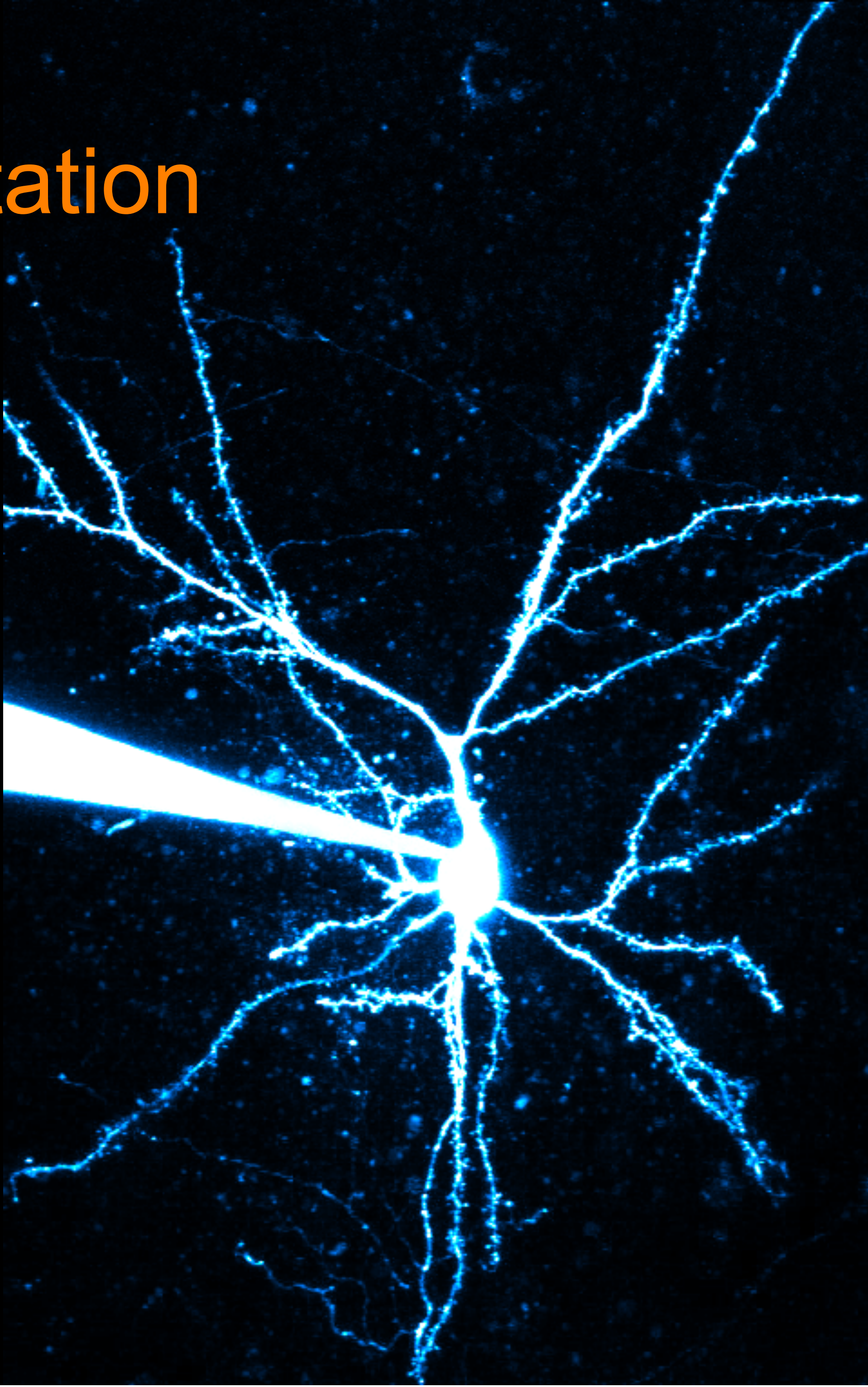
Single neuron computation



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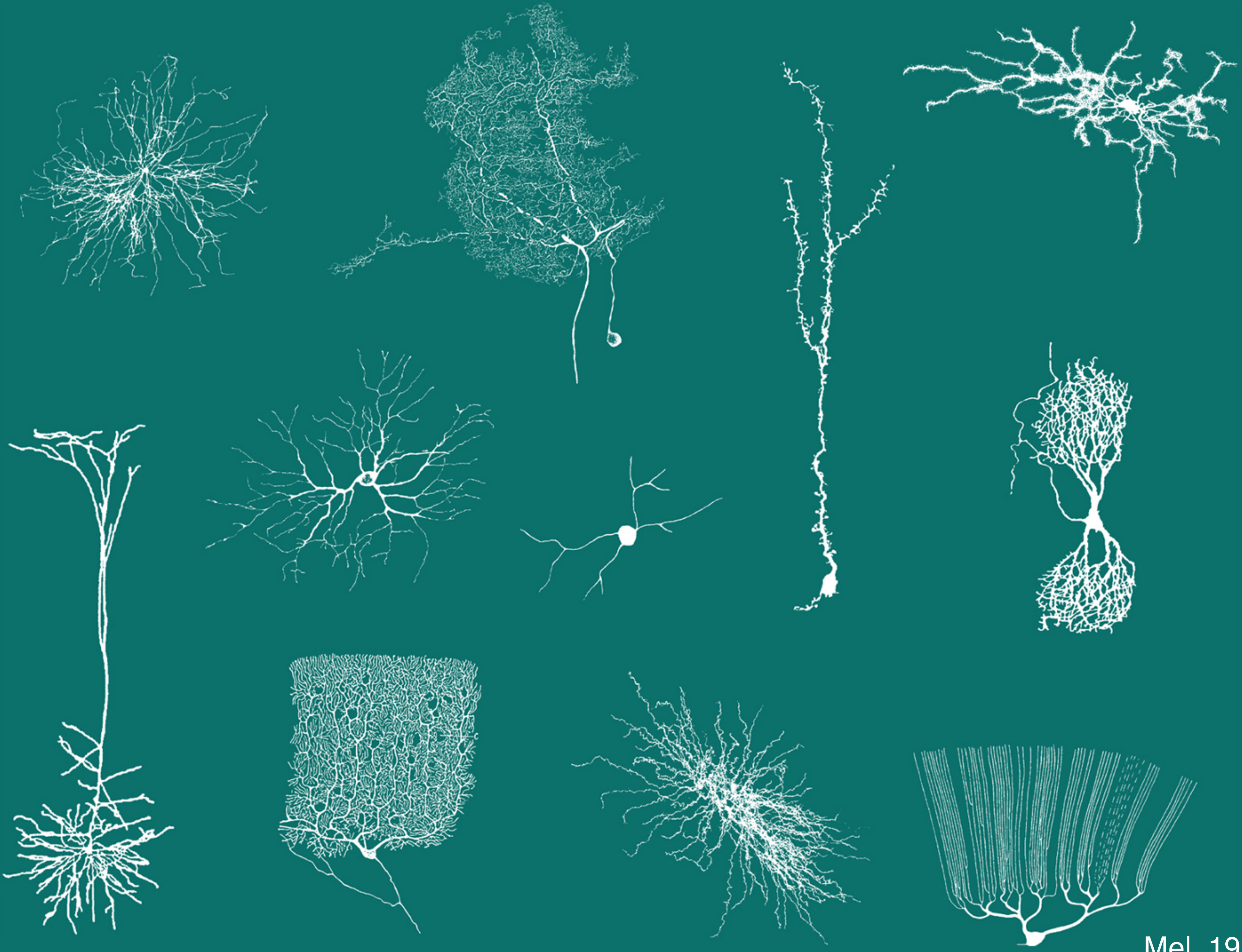
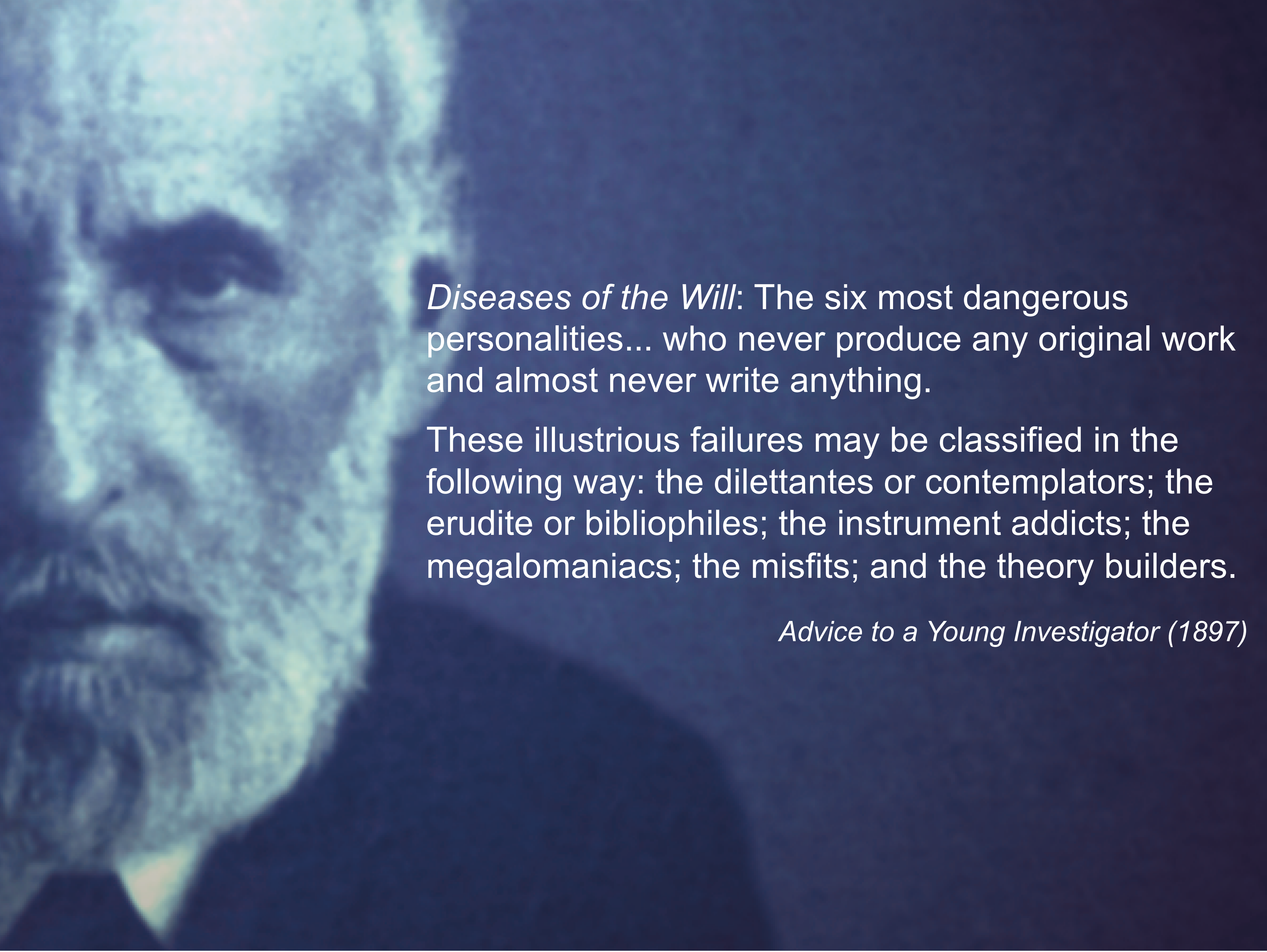
www.dendrites.org

Outline of the lecture

0. Introduction
1. The “Dendritic toolkit” for computation
2. Active dendrites *in vivo*
3. Active dendrites during behaviour
4. Conclusion and perspectives



Mel, 1994



Diseases of the Will: The six most dangerous personalities... who never produce any original work and almost never write anything.

These illustrious failures may be classified in the following way: the dilettantes or contemplators; the erudite or bibliophiles; the instrument addicts; the megalomaniacs; the misfits; and the theory builders.

Advice to a Young Investigator (1897)

Dendritic Computation

Michael London and Michael Häusser

Key Words

dendrites, coding, synaptic integration, spikes, ion channels

Abstract

One of the central questions in neuroscience is how particular tasks, or computations, are implemented by neural networks to generate behavior. The prevailing view has been that information processing in neural networks results primarily from the properties of synapses and the connectivity of neurons within the network, with the intrinsic excitability of single neurons playing a lesser role. As a consequence, the contribution of single neurons to computation in the brain has long been underestimated. Here we review recent work showing that neuronal dendrites exhibit a range of linear and nonlinear mechanisms that allow them to implement elementary computations. We discuss why these dendritic properties may be essential for the computations performed by the neuron and the network and provide theoretical and experimental examples to support this view.

Annu. Rev. Neurosci.
2005. 28:503–32

HOW CAN WE PROVE THAT DENDRITES ARE INVOLVED IN COMPUTATION?

Identify the Computation:

Probing the contribution of dendrites to computation is possible only when the computation of the neuron bearing the dendrites is identified. This requires identifying a simple behavior that involves a recognizable kind of computation (e.g., filtering, convolution, pattern recognition) and tracing it to the neurons responsible.

Defining the Mechanism:

Use recordings (e.g., electrophysiological or imaging) from dendrites of these neurons in an accessible preparation (e.g., brain slices) to define the dendritic signals and biophysical mechanisms that may underlie the behavior.

Correlation in the Intact Preparation:

Use recordings from dendrites in an intact preparation to show strong correlations between dendritic signals linked with the identified computation and the behavior of the animal.

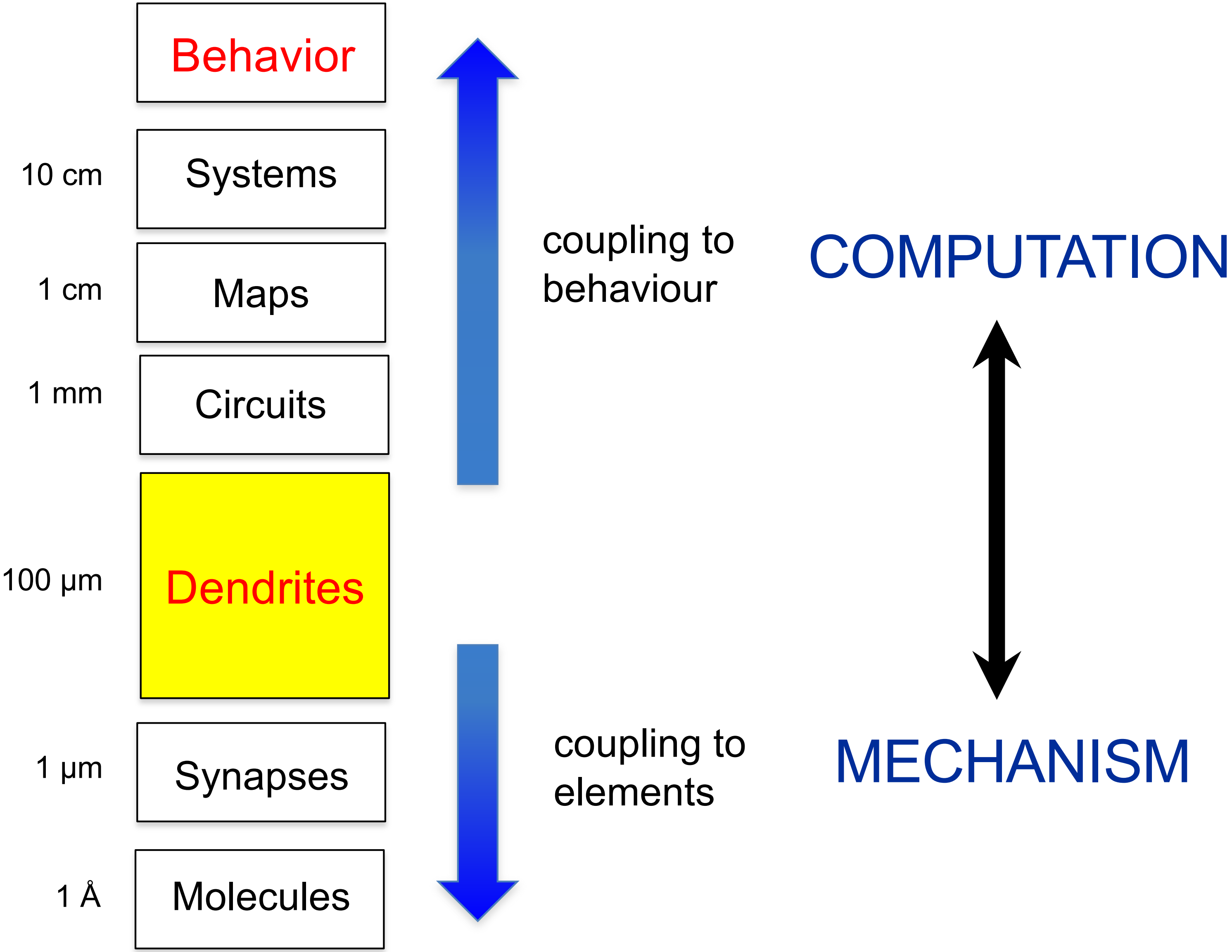
Manipulation to Define a Causal Link:

Manipulate a dendritic mechanism to determine if it is both necessary and sufficient to explain the computation. Selectively knock out the mechanism and demonstrate that the behavior is impaired. Activate or modify the dendritic mechanism to demonstrate that the behavior is modified in the expected direction.

Modeling the Computation:

Use modeling to define an algorithm that describes the computation, or sequence of computations, performed by the dendrites that can plausibly explain the behavior. Modeling of single neurons and neural networks can also be used to confirm that the computation can convey a significant benefit (which can help to establish sufficiency).

The goal: coupling dendritic physiology to behaviour



	Behavior
10 cm	Systems
1 cm	Maps
1 mm	Circuits
100 μm	Dendrites
1 μm	Synapses
1 Å	Molecules

coupling to behaviour

COMPUTATION

MECHANISM

coupling to elements

Current flow in neurons with dendrites

FIG. 1. Diagram illustrating the flow of electric current from a microelectrode whose tip penetrates the cell body (soma) of a neuron. The full extent of the dendrites is not shown. The external electrode to which the current flows is at a distance far beyond the limits of this diagram.

Wilfrid Rall (1922 – 2018)

Neuron

Obituary

Wilfrid Rall (1922–2018)

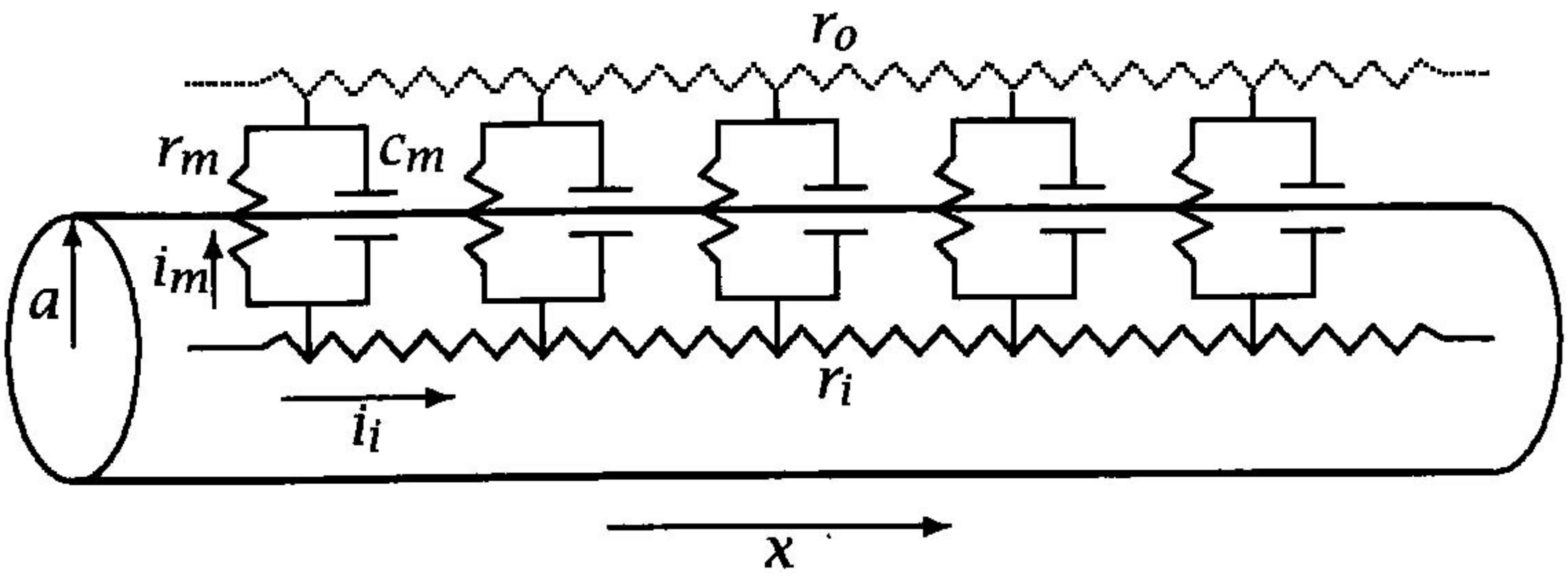
Wilfrid (Wil) Rall was an outstanding scientist and a unique person—warm and modest, despite being a scientific renaissance man. He is the founding father of the field of dendritic modeling and the developer of both cable theory and the compartmental modeling approach for studying dendrites and synaptic integration. He was the first to draw attention to the computational role of dendrites, to dendritic nonlinearities, and to plastic processes in dendritic spines. It is thanks to Rall's 40 years of pioneering theoretical studies, dendrites have become the focus of worldwide research interest, culminating in the recent evidence that local dendritic processing may play a key role in behavior. Rall is among a very few neuroscientists that, almost single-handedly, have changed our understanding of our

The Rall revolution began with a brief paper in *Science* in 1957 with the demonstration that electric current flow in neurons is dominated not by the cell body, as previously thought, but by the extensive dendritic tree. He thus yearned to understand whether, and if so in what way, the branching structure and biophysical properties of dendrites could have functional implications. For a theorist, the message is clear: when estimating parameters like the specific membrane resistivity (R_m) in a spatially distributed system, one should use the appropriate theoretical treatment/formulation. In this case Rall applied cable theory, challenging the "point-neuron model" proposed by Eccles, which overestimated the leakiness (i.e., underestimated the value of R_m) of the dendrites.

science. But good work prevails, and indeed Rall's fundamental and deep insights regarding the implications of cable properties of dendrites gradually penetrated deeply into the scientific community interested in understanding signal flow and synaptic integration in dendrites. The basis of this work was the cable equation (first introduced by Lord Kelvin), which was solved by Rall to describe current flow in dendrites as branching cylindrical structures. This meant solving analytically the cable equation with boundary conditions that represent repeatedly branched cables, each branch having a particular diameter, specific membrane resistivity (R_m), capacitance (C_m), and cytoplasmic resistivity (R_i). Rall's recursive solution method enabled the calculation of the impact of

Neuron, Sept. 5, 2018

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:

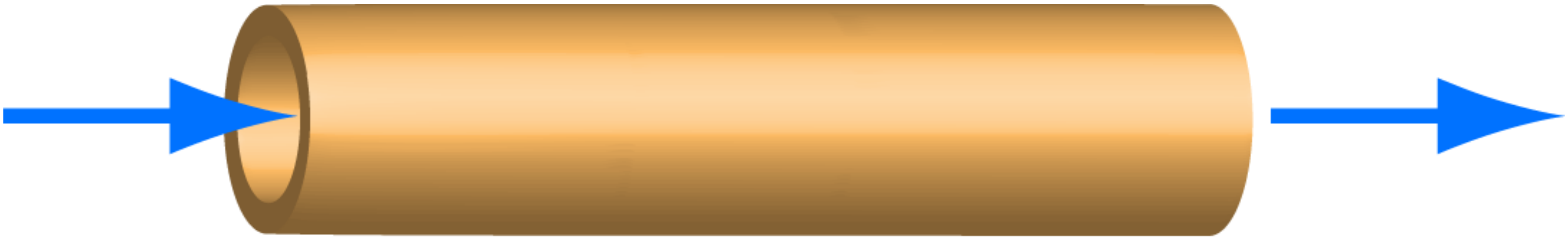
1. Extracellular resistance r_o=0

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

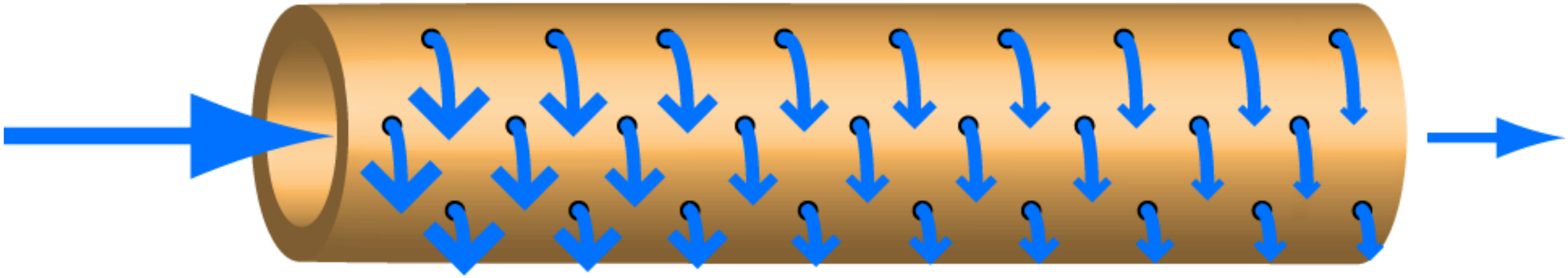
3. Current flow is along a single dimension, x. So, there's no radial current

Passive propagation in cables: the garden hose analogy

Non-leaky hose



Leaky hose



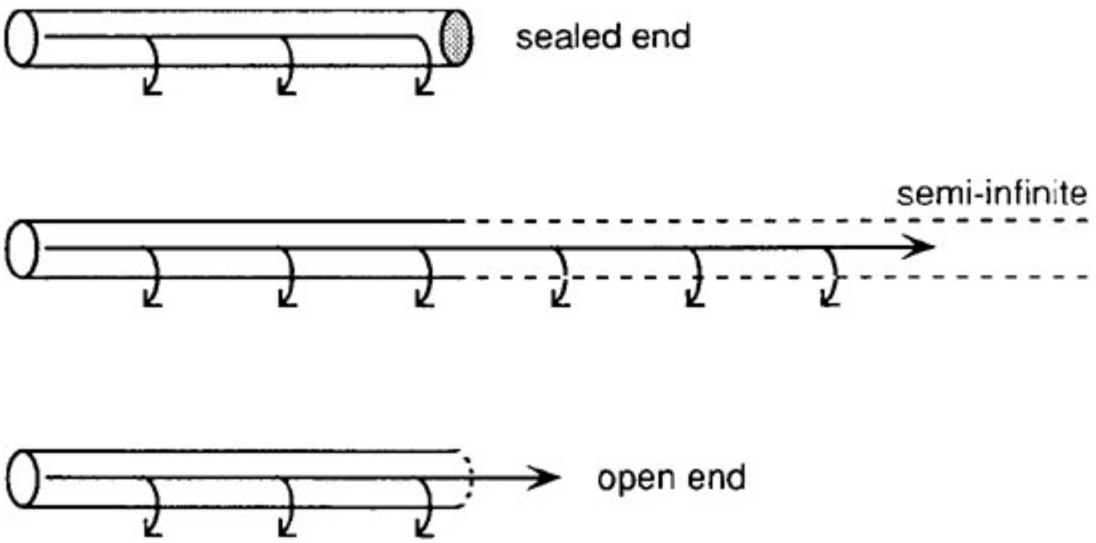
Propagation through neuronal dendrites is similar to water flow through a leaky hose!

