E coli's biased random walk

E. coli



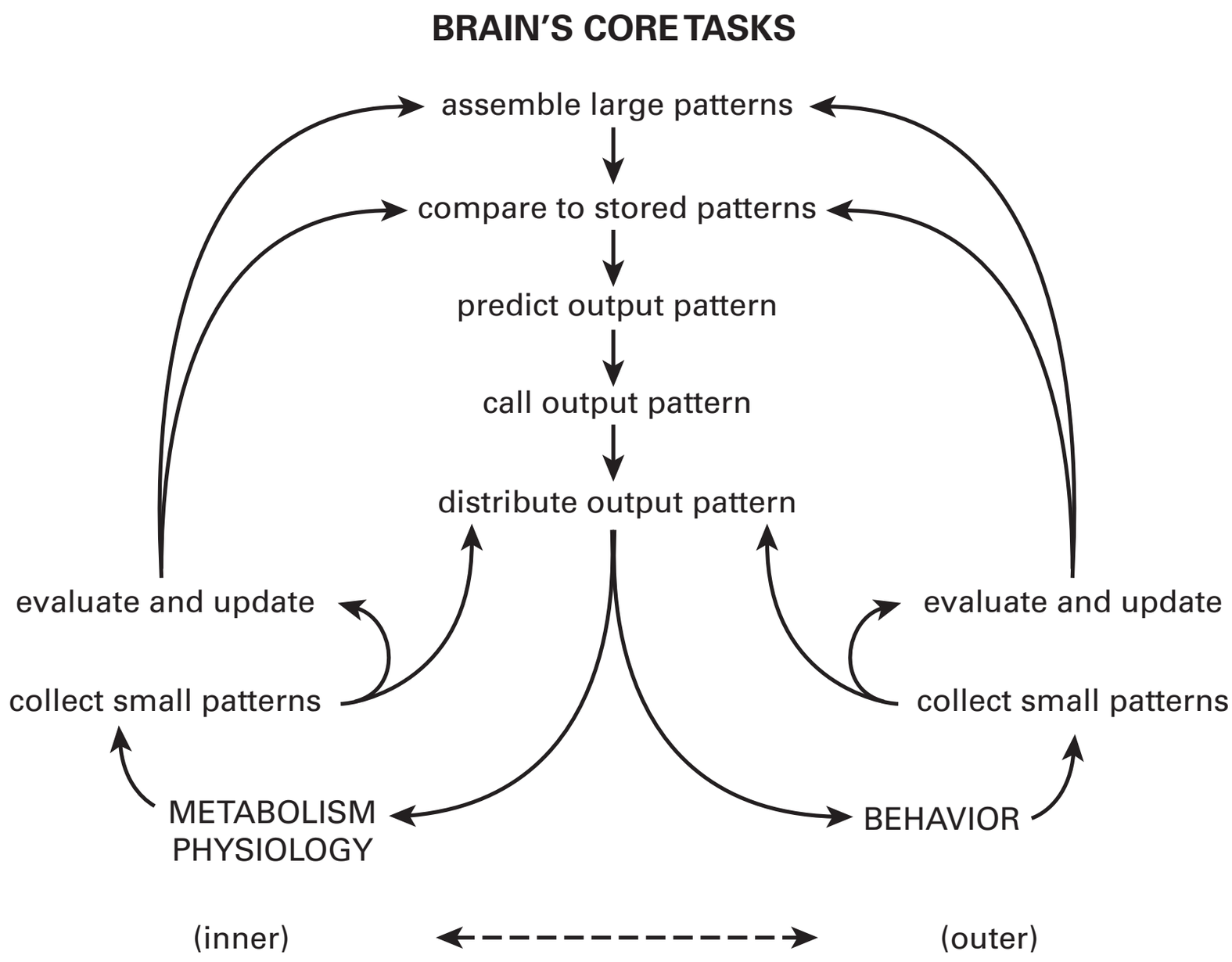


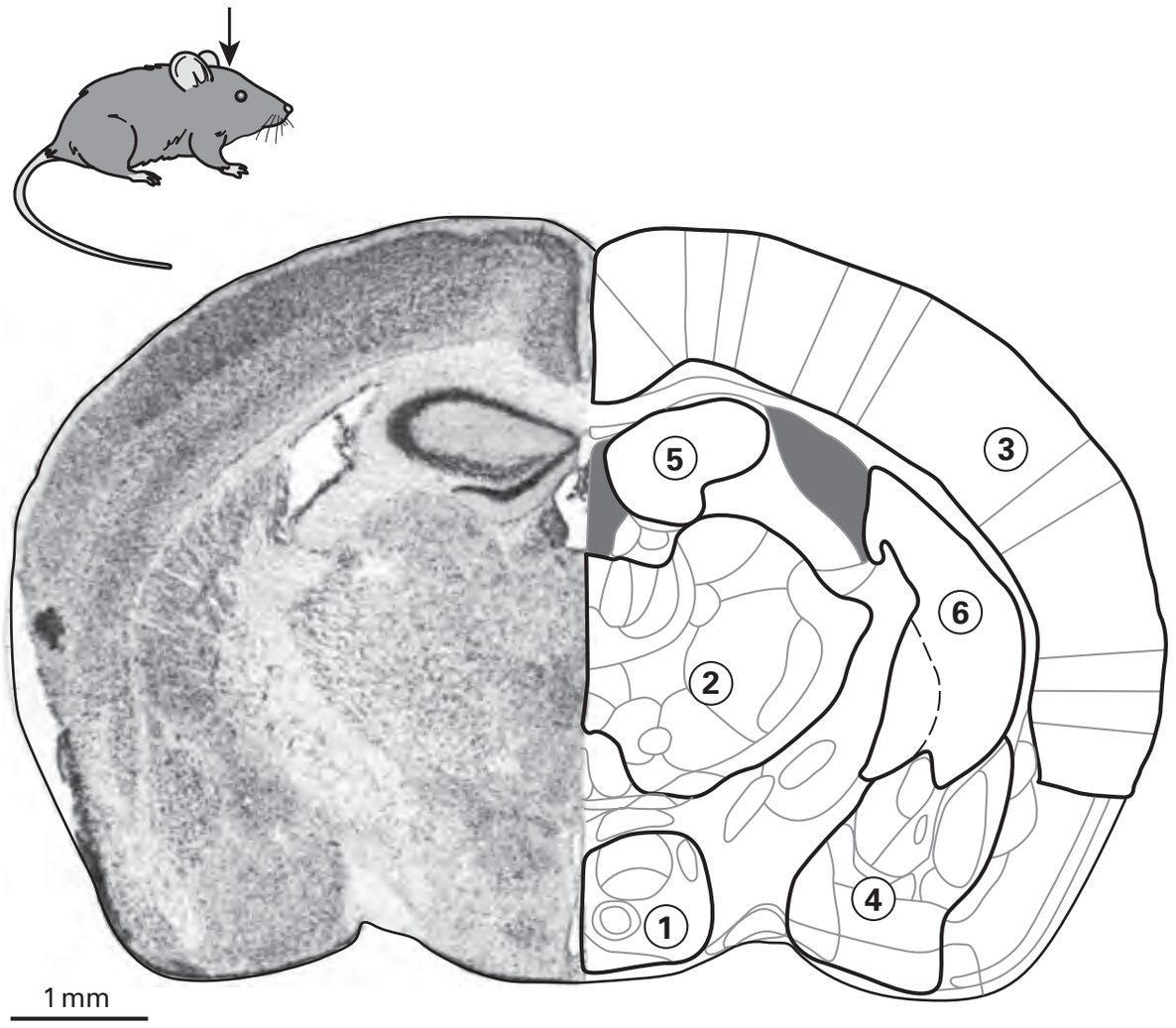
If life is getting better, enjoy more;
If life is getting worse, don't worry about it.

Why do we need a brain?

My brain is my second favorite organ.

Woody Allen

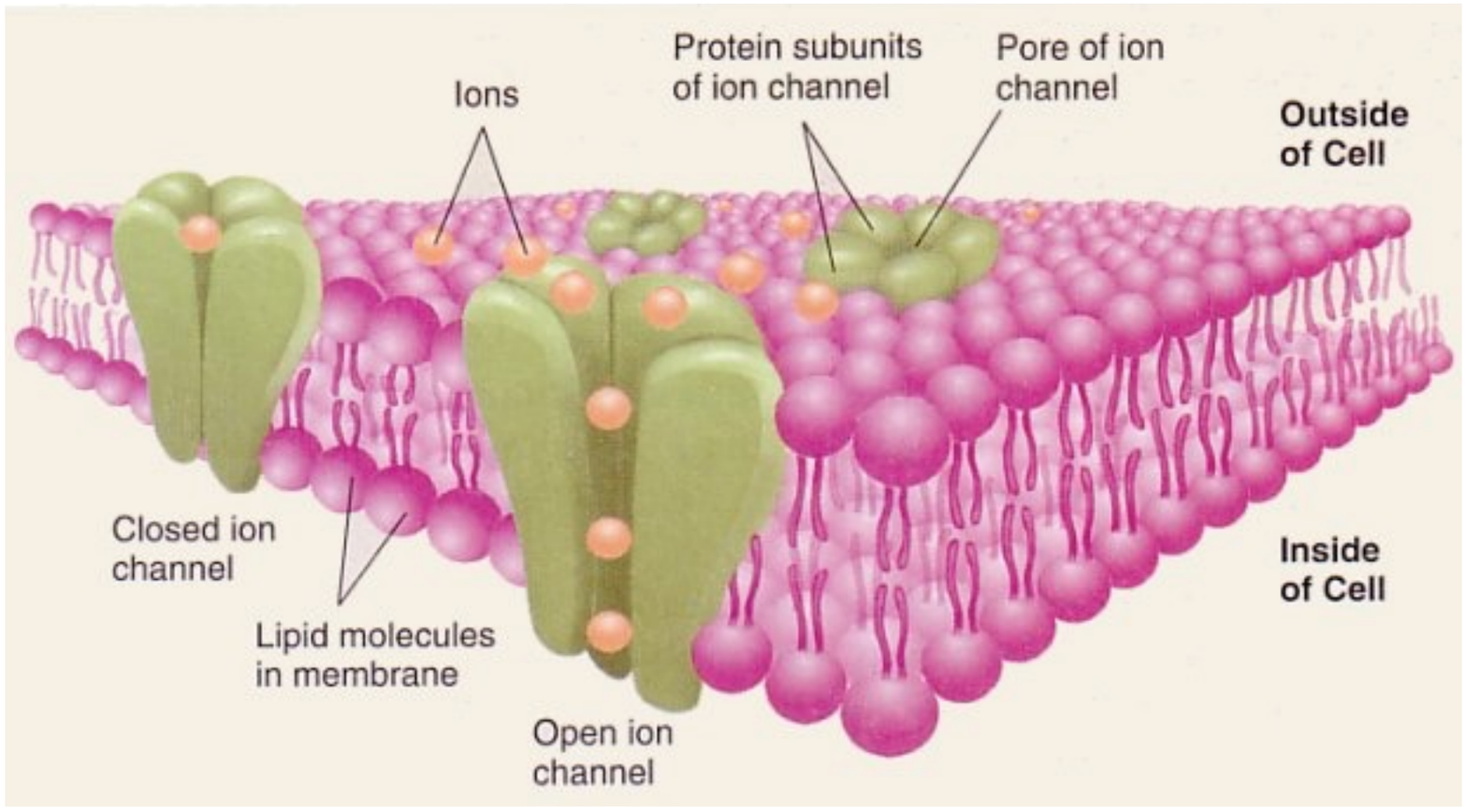

BRAIN'S CORE TASKS
assemble large patterns
compare to stored patterns
predict output pattern
call output pattern
distribute output pattern
evaluate and update
collect small patterns
evaluate and update
collect small patterns
METABOLISM
PHYSIOLOGY
BEHAVIOR
(inner)
(outer)



1. Generate patterns for wireless signaling and appetitive behaviors.
2. “Preprocessing” to shape signals for higher processing.
3. High-level processing: assemble larger patterns, choose behaviors.
4. “Tag” high-level patterns for emotional significance.
5. Store and recall.
6. Evaluate reward predictions.

Single neuron dynamics

My favorite spherical cow

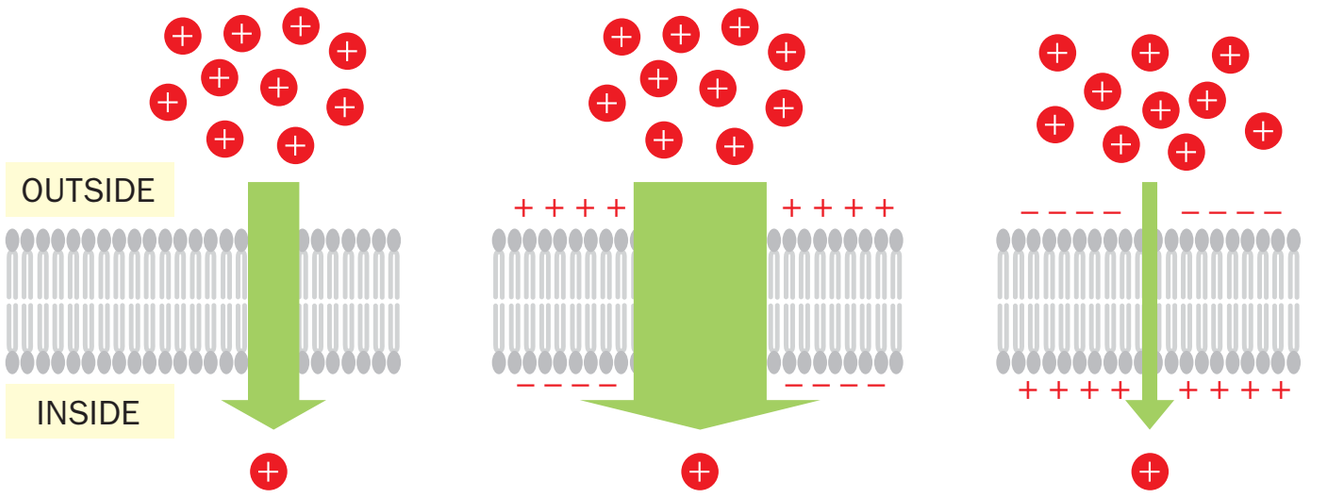


$$qV \sim k_B T$$

$$k_B = 8.6 \times 10^{-5} eV/K$$

$$T = 300\ K$$

What determines the resting potential of a neuron?



chemical gradient alone; no membrane potential

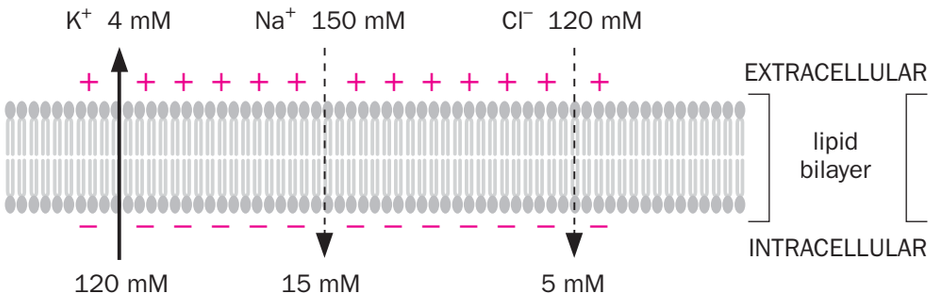
chemical gradient and electrical gradient driving ion movement in the same direction

chemical gradient and electrical gradient driving ion movement in opposing directions

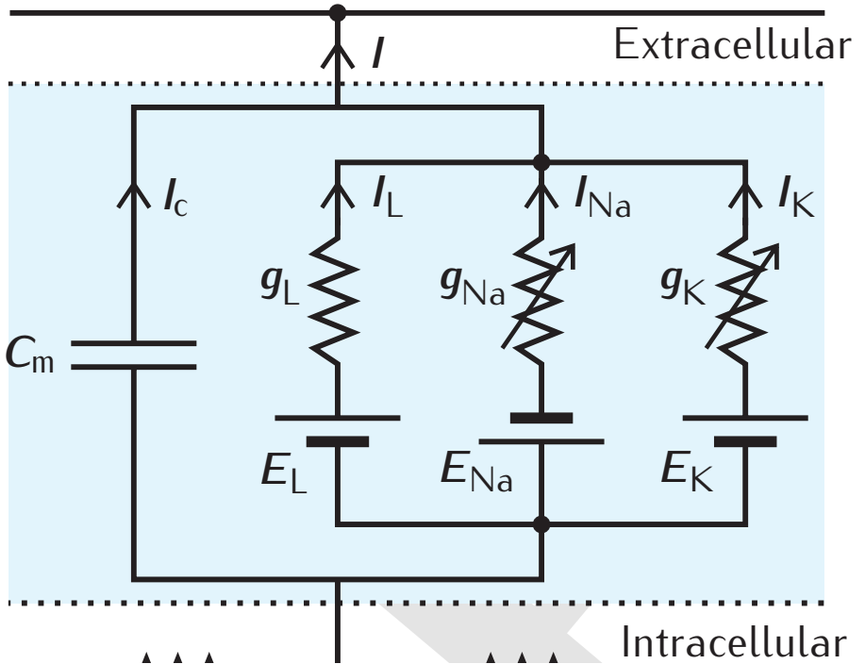
$$E = \frac{k_B T}{ze} \ln \frac{n_{out}}{n_{in}}$$

Ion pump

(A)


K+ 4 mM
Na+ 150 mM
Cl− 120 mM
EXTRACELLULAR
lipid bilayer
INTRACELLULAR
120 mM
15 mM
5 mM

The Equivalent Electronic Circuit of a Neuron



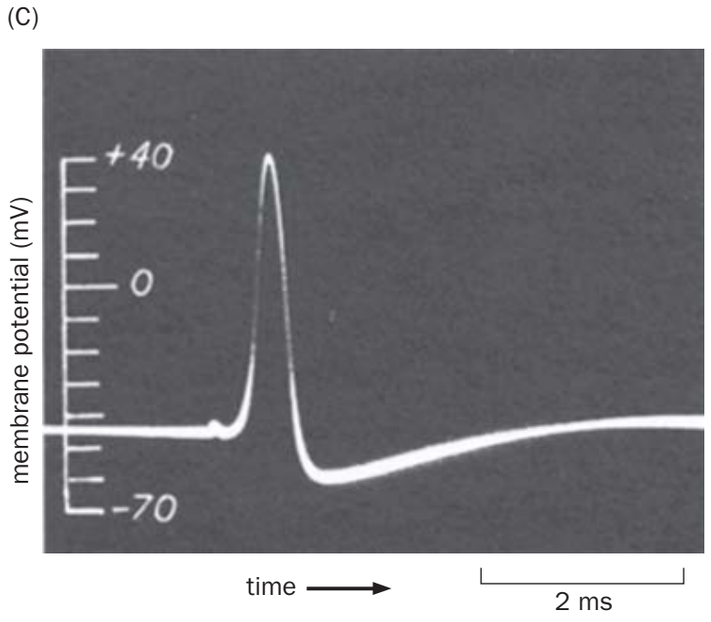
$$C_m \frac{dV}{dt} = -\sum_i g_i(V)(V - E_i) - \bar{g}_L(V - E_L) - I_e$$