THE CABLE EQUATION

$$\frac{\partial V}{\partial T} = -V + \frac{\partial^2 V}{\partial X^2}$$

Rall, 1962, 1977

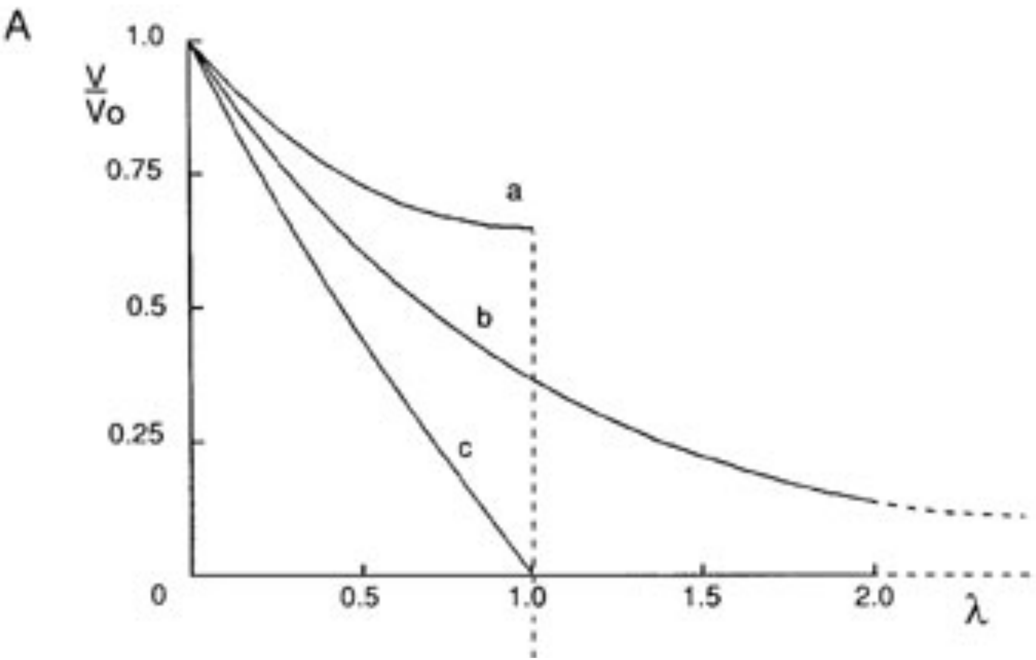
Cable equation describes voltage attenuation in different classes of cables



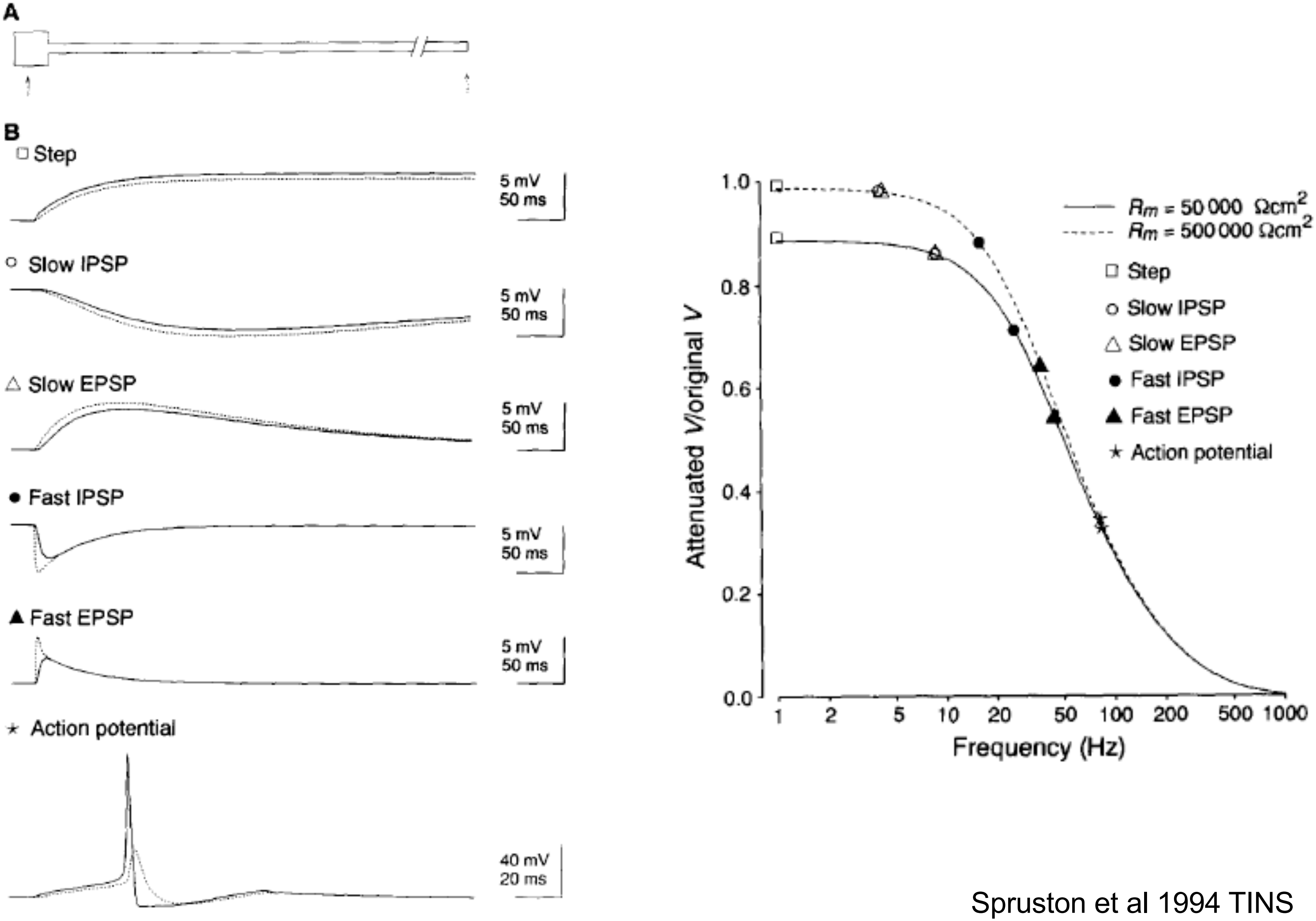
space constant

$$V = V_0 \bullet (1 - e^{-x/\lambda})$$

$$\lambda = \sqrt{\frac{R_m \bullet d}{R_i \bullet 4}}$$



Voltage attenuation is also frequency dependent



Spruston et al 1994 TINS

Rall’s single equivalent cylinder model

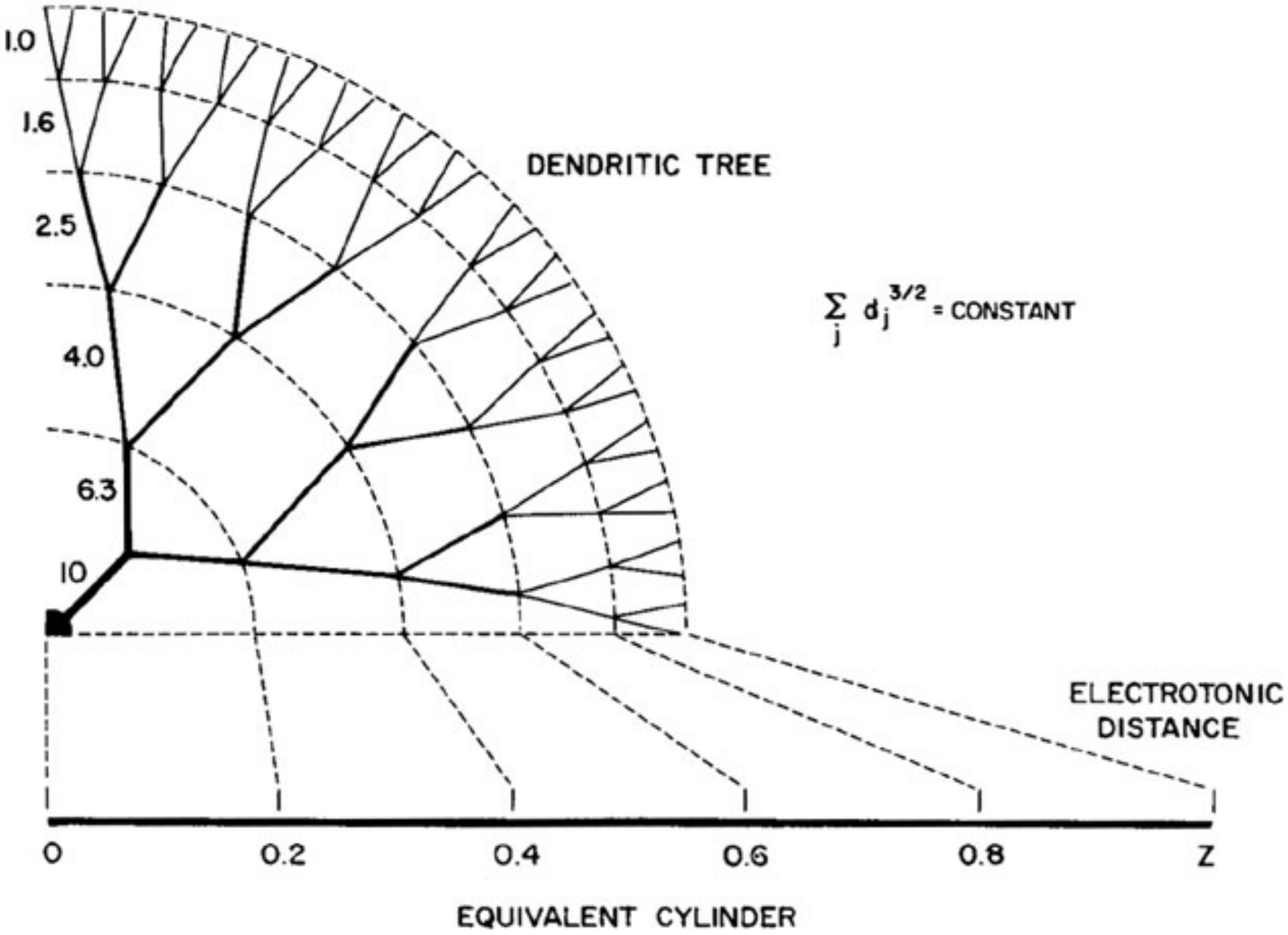
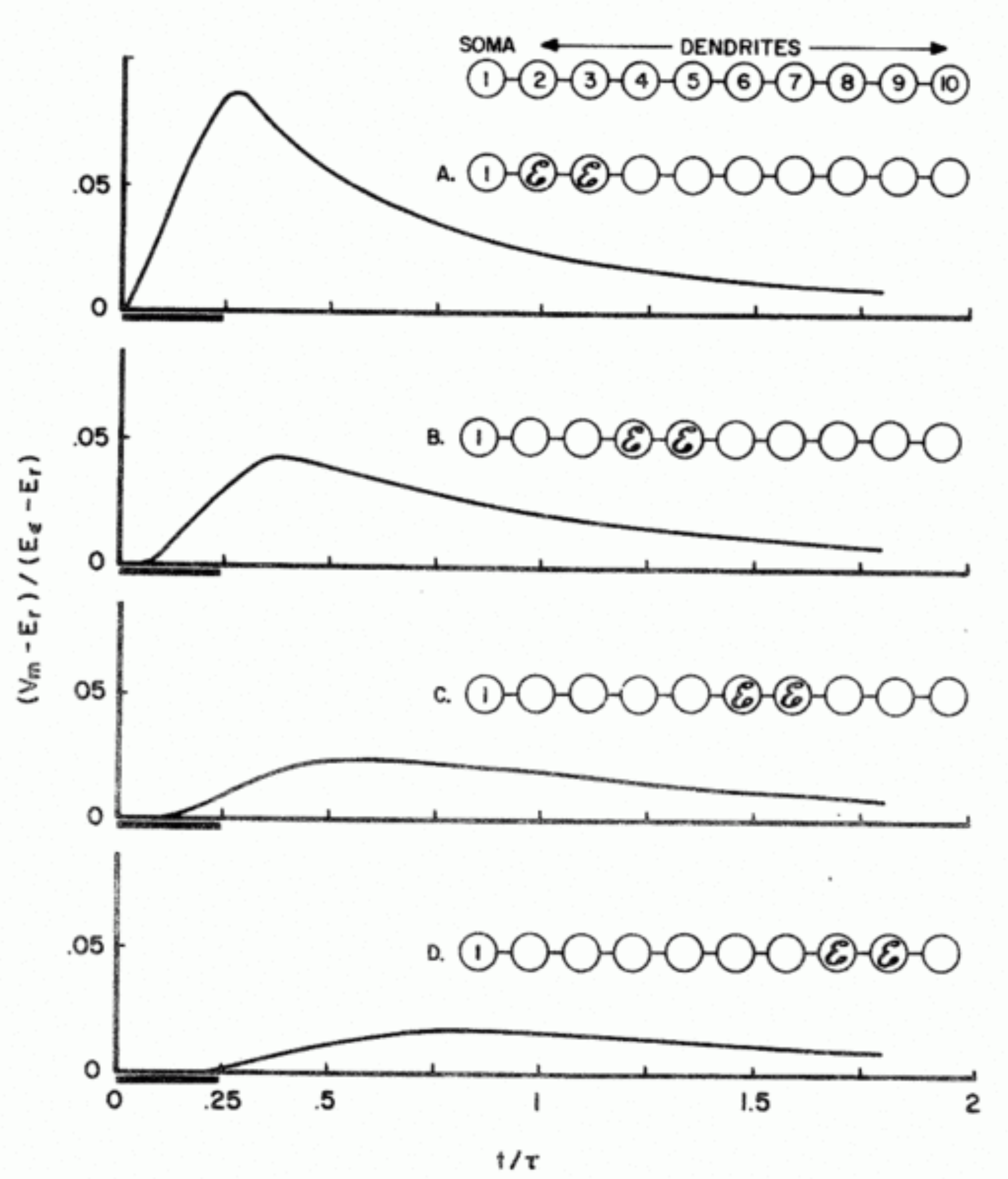


FIG. 4. A dendritic tree illustrative of a class of trees that can be mathematically transformed into an equivalent cylinder. The diagram corresponds to a specific numerical example (Rall, 1962a, Table I) of a symmetric tree with a radial extent of about 800 μ, and with cylindrical diameters decreasing from a trunk of 10 μ to peripheral branches of 1 μ. The dashed lines connect points having the same Z-value (electrotonic distance) in both tree and cylinder. Z is defined by

Rall, 1964

Attenuation of EPSPs in the single equivalent cylinder



⇒ the size and shape of somatic EPSPs depends on location of dendritic origin

Rall, 1964

The NEURON simulation environment

NEURON *for empirically-based simulations of neurons and networks of neurons*

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- What is it?
- System requirements

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- Research using NEURON

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an archive of published models that are ready to run!

Demonstrations and Examples

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where John Moore distributes NEURON plus a large collection of helpful documents on its use in education and research

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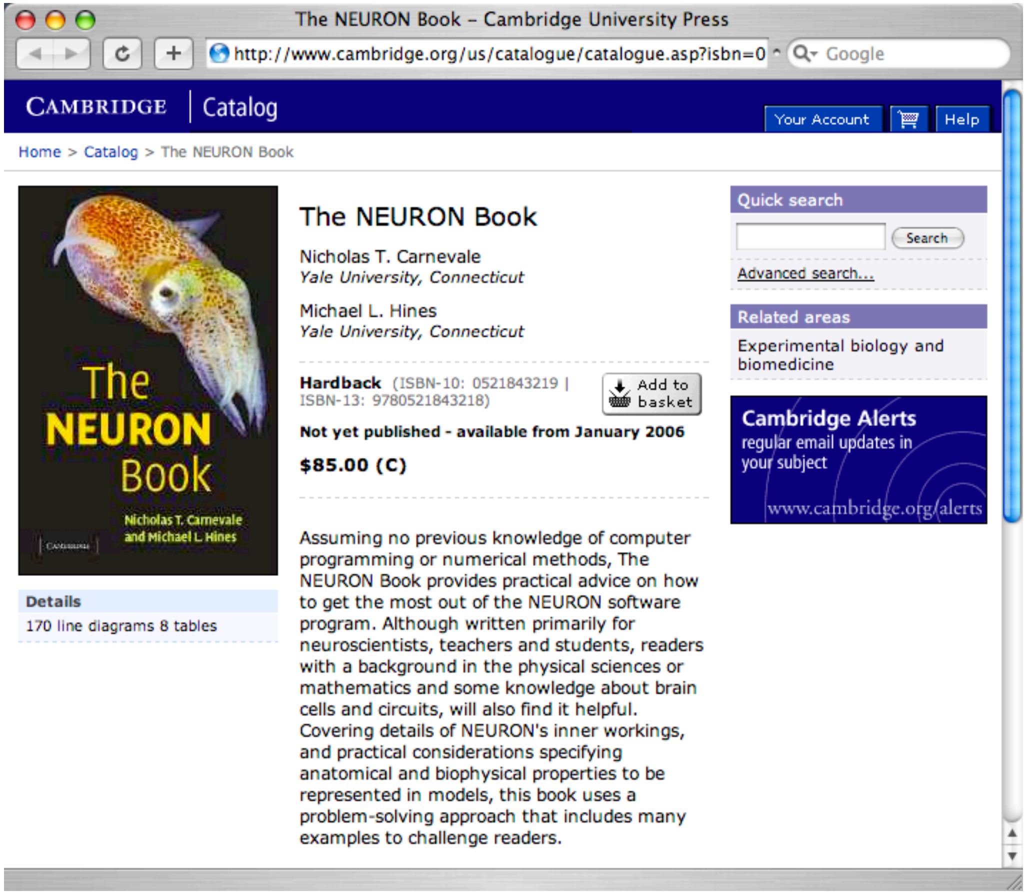

Home > Catalog > The NEURON Book

The NEURON Book

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Yale University, Connecticut

Michael L. Hines
Yale University, Connecticut

Hardback (ISBN-10: 0521843219 | ISBN-13: 9780521843218)

Not yet published - available from January 2006

$85.00 (C)

Assuming no previous knowledge of computer programming or numerical methods, The NEURON Book provides practical advice on how to get the most out of the NEURON software program. Although written primarily for neuroscientists, teachers and students, readers with a background in the physical sciences or mathematics and some knowledge about brain cells and circuits, will also find it helpful. Covering details of NEURON's inner workings, and practical considerations specifying anatomical and biophysical properties to be represented in models, this book uses a problem-solving approach that includes many examples to challenge readers.

Details
170 line diagrams 8 tables

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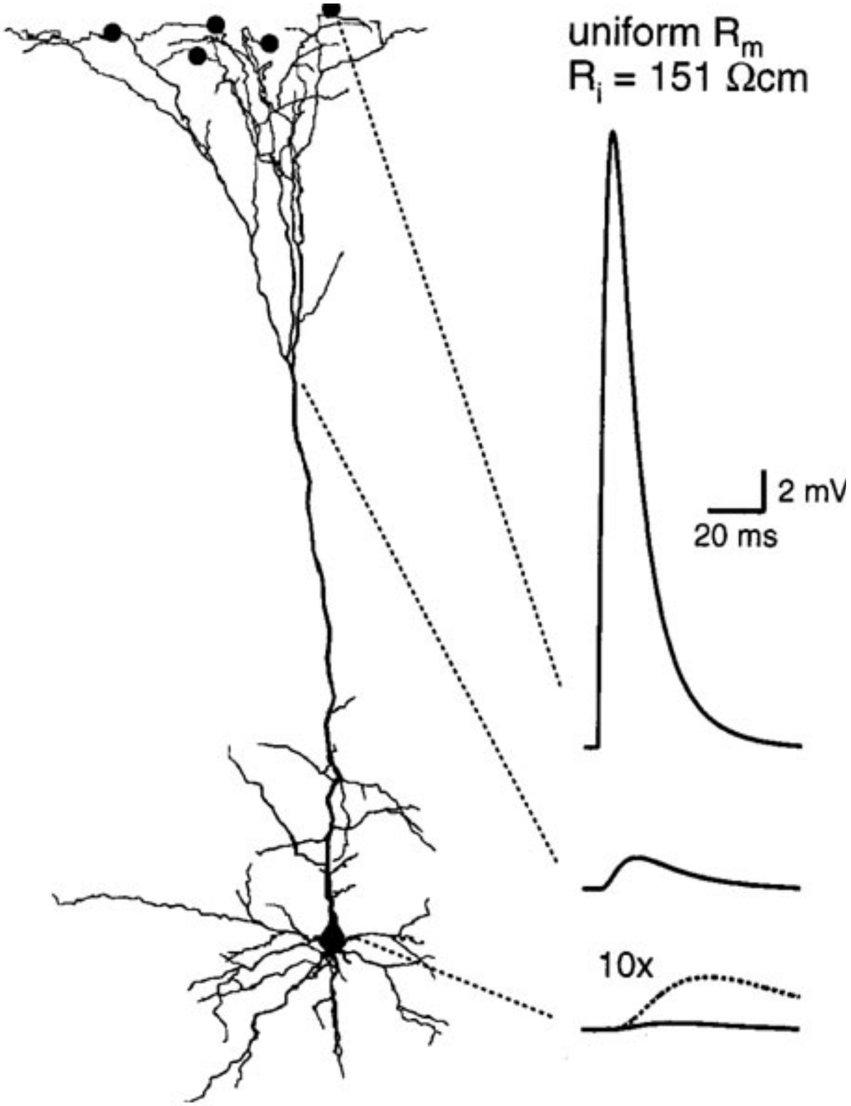
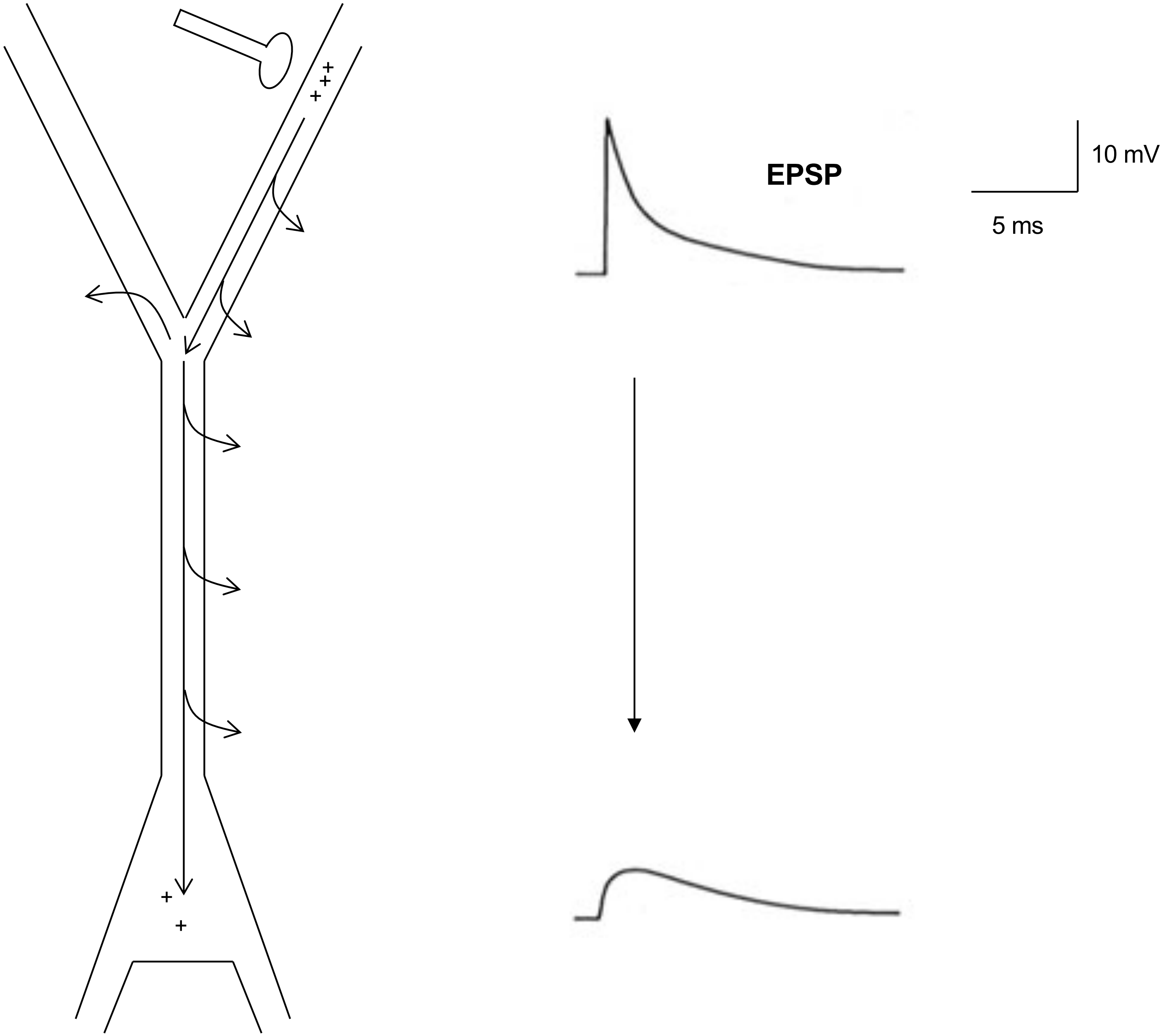
www.neuron.yale.edu **Cambridge UP, 2006**

Using a compartmental model to estimate attenuation of distally generated EPSPs



Stuart & Spruston, 1998

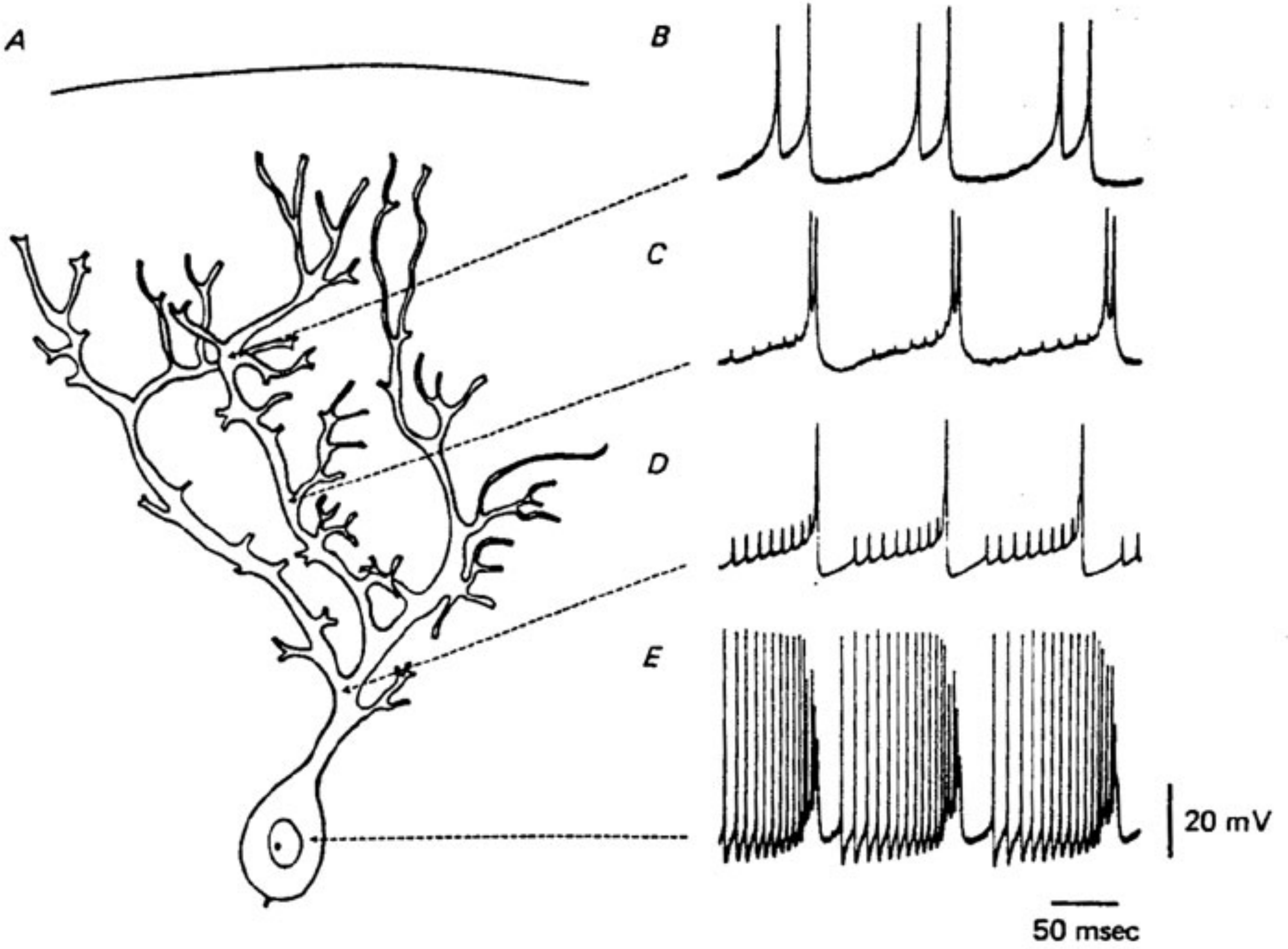
Summary: dendrites attenuate and slow EPSPs arriving at the soma



⇒ the size and shape of somatic EPSPs depends on location of dendritic origin

What about active dendrites?

Compartmentalization of the dendritic tree by Na^+ and Ca^{2+} spikes



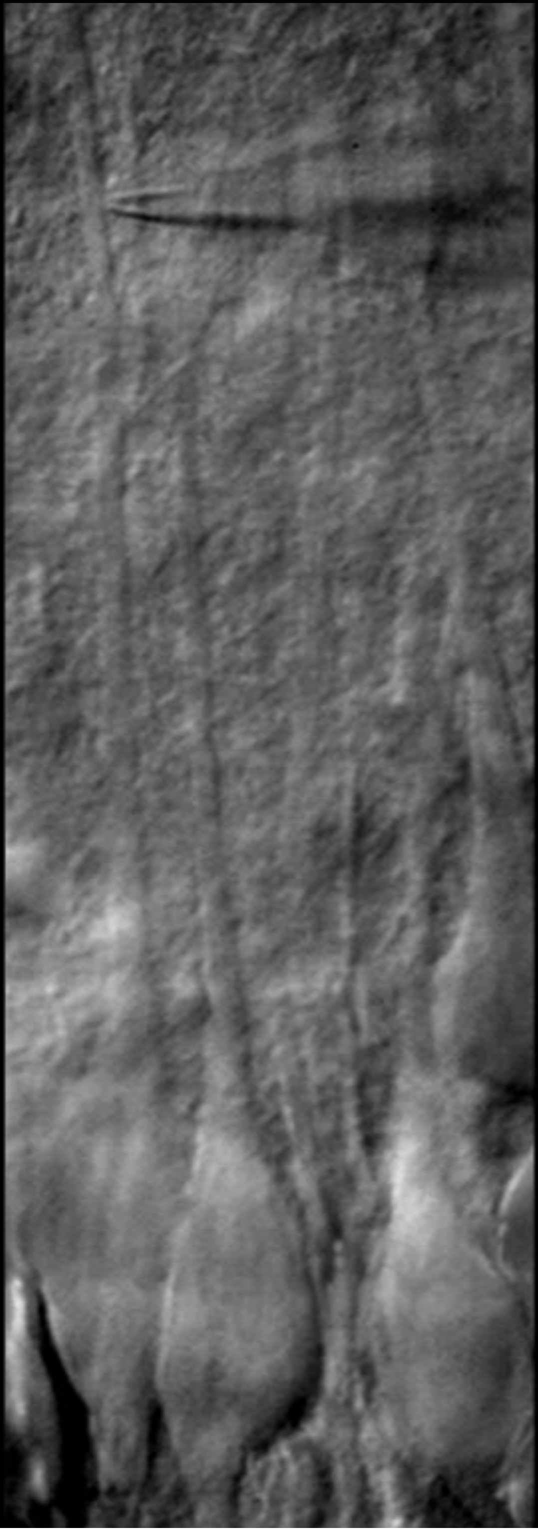
Ca^{2+} spikes

Na^+ spikes

Fig. 4. Composite picture showing the relationship between somatic and dendritic action potentials following DC depolarization through the recording electrode. A clear shift in amplitude of the s.s. against the dendritic Ca-dependent potentials is seen when comparing the more superficial recording in *B* with the somatic recording in *E*. Note that at increasing distances from the soma the fast spikes are reduced in amplitude and are barely noticeable in the more peripheral recordings. However, the prolonged and slow-rising burst spikes are more prominent at dendritic level.

from Llinas & Sugimori 1980

Dendritic patch-clamp recording

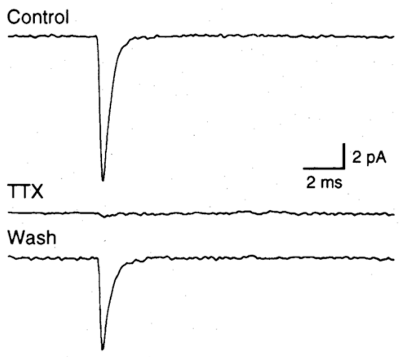


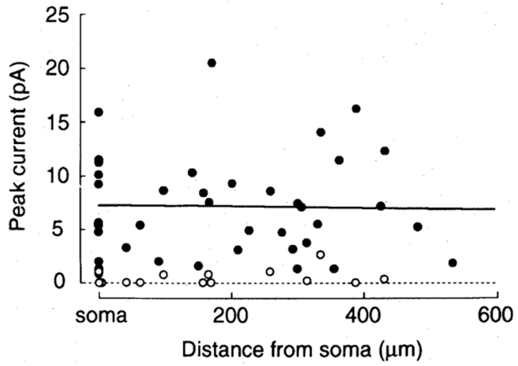
Stuart et al., Pflüger’s Archiv, 1993

Spruston et al., 1995

Voltage-gated channels in dendrites

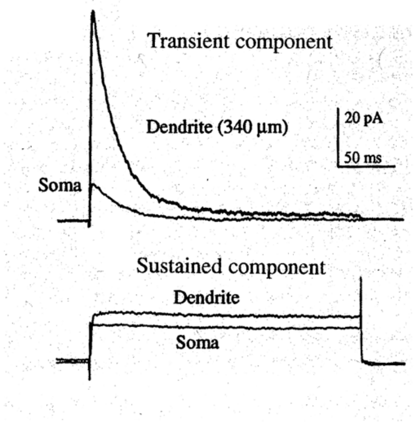
Na channels

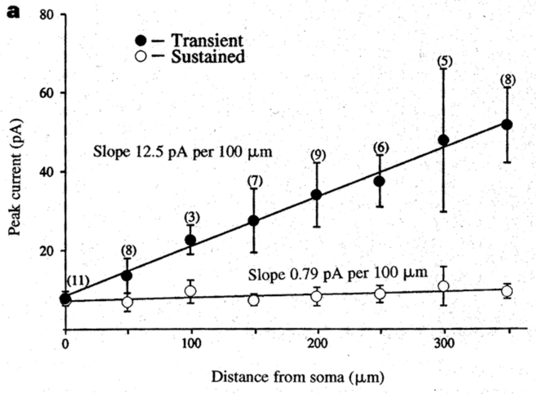




Stuart & Sakmann, 1994

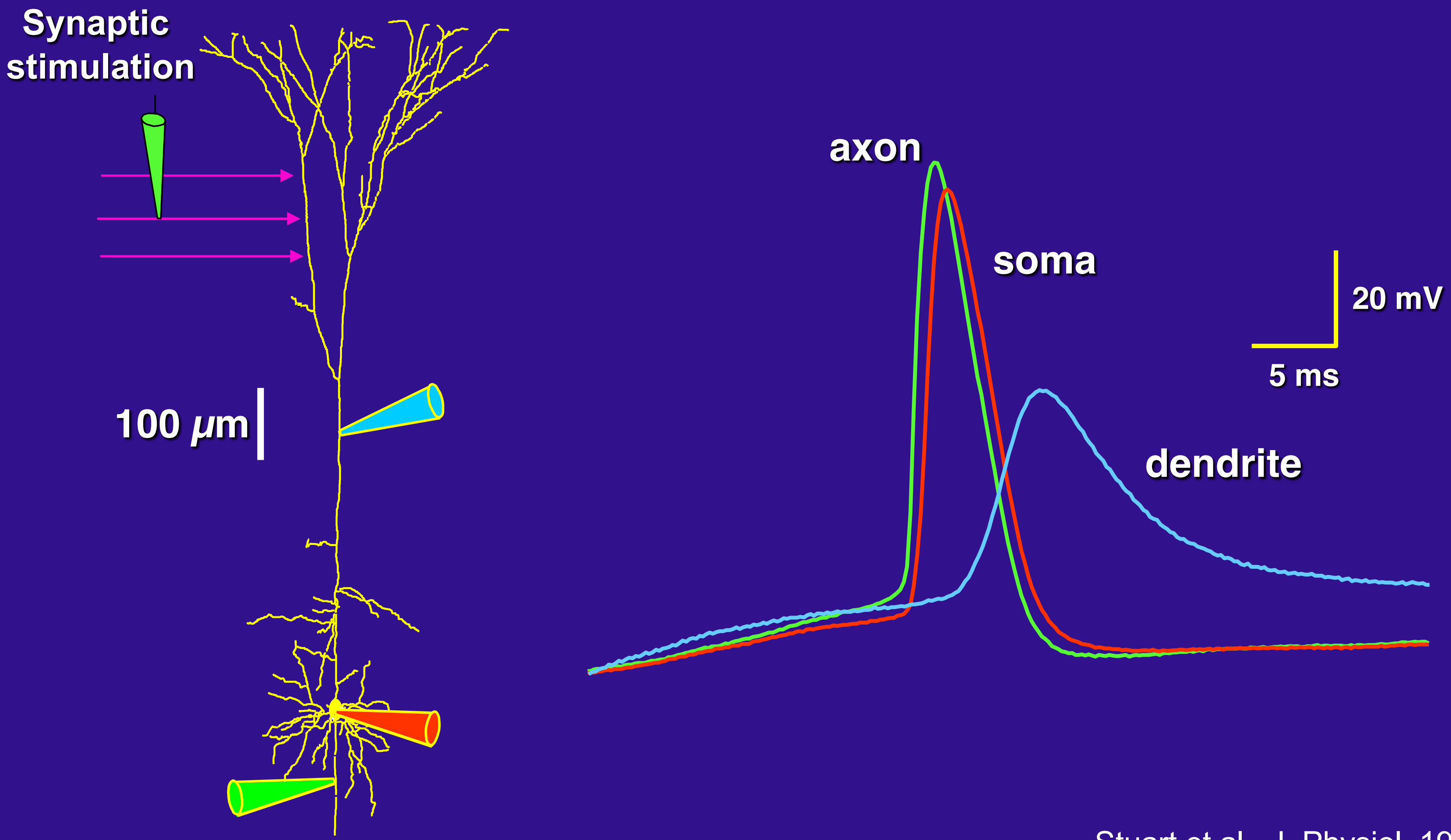
A-type K channels





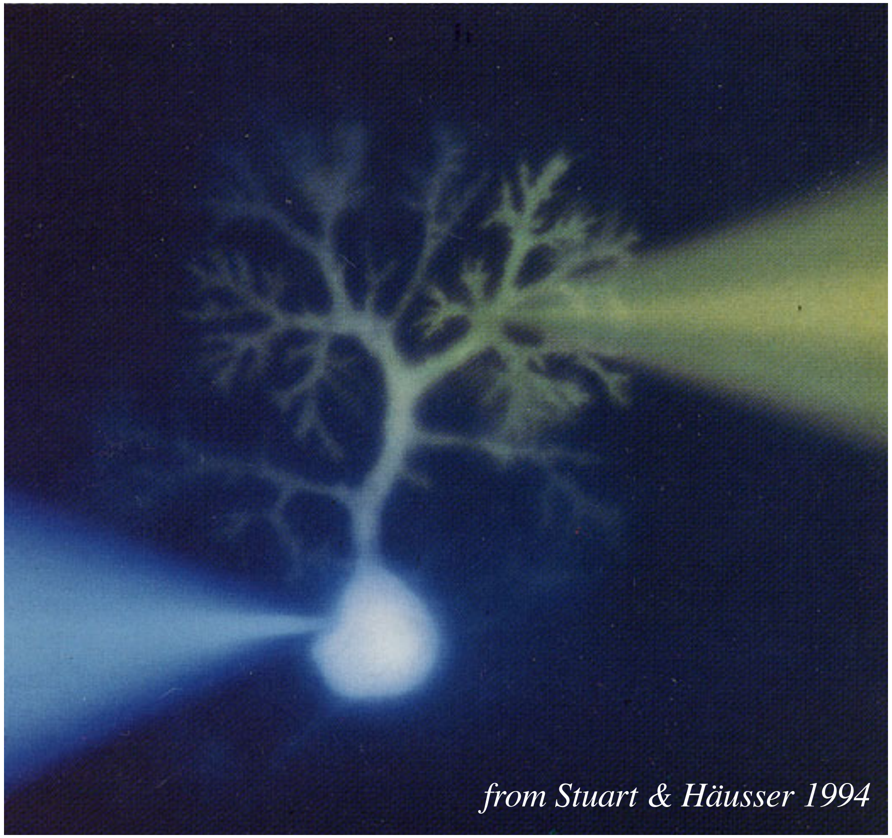
Hoffman et al., 1997

Action potential initiation and backpropagation in pyramidal neurons

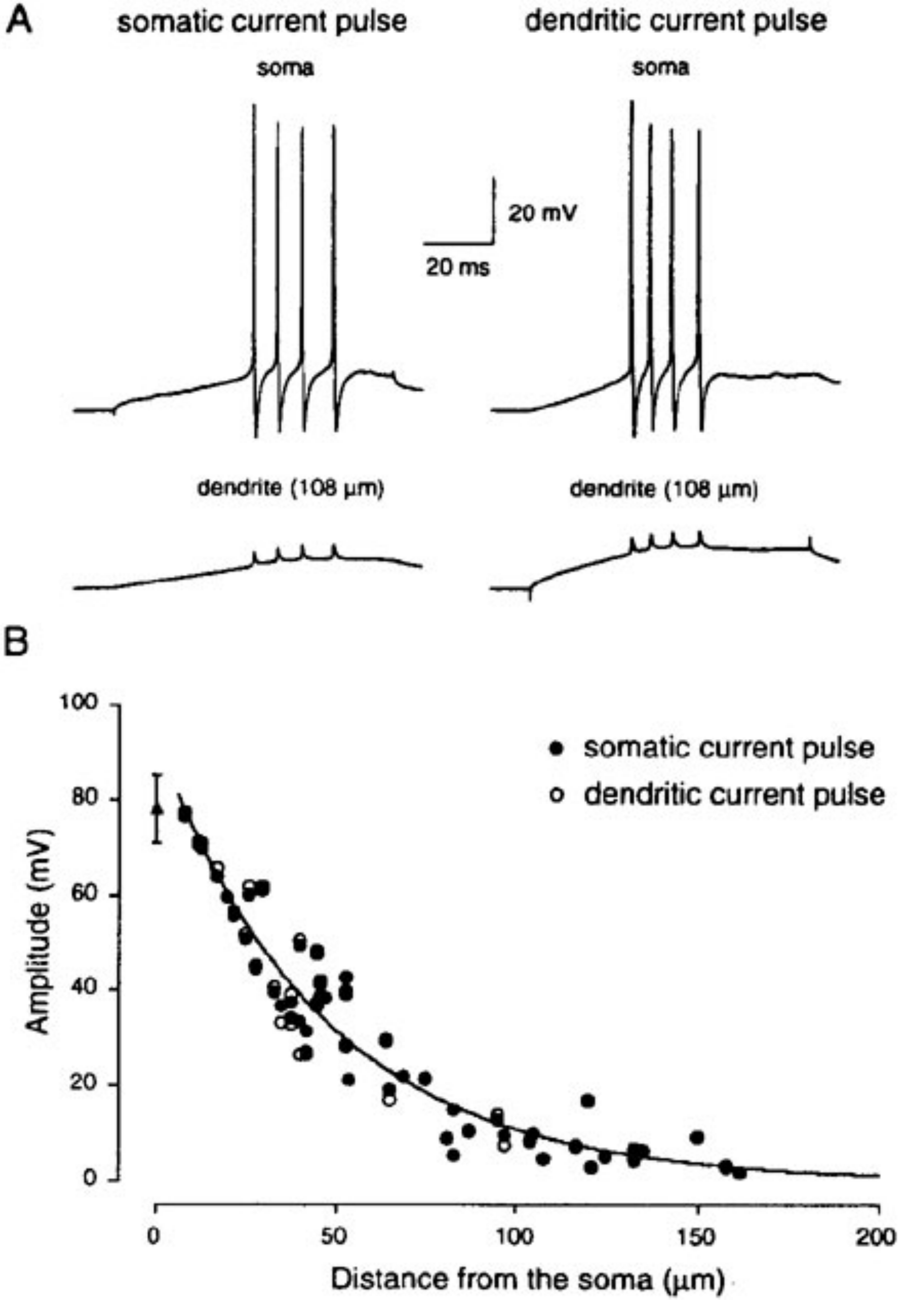


Stuart et al., J. Physiol. 1997

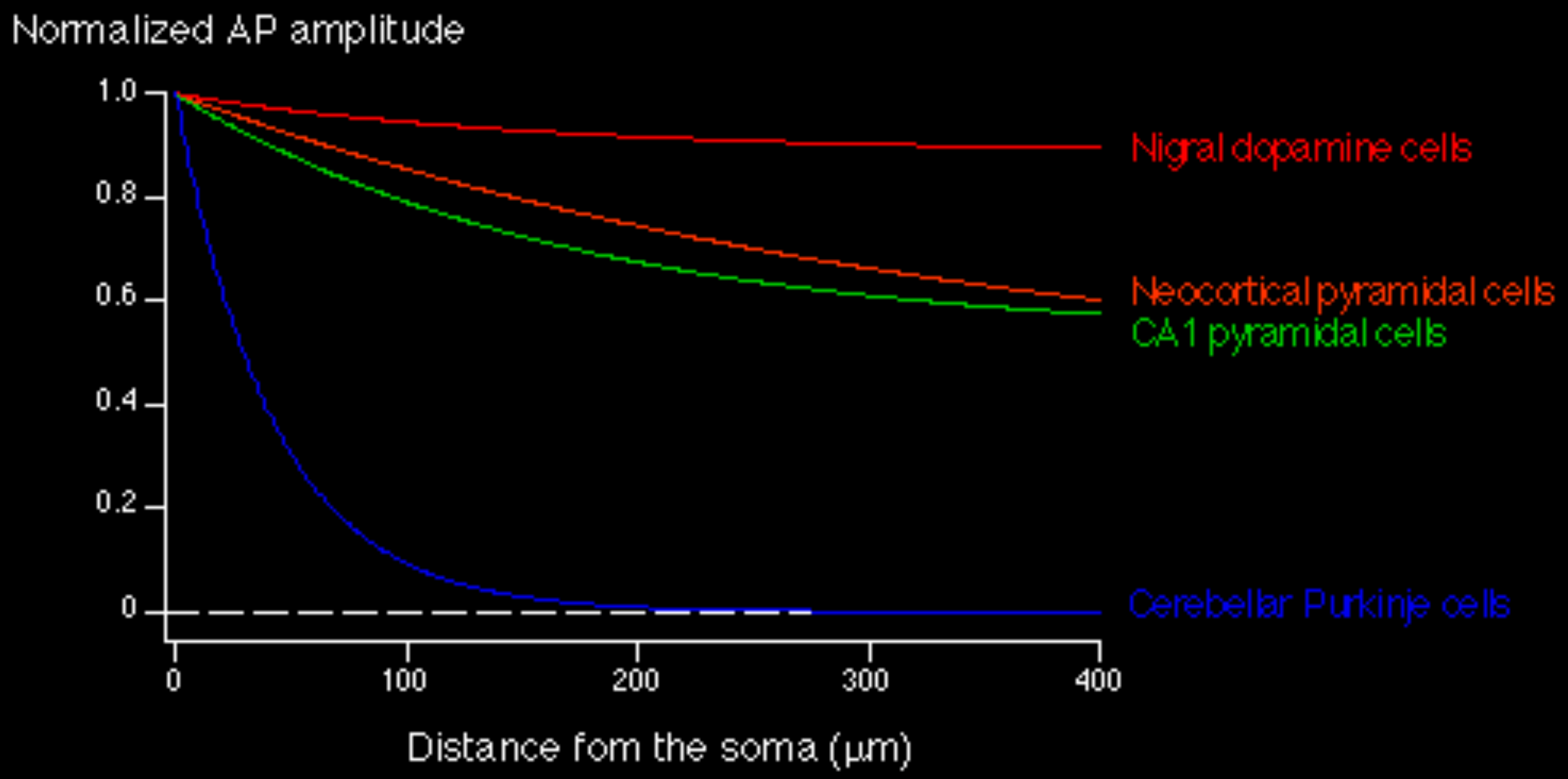
Backpropagation is not present in all neurons (e.g. Purkinje cells)



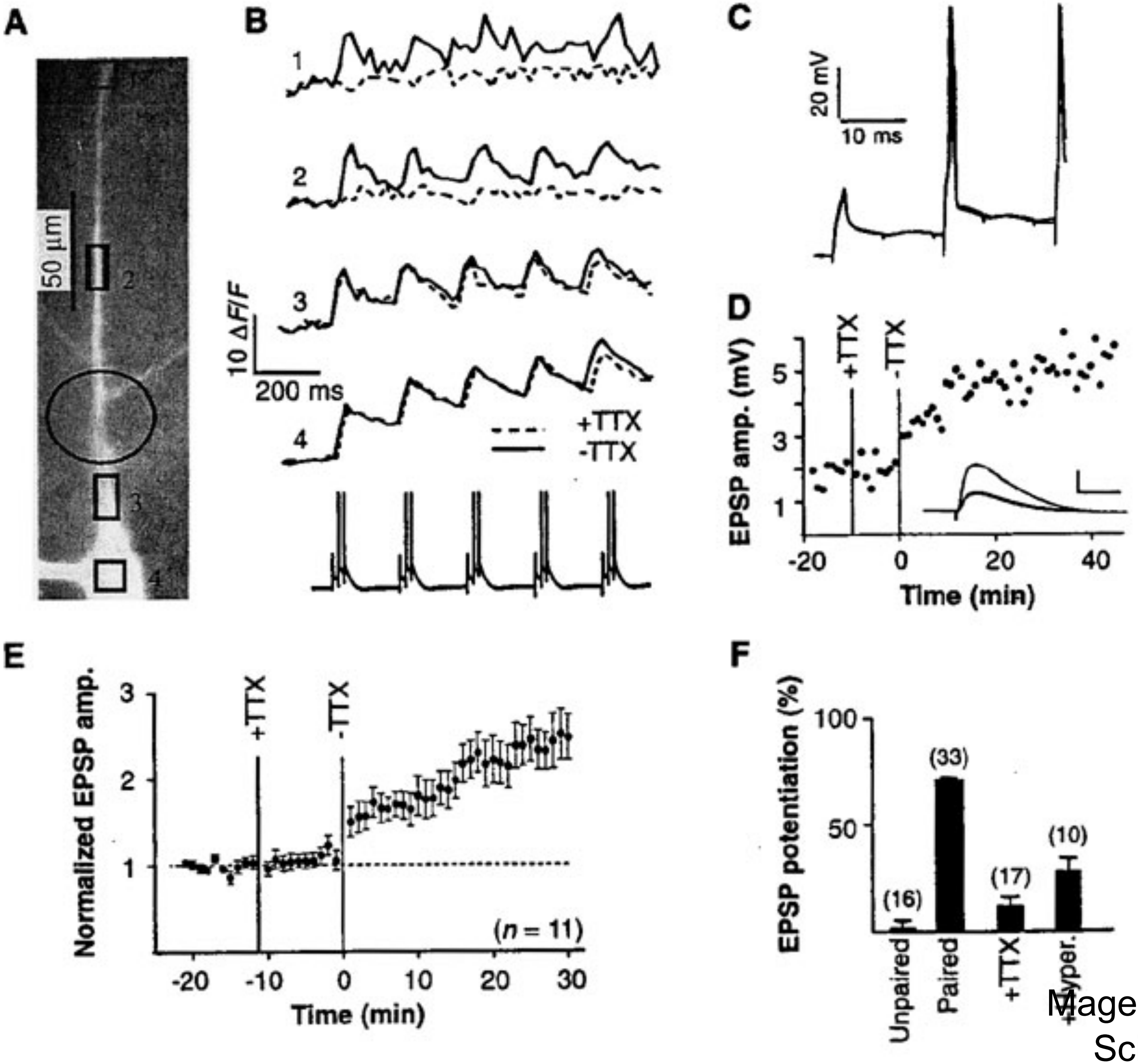
from Stuart & Häusser 1994



Backpropagation is cell-type specific

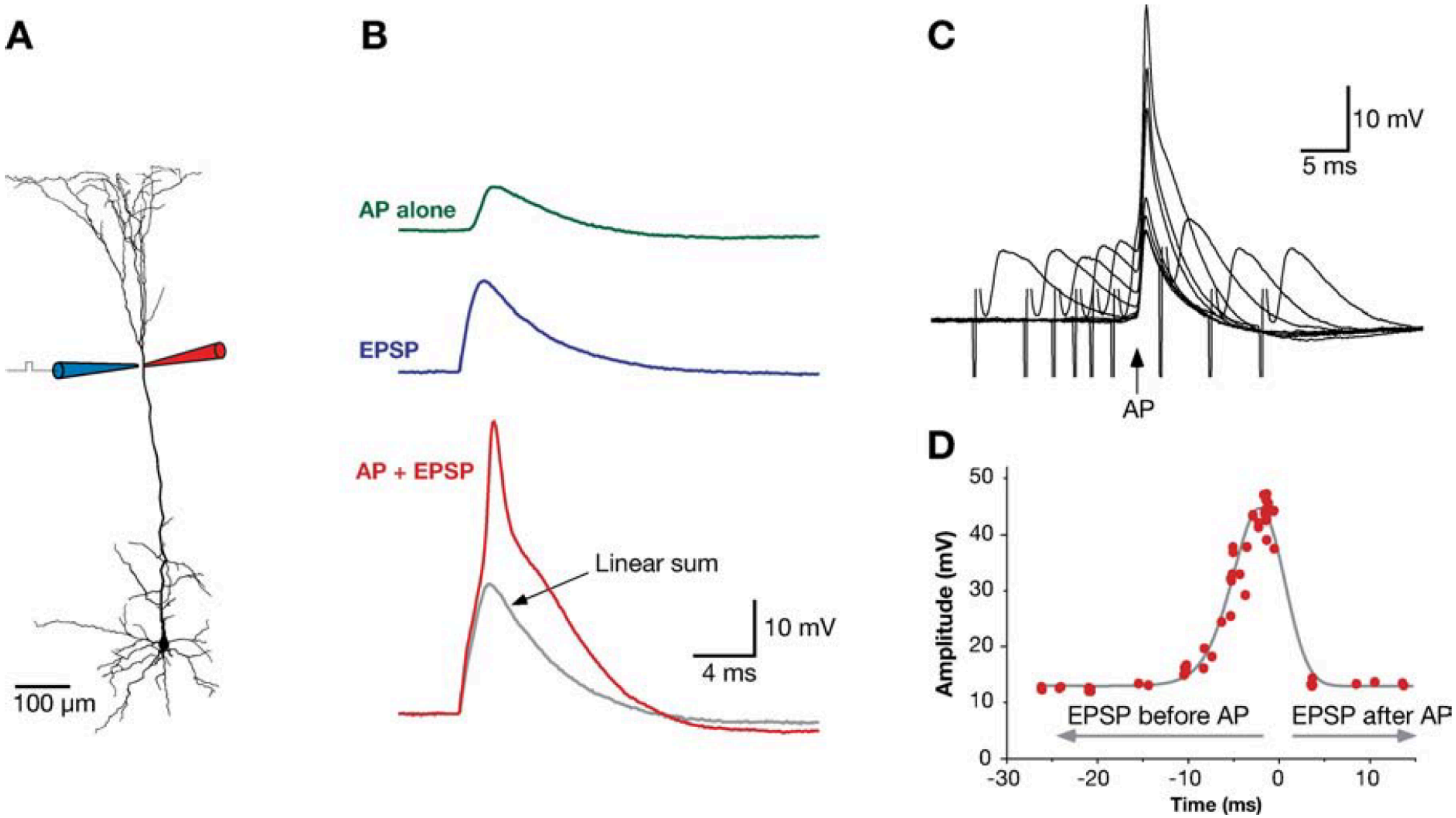


Backpropagation gates the induction of LTP



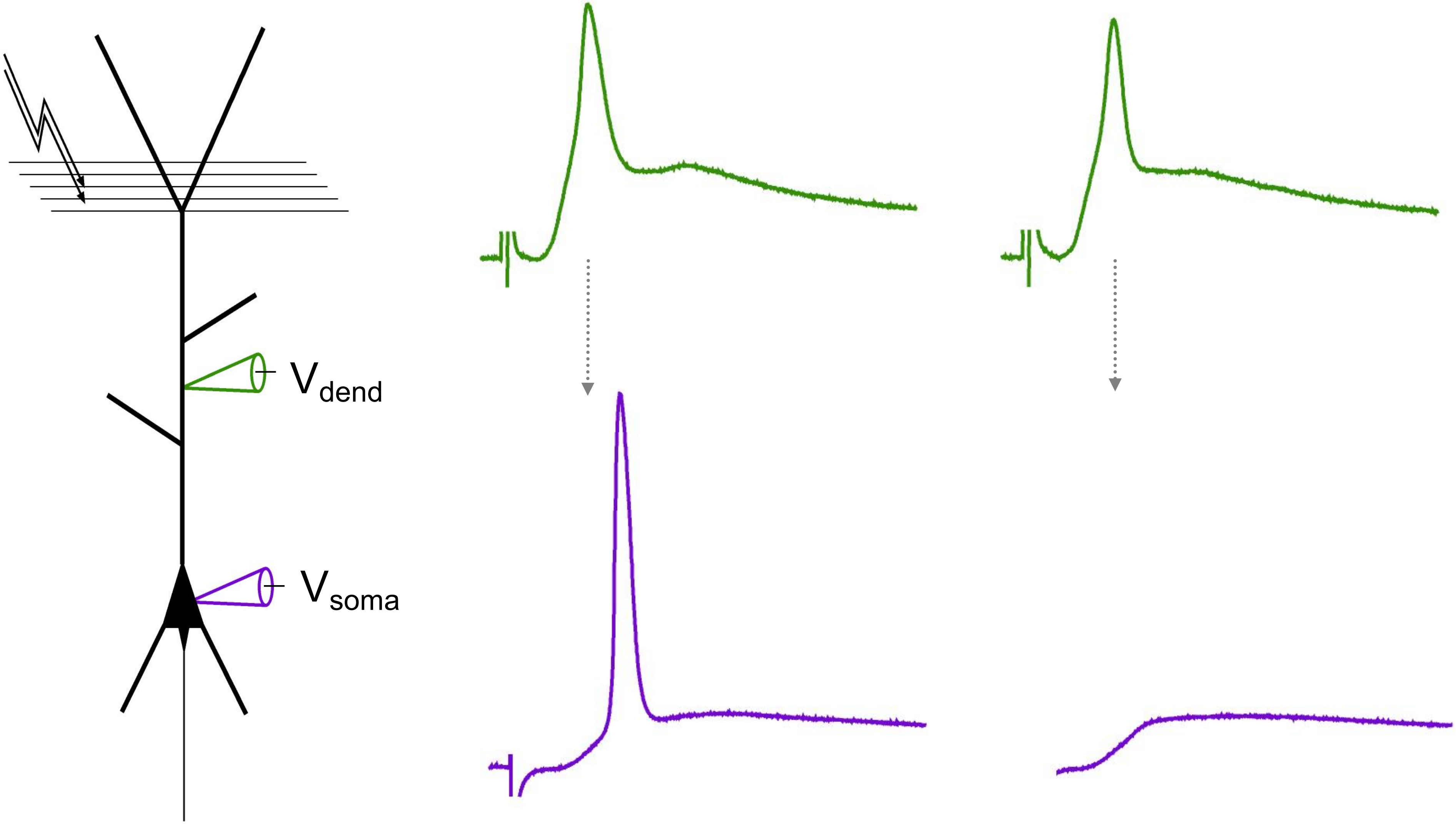
Magee & Johnston,
Science 1997

Local coincidence detection of APs and EPSPs in dendrites



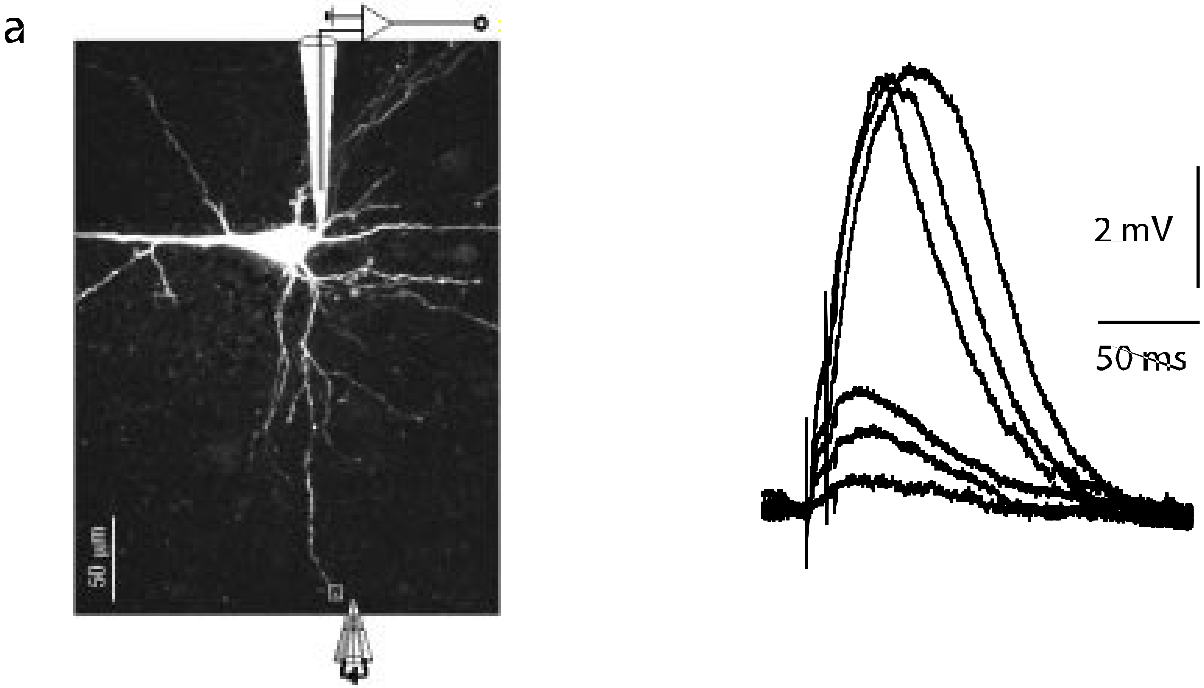
Stuart and Häusser, *Nature Neuroscience* 2001