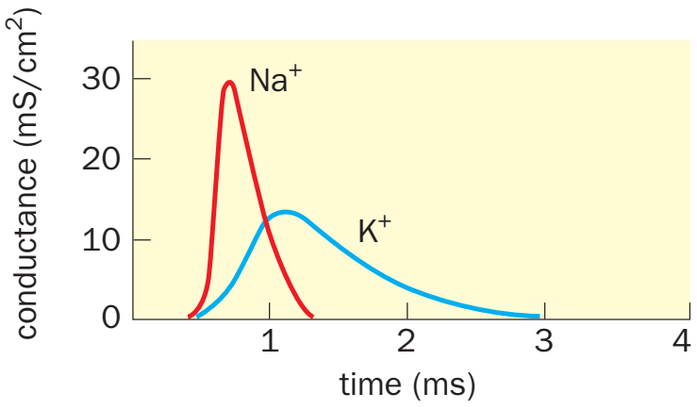
$C_m \approx 0.1 - 1$ nF

$r_m = 1/g \approx 10 - 100$ MΩ

$\tau_m = C_m r_m \approx 10 - 100$ ms

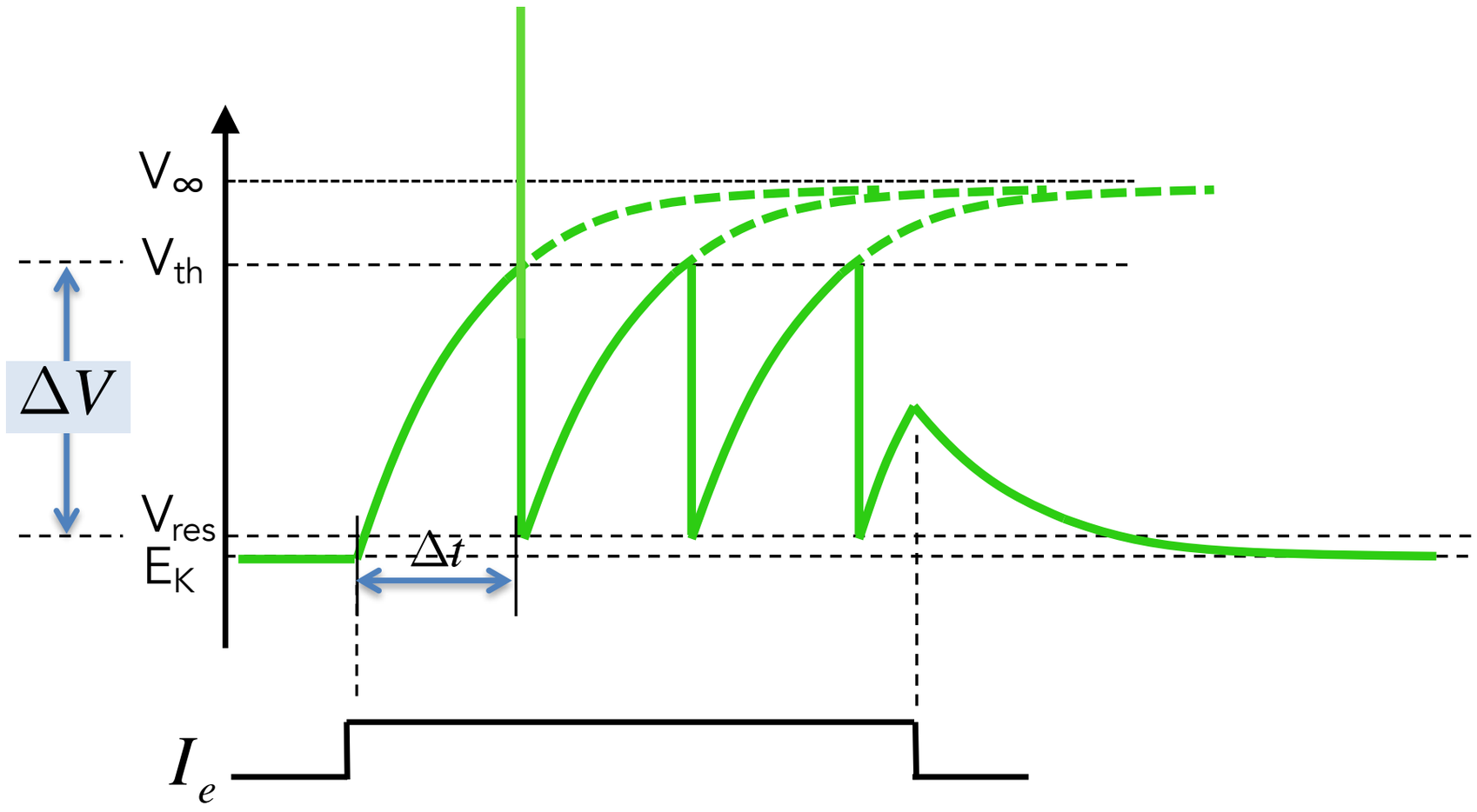
The Hodgkin-Huxley model





$$C\frac{dV}{dt} = -g_K n^4 (V - E_K) - g_{Na} m^3 h (V - E_{Na}) - g_L (V - E_L) - I_e$$

Integrate-and-Fire model



$$C\frac{dV}{dt} = -g(V - E_K) + I_e$$

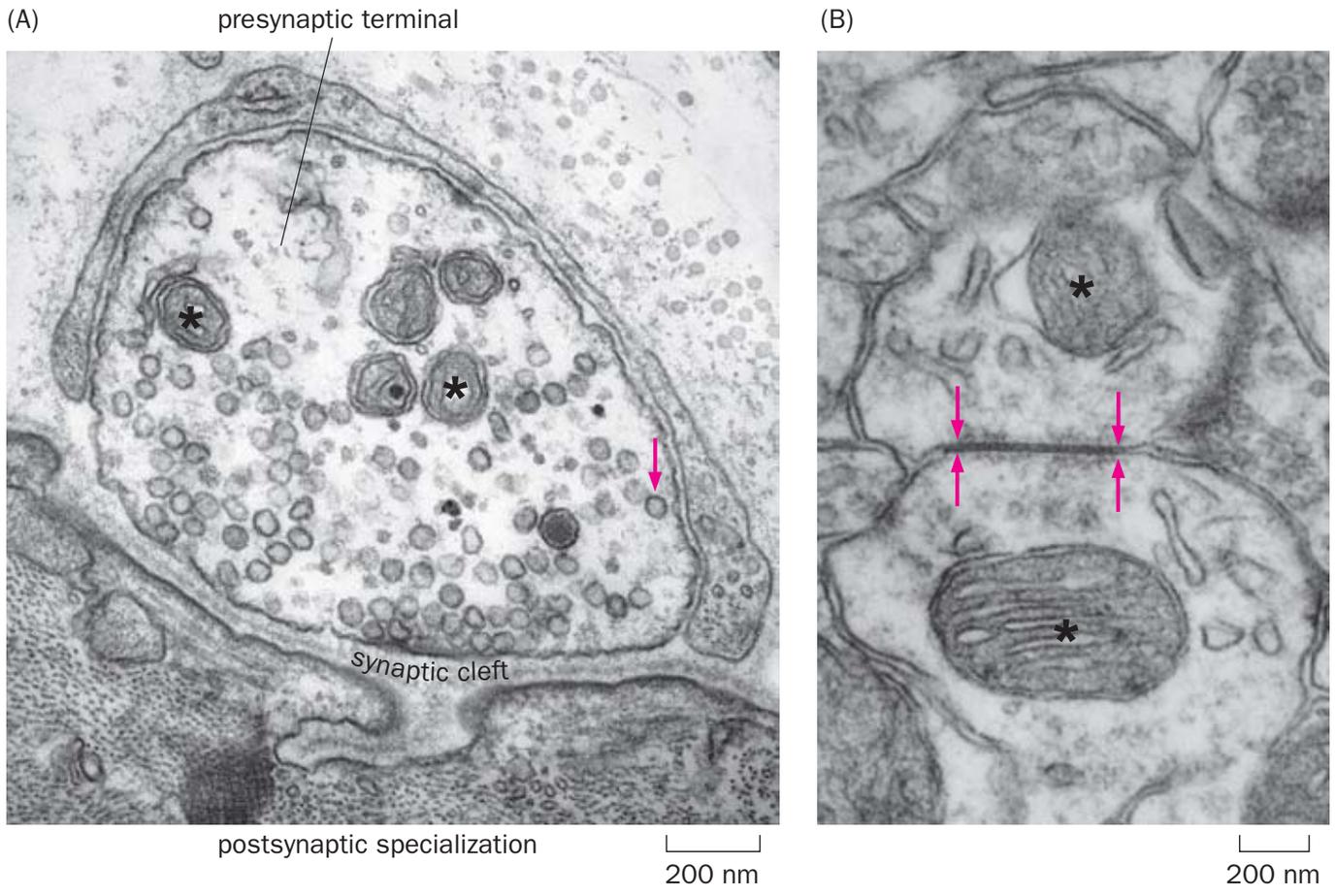
$$V(t^-_{spike}) = V_{th}$$

$$V(t^+_{spike}) = V_{res}$$

How neurons communicate with each other?

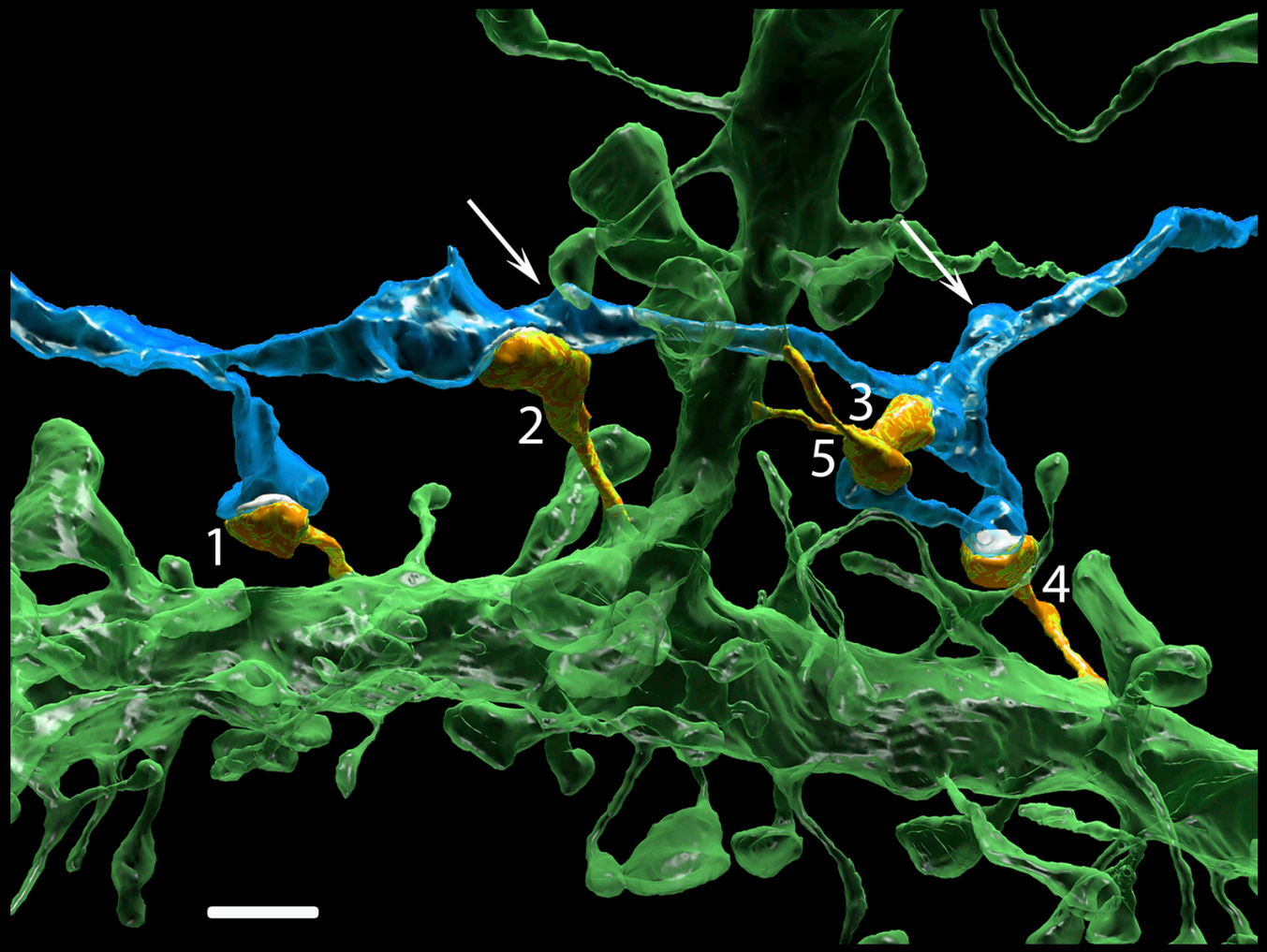
Nerve cells are related by contiguity rather than continuity

Santiago Ramon y Cajal



Chemical and electrical synapses

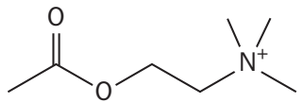
Synaptic Connectivity



Kasthuri et. al, Cell 2015

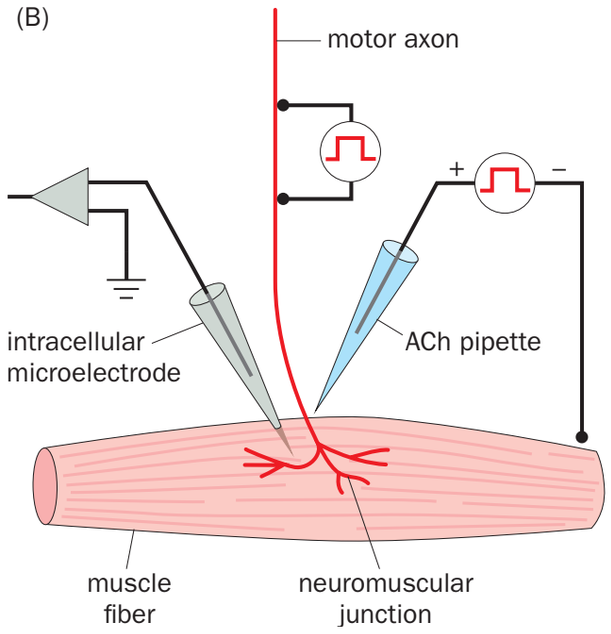
Neurotransmitter release evokes membrane potential change in the postsynaptic neuron

(A)

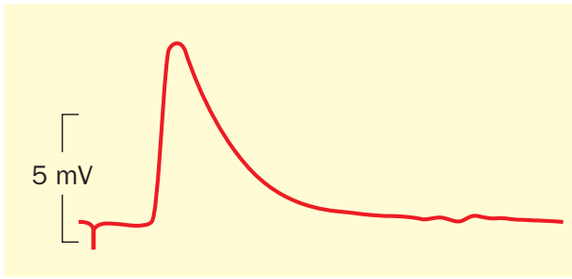


acetylcholine (ACh)

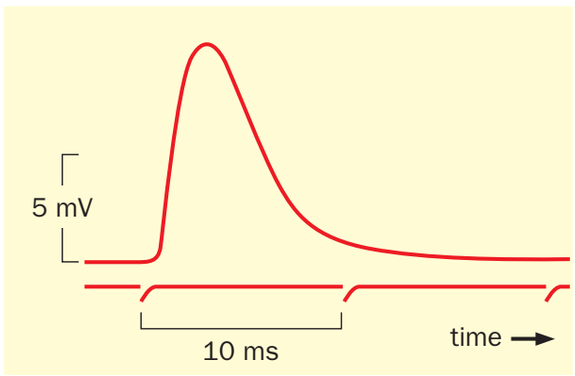
(B)



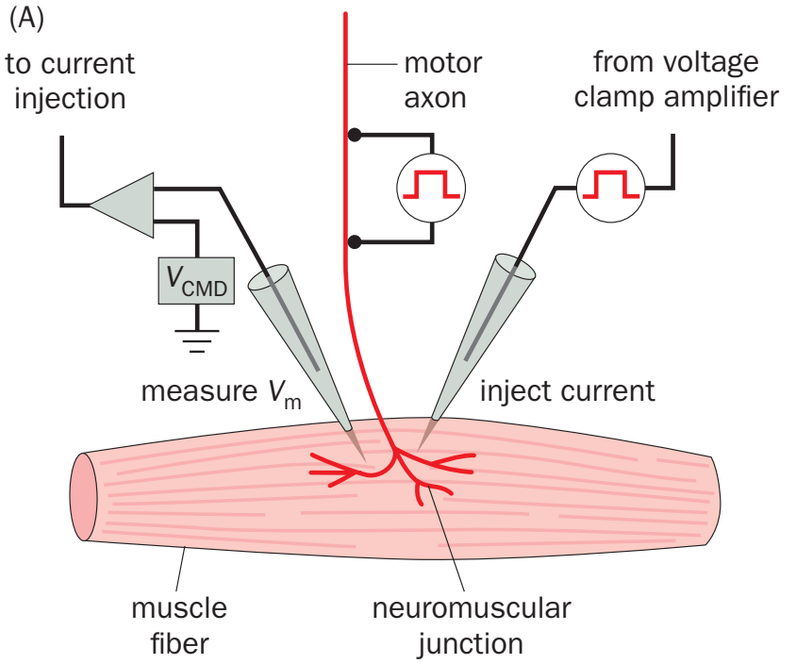
(C) nerve stimulation

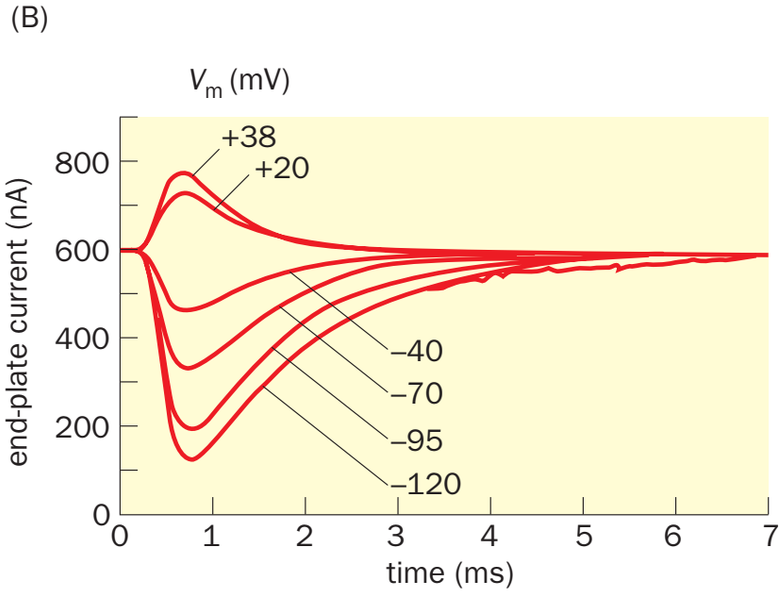


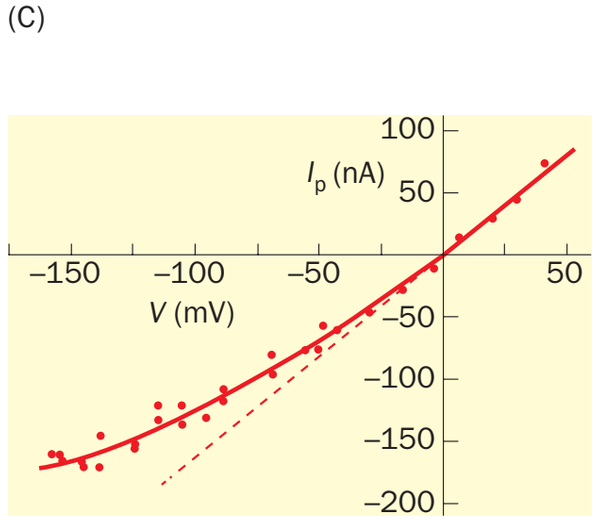
ACh iontophoresis



Reversal potential of a synapse







Modelling synaptic transmission

Release probability (u)

$$I = \bar{g}_s u(V - E_s) \approx Au$$

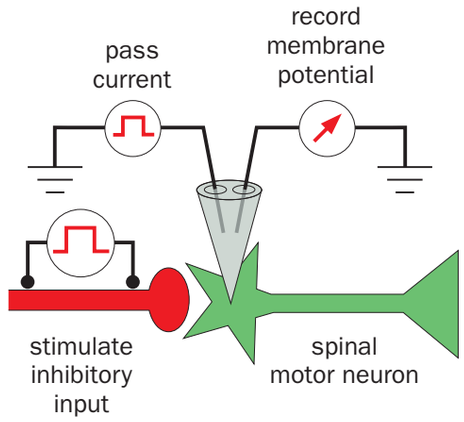
$$u = u_0 e^{-(t-t_{spike})/\tau_s}, \textbf{ for } t > t_{spike}$$

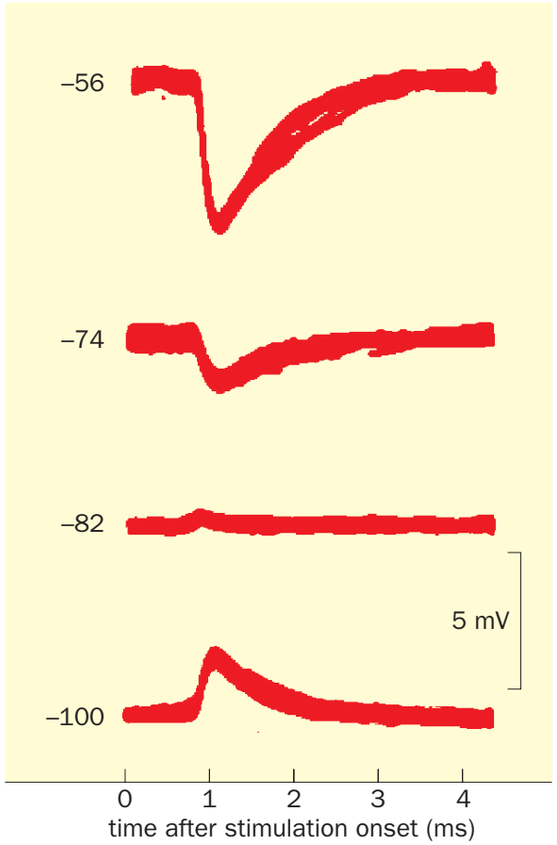
$$\frac{dI}{dt} = -\frac{I}{\tau_s} + Au_0\delta(t - t_{spike})$$

Excitatory and Inhibitory Synapses

Table 3–2: Commonly used neurotransmitters

Neurotransmitter	Major uses in the vertebrate nervous system[1]
Acetylcholine	motor neurons that excite muscle; ANS[2] neurons; CNS excitatory and modulatory neurons
Glutamate	most CNS excitatory neurons; most sensory neurons
GABA	most CNS inhibitory neurons
Glycine	some CNS inhibitory neurons (mostly in the brainstem and spinal cord)
Serotonin (5-HT)	CNS modulatory neurons
Dopamine	CNS modulatory neurons
Norepinephrine	CNS modulatory neurons; ANS[2] neurons
Histamine	CNS modulatory neurons
Neuropeptides	usually co-released from excitatory, inhibitory, or modulatory neurons; neurosecretory cells