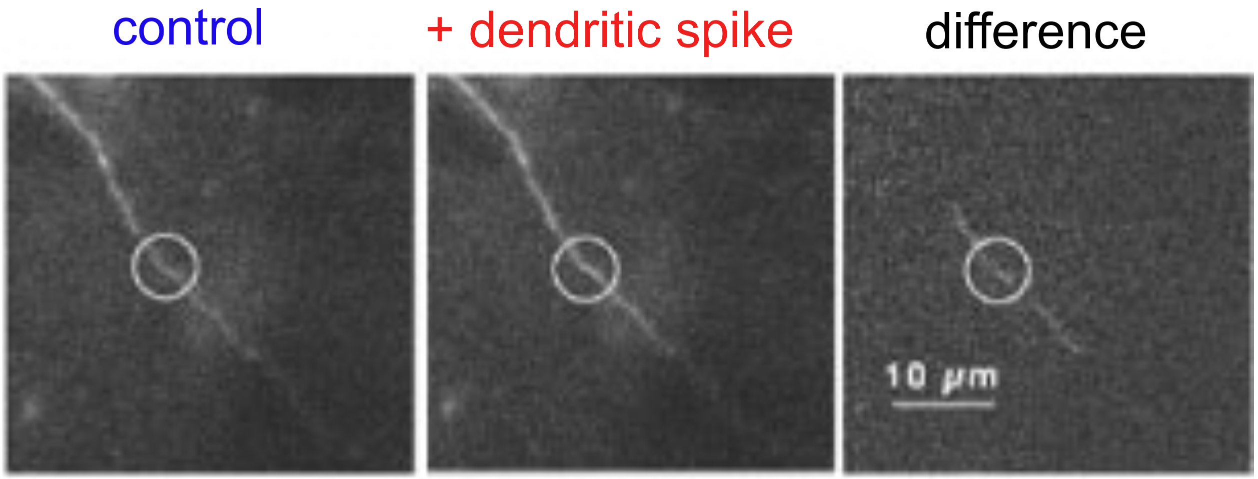
Dendrites can initiate local spikes which may or may not trigger output



Golding and Spruston 1998

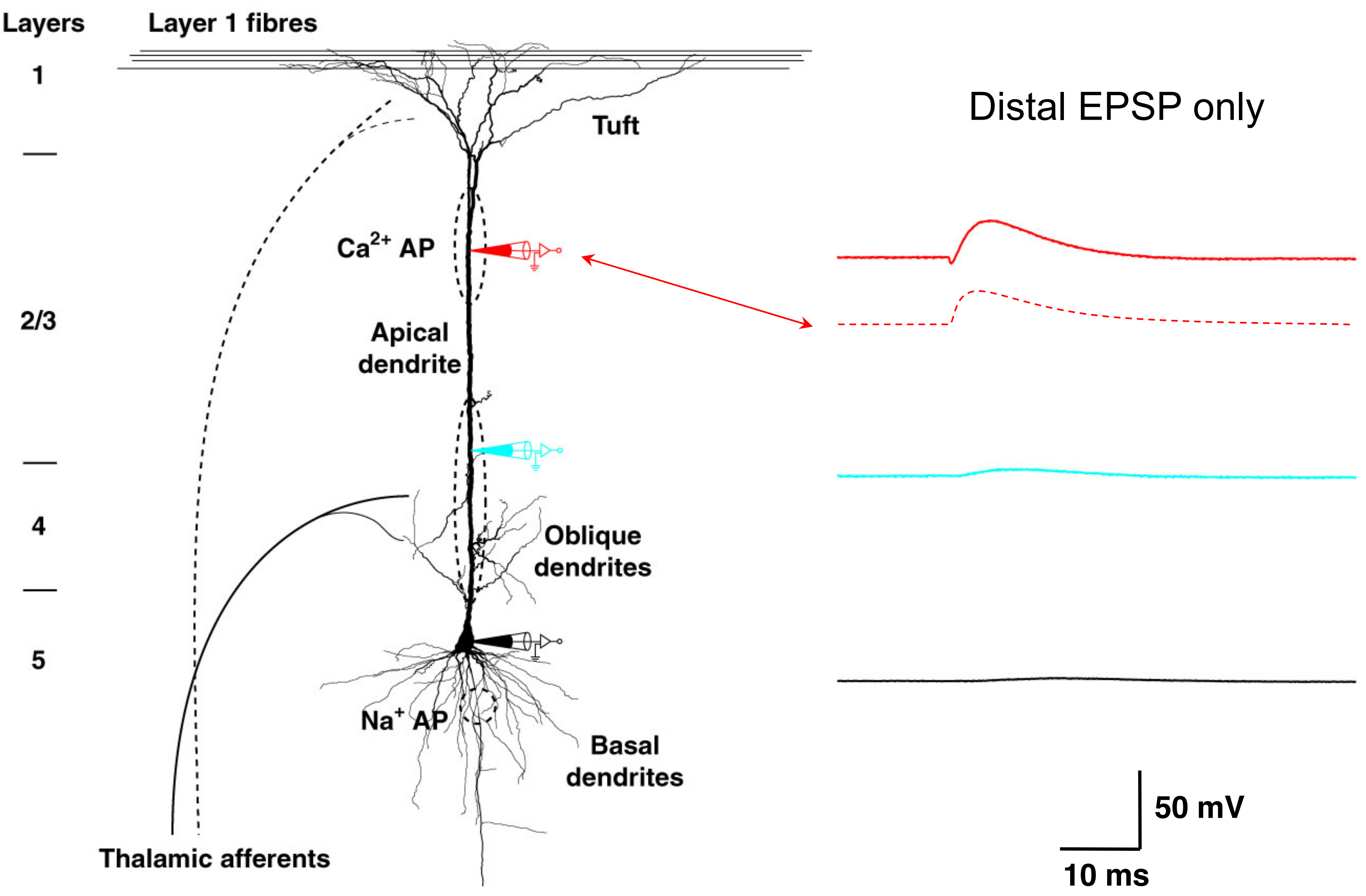
Dendritic spikes cause local calcium influx





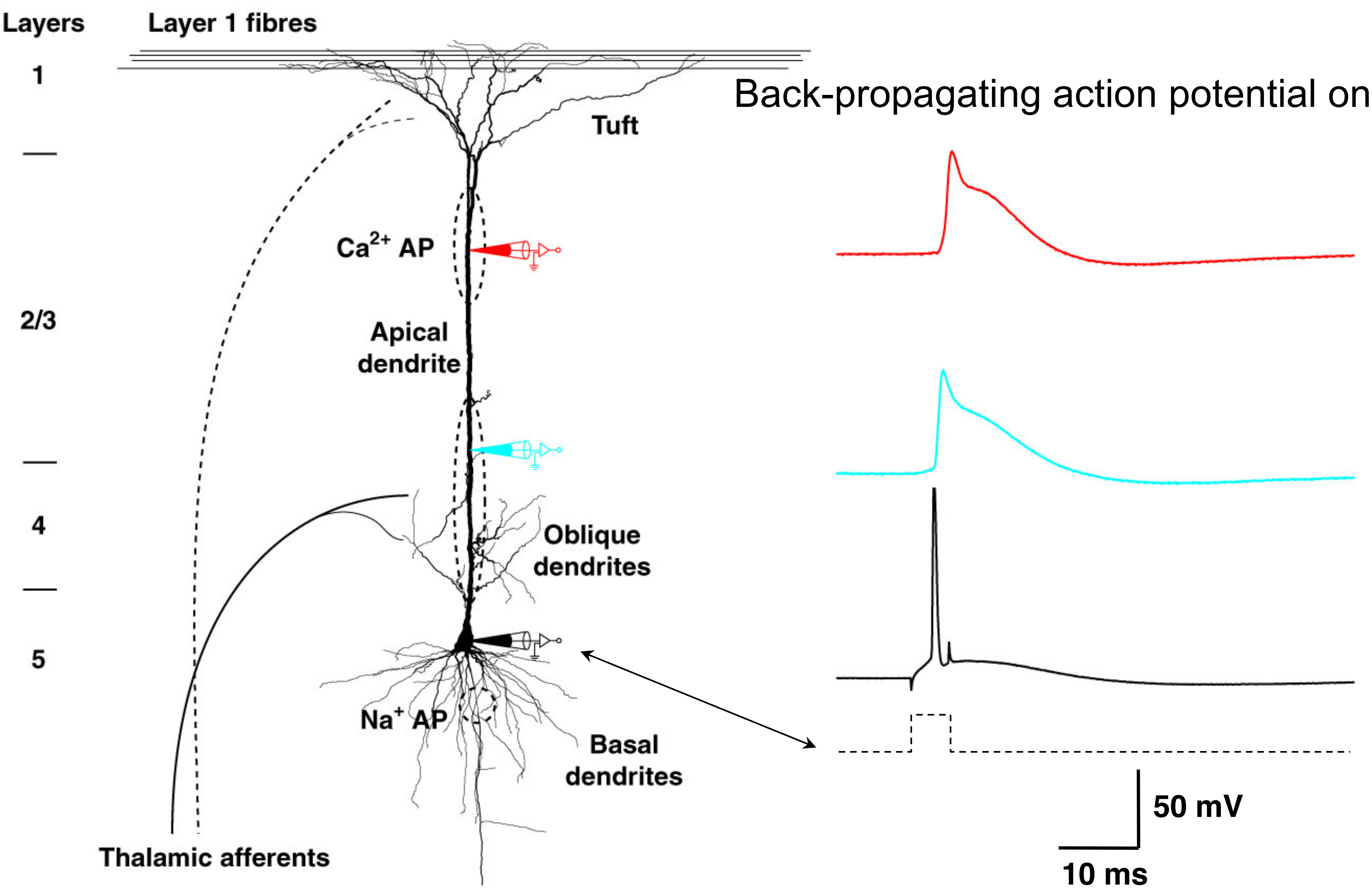
Schiller et al., *Nature* 2000

Interaction between backpropagating APs and distal Ca spikes



Larkum, Zhu & Sakmann - Nature, 1999

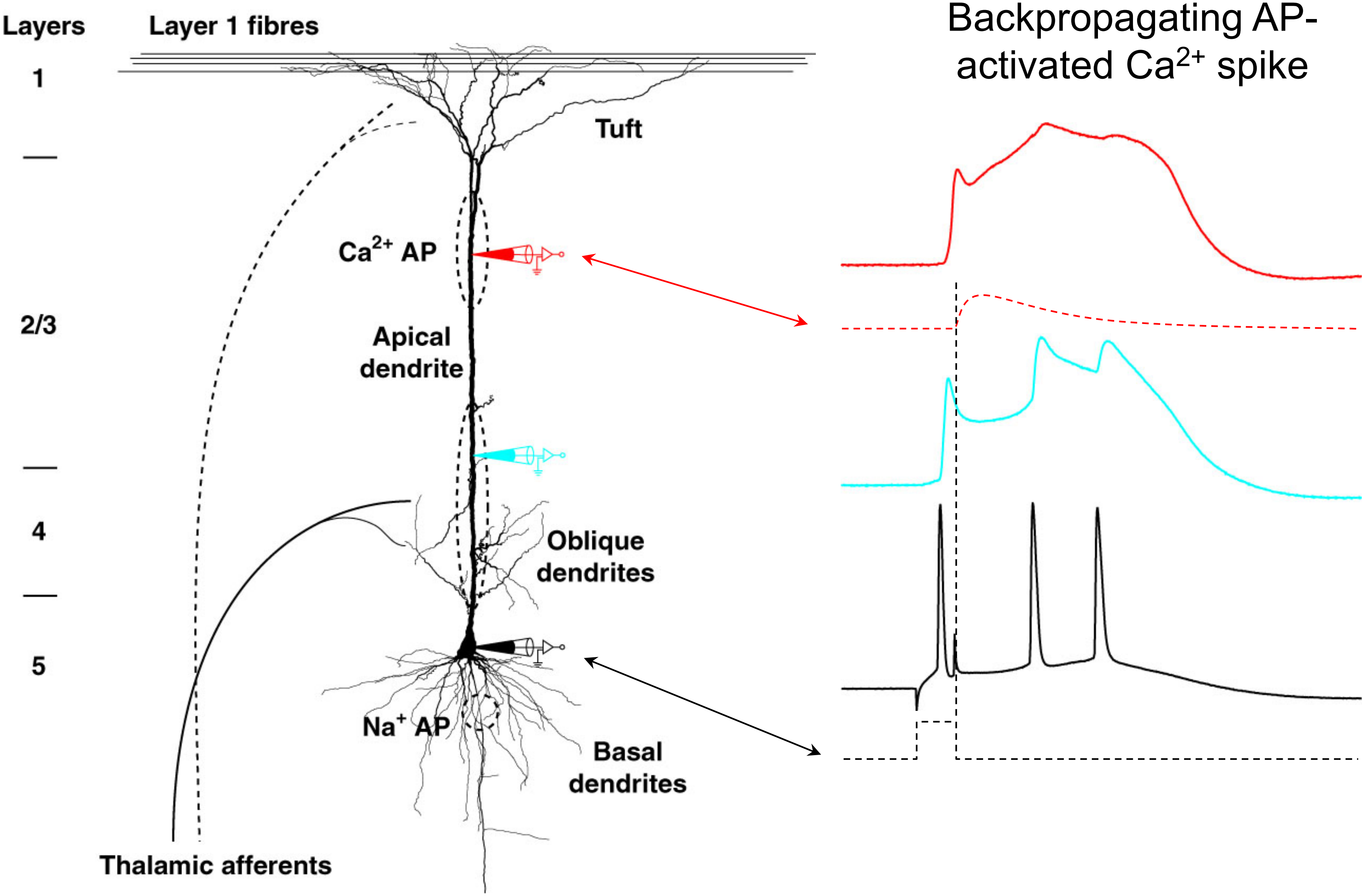
Interaction between backpropagating APs and distal Ca spikes



Larkum, Zhu & Sakmann - Nature, 1999

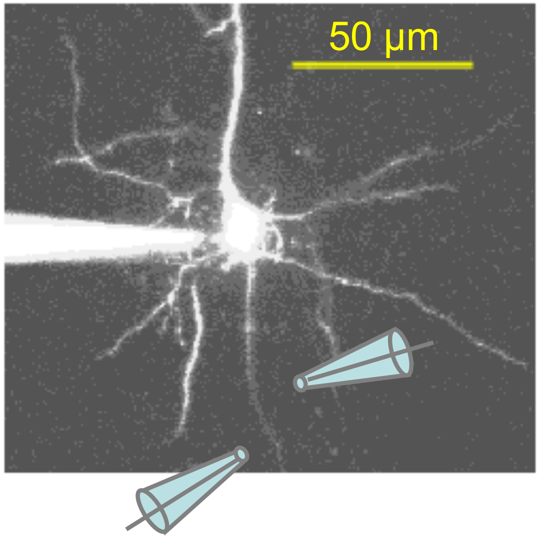
Interaction between backpropagating APs and distal Ca spikes

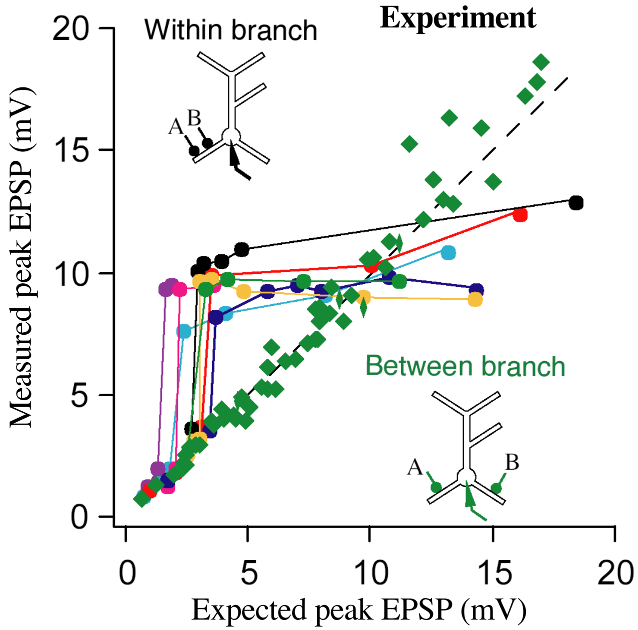
Backpropagating AP-activated Ca^{2+} spike

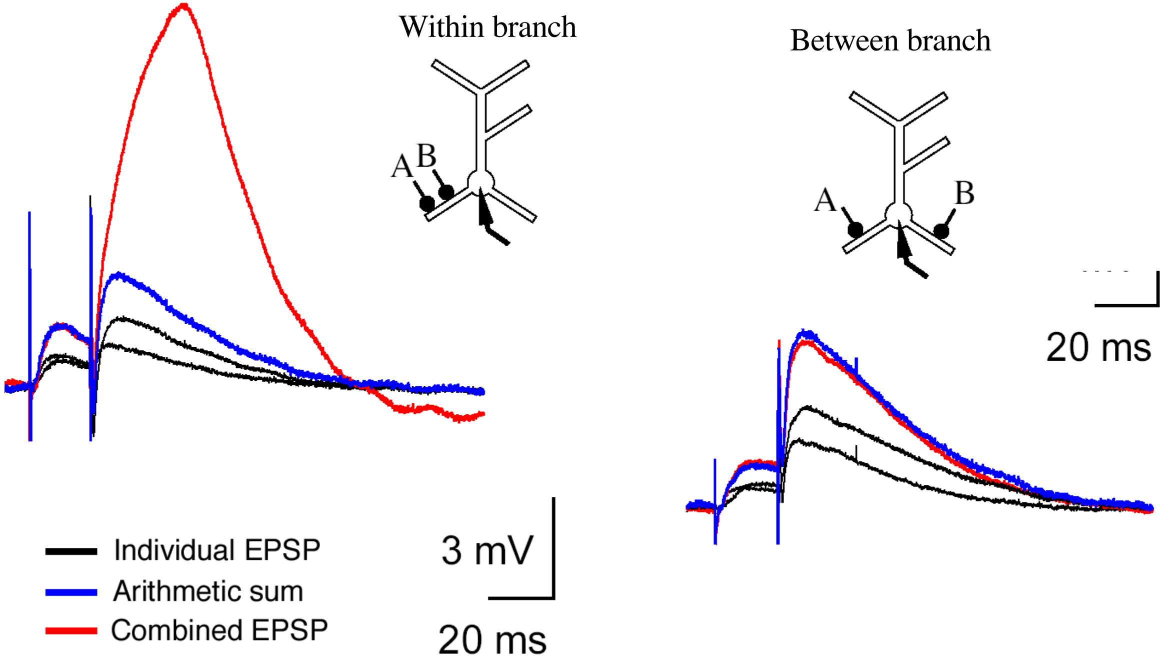


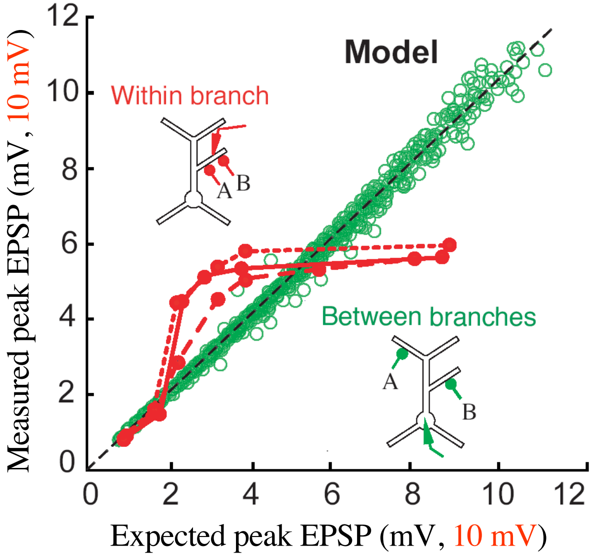
Larkum, Zhu & Sakmann - Nature, 1999

Computational subunits in thin dendrites of cortical pyramidal cells





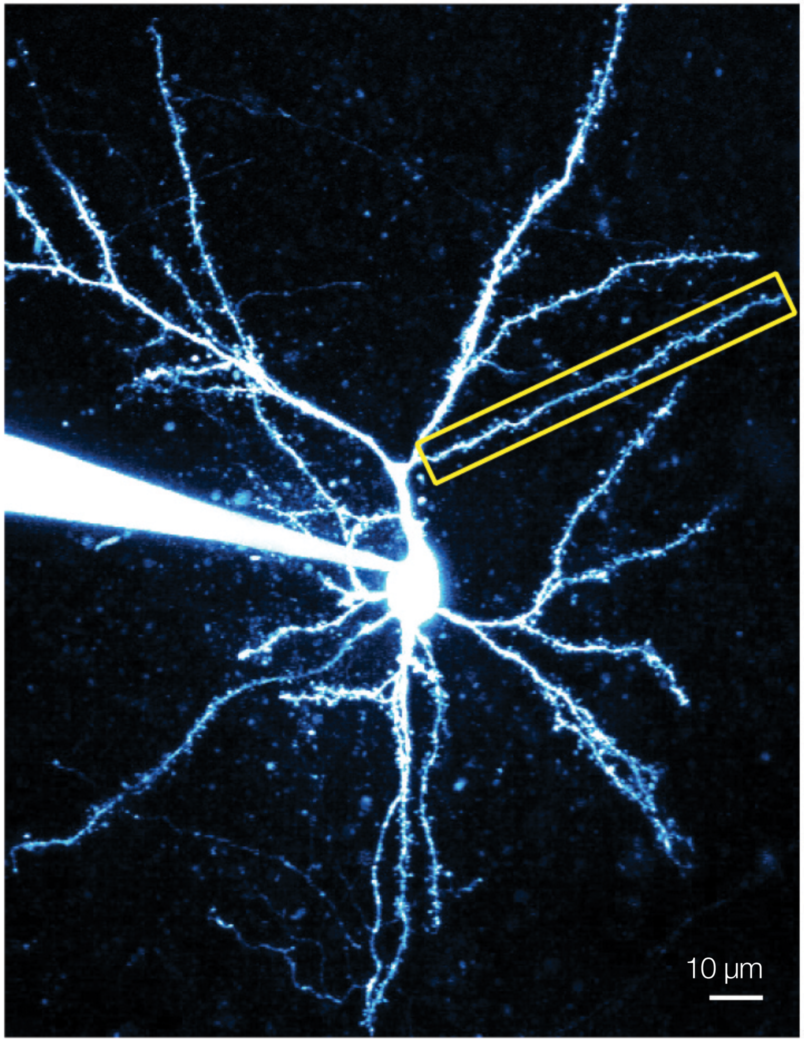




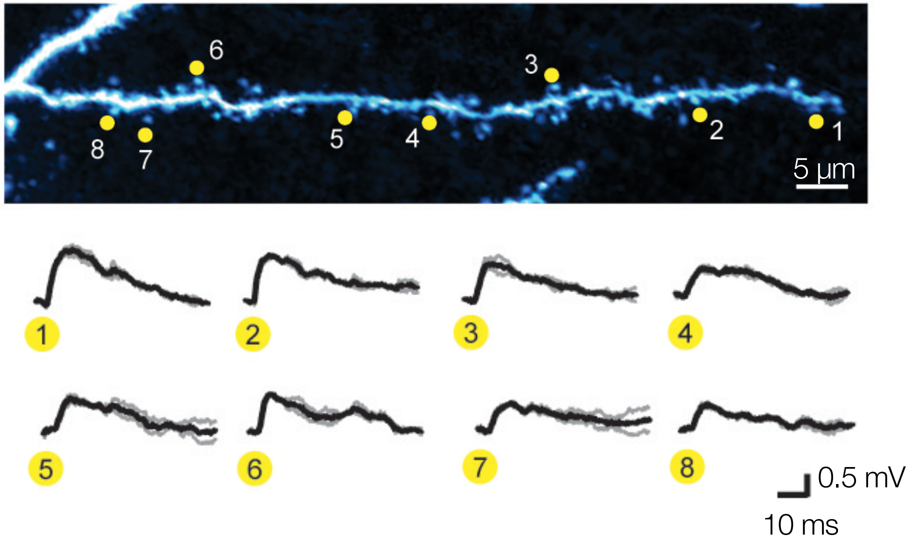
Polsky, Mel, Schiller, 2004

Can single pyramidal cell dendrites read out spatiotemporal sequences?