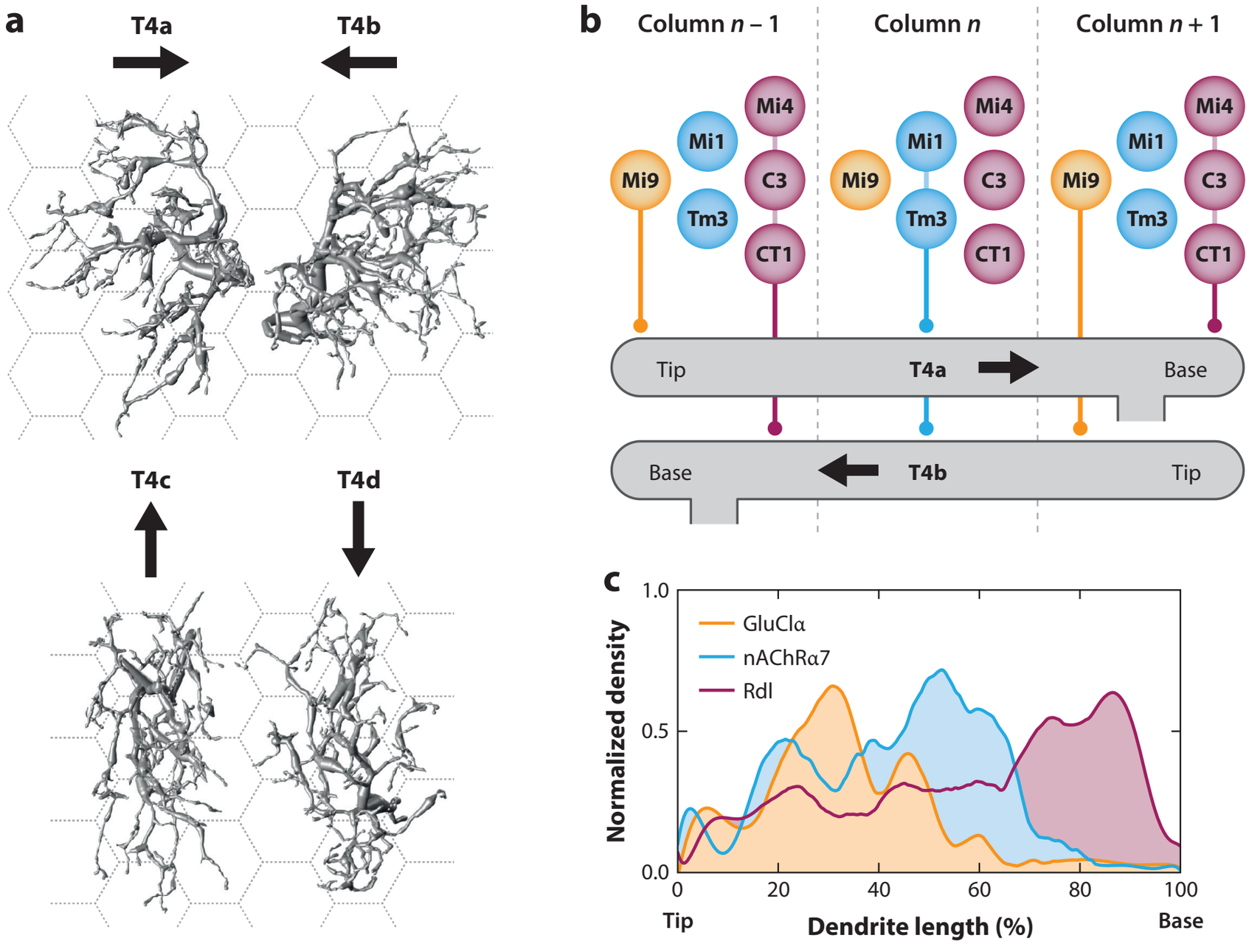


Shunting inhibition and divisive operation

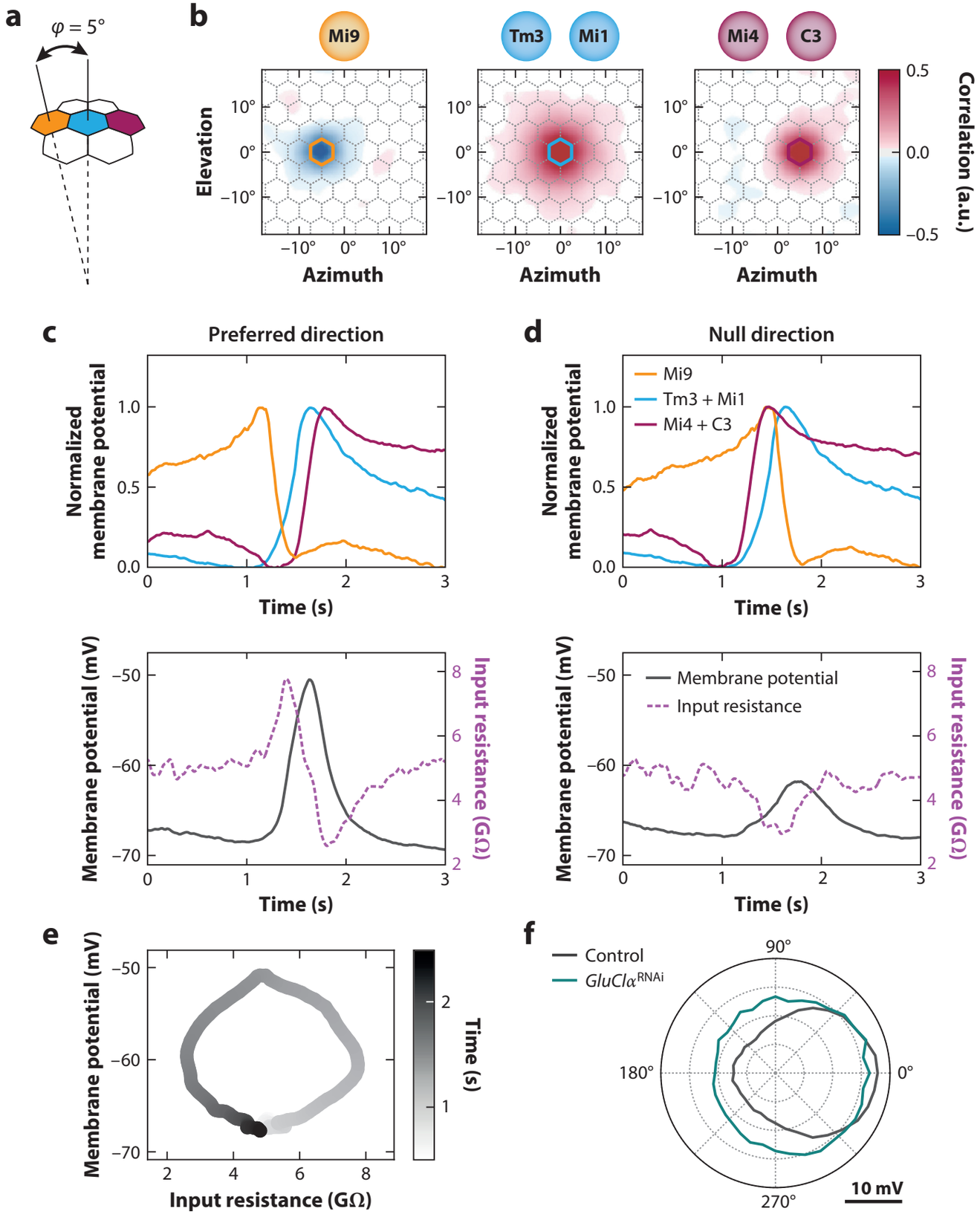
$$C_m \frac{dV}{dt} = -g_L(V - E_L) - g_{inh}(V - E_L) - g_{exc}(V - E_0)$$

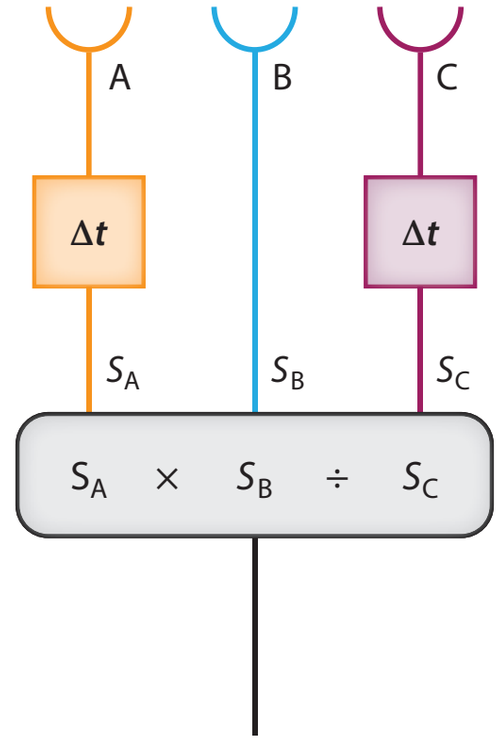
$$V = \frac{(g_L + g_{inh})E_L + g_{exc}E_0}{g_L + g_{inh} + g_{exc}}$$

$$g_{inh} \gg g_L + g_{exc} \qquad V \approx E_L + \frac{g_{exc}}{g_{inh}}E_0$$



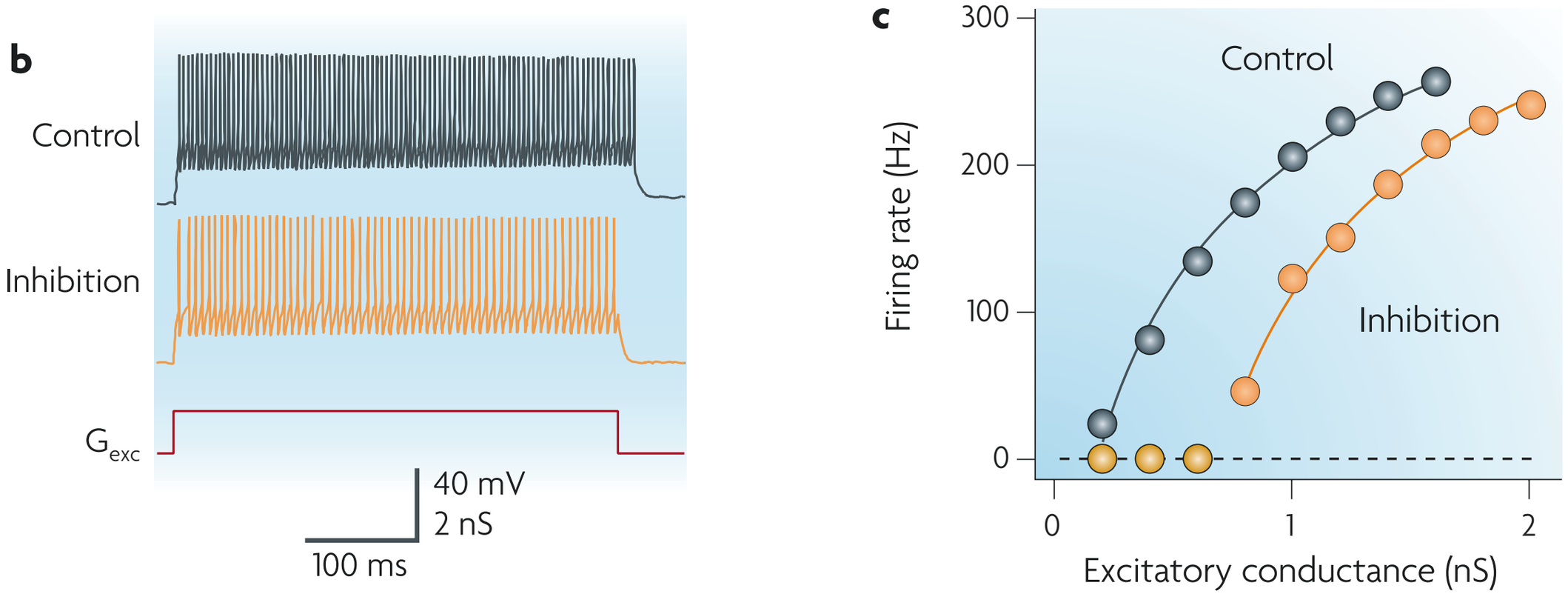
Borst & Groschner, Annual Review Neuroscience 2023





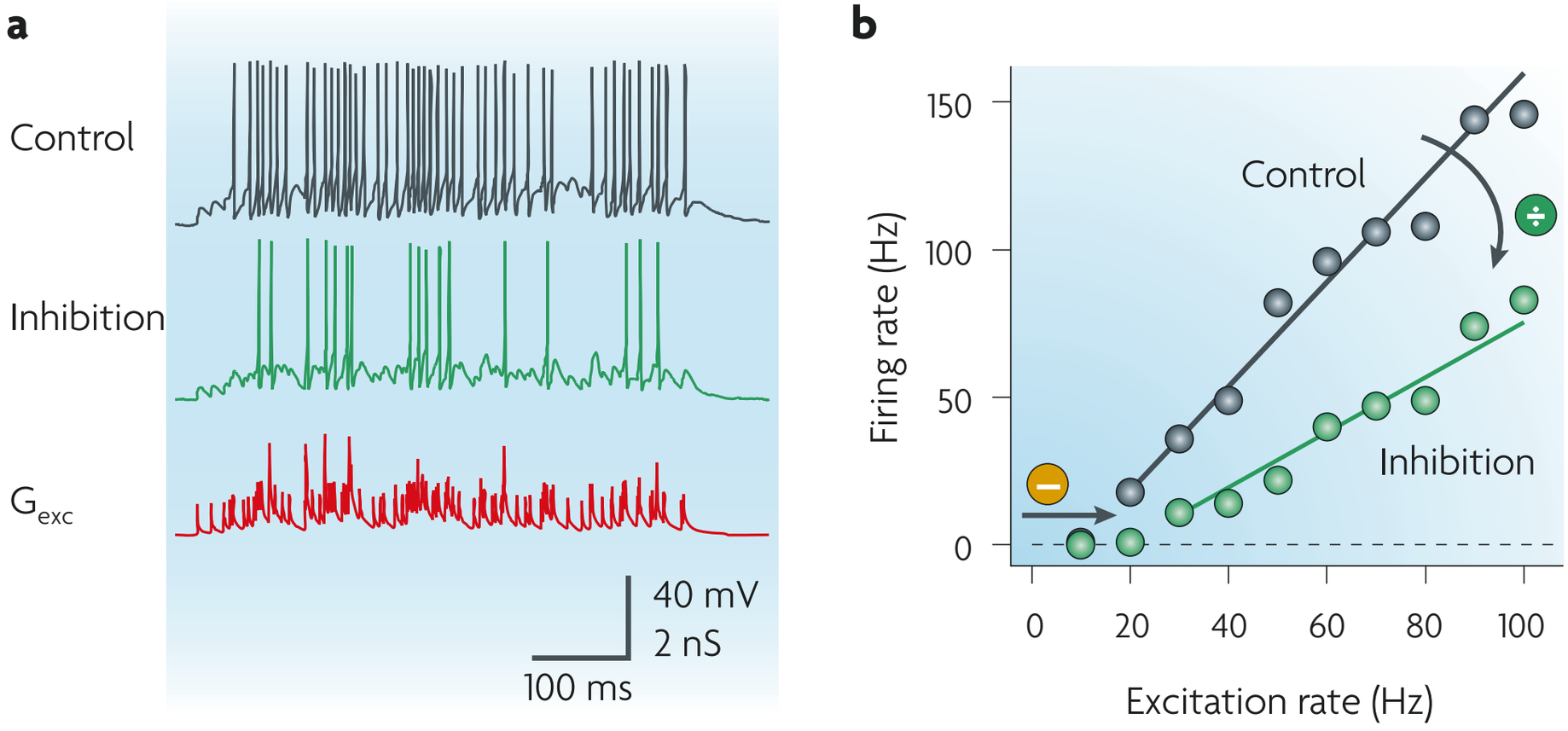
Gonzalez-Suarez AD et. al.,
Current Biology 2022

However, shunting inhibition becomes subtractive for firing rate



Why? (Your homework)

But Shunting inhibition can become divisive in the presence of large synaptic input noise



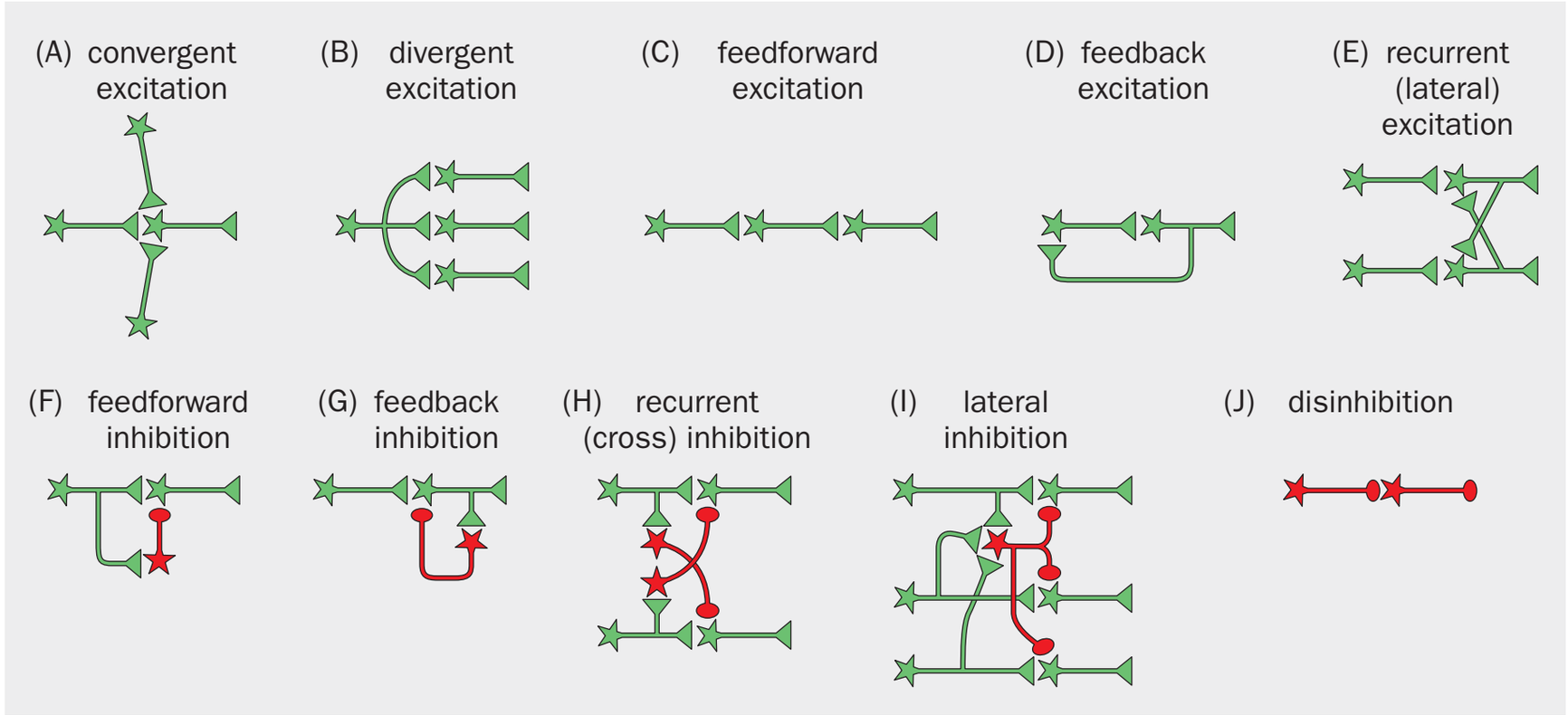
Angus Silver Nature Review Neuroscience 2010

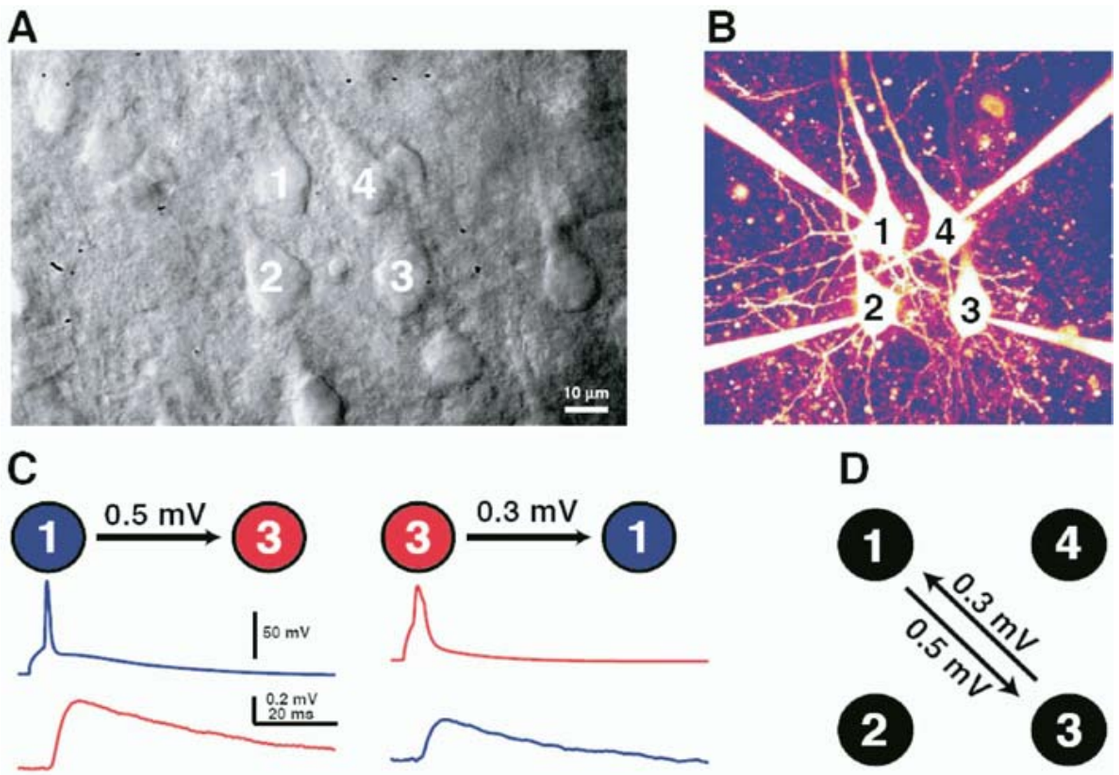
The organization of neural circuits

Circuit diagrams or connectomes are *absolutely* necessary but *completely* insufficient for understanding nervous system function.