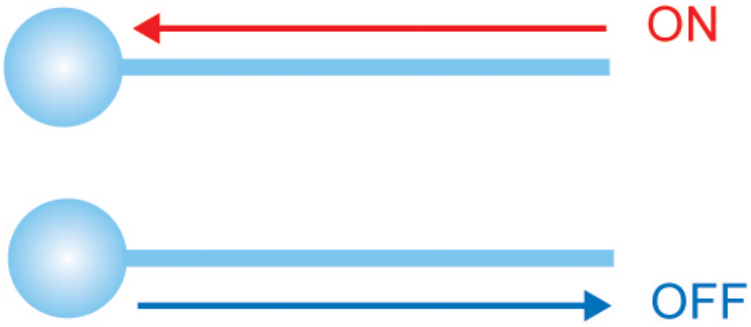
Pyramidal cell



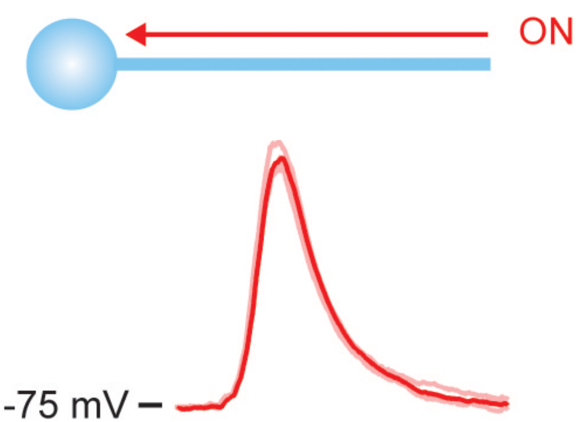
Individual responses

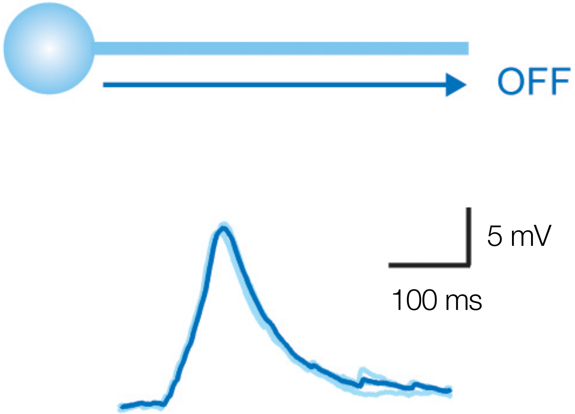


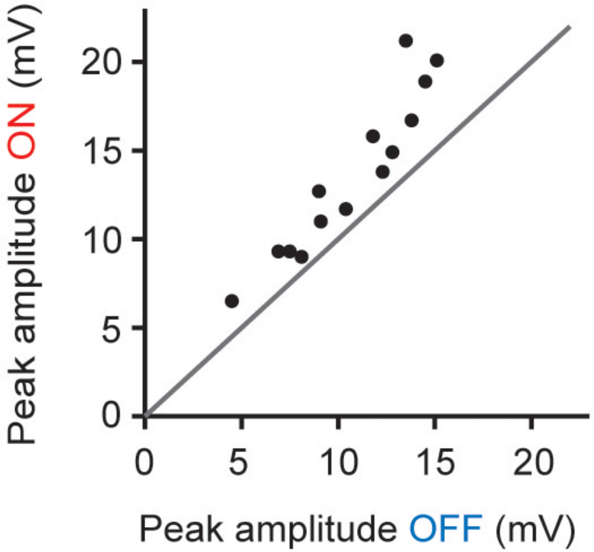
Sequential activation

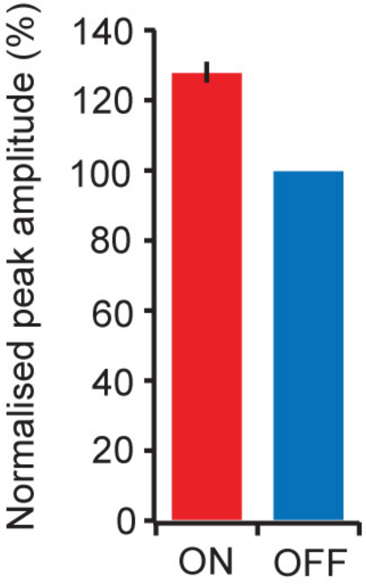


Integration is sensitive to sequence direction

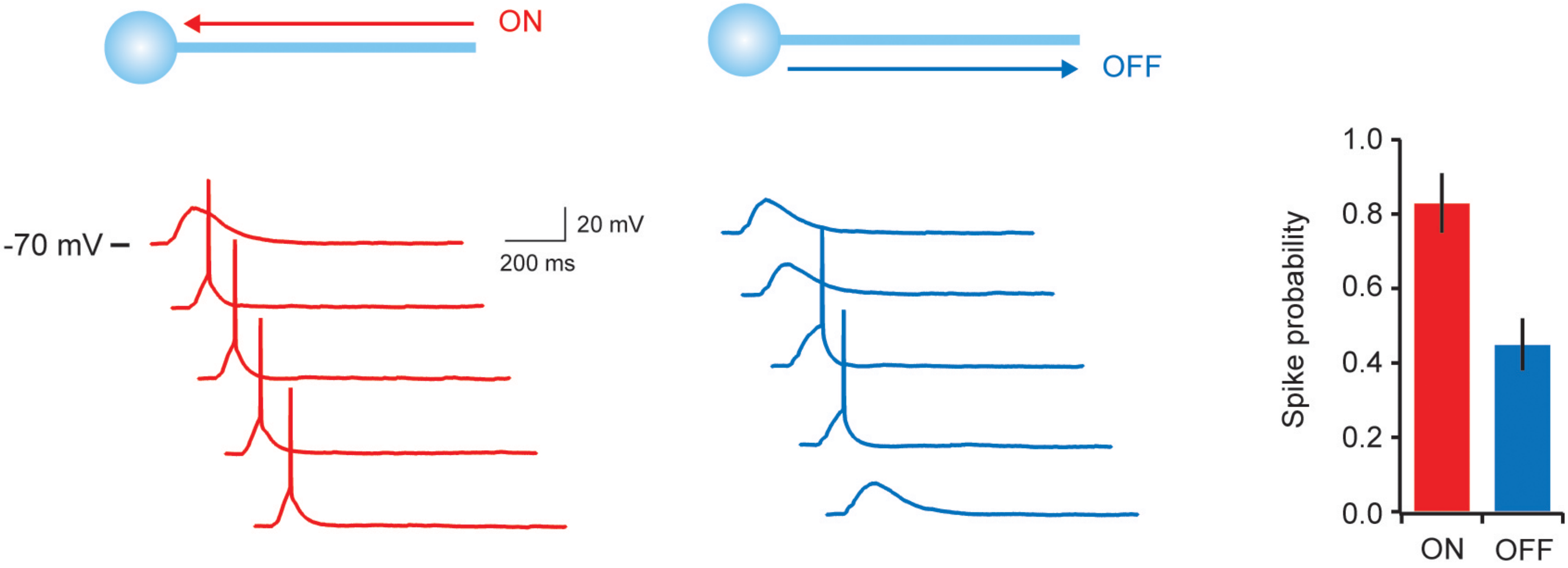








Sequence-dependent spike output



➡ Sequence sensitivity modulates spike output

Branco et al., Science 2010

Article

Cell

Enhanced Dendritic Compartmentalization in Human Cortical Neurons

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https://doi.org/10.1016/j.cell.2018.08.045

SUMMARY

The biophysical features of neurons shape information processing in the brain. Cortical neurons are larger in humans than in other species, but it is unclear how their size affects synaptic integration. Here, we perform direct electrical recordings from human dendrites and report enhanced electrical compartmentalization in layer 5 pyramidal neurons. Compared to rat dendrites, distal human dendrites provide limited excitation to the soma, even in the presence of dendritic spikes. Human somas also exhibit less bursting due to reduced recruitment of dendritic electrogenesis. Finally, we find that decreased ion channel densities result in higher input resistance and underlie the lower coupling of human dendrites. We conclude that the increased length of human neurons alters their input-output properties, which will impact cortical computation.

2017; Häusser and Mel, 2003; Jadi et al., 2014; London and Häusser, 2005; Poirazi et al., 2003; Polsky et al., 2004; Tran-Van-Minh et al., 2015).

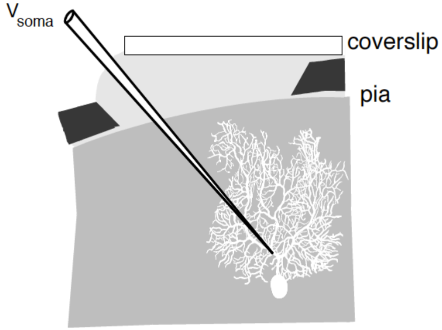
We reasoned that the increased length of human dendrites could further compartmentalize synaptic integration and information processing within individual neurons. However, because compartmentalization critically relies upon details of membrane properties and active conductances (Atkinson and Williams, 2009; Stuart and Spruston, 1998), which cannot be predicted by anatomical features alone, it is not known to what degree human neurons differ from their non-human counterparts. Here, we employ direct patch-clamp electrophysiology to test the hypothesis that dendritic integration is more functionally segregated in human pyramidal neurons.

RESULTS

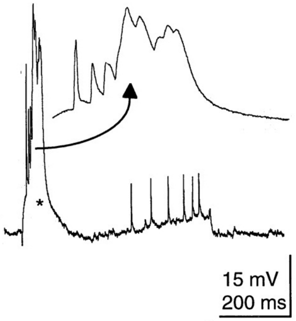
Reduced Burst Firing in Human Neurons

We performed whole-cell recordings from layer 5 (L5) pyramidal neurons in acute human brain slices obtained from the anterior temporal lobe of neurosurgical patients (Figure 1A; STAR Methods). Compared to rat temporal association cortex (TEA) (Eyal et al., 2016; Mohan et al., 2015) somas, human somas

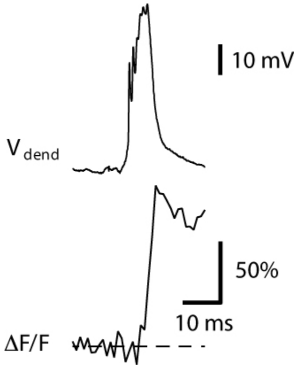
What about *in vivo*?



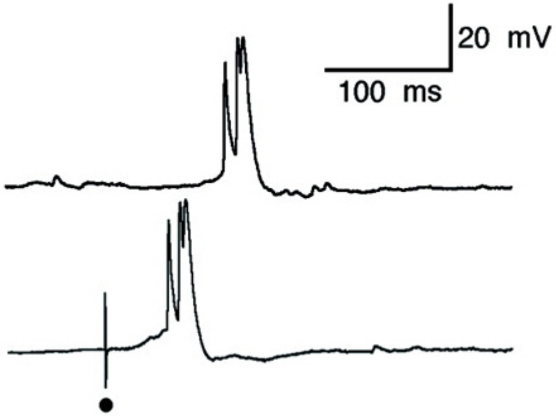
Early efforts to record from dendrites *in vivo*



Kamondi, Acsady, Buzsaki, 1998

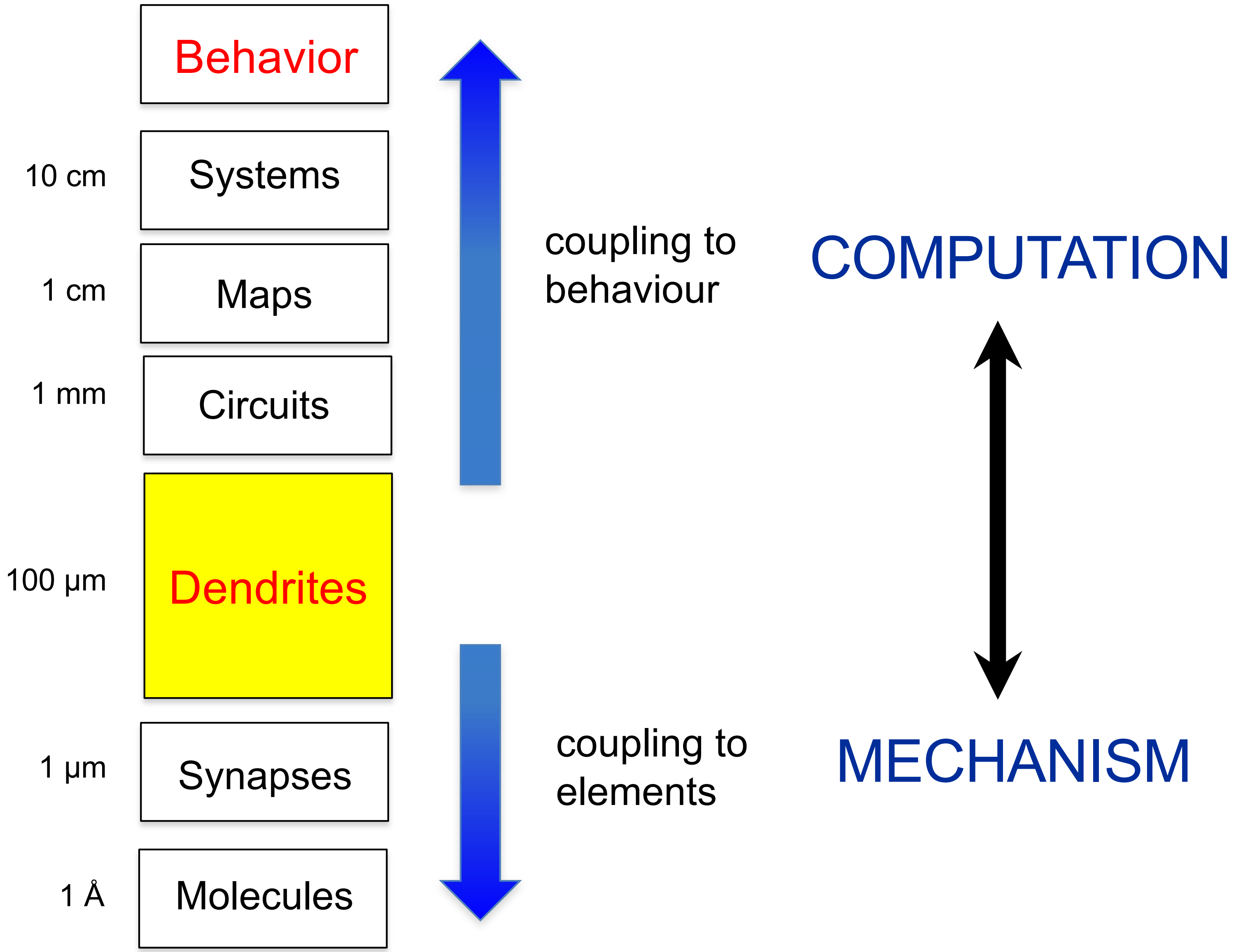


Helmchen et al., 1999



Zhu & Larkum, 2002

The goal: coupling dendritic physiology to behaviour



Behavior

10 cm Systems

1 cm Maps

1 mm Circuits

100 µm Dendrites

1 µm Synapses

1 Å Molecules

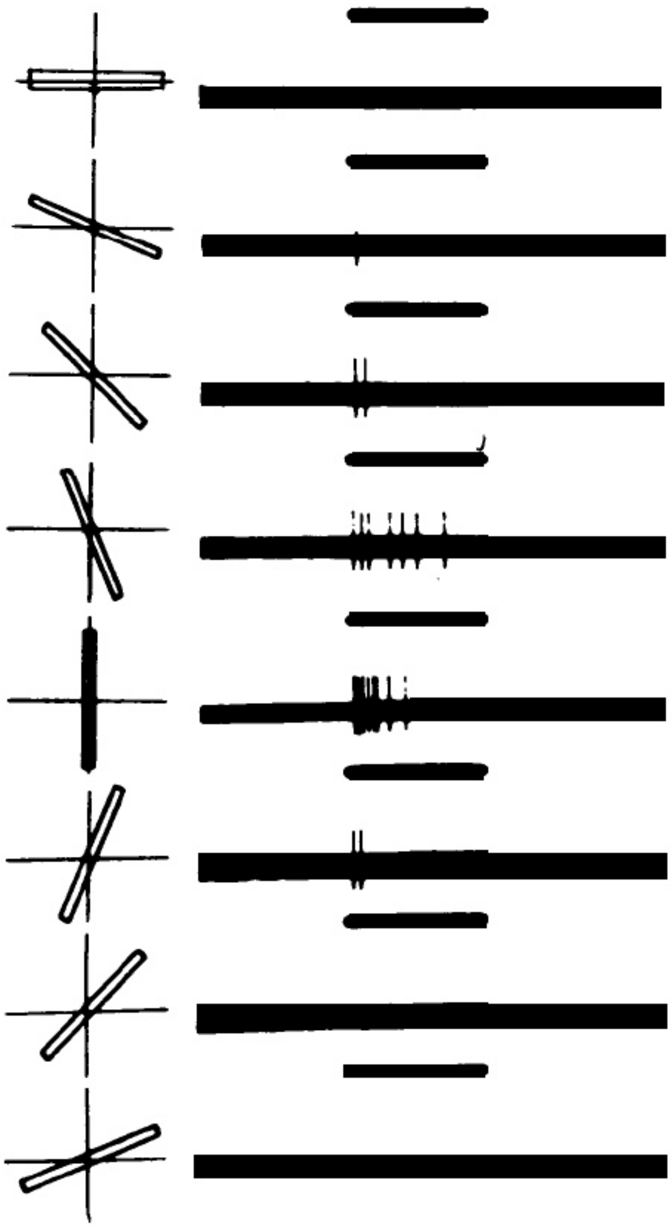
coupling to behaviour

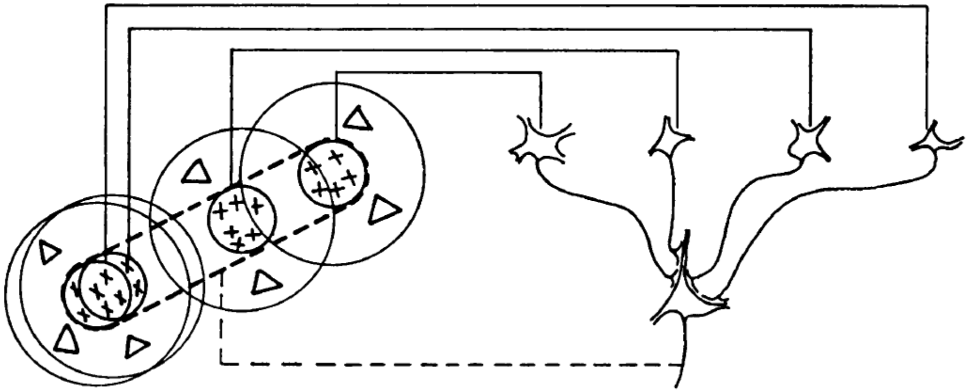
coupling to elements

COMPUTATION

MECHANISM

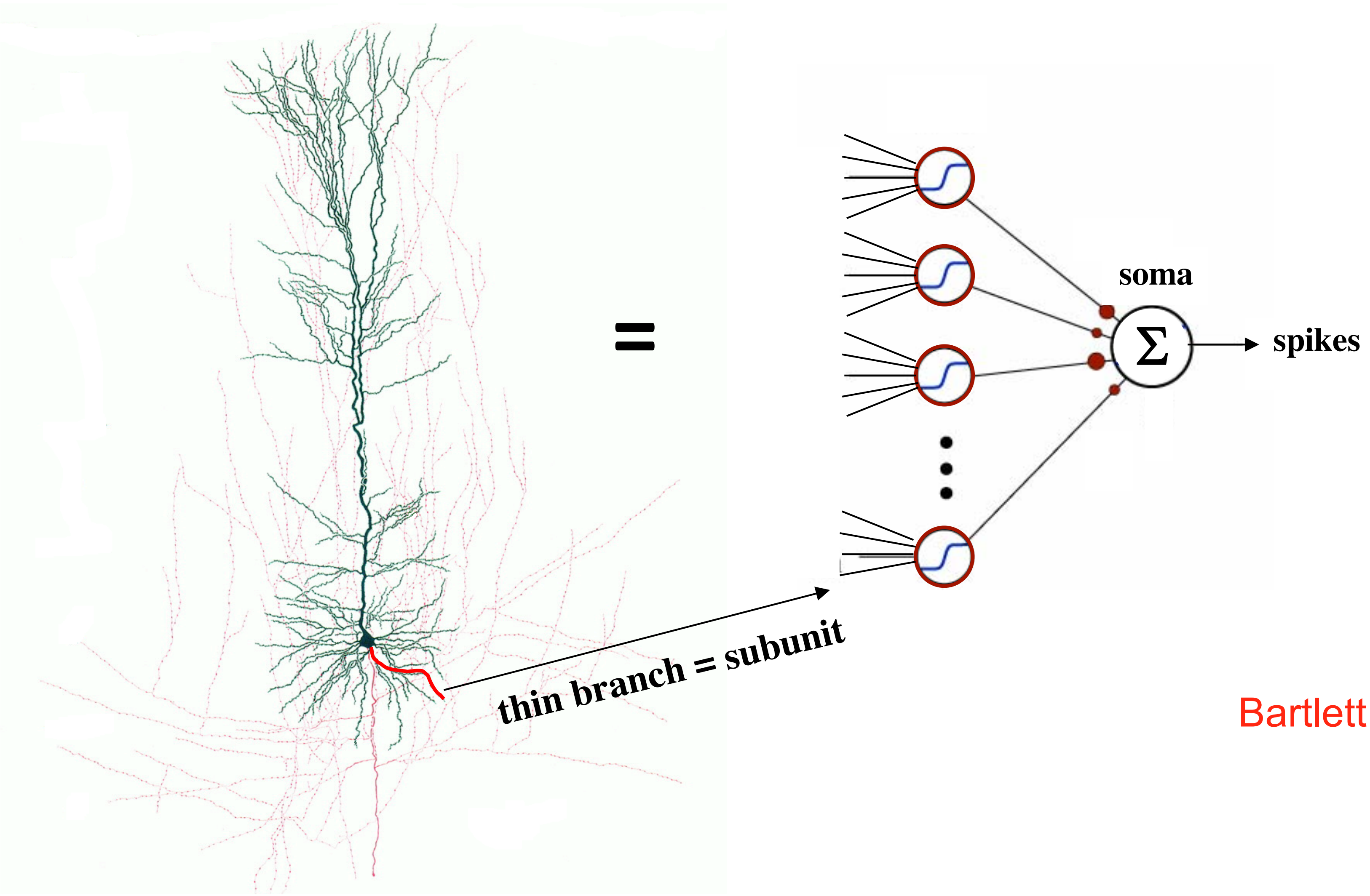
Orientation selectivity in primary visual cortex





Hubel & Wiesel, 1962

Dendritic nonlinearities create independent processing compartments

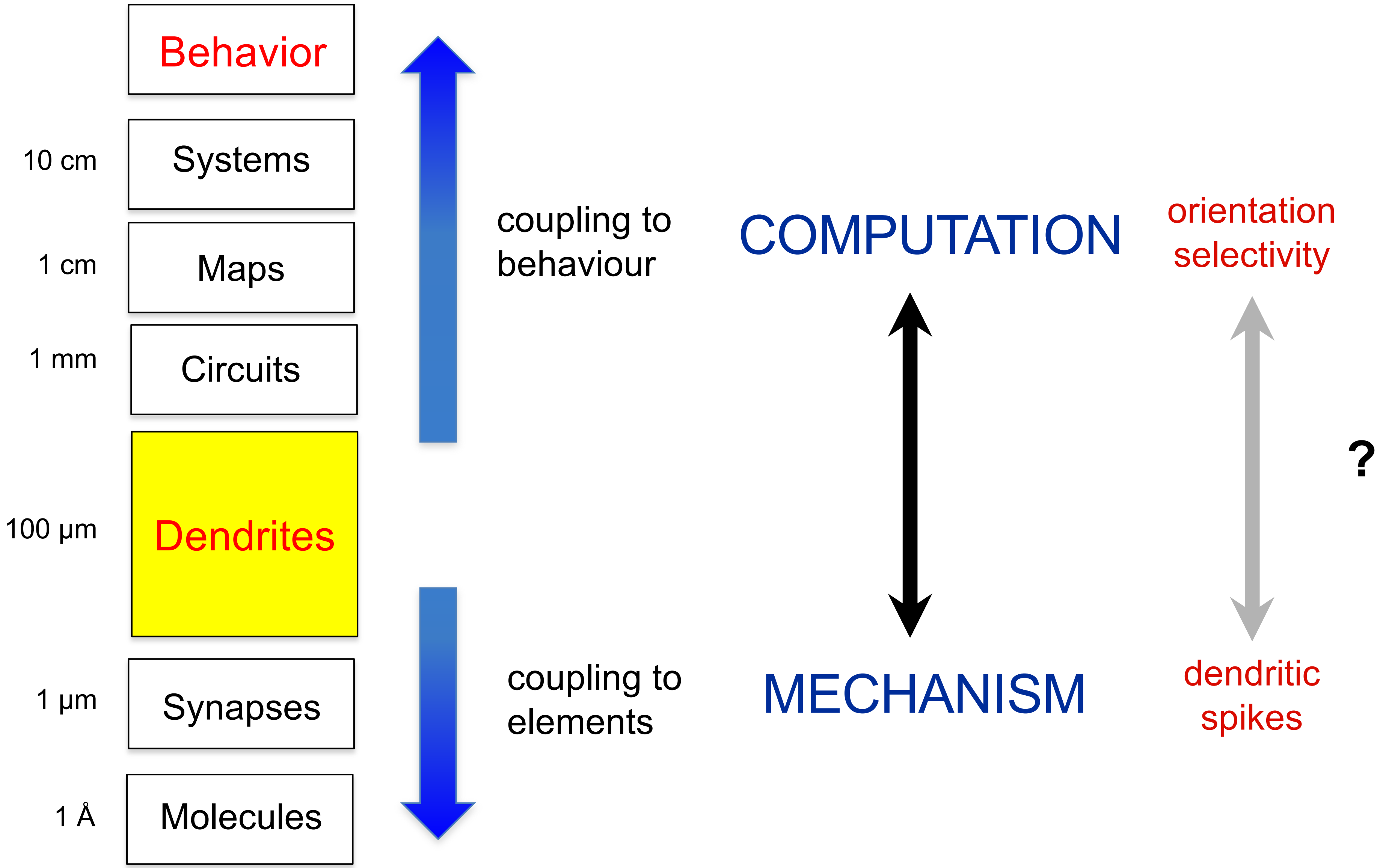


Bartlett Mel

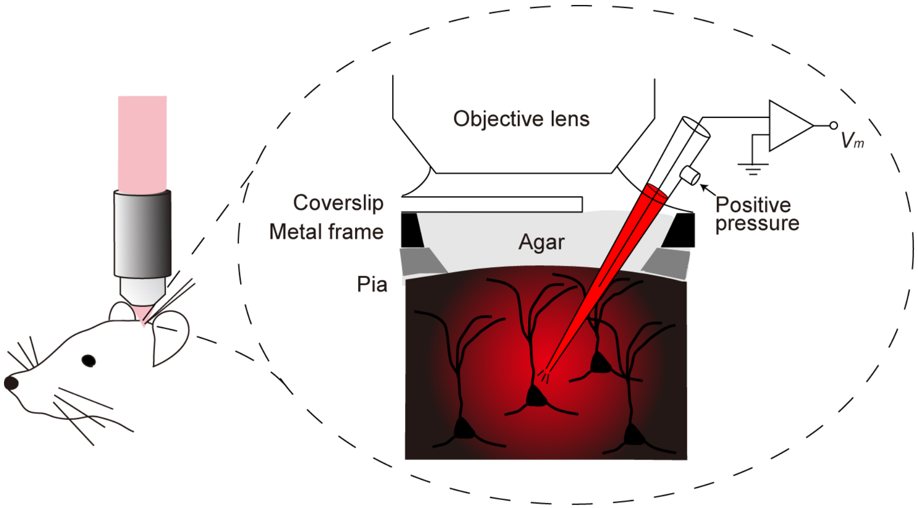
"One has to consider the possibility that in the monkey the simple-cell step may be skipped, perhaps by summing the inputs from cells in layer 4 on dendrites of complex cells. In such a scheme each main dendritic branch of a complex cell would perform the function of a simple cell."