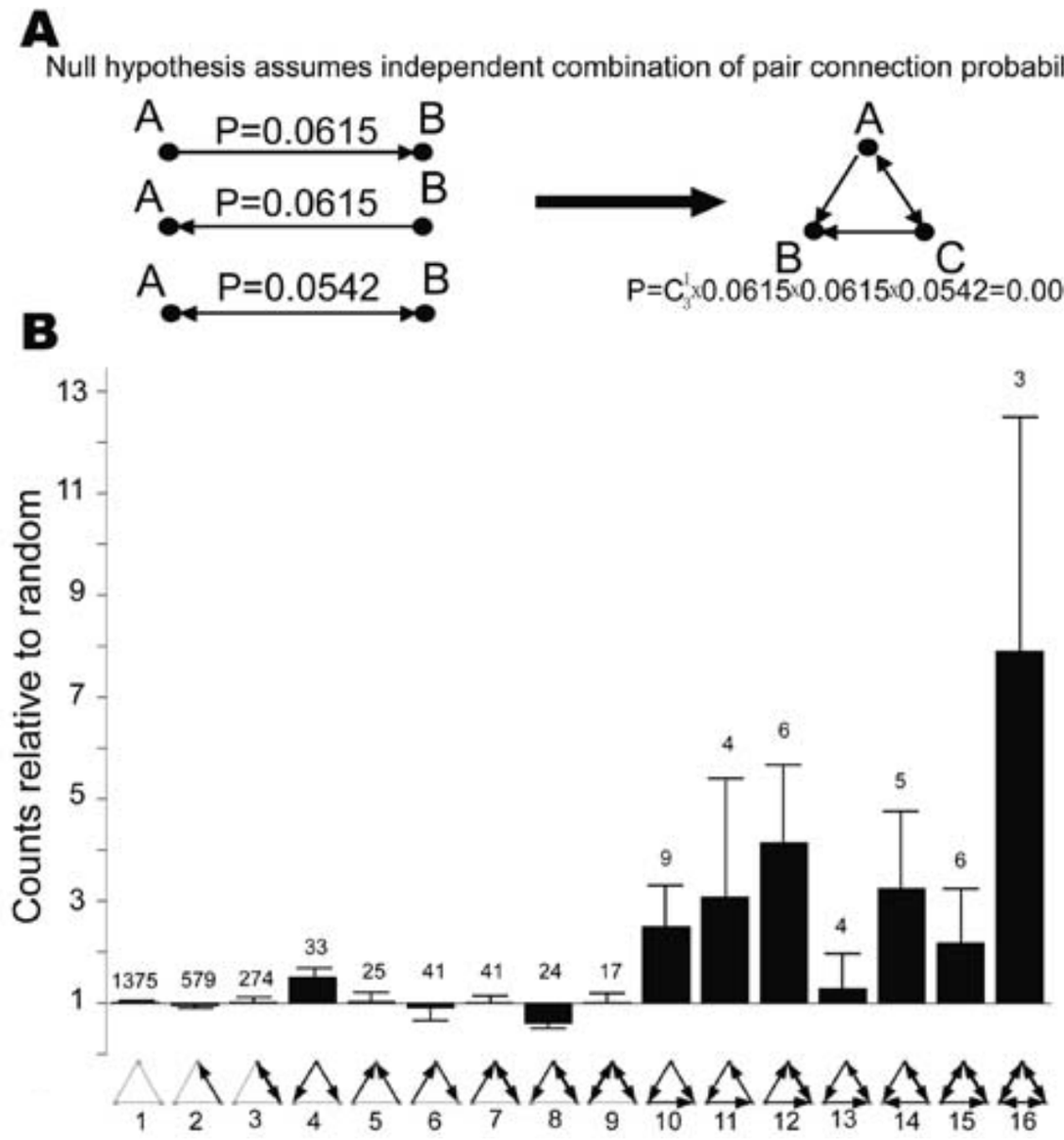
Eve Marder

Circuit motifs



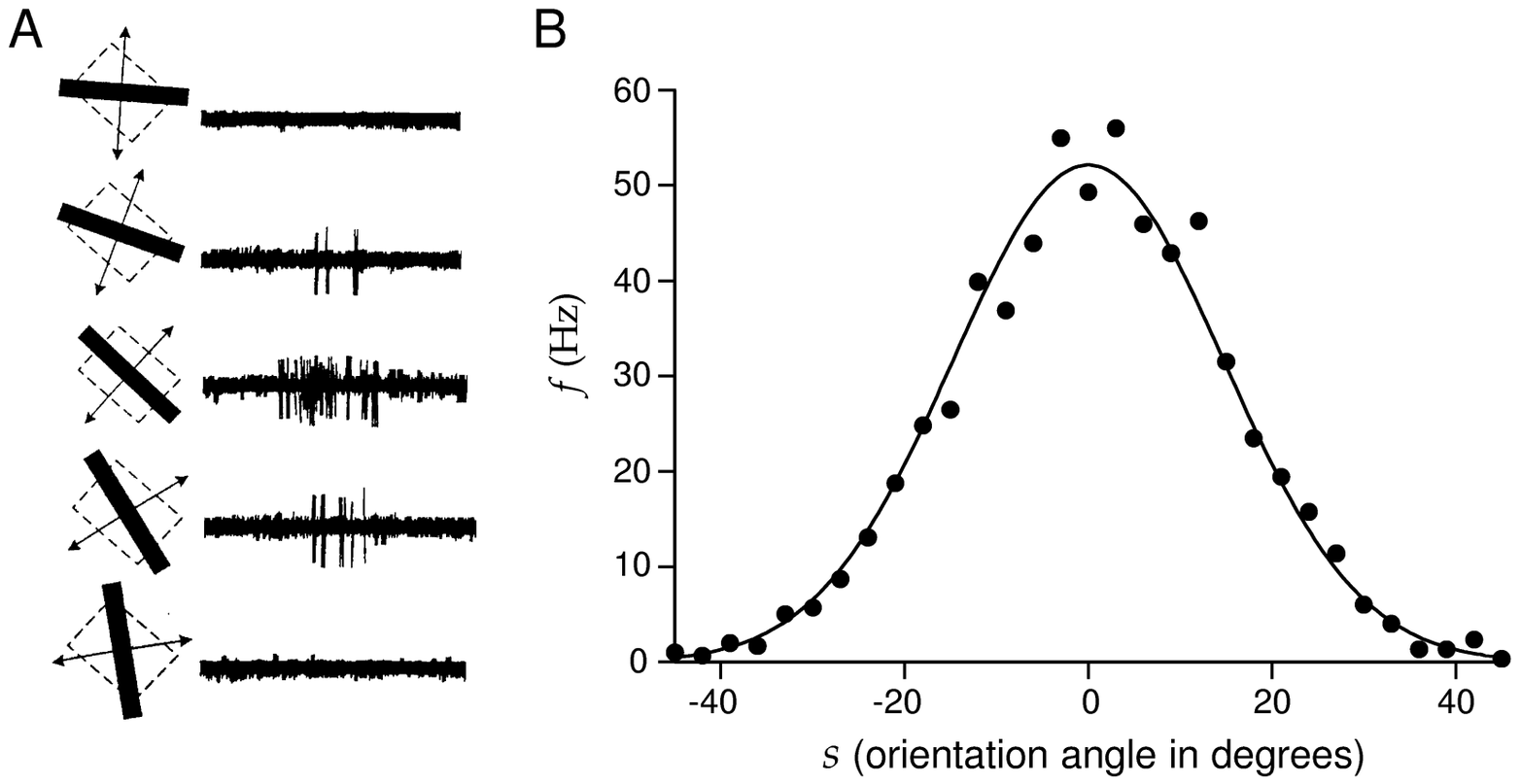

A
1
4
2
3
10 µm
B
1
4
2
3
C
1
0.5 mV
3
50 mV
0.2 mV
20 ms
3
0.3 mV
1
D
1
4
0.3 mV
0.5 mV
2
3

Some circuit motifs are over-represented

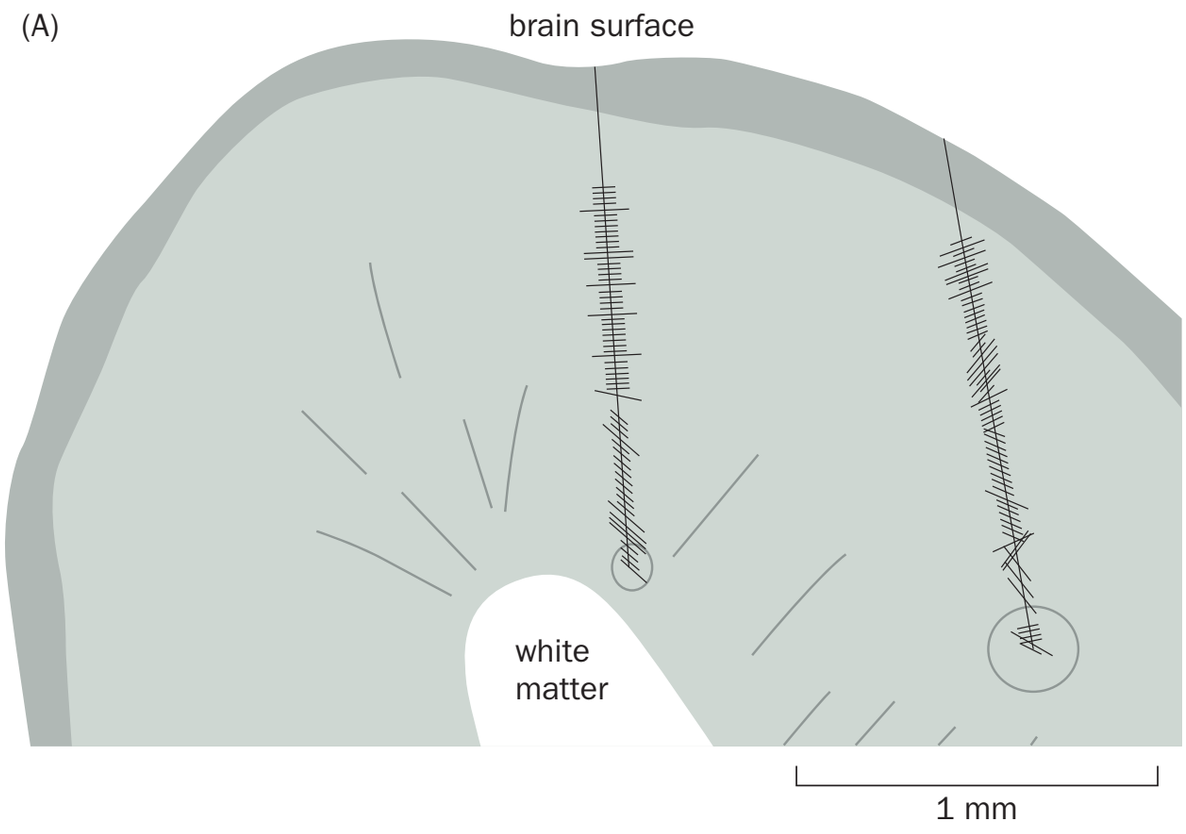


Song S, et.al, PloS Biology 2005

The cortex uses maps to organize information

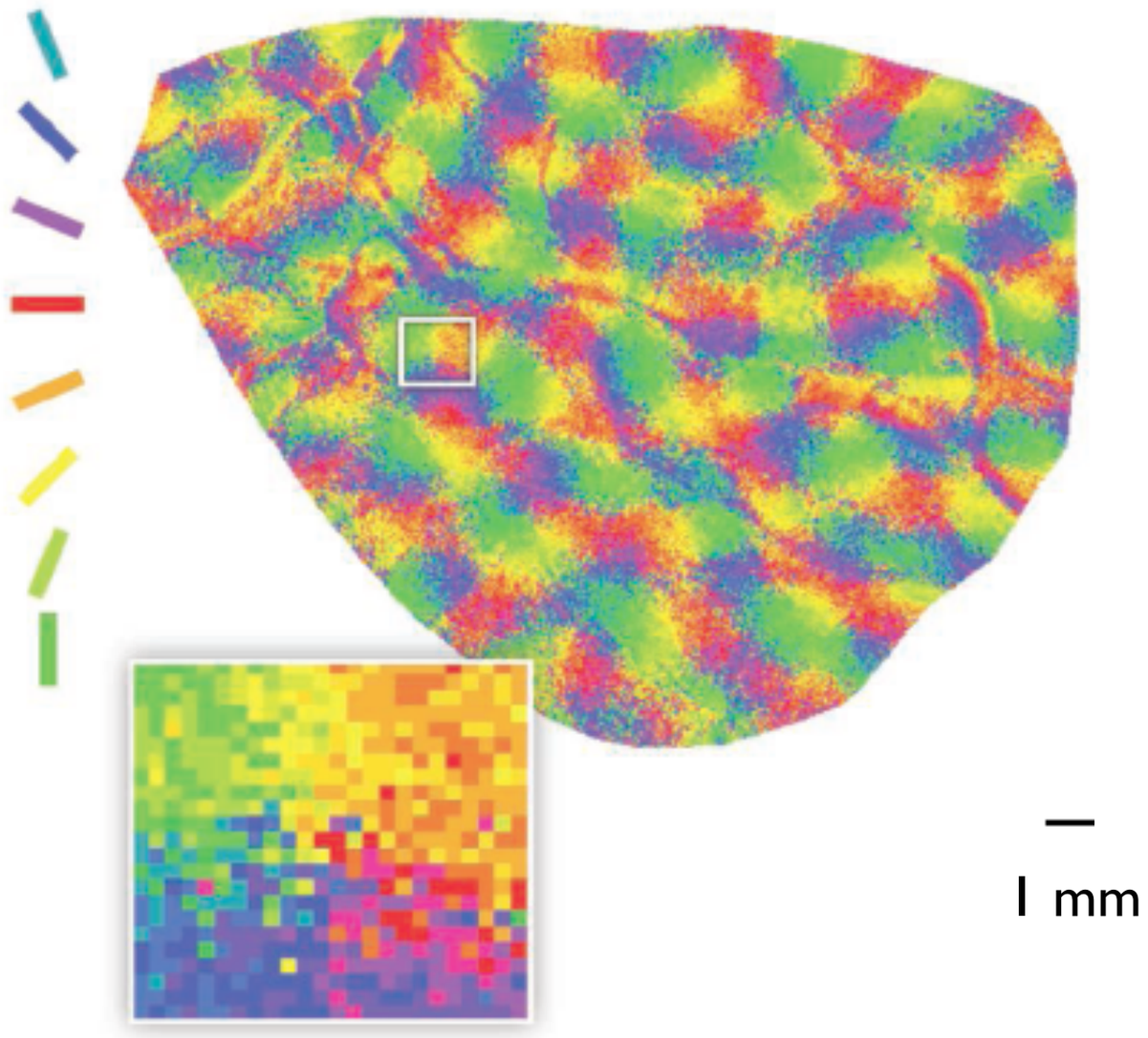


The Cortical Column

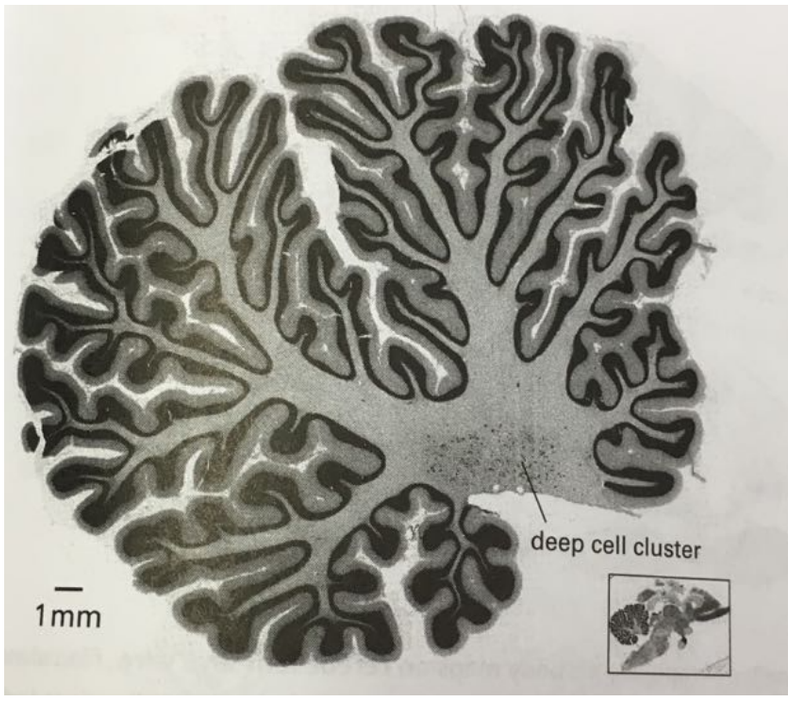


Hubel DH & Wiesel TN (1962) J Physiology 160: 106-154

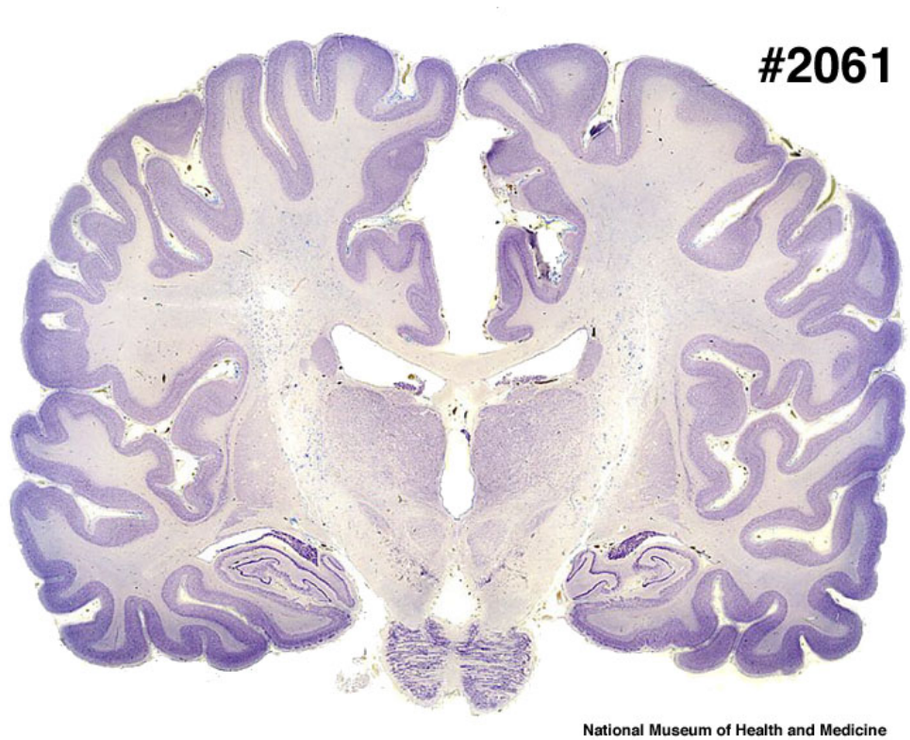
The cortex uses maps to organize information



cerebral cortex vs. cerebellar cortex



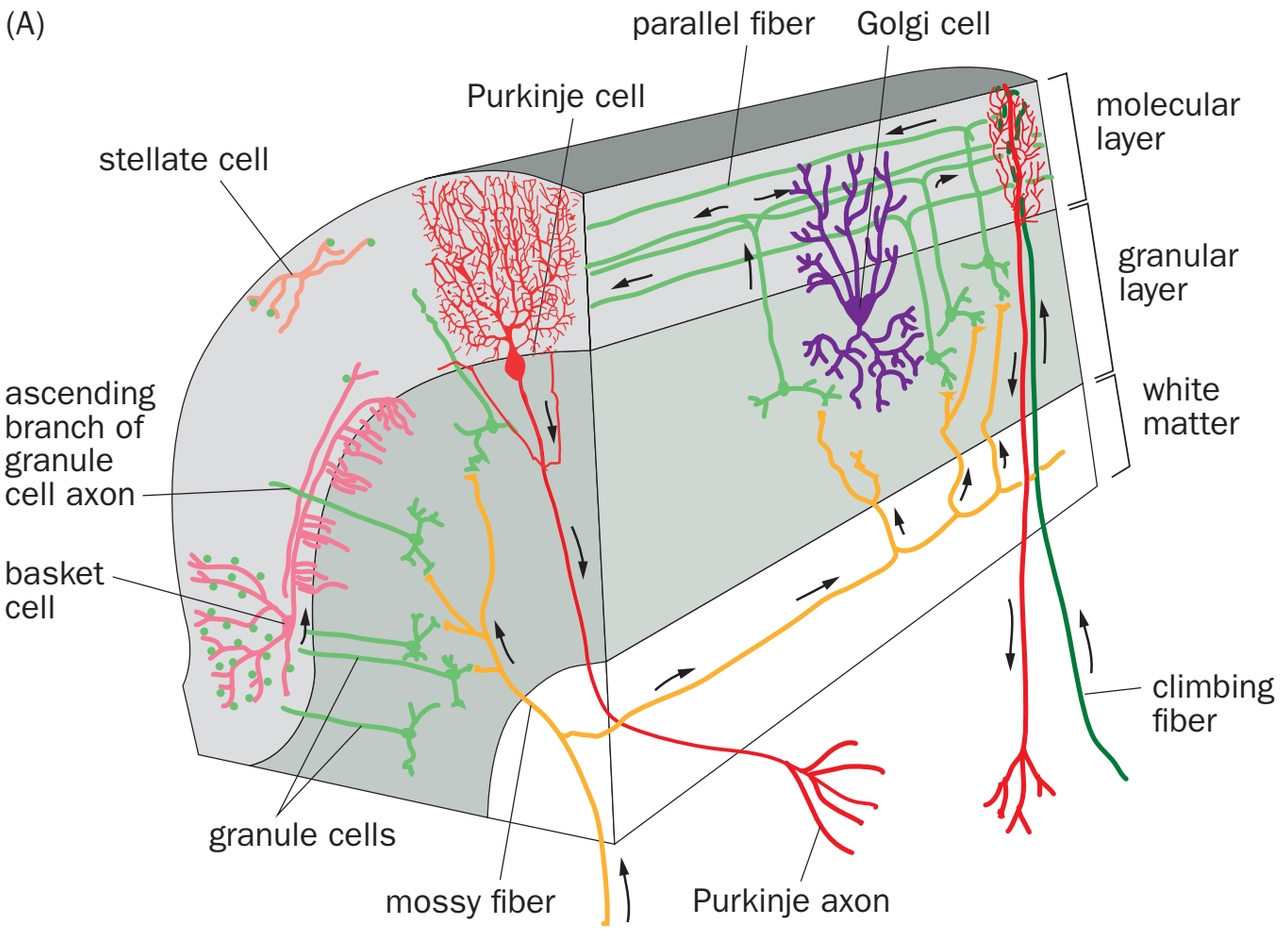
cerebellum



cerebral cortex

Connecting dense array to sparse array with extreme convergence and divergence

The organization of cerebellar cortex



$$N_g D = N_p C$$

$$N_g \gg N_p$$

$$C \gg D$$

Connecting many dense arrays to many other dense arrays with moderate convergence and divergence

The organization of the cortical column

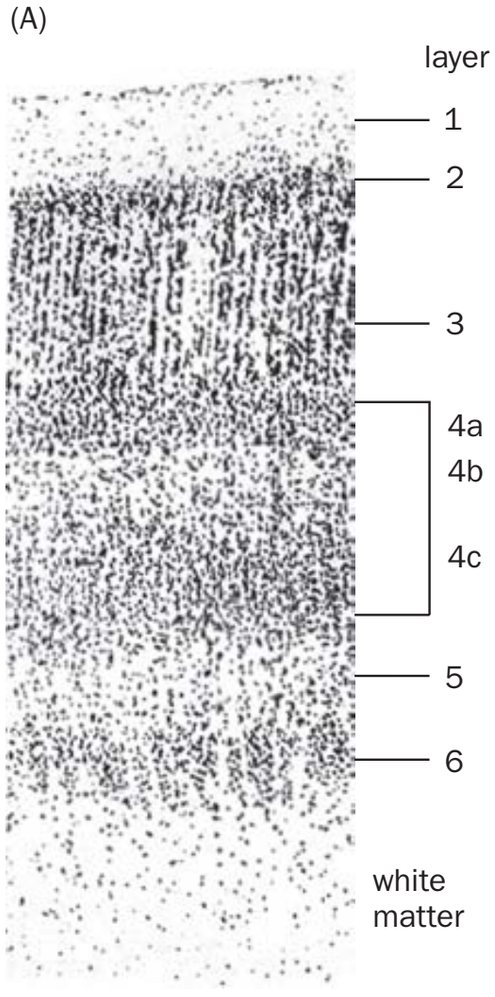
85% excitatory cells

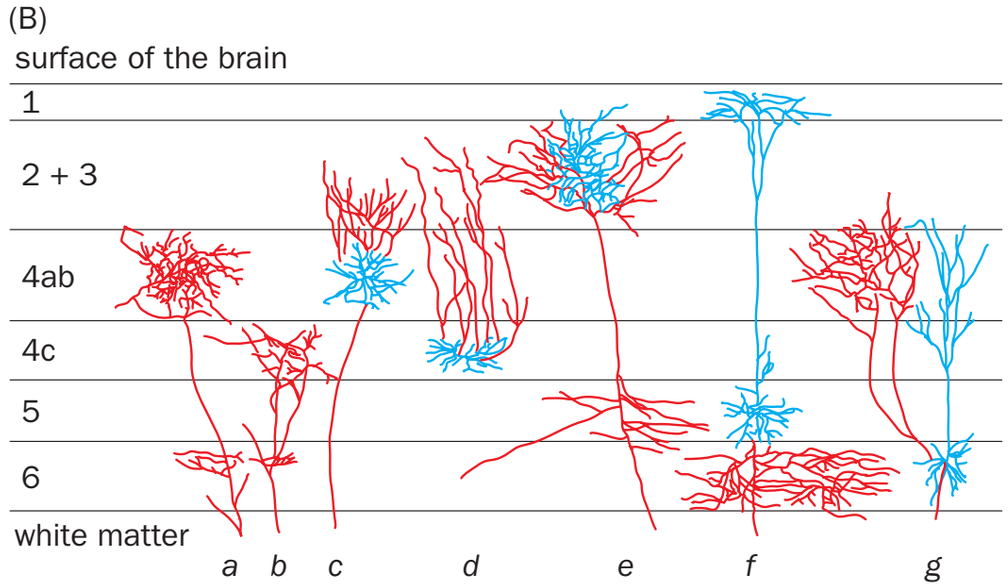
15% inhibitory cells

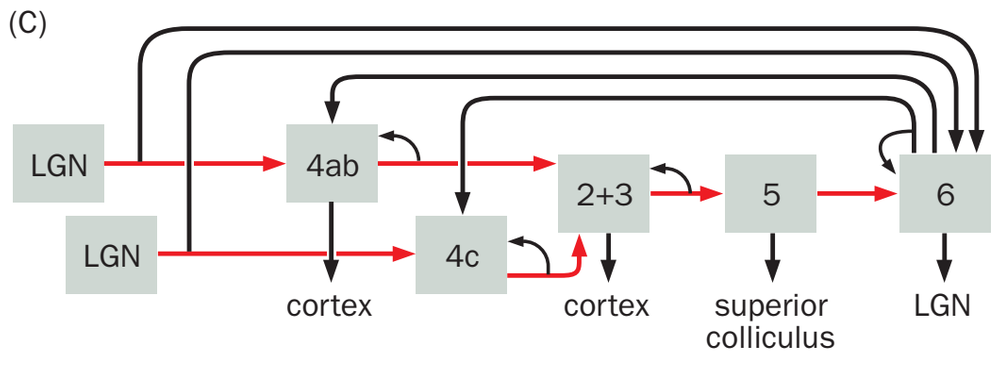
10^5 neurons

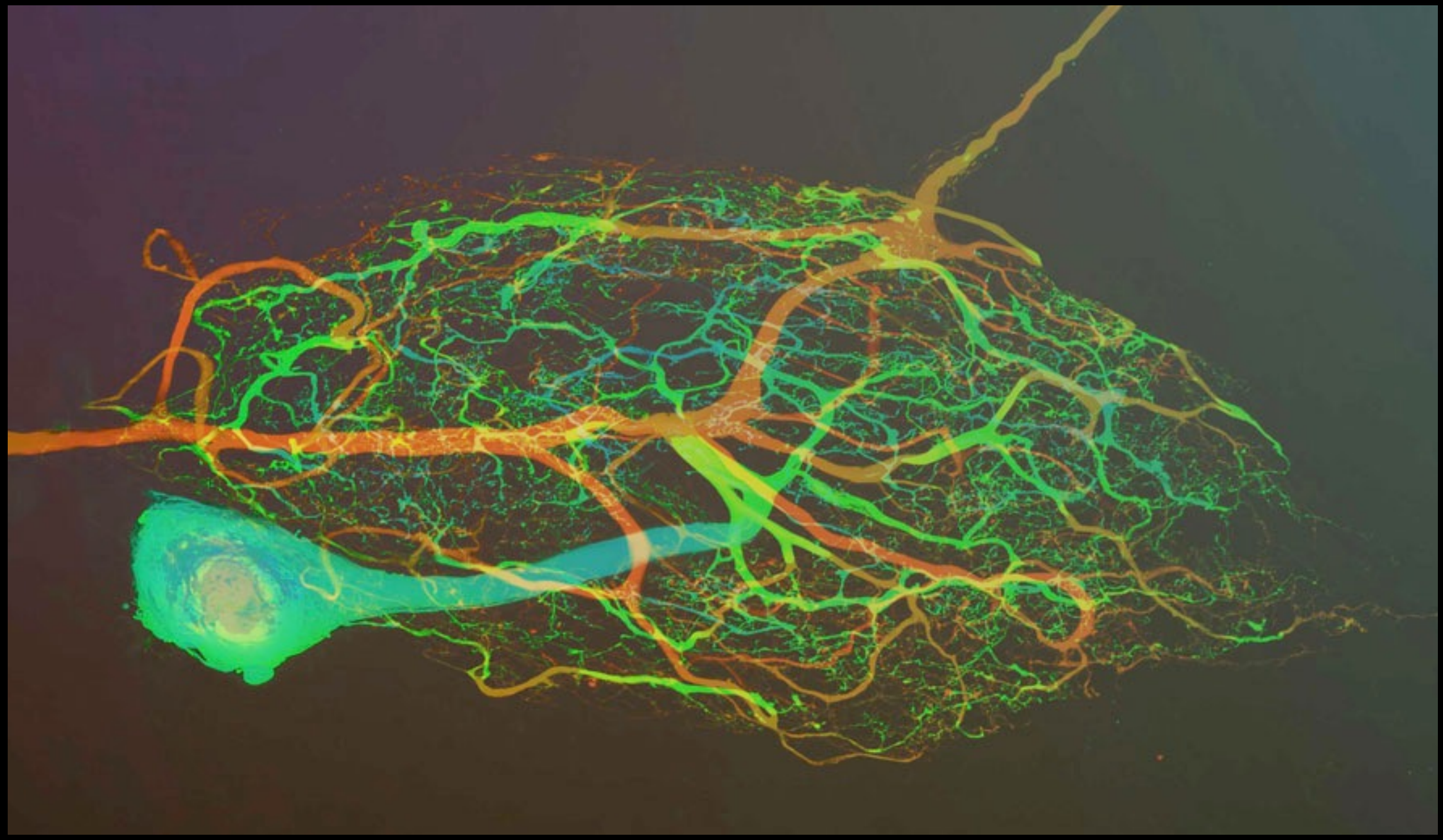
10^9 synapses

5000 m wires



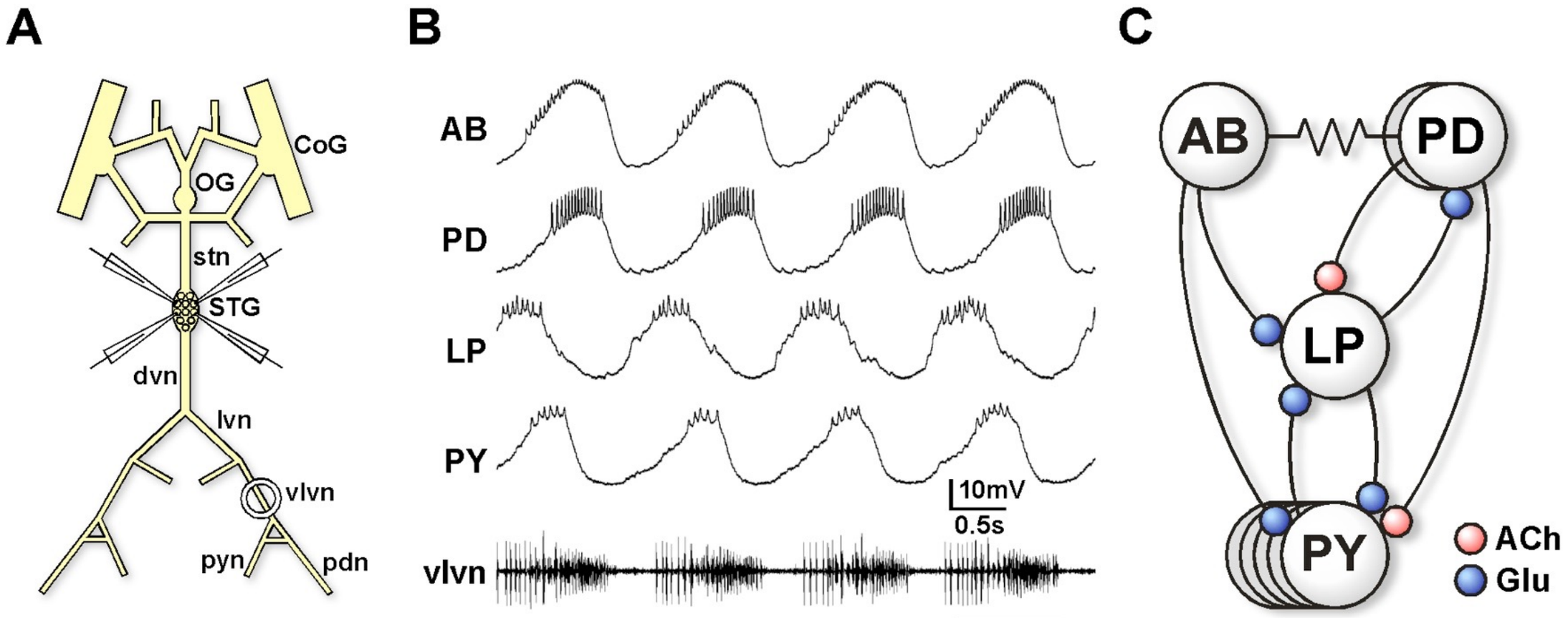




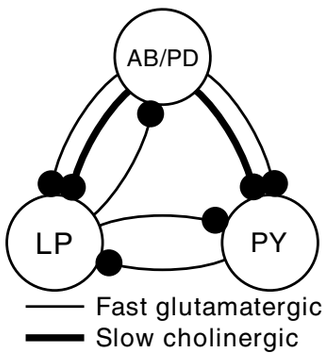


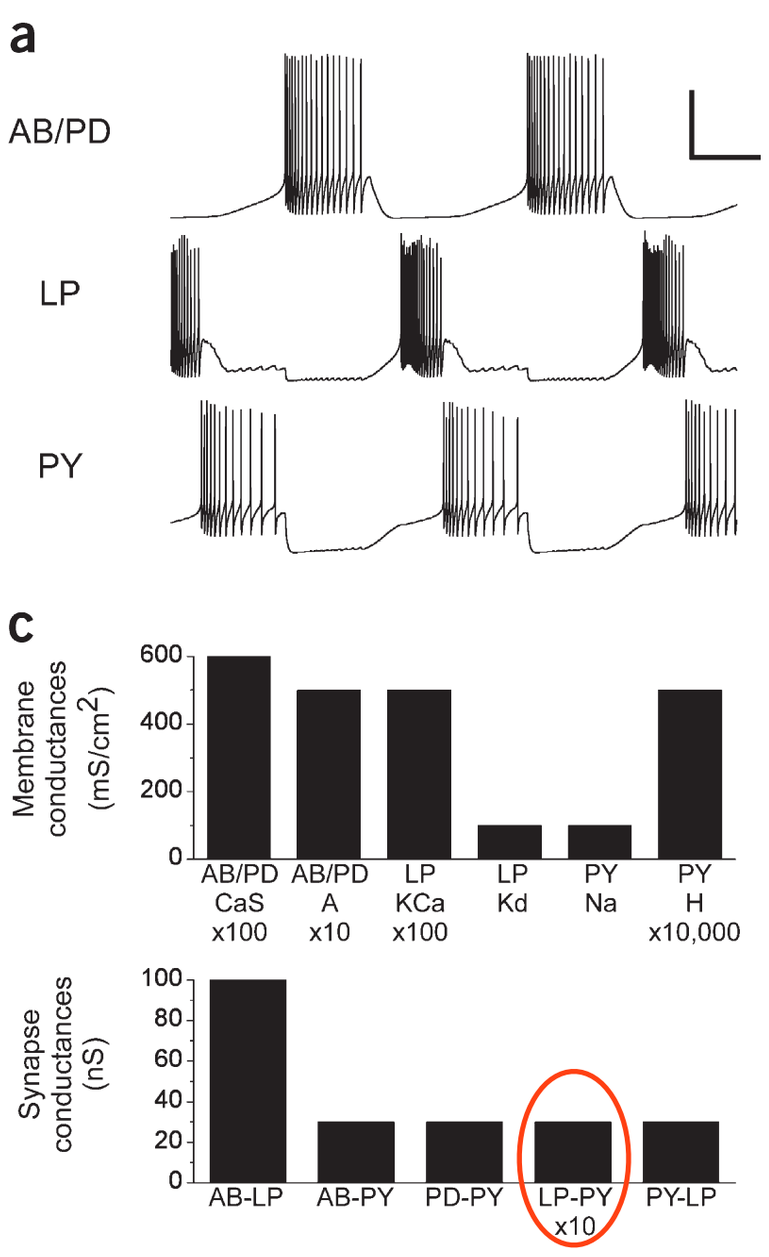
Eve Marder

STG has identified neurons with stereotypical activity patterns



Similar neural activities with widely different model-network properties





Prinz, Bucher and Marder
Nature Neuroscience Dec 2004


樹突
dendrite
軸突
axon
樹突
dendrite
細胞体
soma
軸突
axon

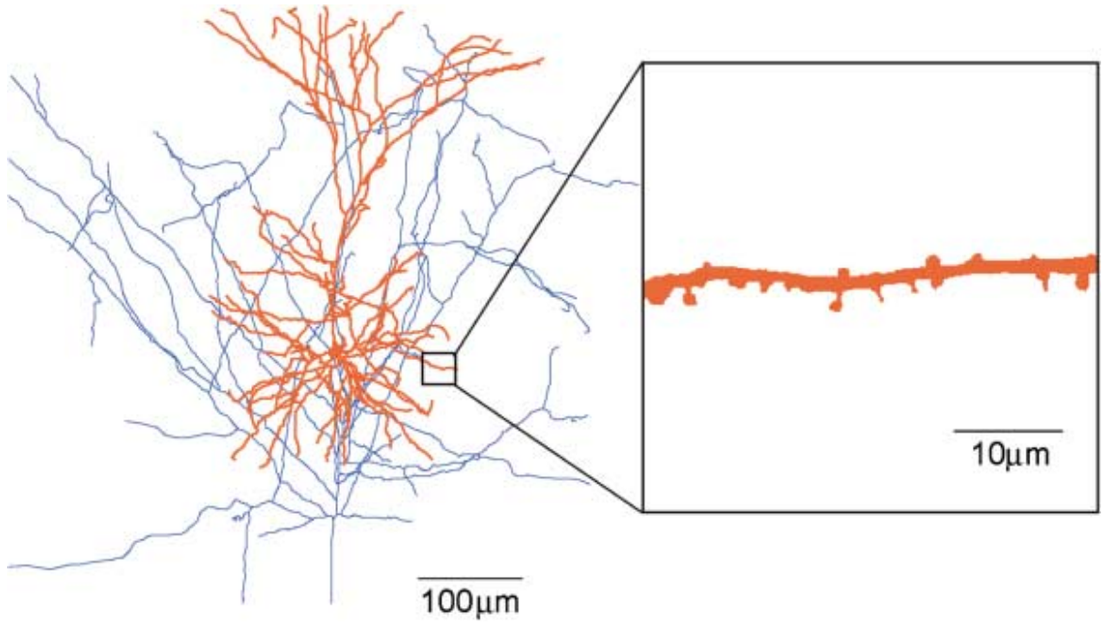
Why do we need axons and dendrites?