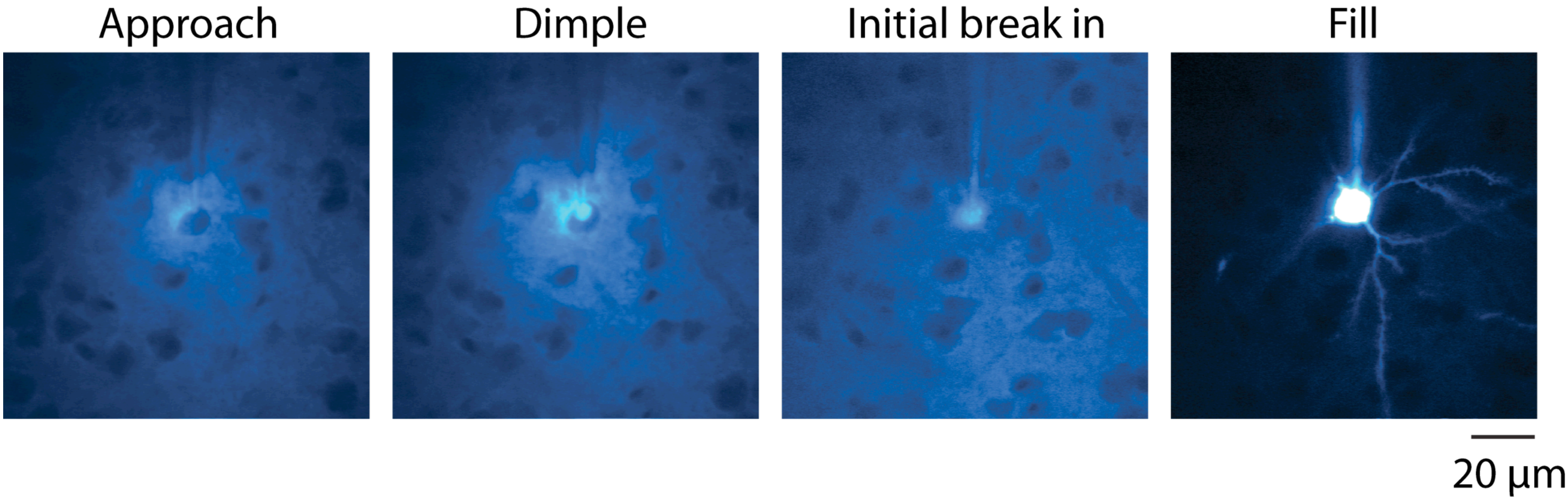
David Hubel, Nature 299: 515-524, 1982

The goal: coupling dendritic physiology to behaviour



In vivo patch-clamp recordings in mouse visual cortex

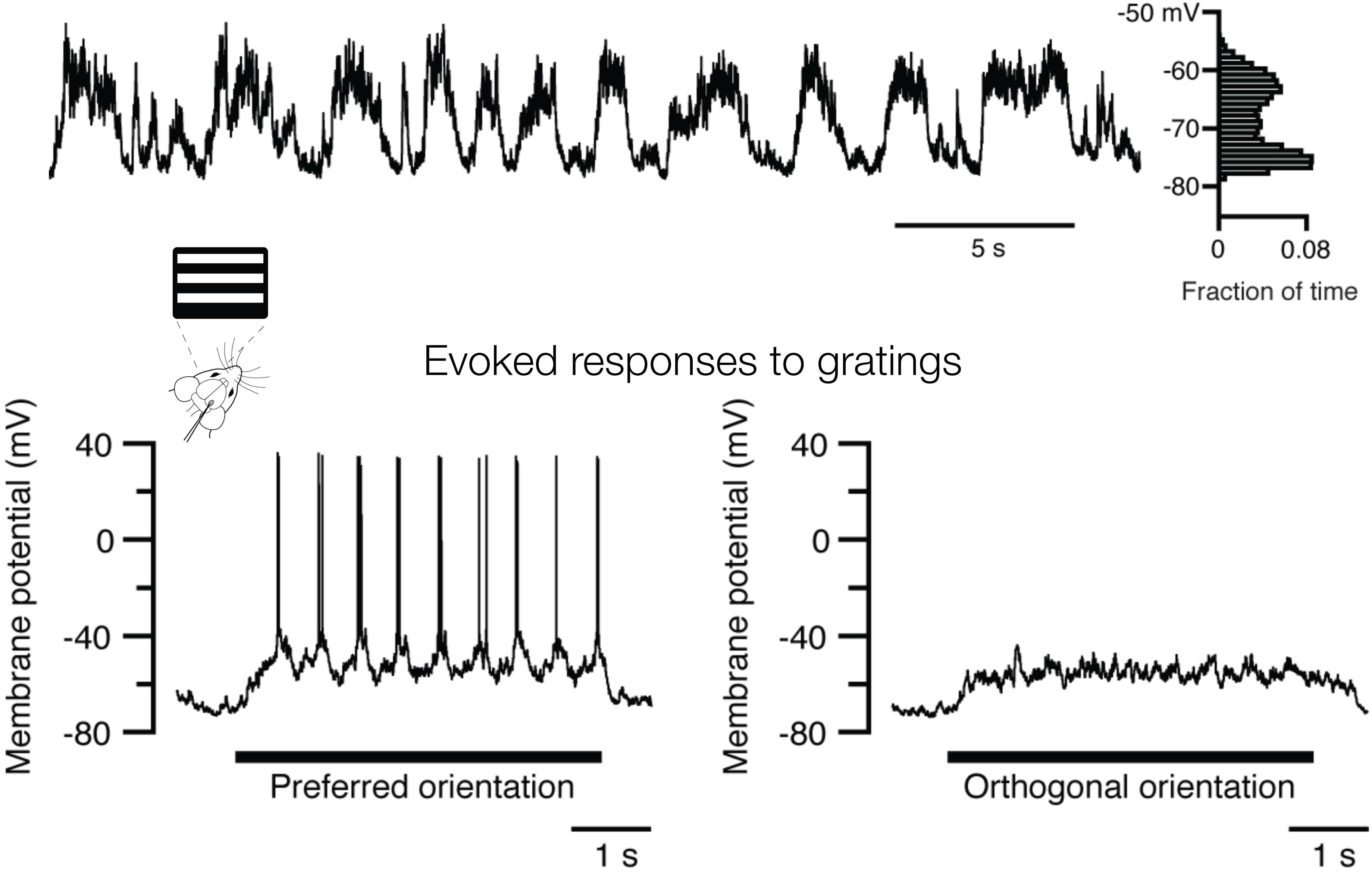




“Shadowpatching” - Kitamura et al., *Nature Methods* 2008

Physiology of neurons in mouse visual cortex

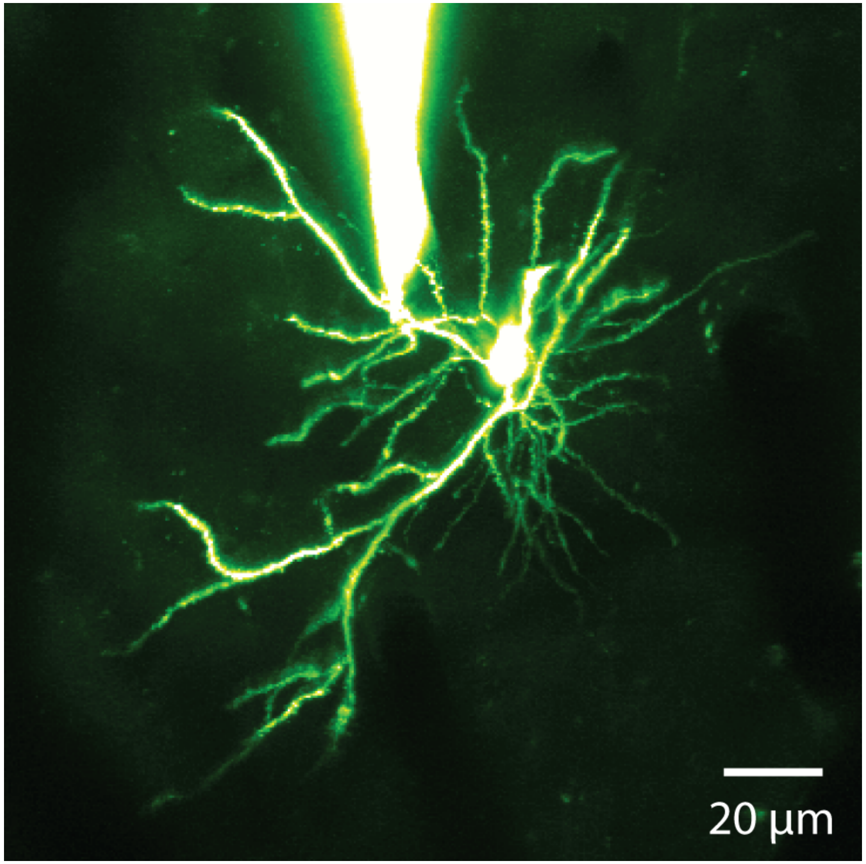
Spontaneous



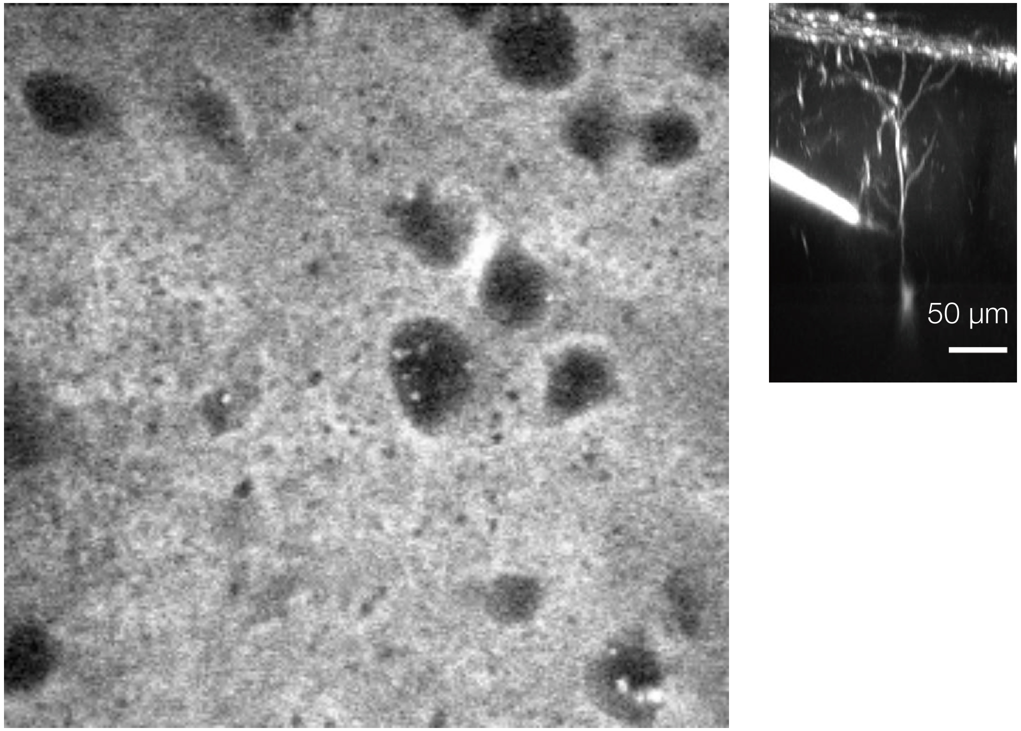
Evoked responses to gratings

Imaging-guided dendritic patch recordings

1. Blind, fill, visualize

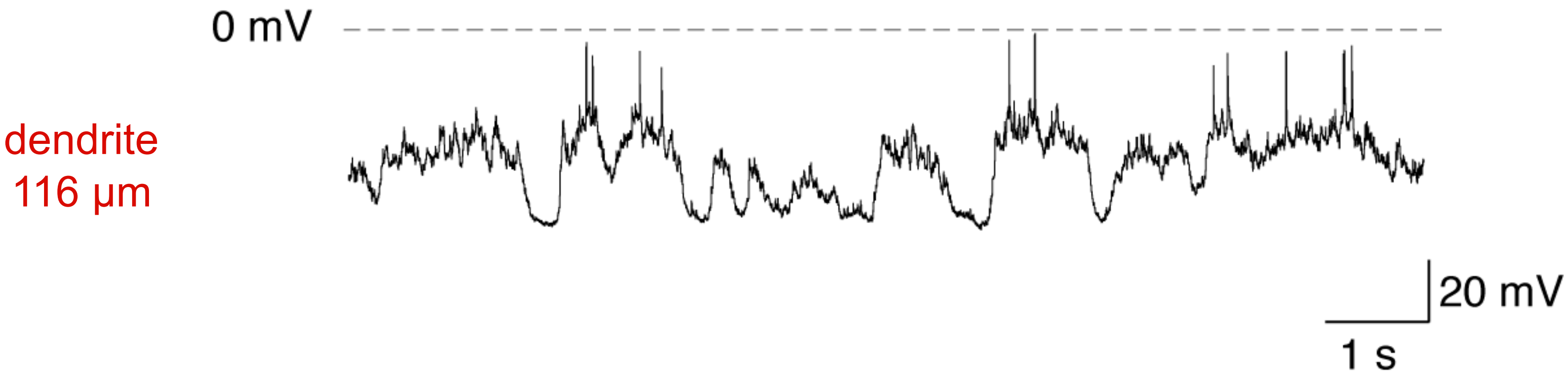


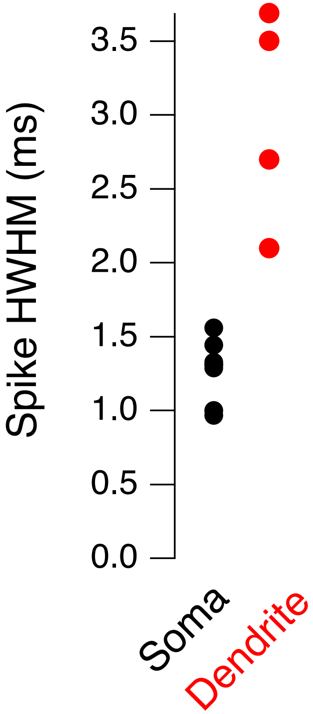
2. Shadowpatching

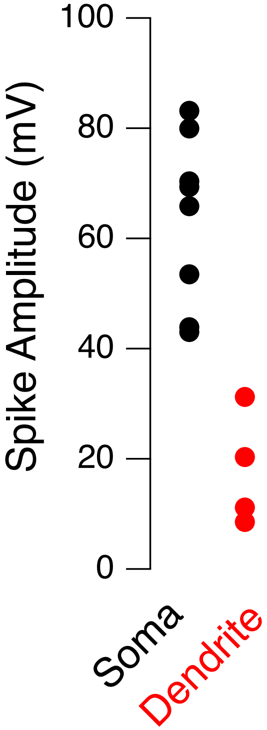


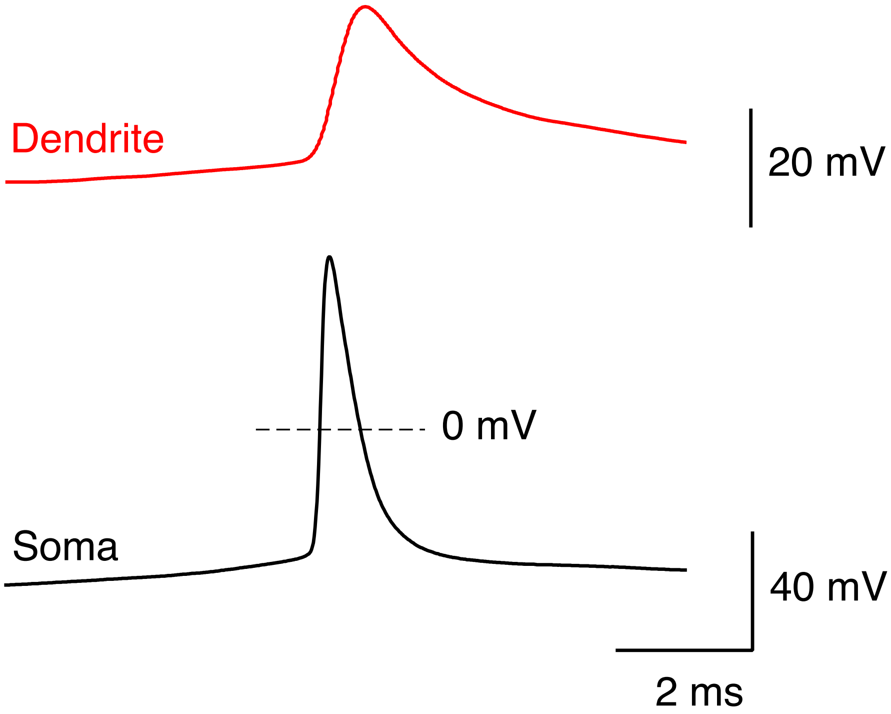
Layer 2/3 pyramidal neurons

Spontaneous backpropagating APs in dendrites



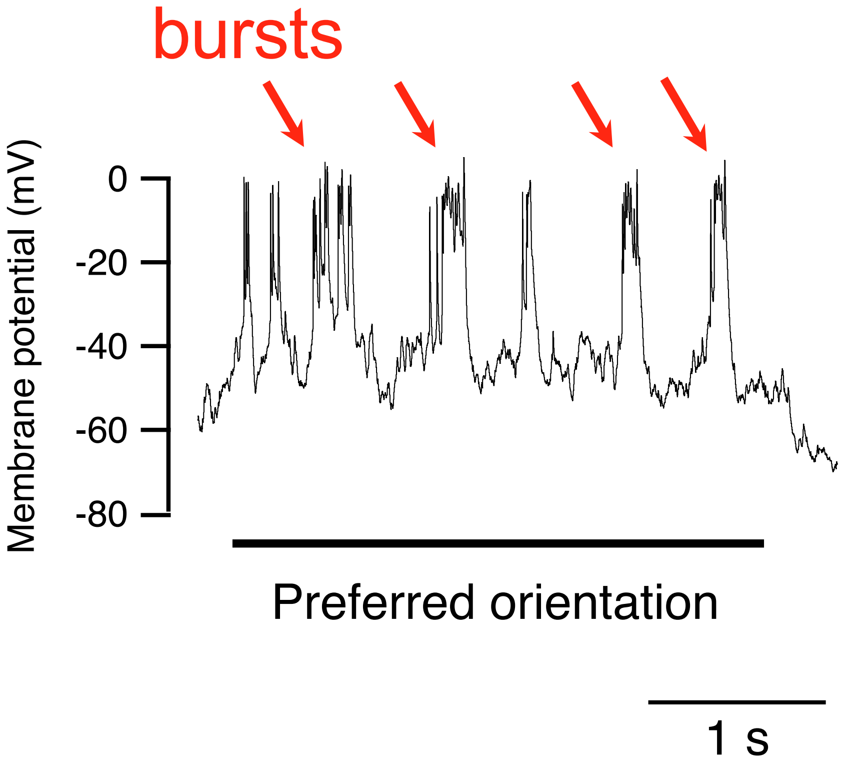




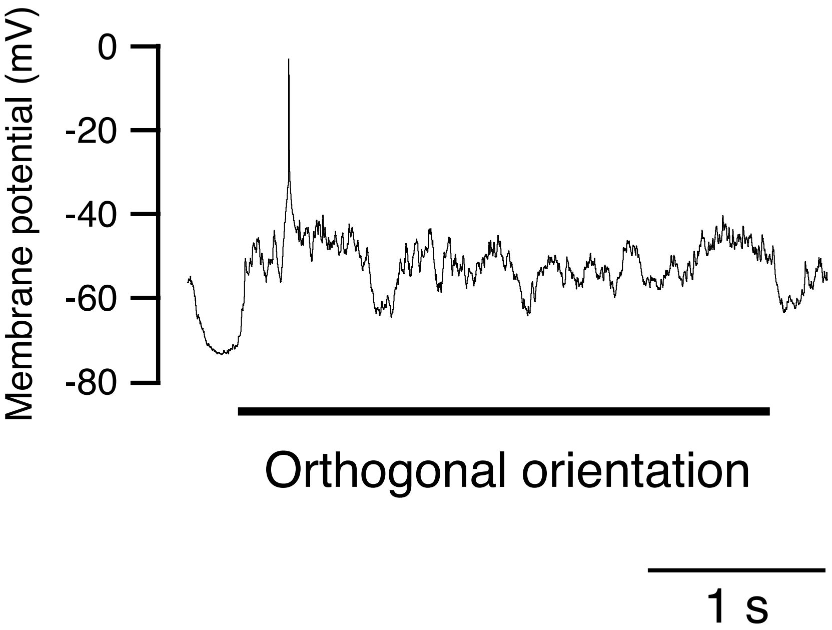


(cf. Waters, Larkum, Sakmann, Helmchen, 2003)