Wiring Optimization of Neural Circuit

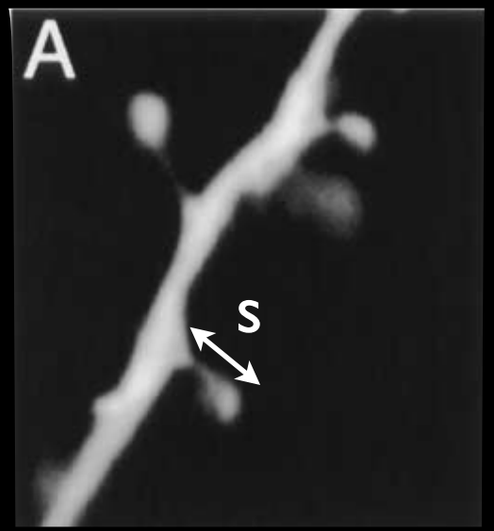
“After the many shapes assumed by neurons, we are now in a position to ask whether this diversity ... has been left to chance and is insignificant, or whether it is tightly regulated and provides an advantage to the organism. ... we realized that all of the various conformations of the neuron and its various components are simply morphological adaptations governed by laws of conservation for time, space, and material.”

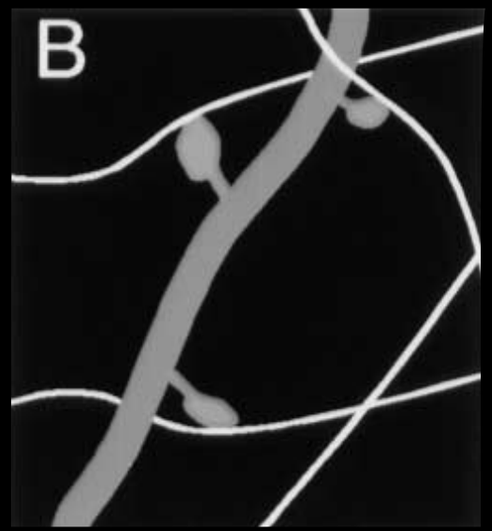
Ramon y Cajal

A toy problem: why do we need axons, dendrites and spines?

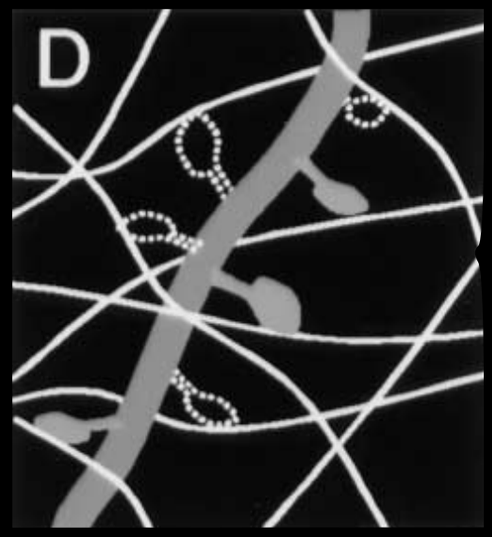


Structural Plasticity of Synaptic Connectivity





$$f = \frac{2}{\pi s L_d b n}$$

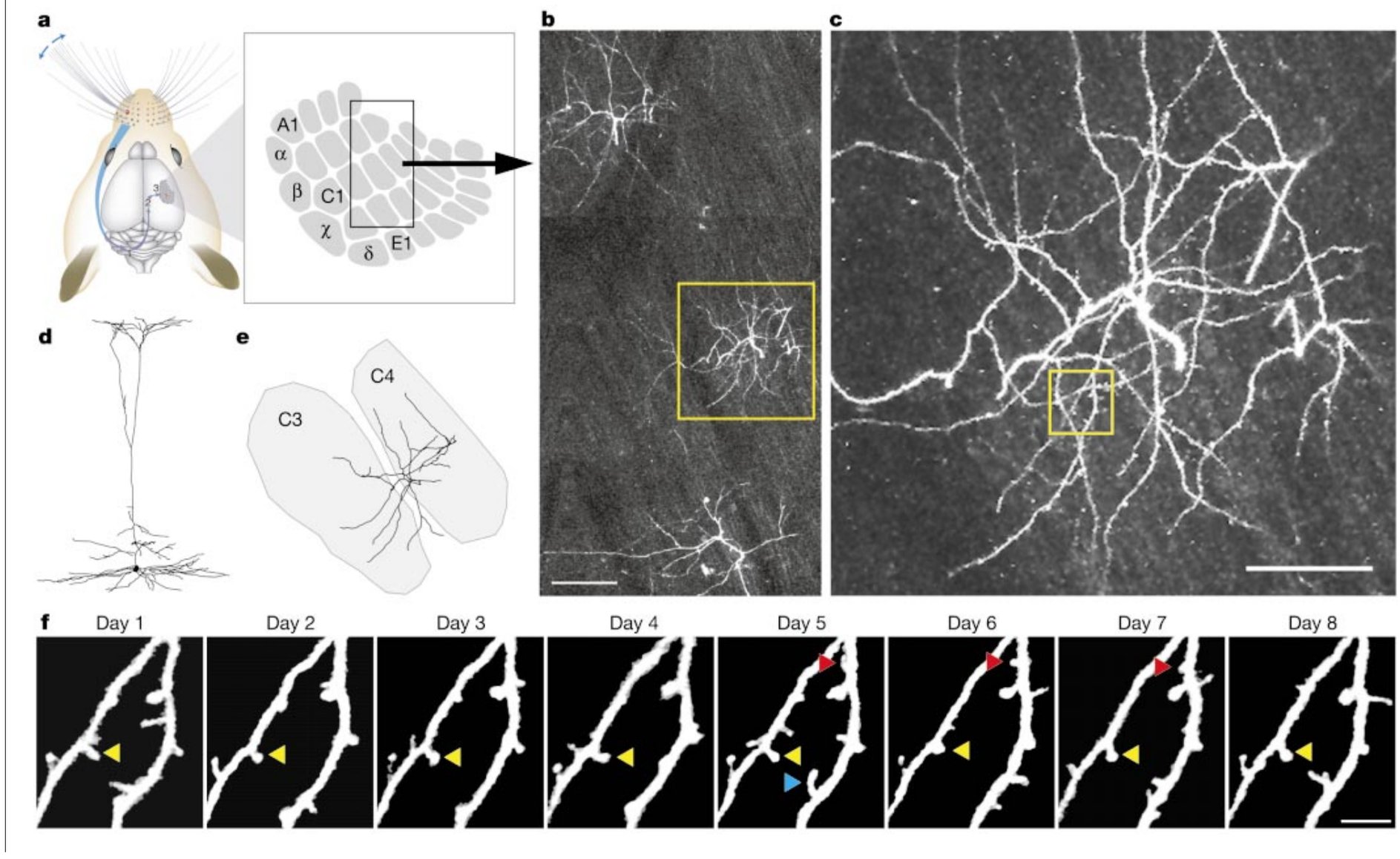


filling fraction = 3/7

s: spine length
L_d: total dendritic length per neuron
b: inter-bouton distance
n: neuronal density

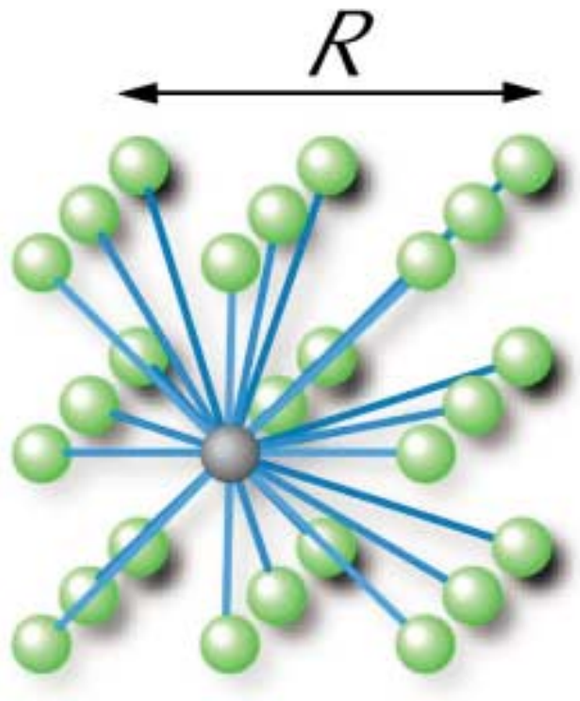
Stepanyants et. al., *Neuron* 2001

Structural Plasticity of Synaptic Connectivity



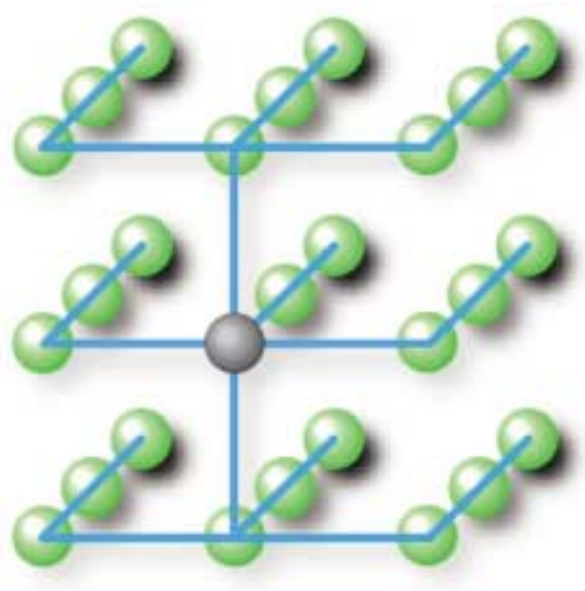
Trachtenberg et., al. *Nature* 2002

A toy problem: why do we need axons and dendrites?



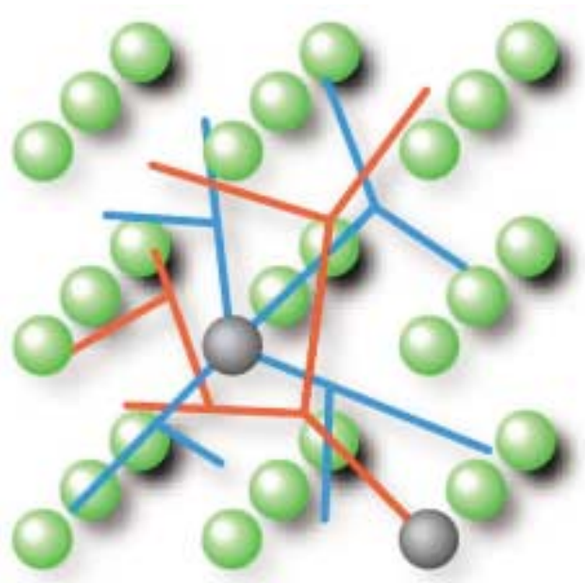
Design 1

A toy problem: why do we need axons and dendrites?



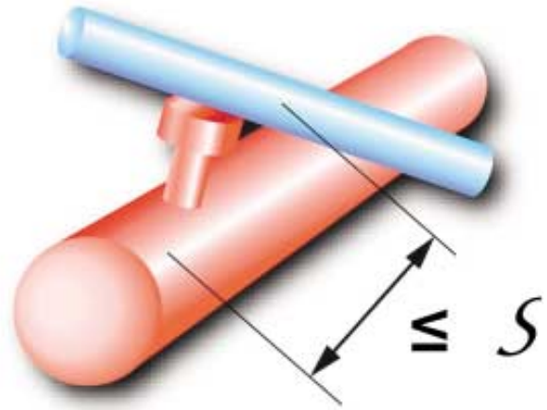
Design II

A toy problem: why do we need axons and dendrites?



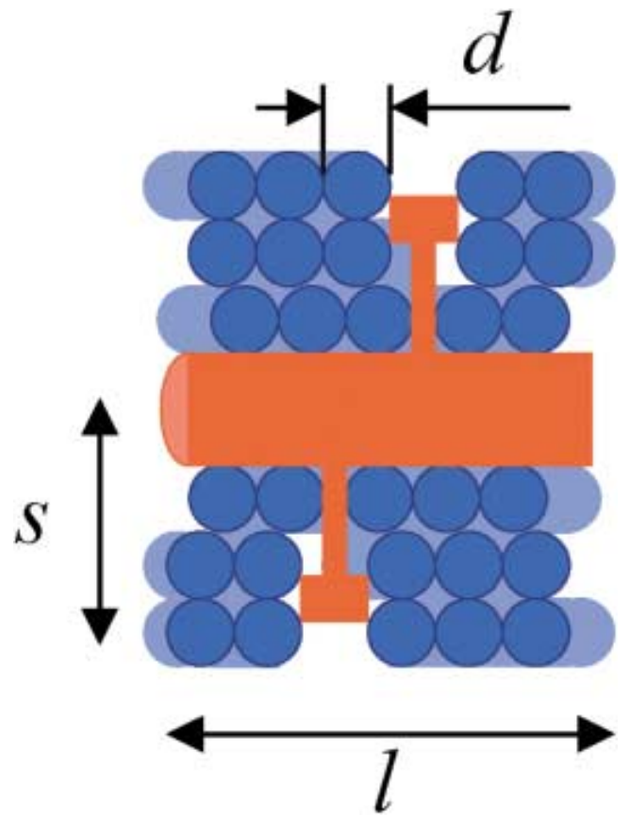
Design III

A toy problem: why do we need axons and dendrites?



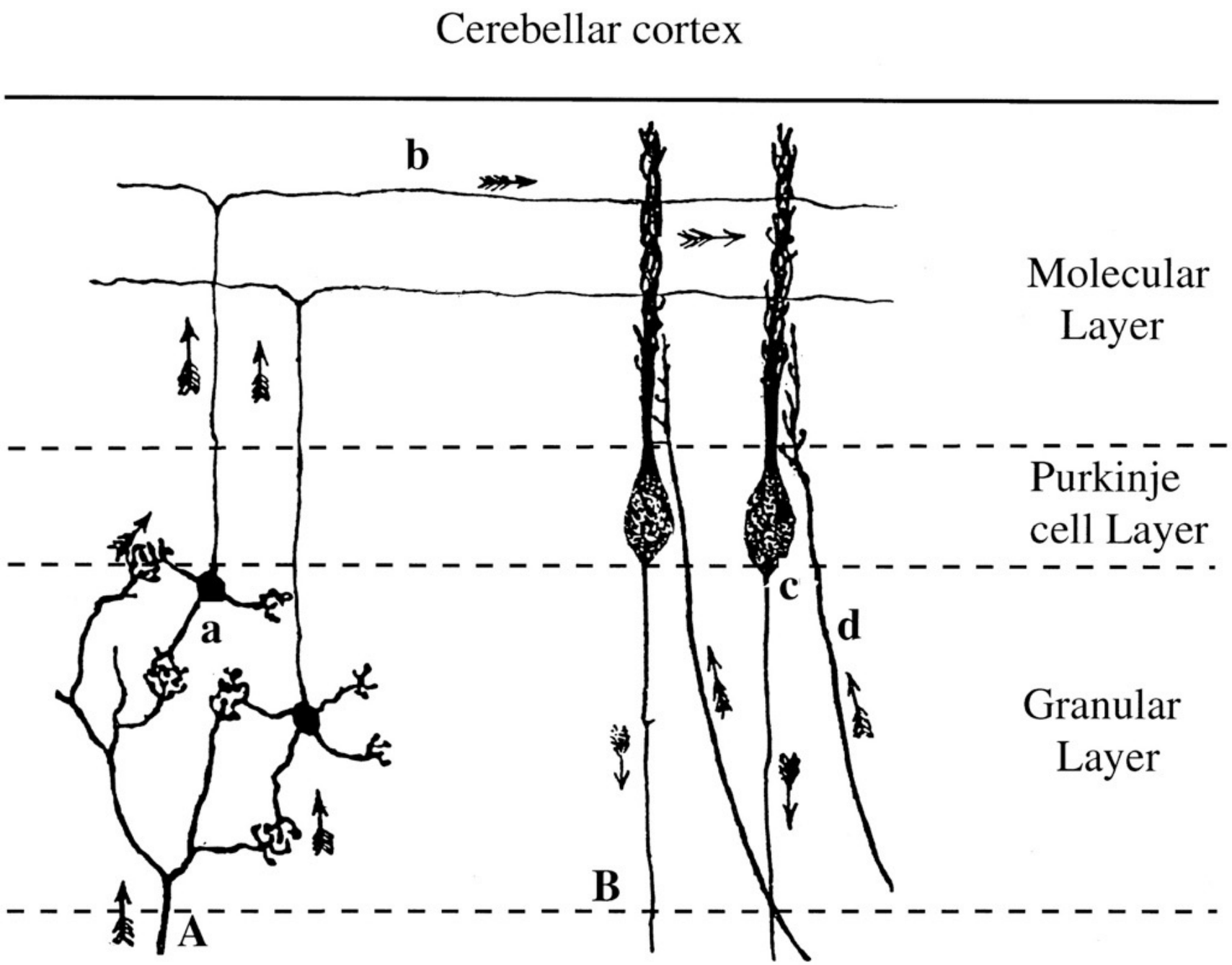
Design IV

Why do we need axons and dendrites?



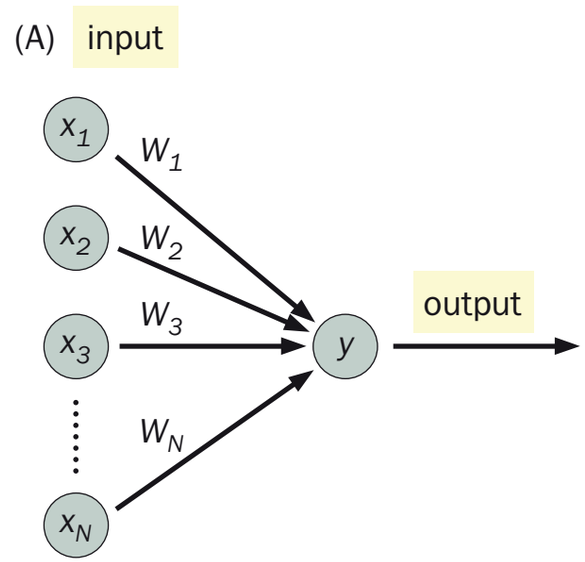
The Optimality of the design

Chklovskii *Neuron* 2004



Cajal's drawing of the cerebellar cortex

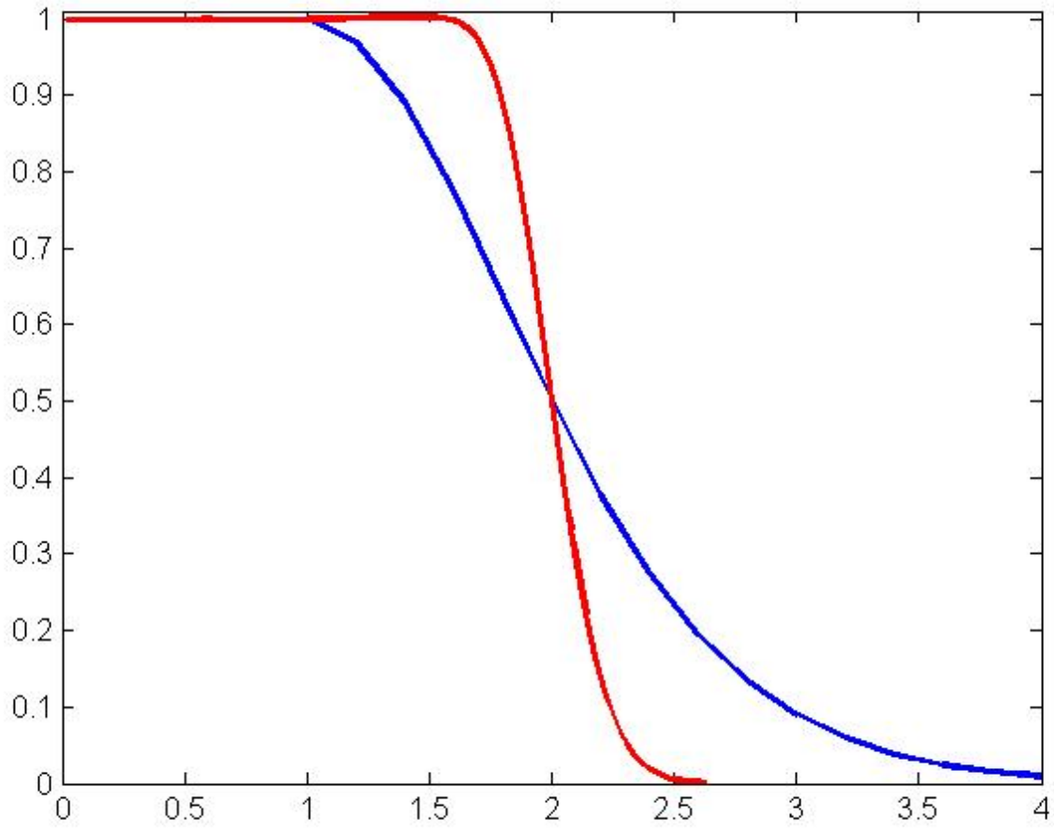
Mcculloch-Pitts neuron and the Perceptron model



$$y = \text{sign}\left(\sum_{i=1}^{N} W_i x_i - \theta \right)$$

Critical Capacity

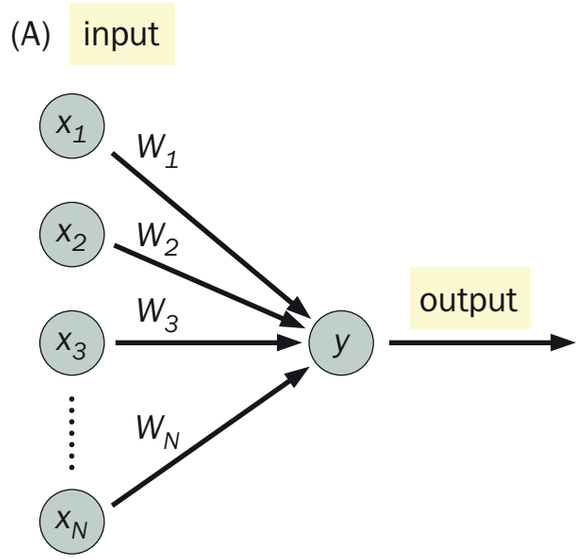
$$\frac{C(P,N)}{2^P}$$



$$\alpha = P/N$$

$$C(P,N) = 2\sum_{k=0}^{N-1}\binom{P-1}{k}$$

The Perceptron learning algorithm

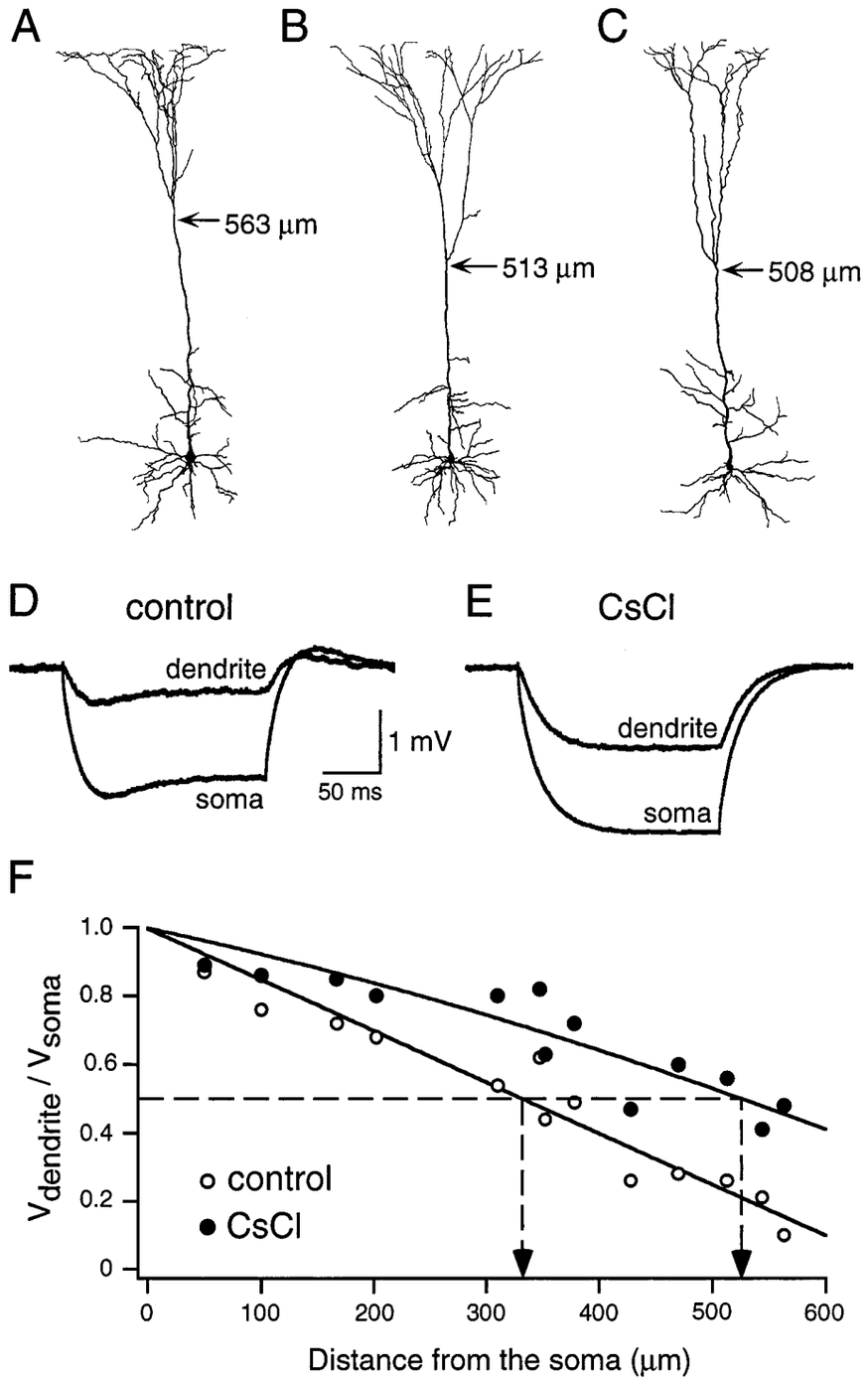


$$y = \text{sign}\left(\sum_{i=1}^{N} w_i x_i - \theta\right)$$

$$\mathbf{W} \leftarrow \mathbf{W} + \eta(y_0^n - y)\mathbf{X^n}$$

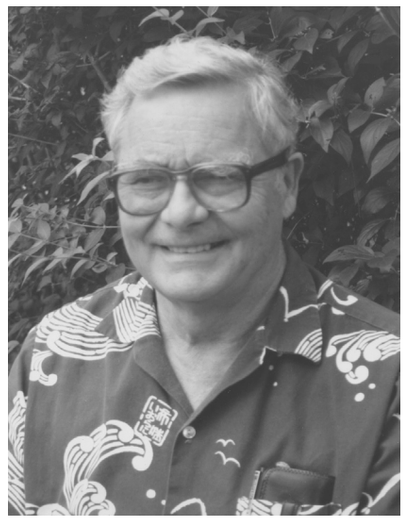
The roles of dendrites beyond connectivity

One of the hidden features that you cannot see in the wiring diagram



Stuart & Spruston J Neuroscience 1998

Wilfred Rall and the cable equation



Wilfrid Rall

Fundamental Equations

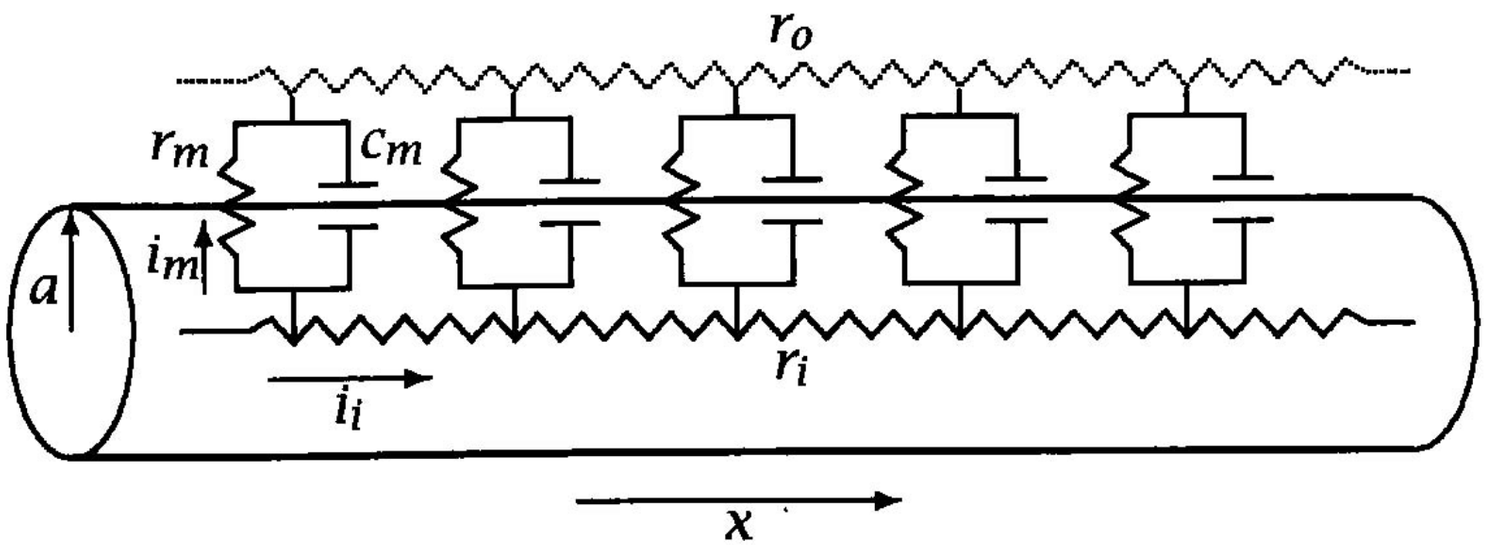
The derivation of the differential equation for distributions of passive electrotonic potential in uniform cylinders is well established in the theory developed for axons (5, 9, 20). In regions containing no sources or sinks of externally applied current, this differential equation can be expressed

$$\lambda^2 \frac{\partial^2 V}{\partial x^2} = V + \tau \frac{\partial V}{\partial t}, \qquad [1]$$

where $V = V_m - E$ is the electrotonic potential, x represents distance along the axis of the cylinder, $\tau = R_m C_m$ is the membrane time constant, and $\lambda = [(d/4)(R_m/R_i)]^{1/2}$ is the characteristic length constant.[3]

Experimental Neurology 1959

The basic assumption of cable theory: dendrites are cylinders!



r_i = axial resistance (Ω/cm)

r_m = membrane resistance (Ω-cm)

c_m = membrane capacitance (F/cm)

Simplifying assumptions:

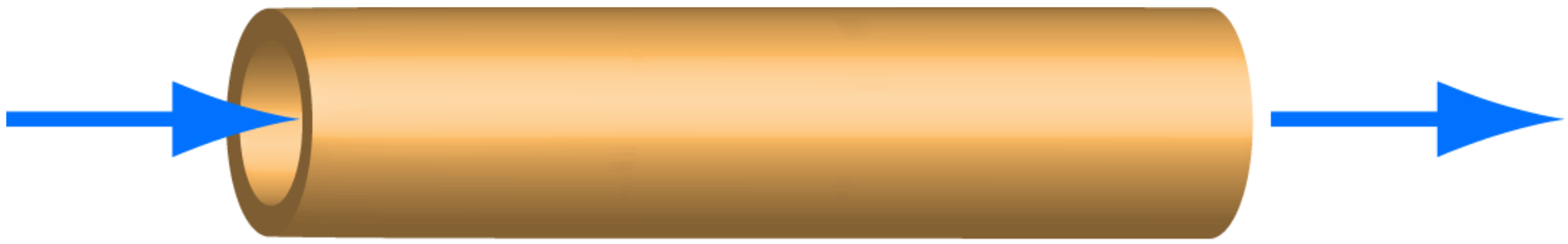
1. Extracellular resistance r_o=0

2. Membrane properties are uniform throughout, for all parts of the cylinder and are independent of membrane potential – no voltage gated channels.

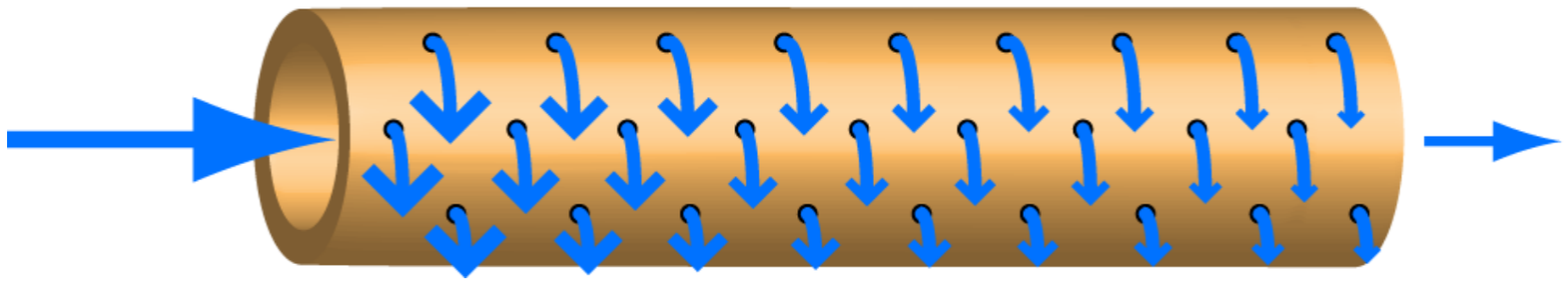
3. Current flow is along a single dimension, *x*. So, there's no radial current

Cable equation: a garden hose analogy

Non-leaky hose



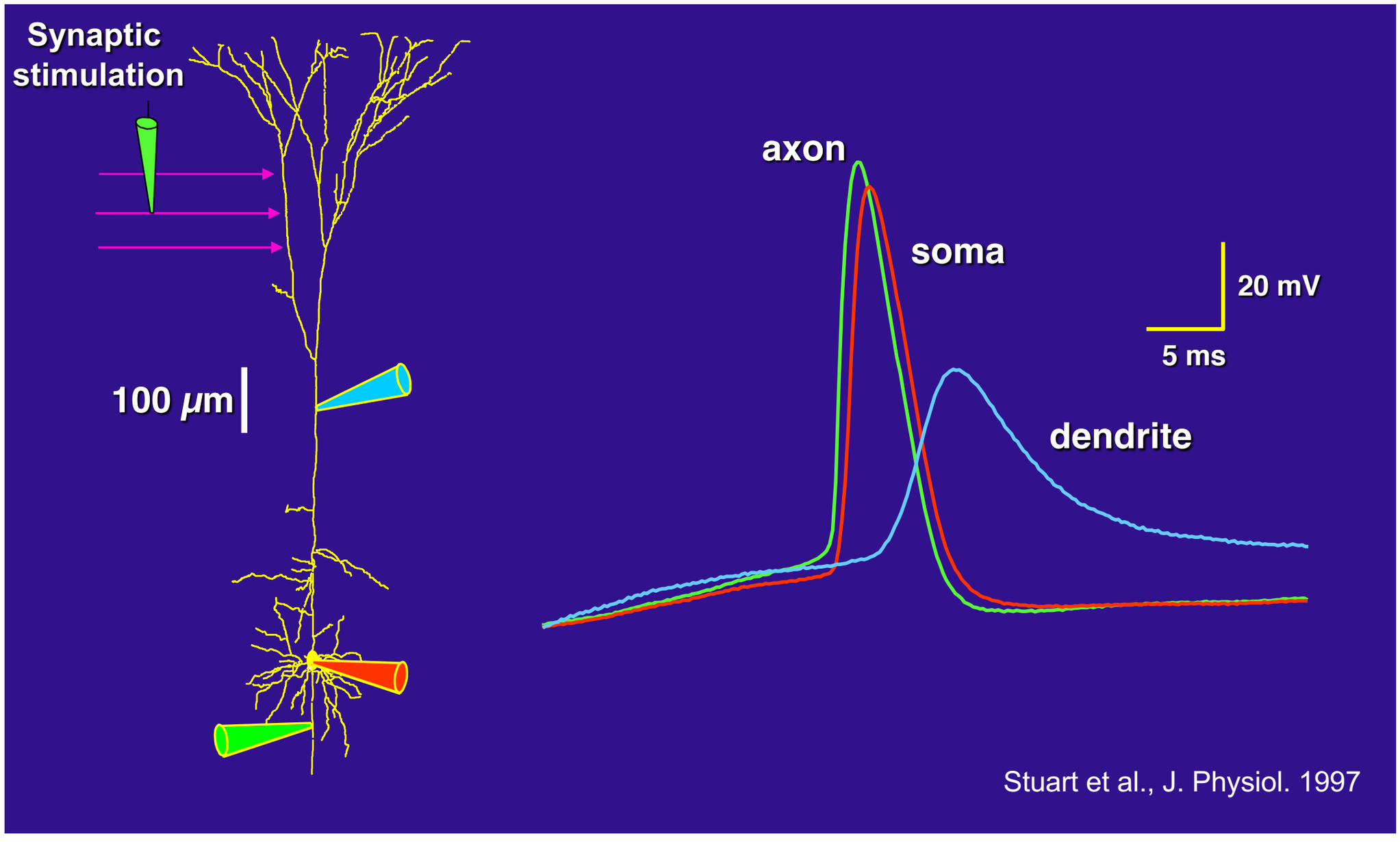
Leaky hose



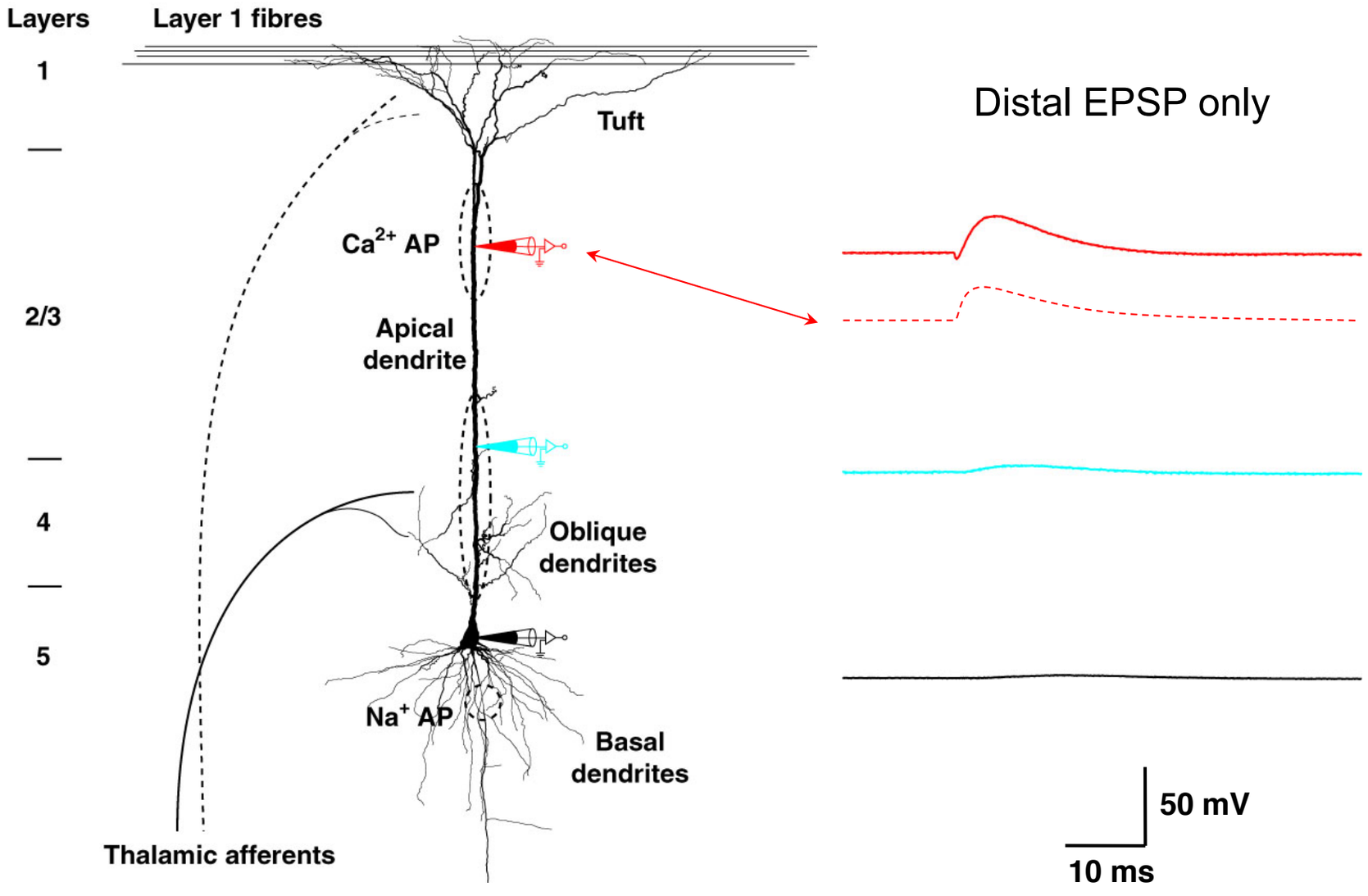
Propagation through neuronal dendrites is similar to water flow through a leaky hose!