Visually evoked responses in distal dendrites

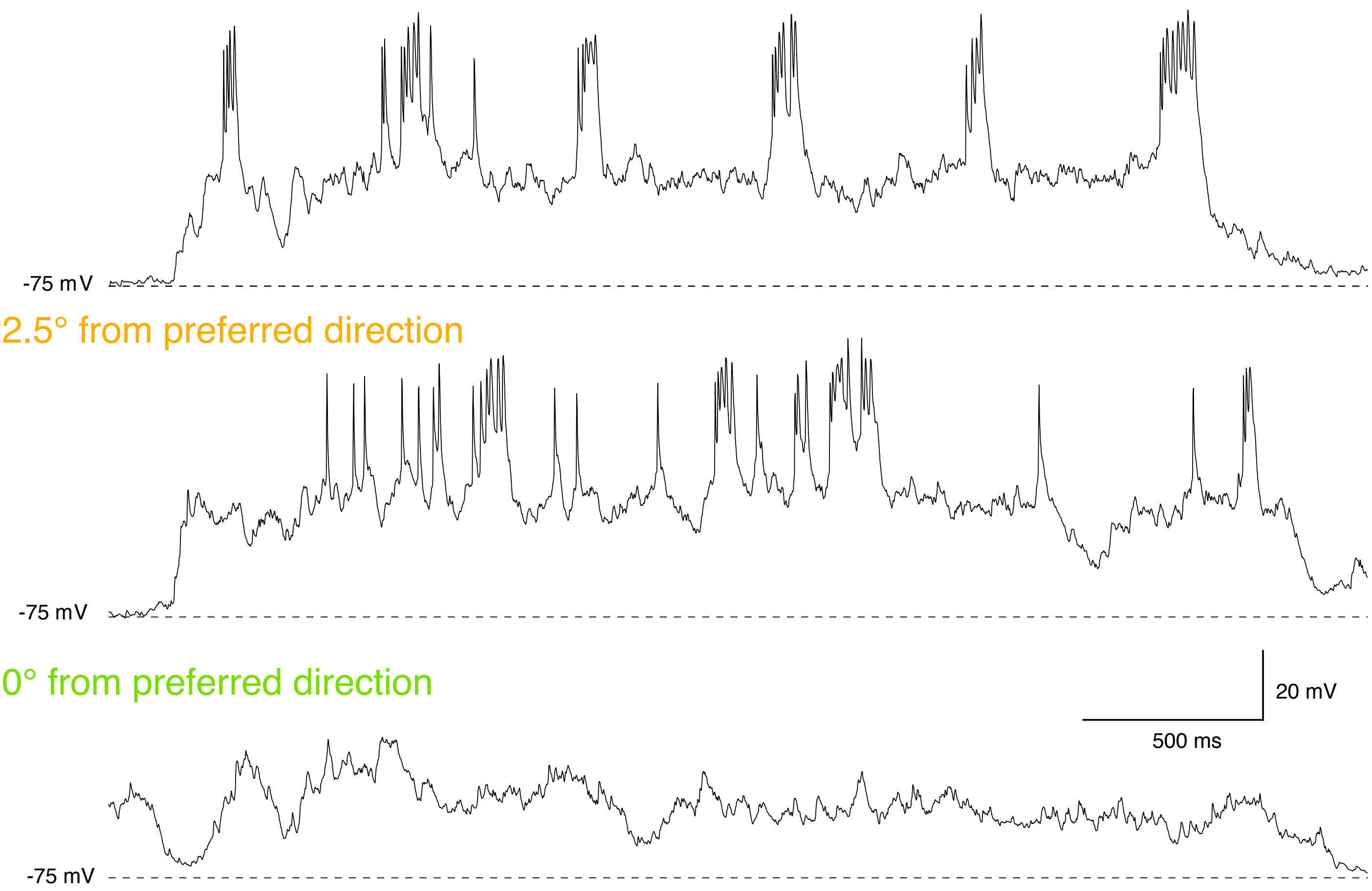


Preferred orientation



Orthogonal orientation

Dendritic bursts are orientation tuned

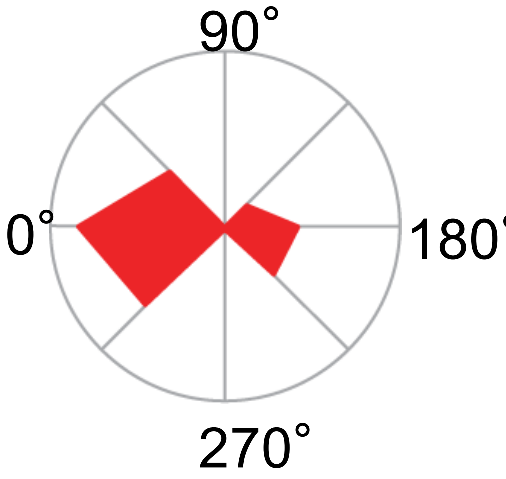

Preferred direction

22.5° from preferred direction

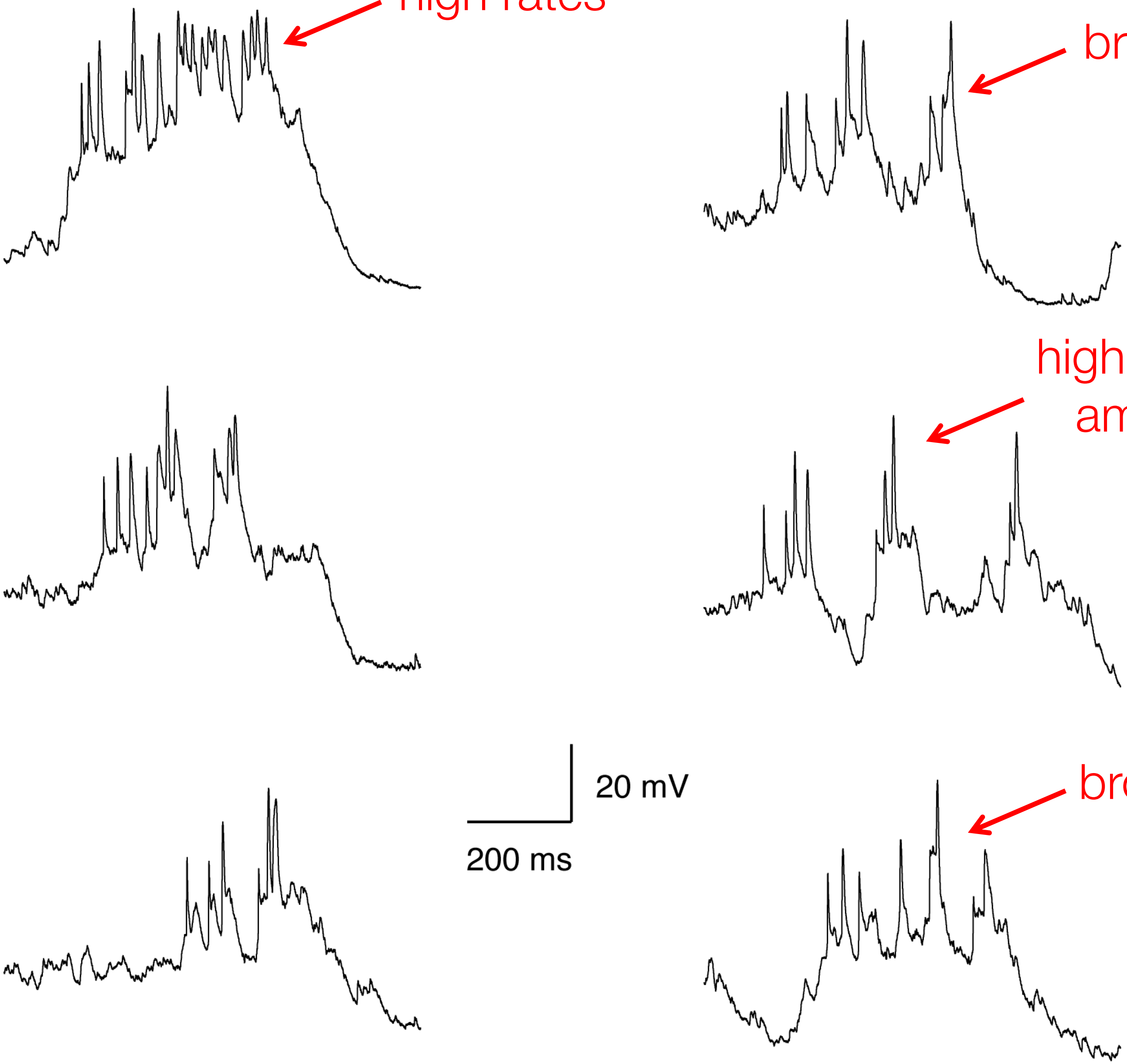
90° from preferred direction

Orientation tuning

Bursts



Visually evoked bursts are highly heterogeneous



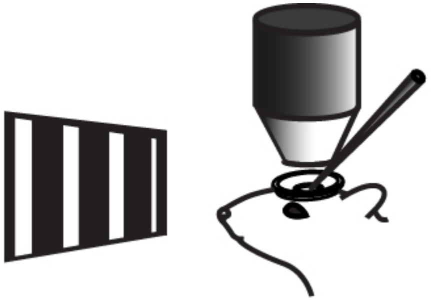
high rates

broad spikes

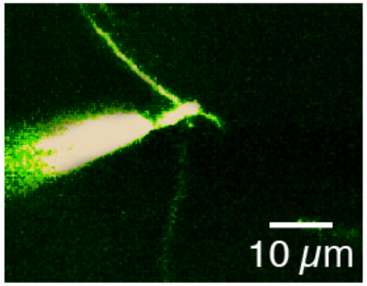
highly variable amplitudes

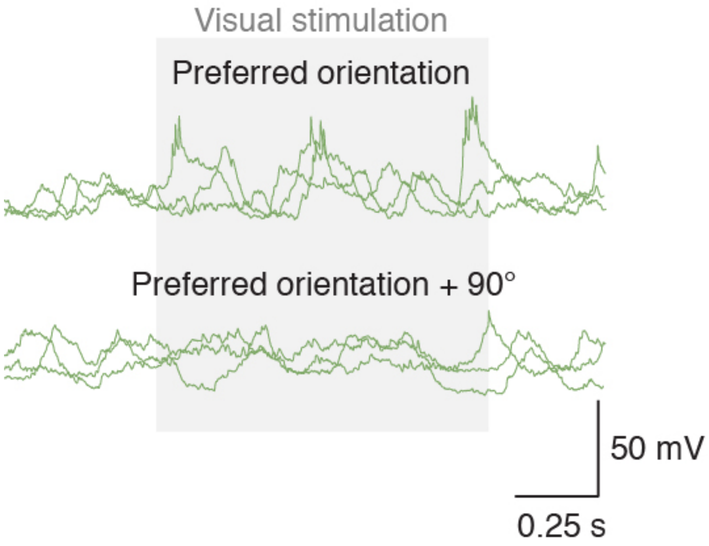
broad spikes

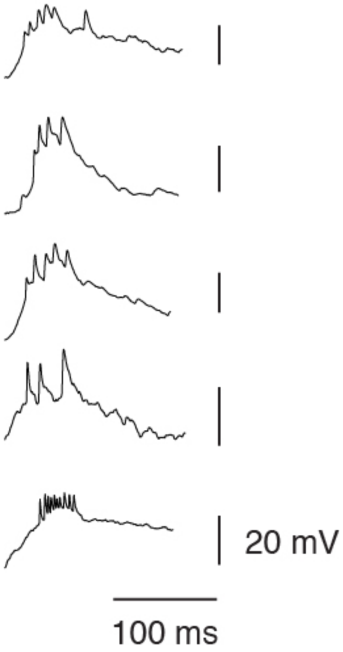
Visually evoked bursts in awake mice



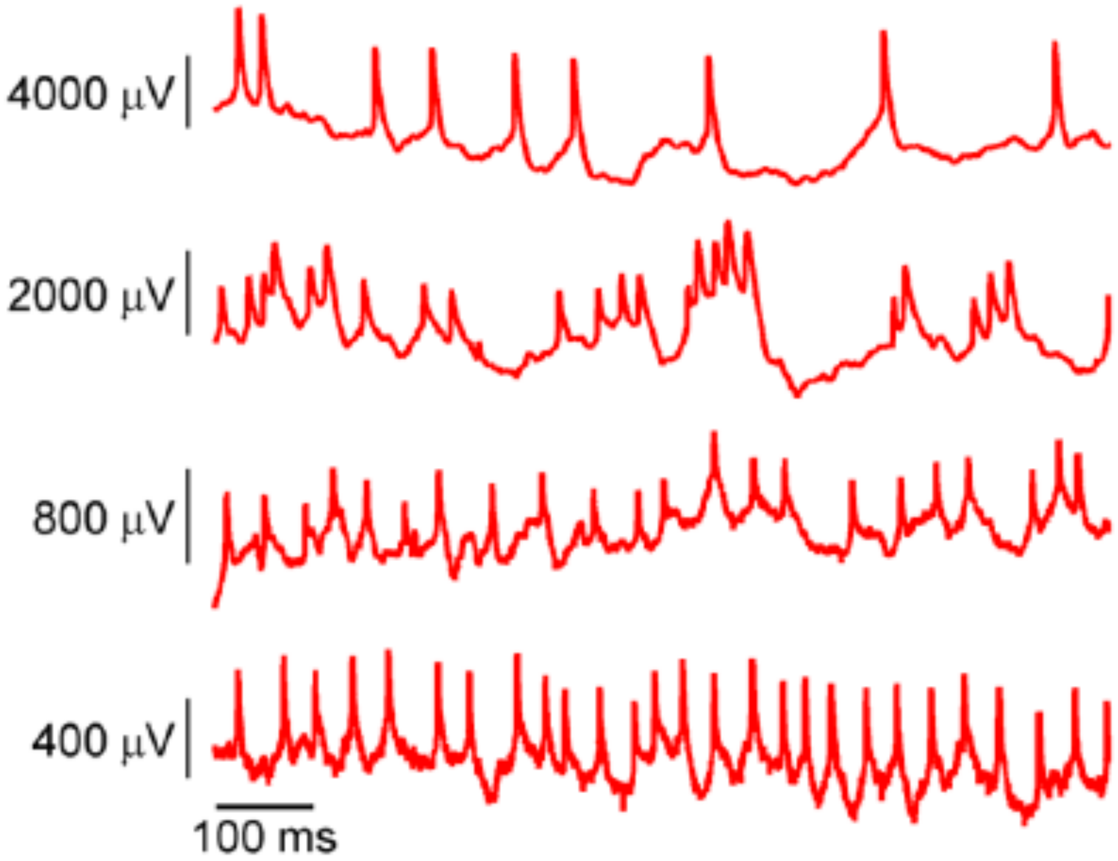
Awake





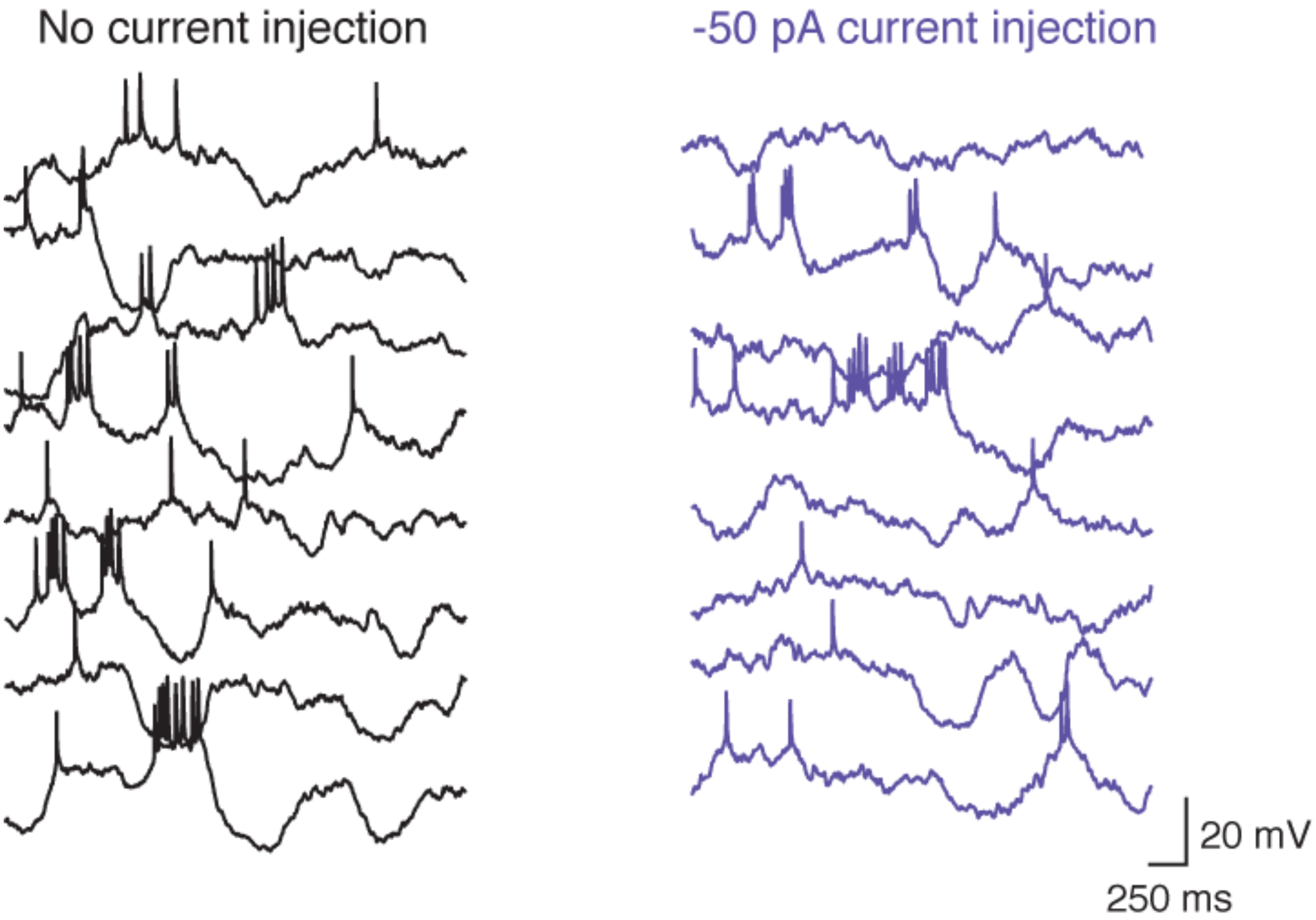


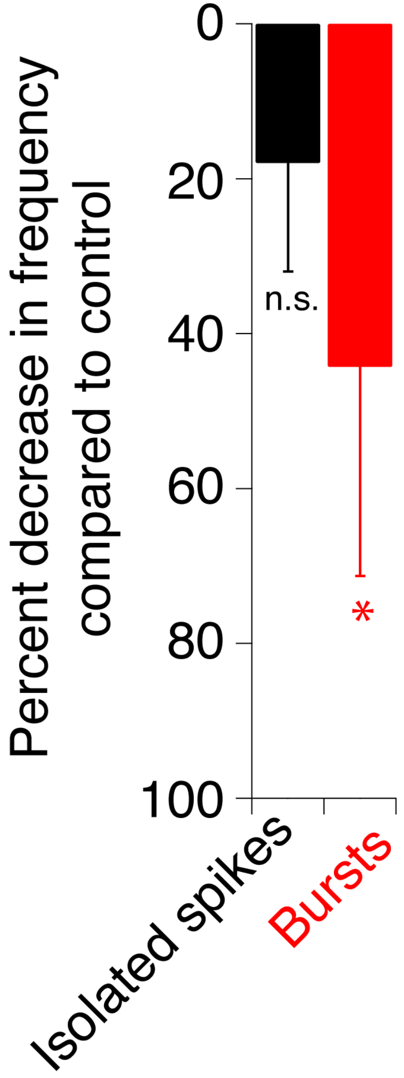
Putative tetrode recordings from dendrites in freely-moving animals



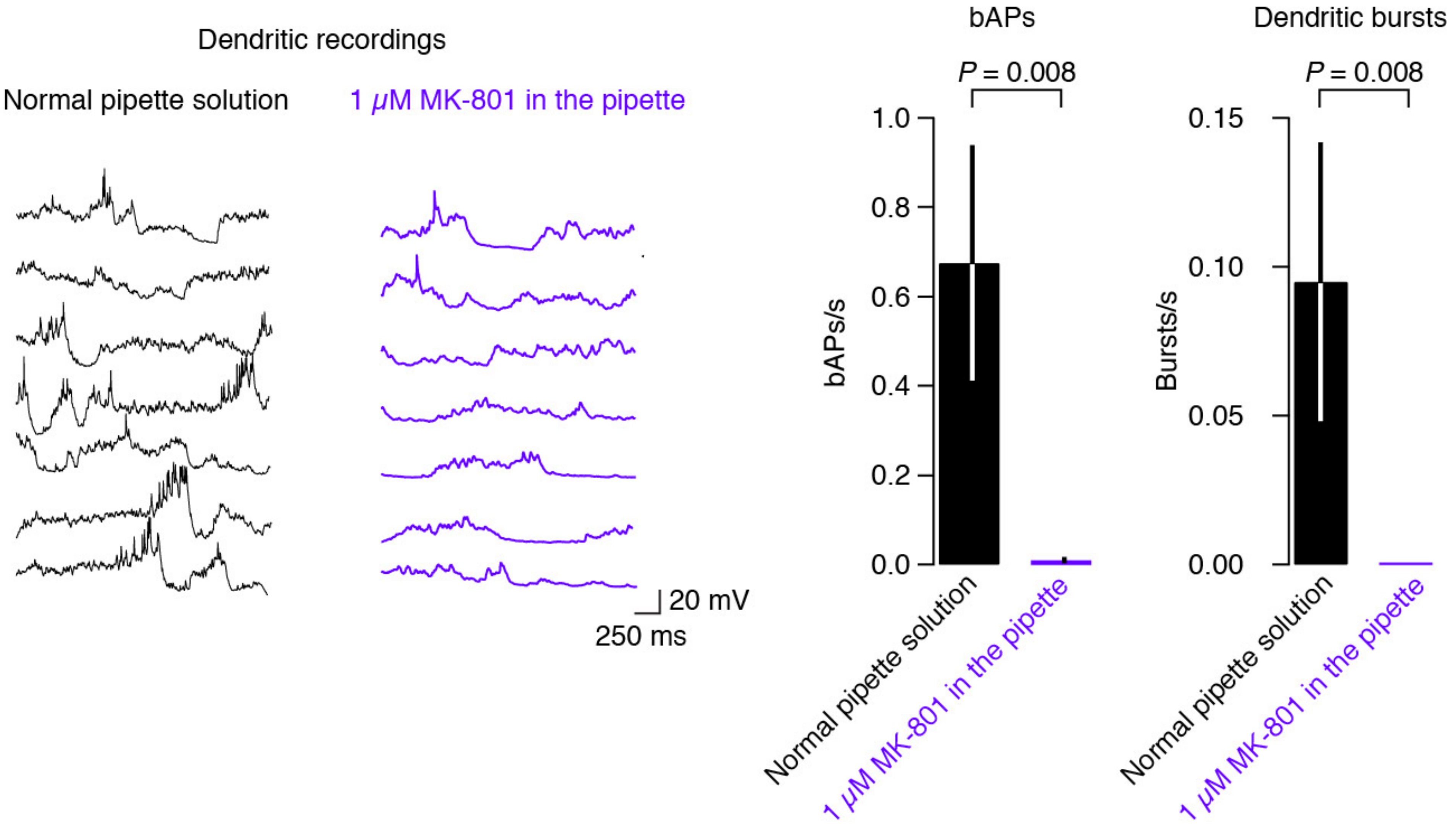
Moore… Mehta *Science* 2016

Dendritic spike bursts are highly sensitive to hyperpolarization



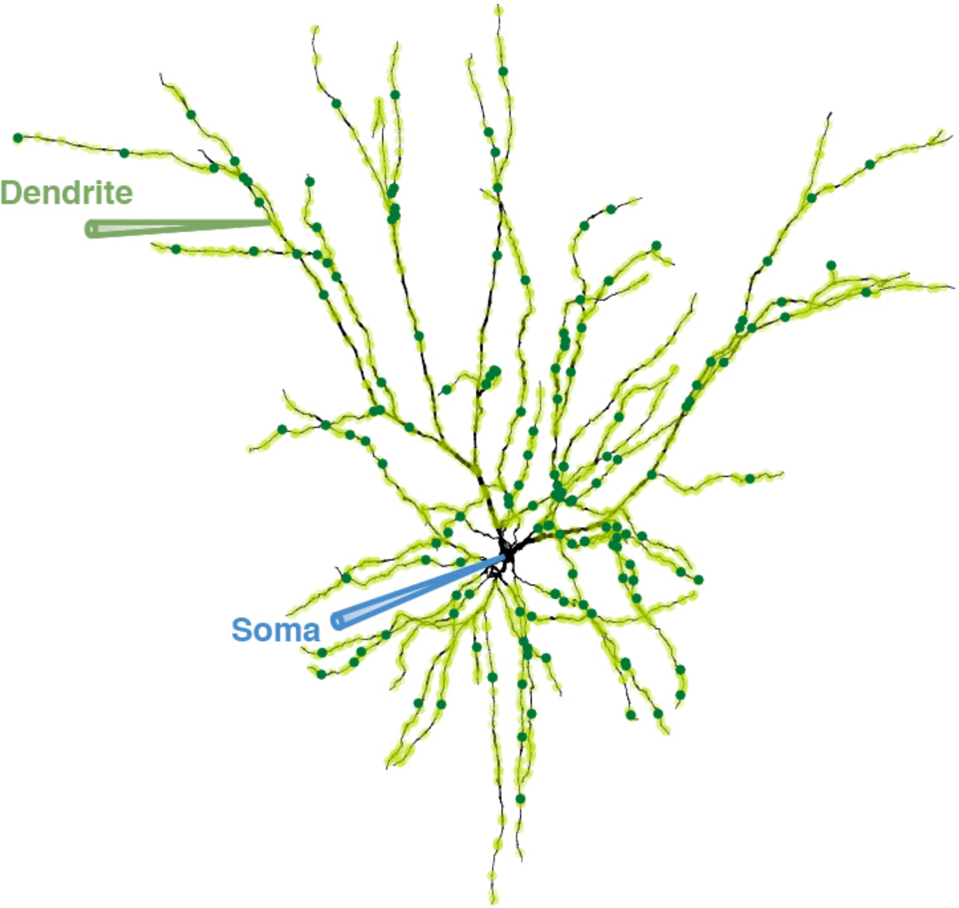


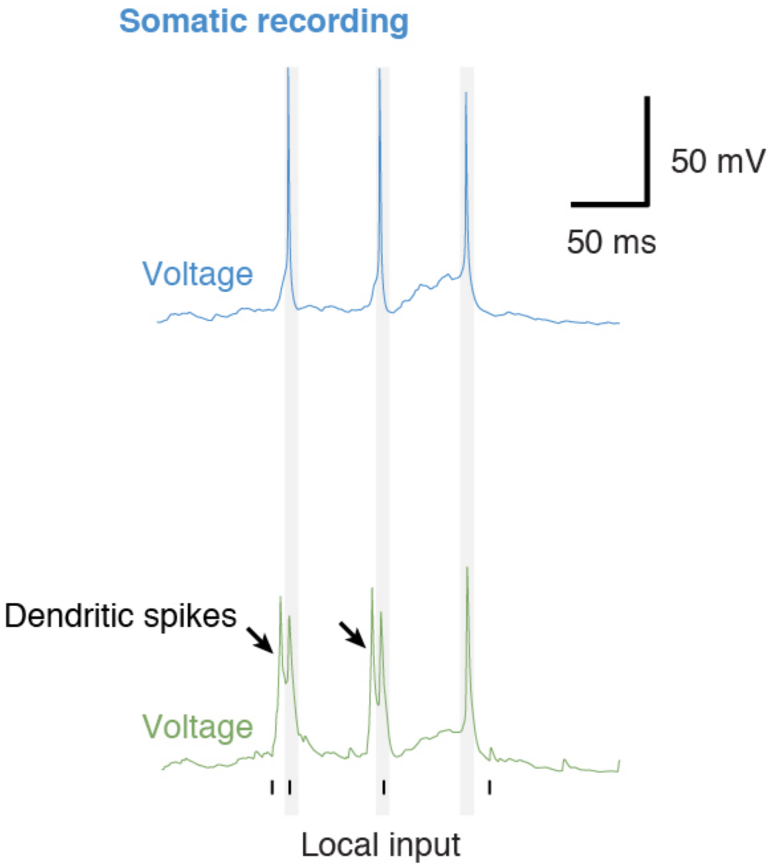
Dendritic spike bursts are highly sensitive to NMDA-R block



M
O
D
E
L

Distributed input triggers dendritic spikes in a pyramidal cell model

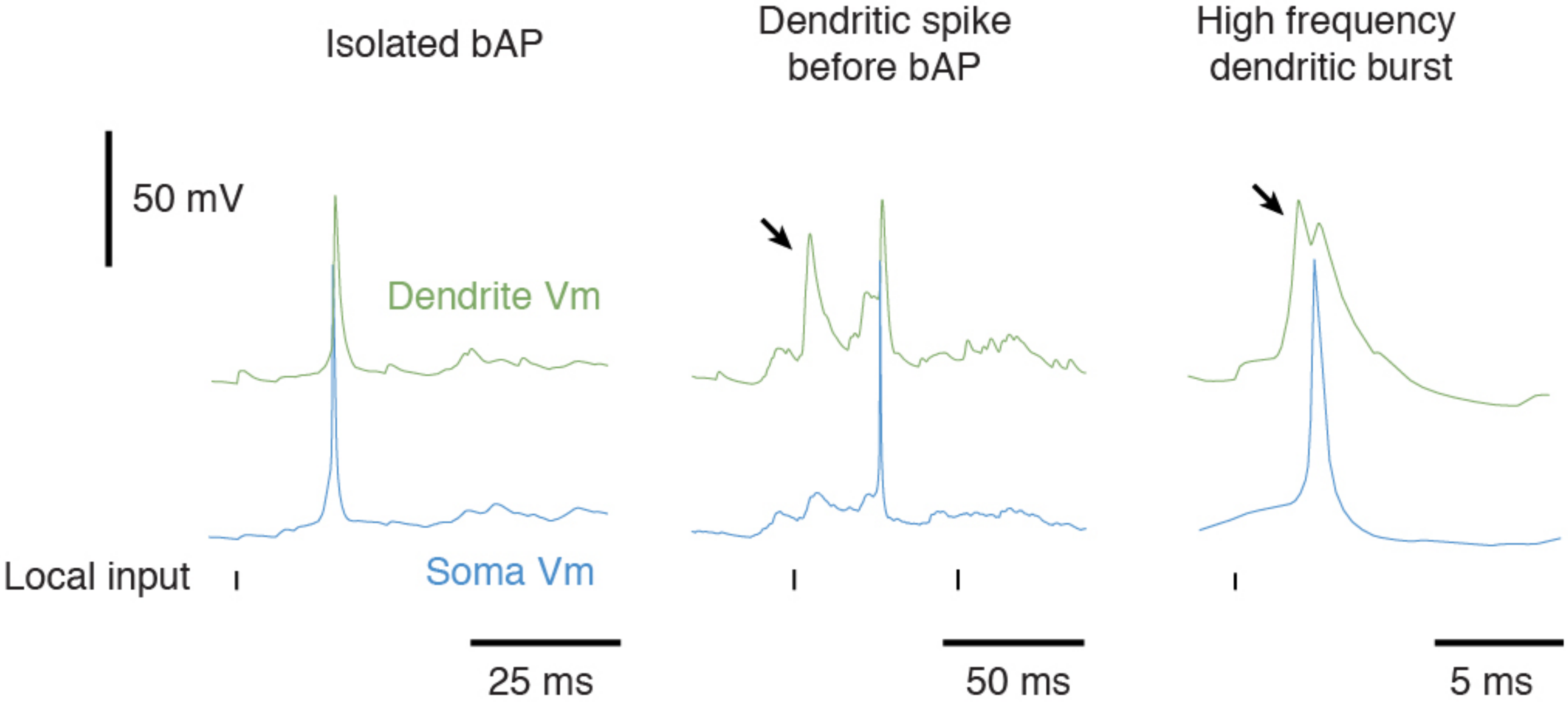




Active compartmental model of a layer 2/3 pyramidal neuron with glutamatergic (AMPA & NMDA) and GABAergic synapses activated in distributed spatiotemporal patterns: background @ 0.5 Hz, signal (10%) @ 5 Hz

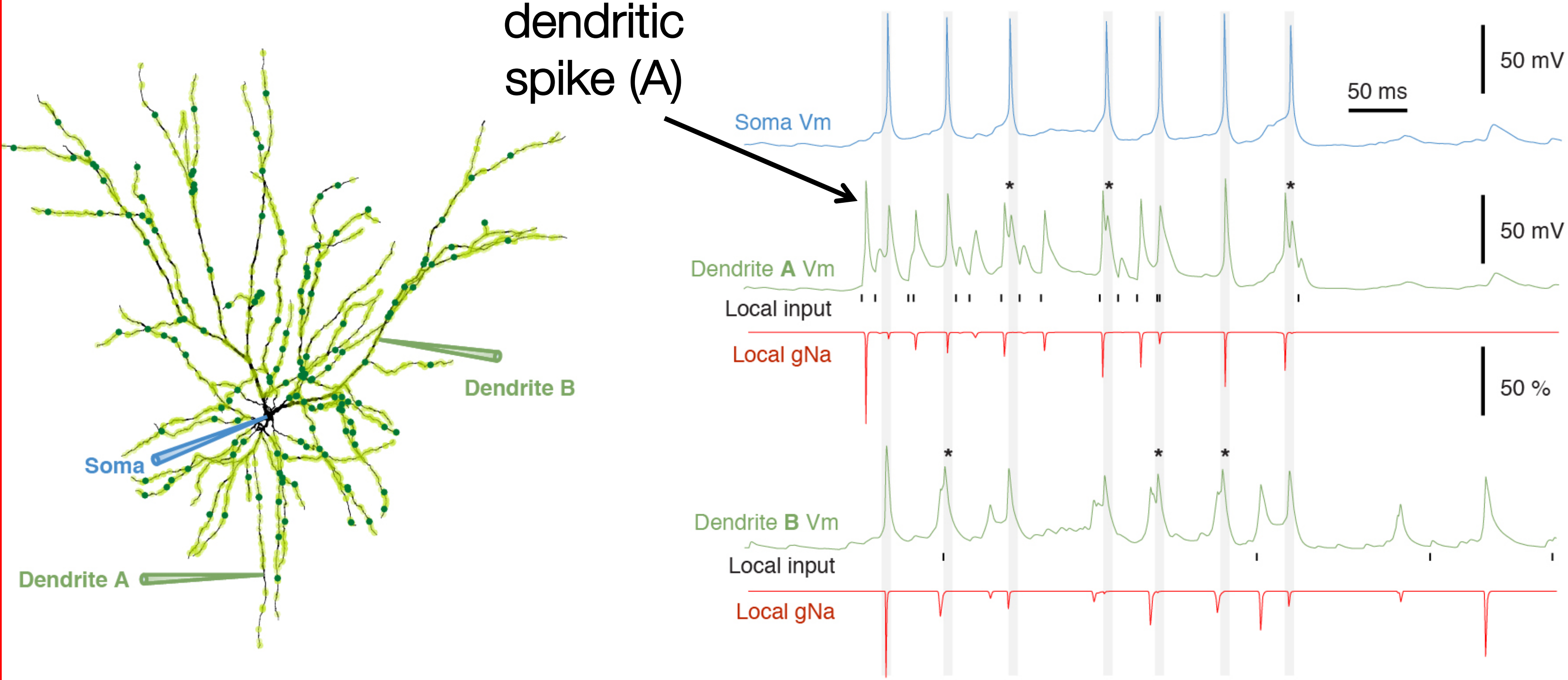
M
O
D
E
L

Different types of active events in the pyramidal cell model



M
O
D
E
L

Distributed initiation explains high frequency of dendritic spikes



Mixture of dendritic spikes & bAP

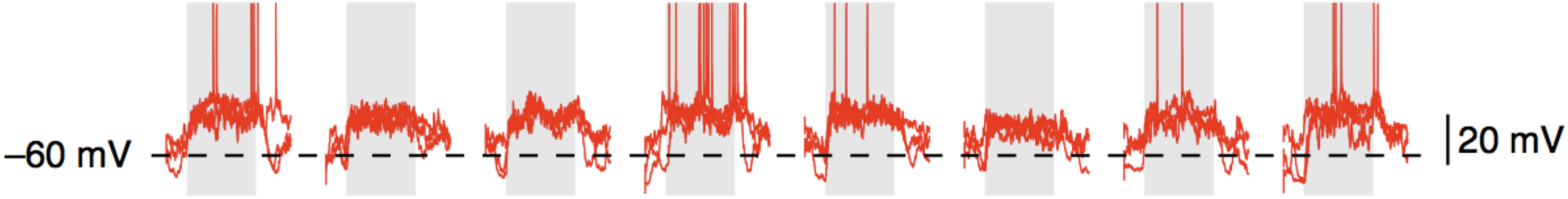
dendritic spike (A)

dendritic spike (B)

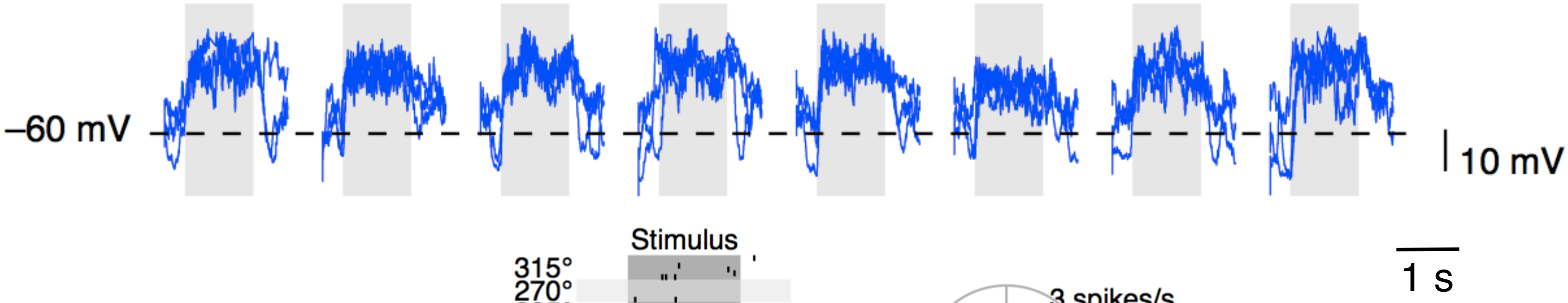
Interim summary

- Visual input triggers large, bursty events in distal dendrites
- These events cannot be accounted for by backpropagating APs, and thus are likely to be **dendritic spikes**
- The dendritic spikes are tuned to sensory stimuli
- Dendritic spikes are blocked by hyperpolarization and intracellular MK-801
- Modelling reveals that dendritic spikes can be triggered by distributed input and can initiate across multiple branches