A derivation

Action potential generation and back propagation in dendrites

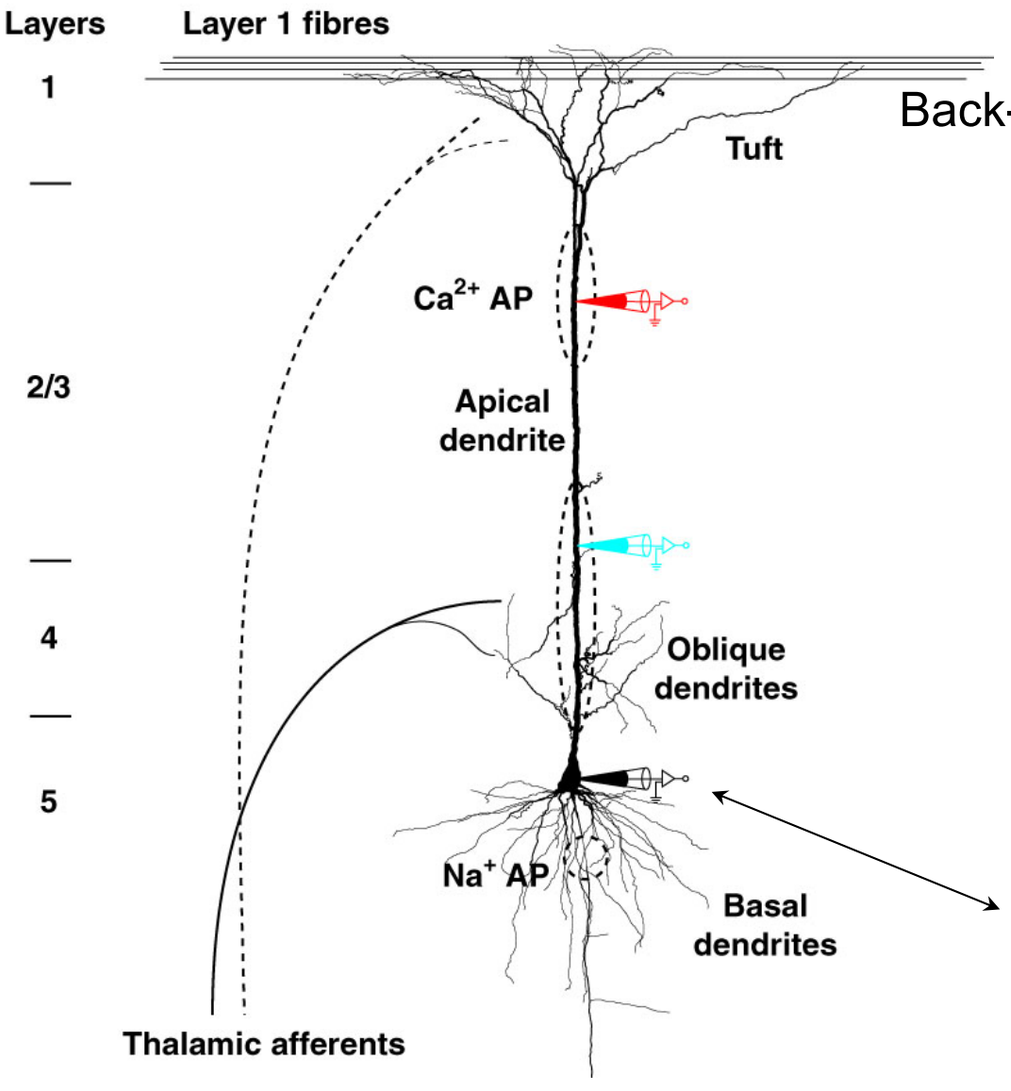


Interaction between back-propagation of action potentials and Ca^{2+} spike

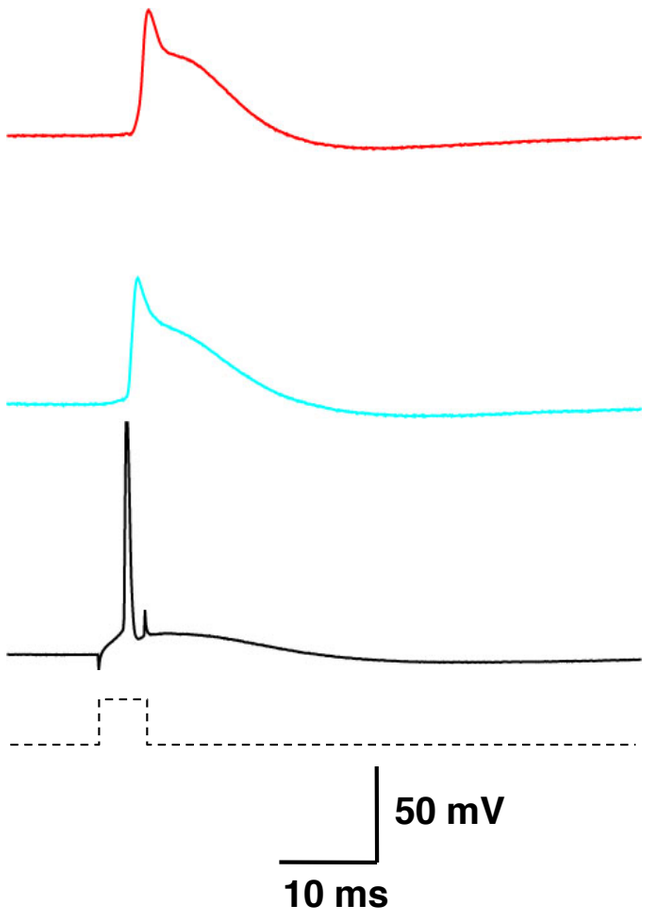


Larkum, Zhu & Sakmann - Nature, 1999

Interaction between back-propagation of action potentials and Ca^{2+} spike



Back-propagating action potential only



Larkum, Zhu & Sakmann - Nature, 1999

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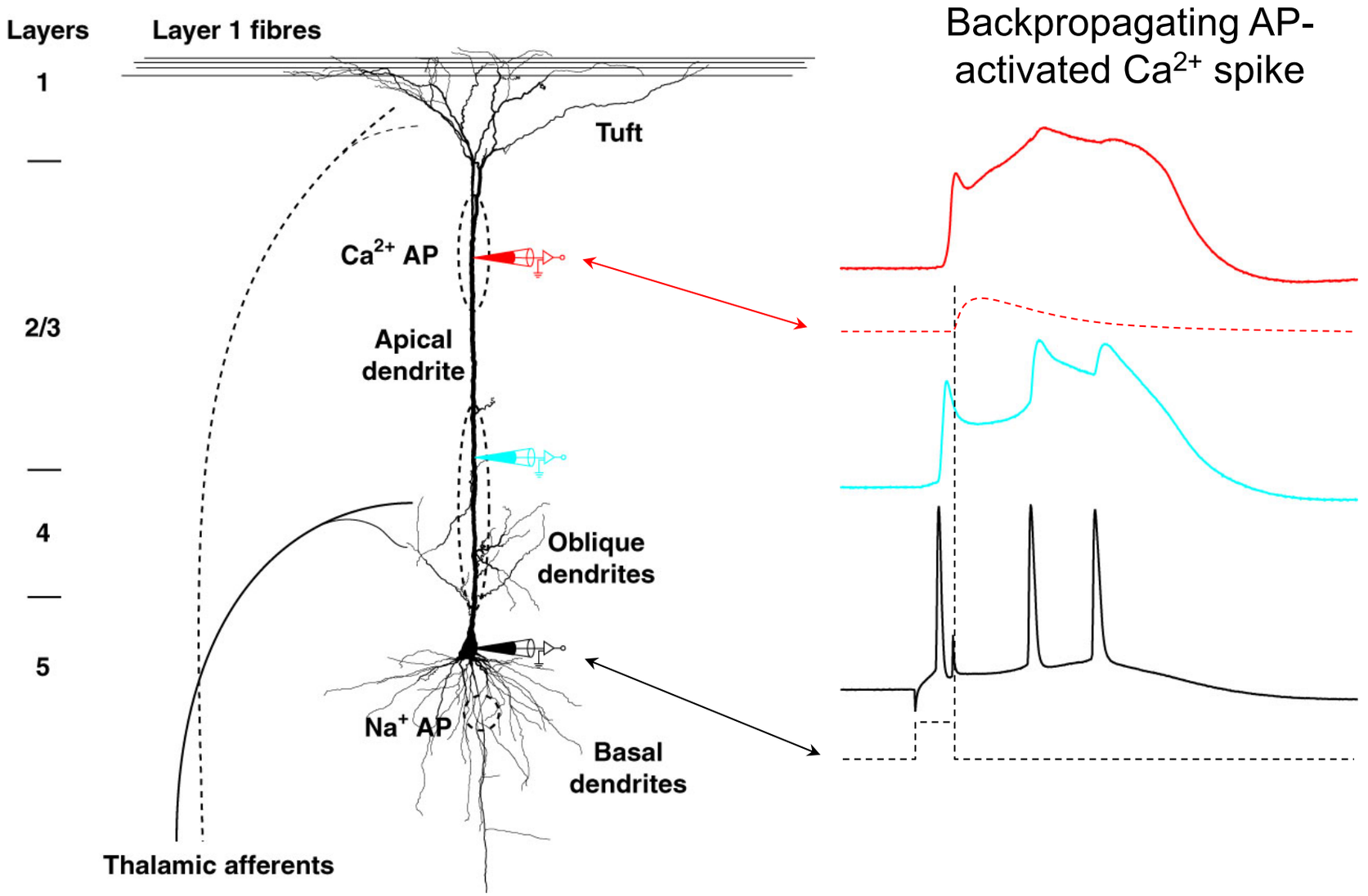
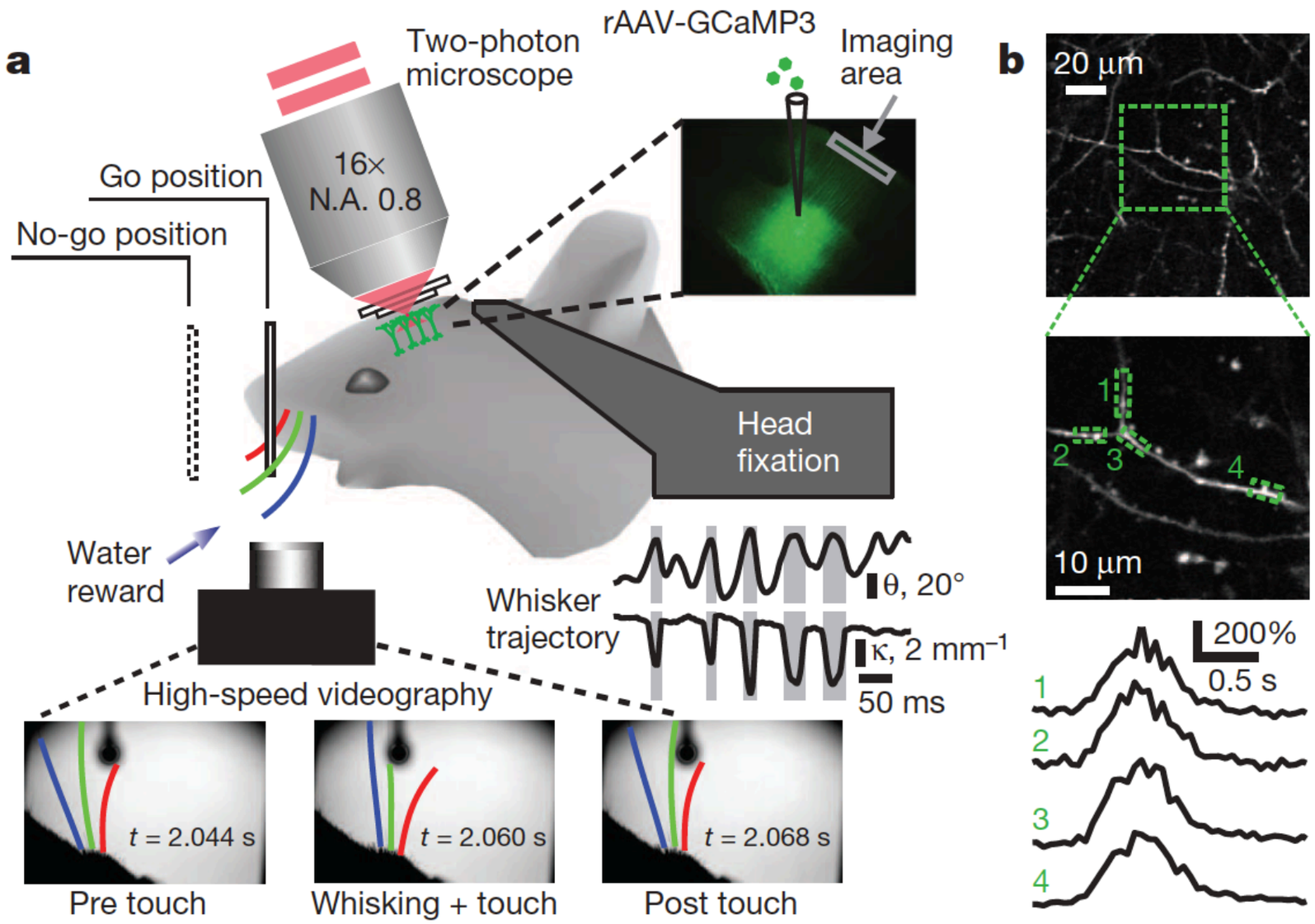


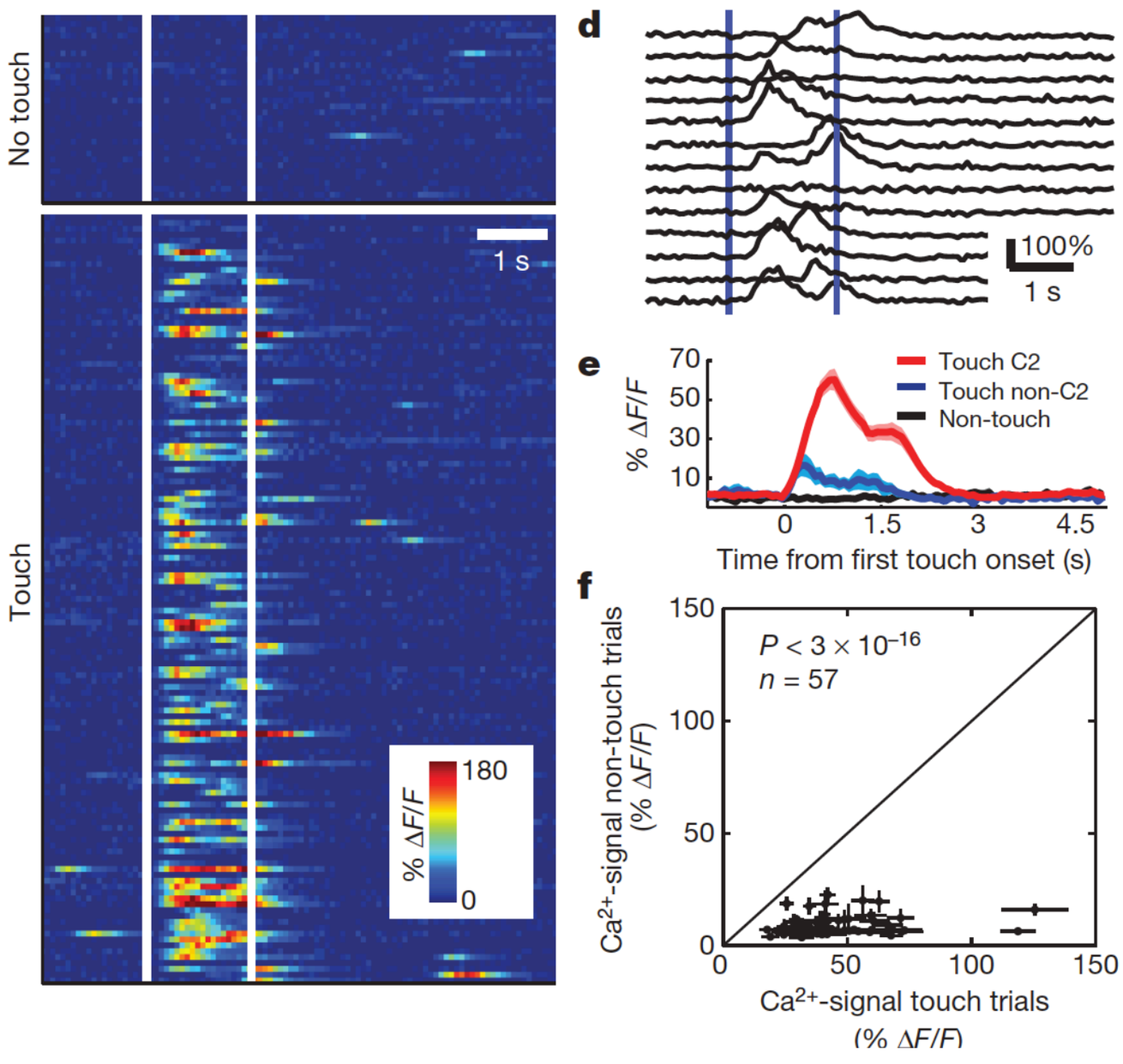
Larkum, Zhu & Sakmann - Nature, 1999

Specific dendritic Ca^{2+} signal during active sensing



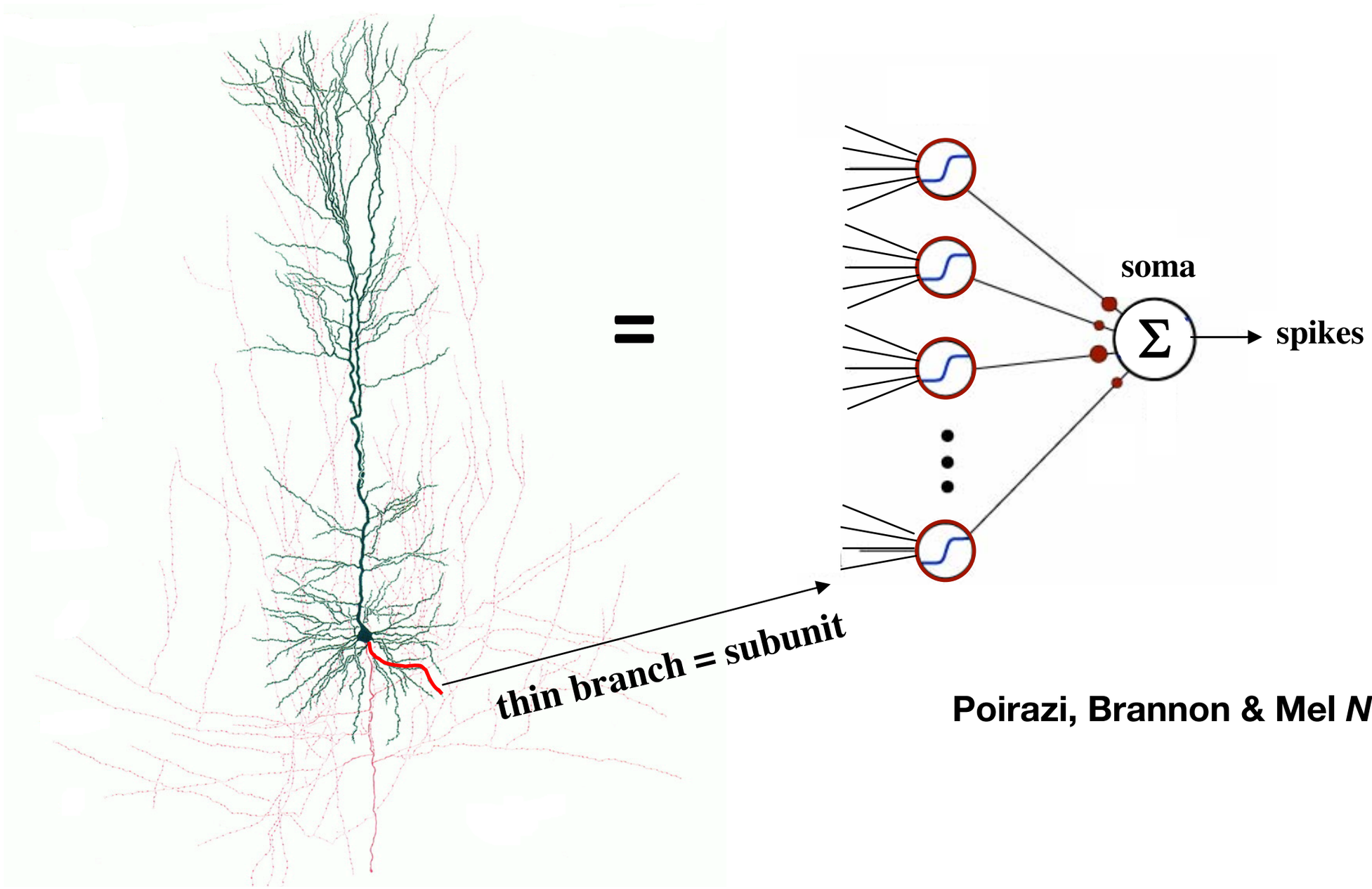
Xu et al *Nature* 2012

Specific dendritic Ca^{2+} signal during active sensing



Xu et al *Nature* 2012

Dendritic compartment and nonlinear integration



Poirazi, Brannon & Mel *Neuron 2003*

Single Cortical Neurons as Deep Artificial Neural Networks

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Can Single Neurons Solve MNIST? The Computational Power of Biological Dendritic Trees

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