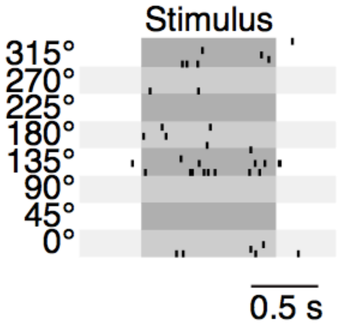
Subthreshold tuning of membrane potential

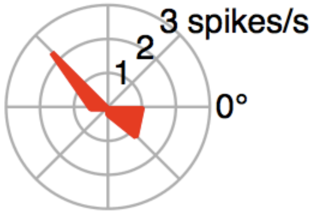


Spikes blanked (50 ms window)

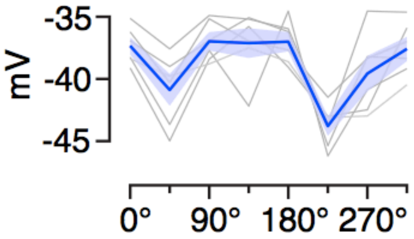


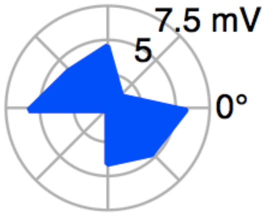
Spikes:



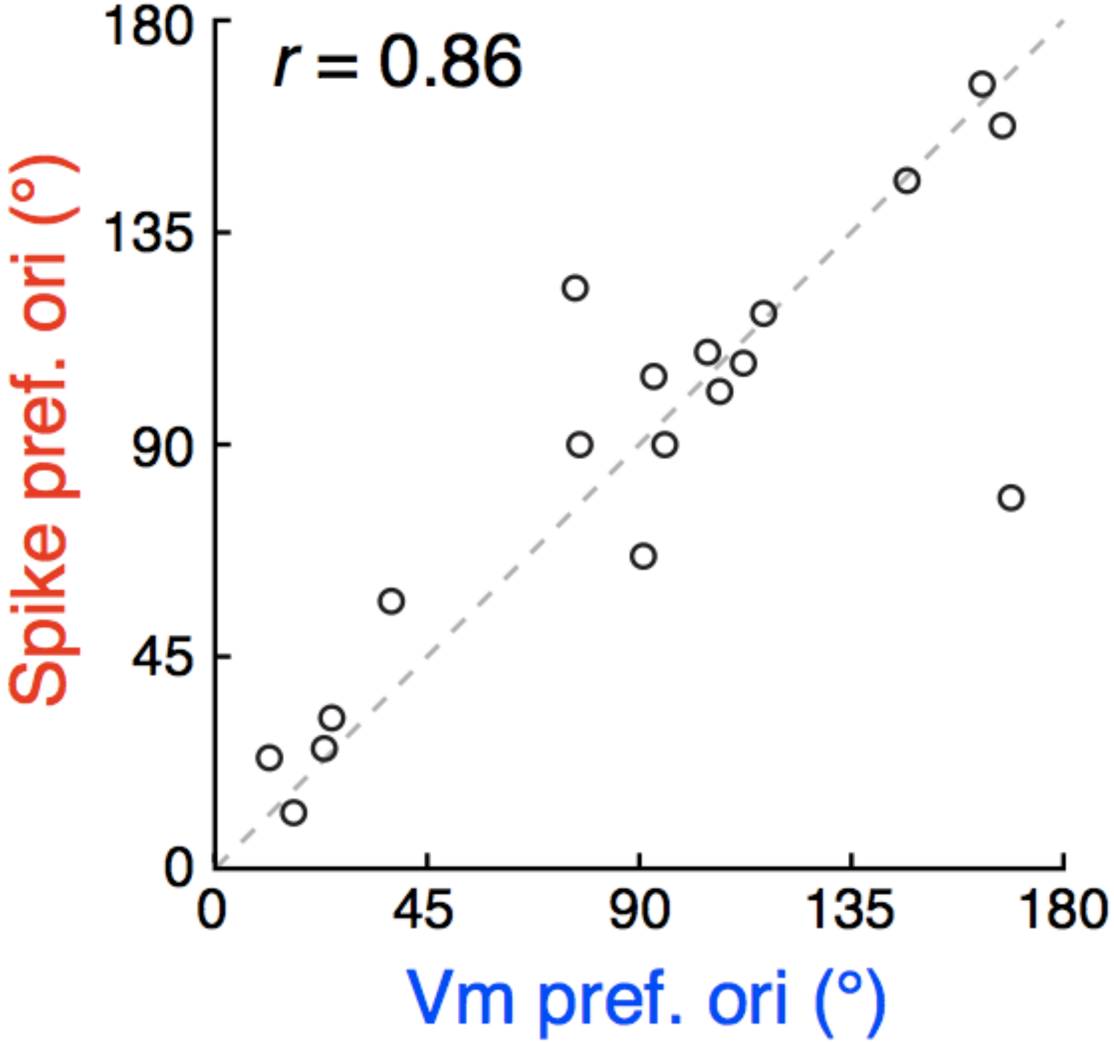


Subthreshold Vm:

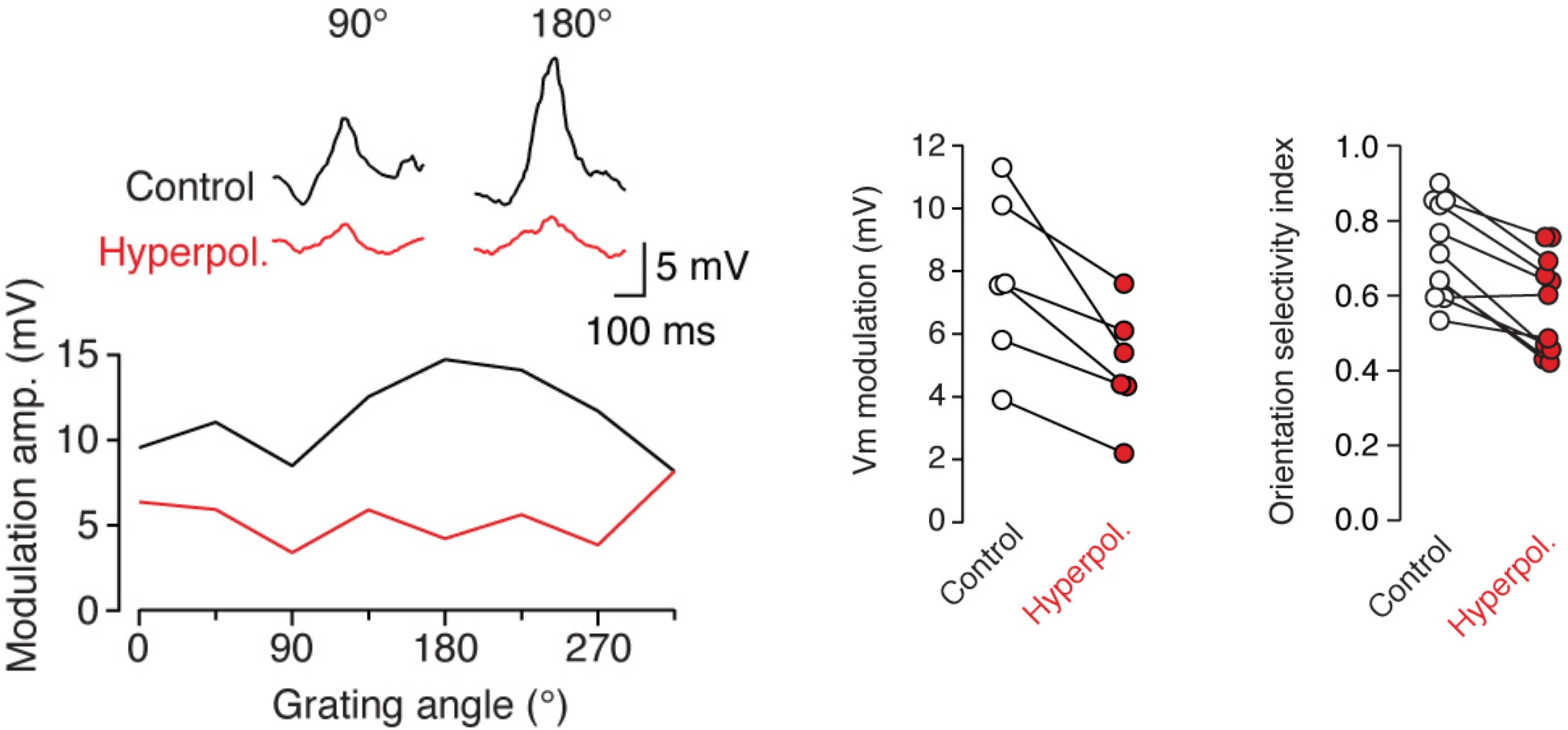




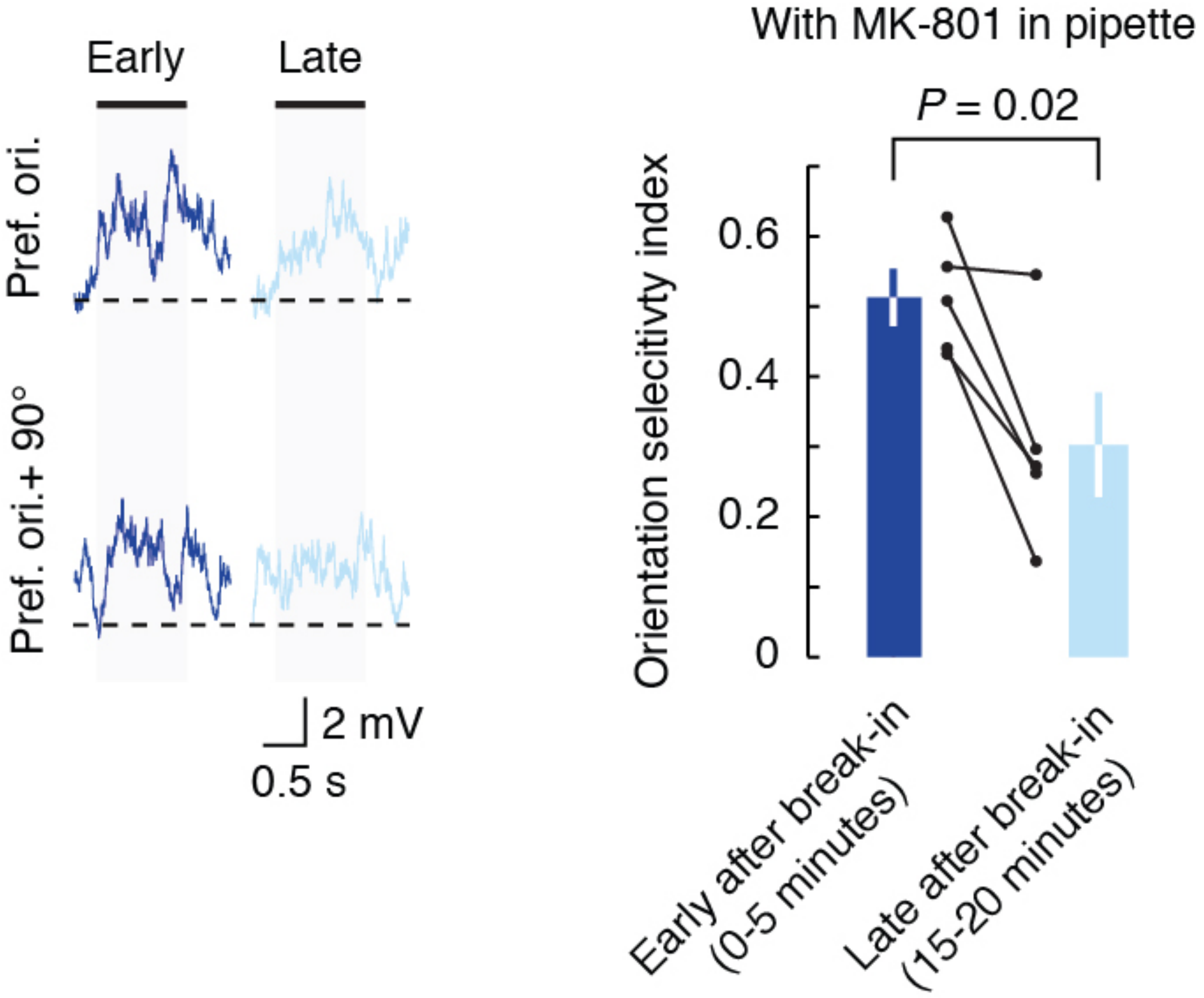
Subthreshold V_m tuning matches spike tuning



Hyperpolarization blocks subthreshold tuning



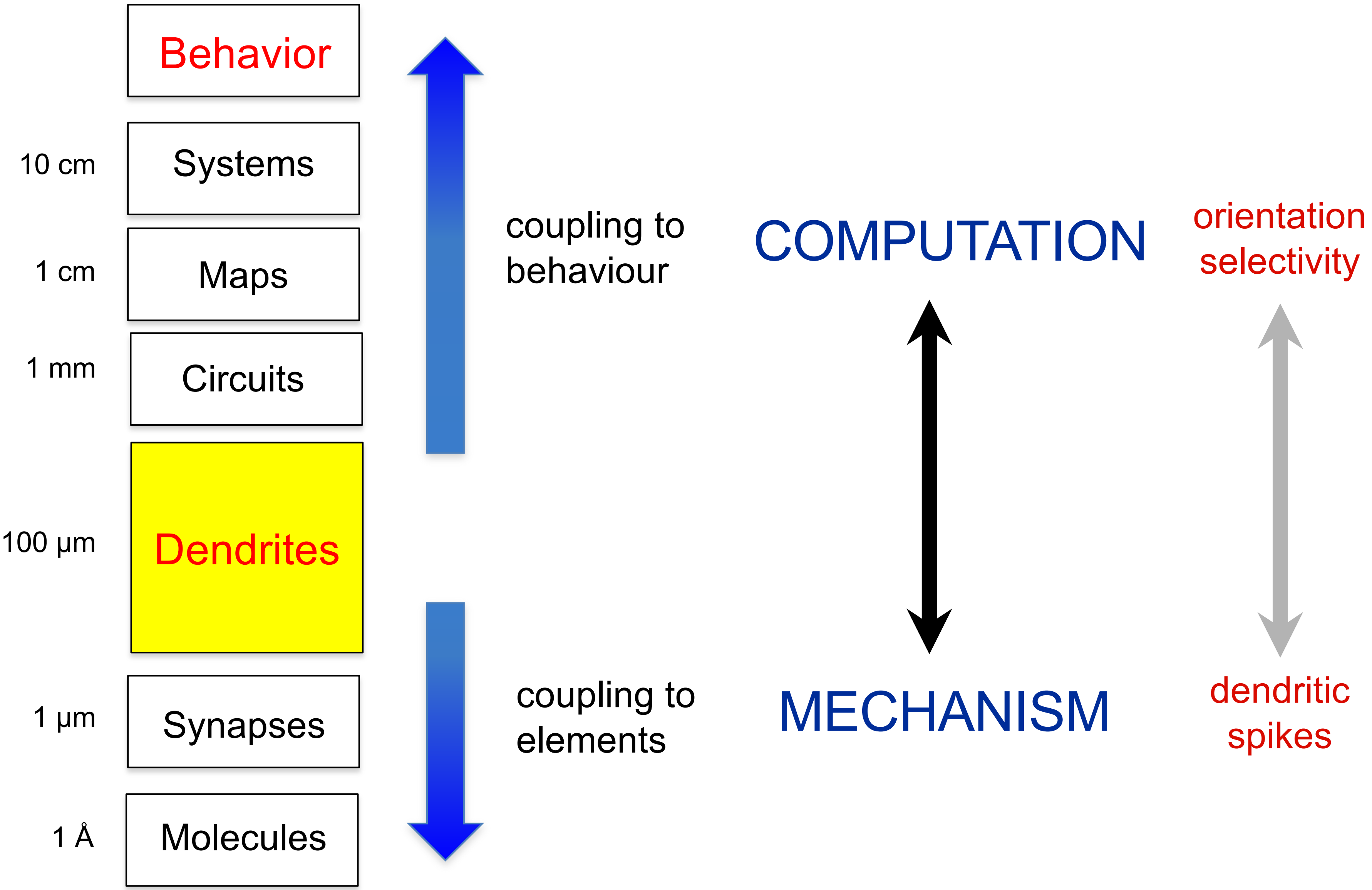
Intracellular block of NMDA-Rs reduces subthreshold tuning



Summary

- Dendritic spikes are evoked by visual stimulation in an orientation-tuned manner
- Dendritic spikes are sensitive to hyperpolarization
- The subthreshold membrane potential at the soma is orientation tuned
- Subthreshold tuning is reduced on hyperpolarization or with NMDA-R block
- Dendritic spikes contribute to orientation tuning

The goal: coupling dendritic physiology to behaviour



Behavior

10 cm Systems

1 cm Maps

1 mm Circuits

100 µm Dendrites

1 µm Synapses

1 Å Molecules

coupling to behaviour

coupling to elements

COMPUTATION

MECHANISM

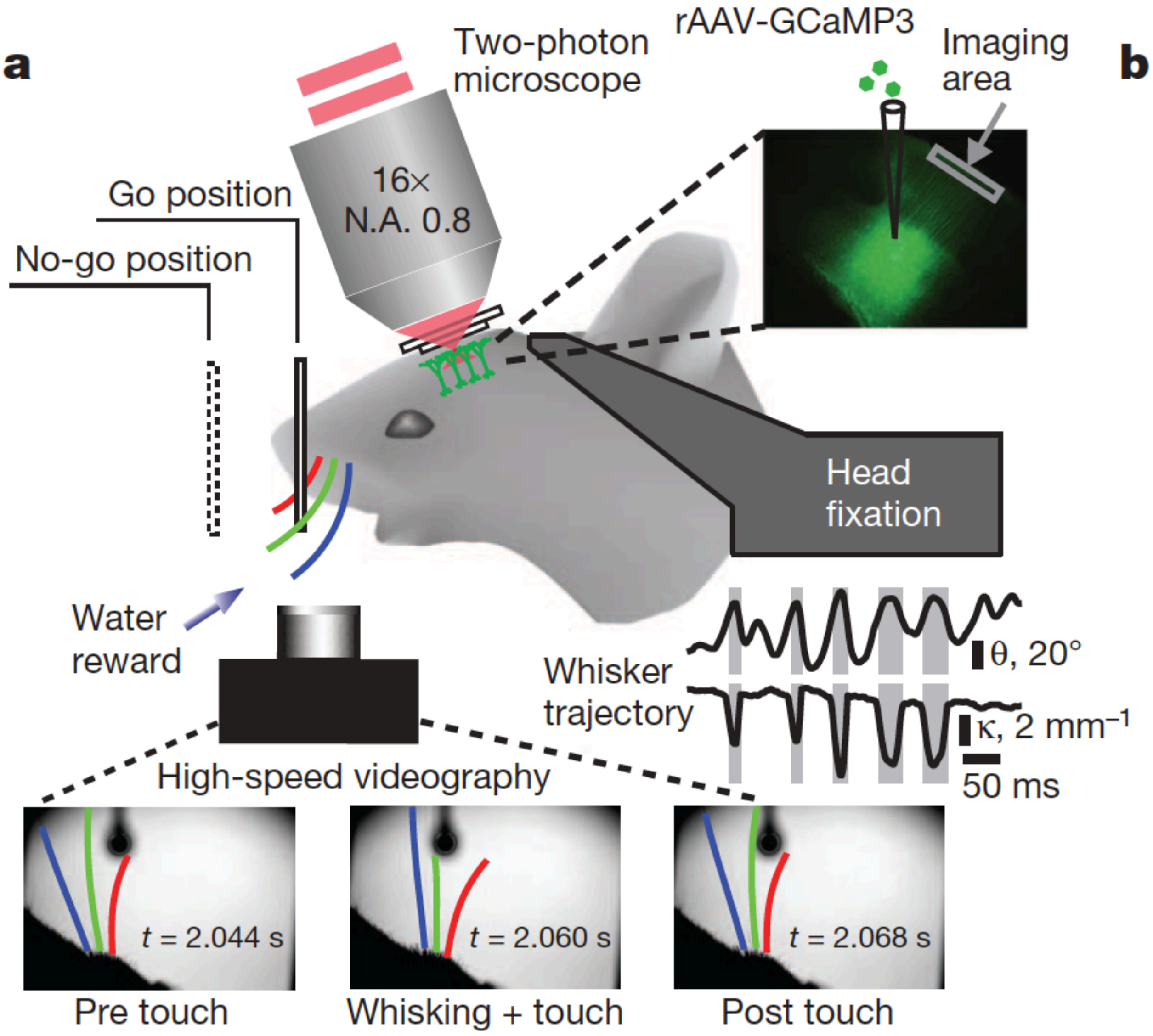
orientation selectivity

dendritic spikes

Smith et al. *Nature* 2013

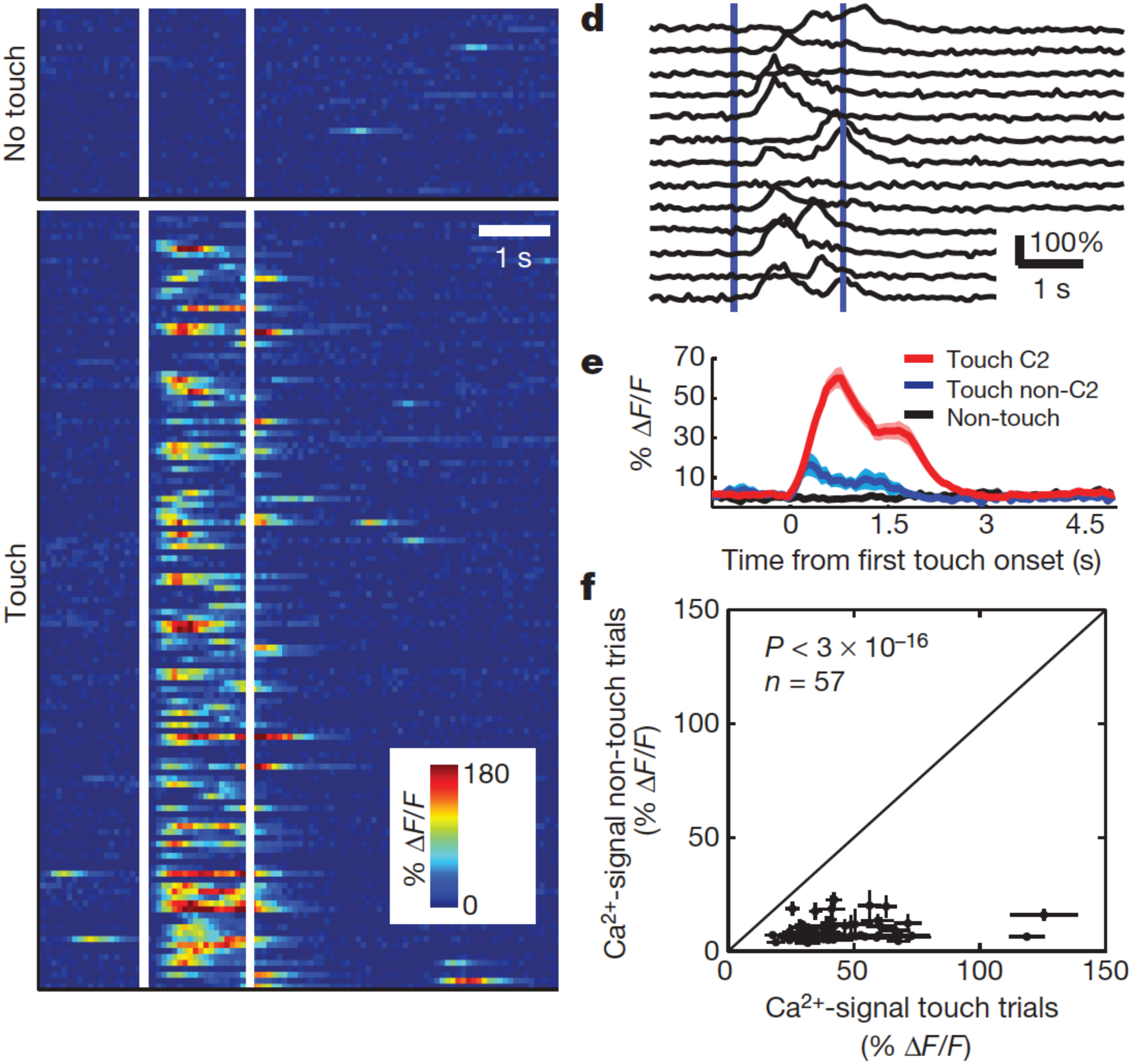
What about behaviour?

Specific dendritic tuft Ca^{2+} signals during active sensing



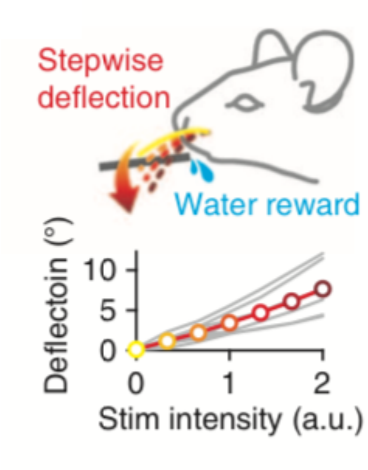
Xu... Magee & Svoboda, Nature 2012

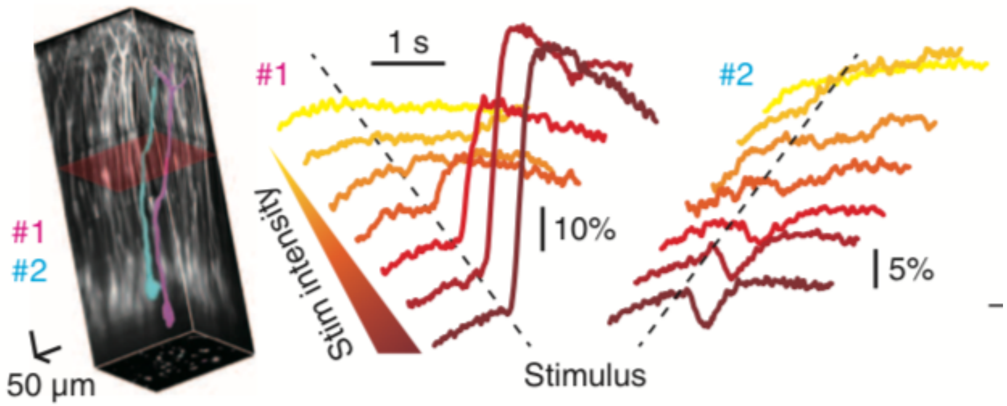
Specific dendritic tuft Ca^{2+} signals during active sensing

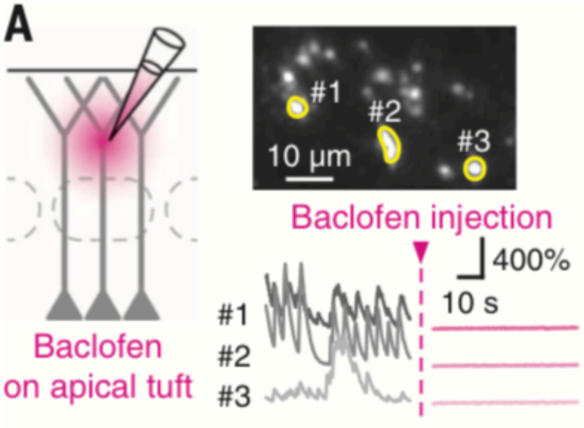


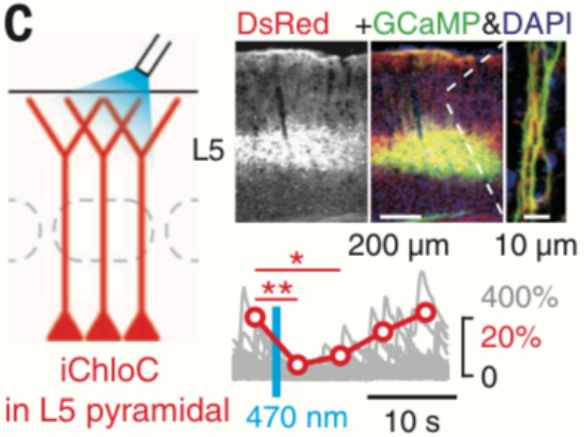
Xu... Magee & Svoboda, Nature 2012

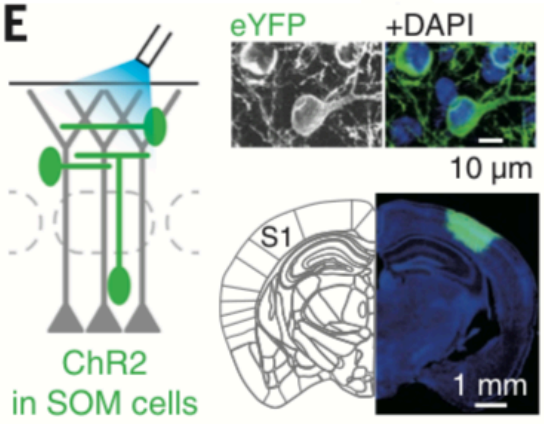
Manipulation of L5 apical dendrites modulates stimulus perception



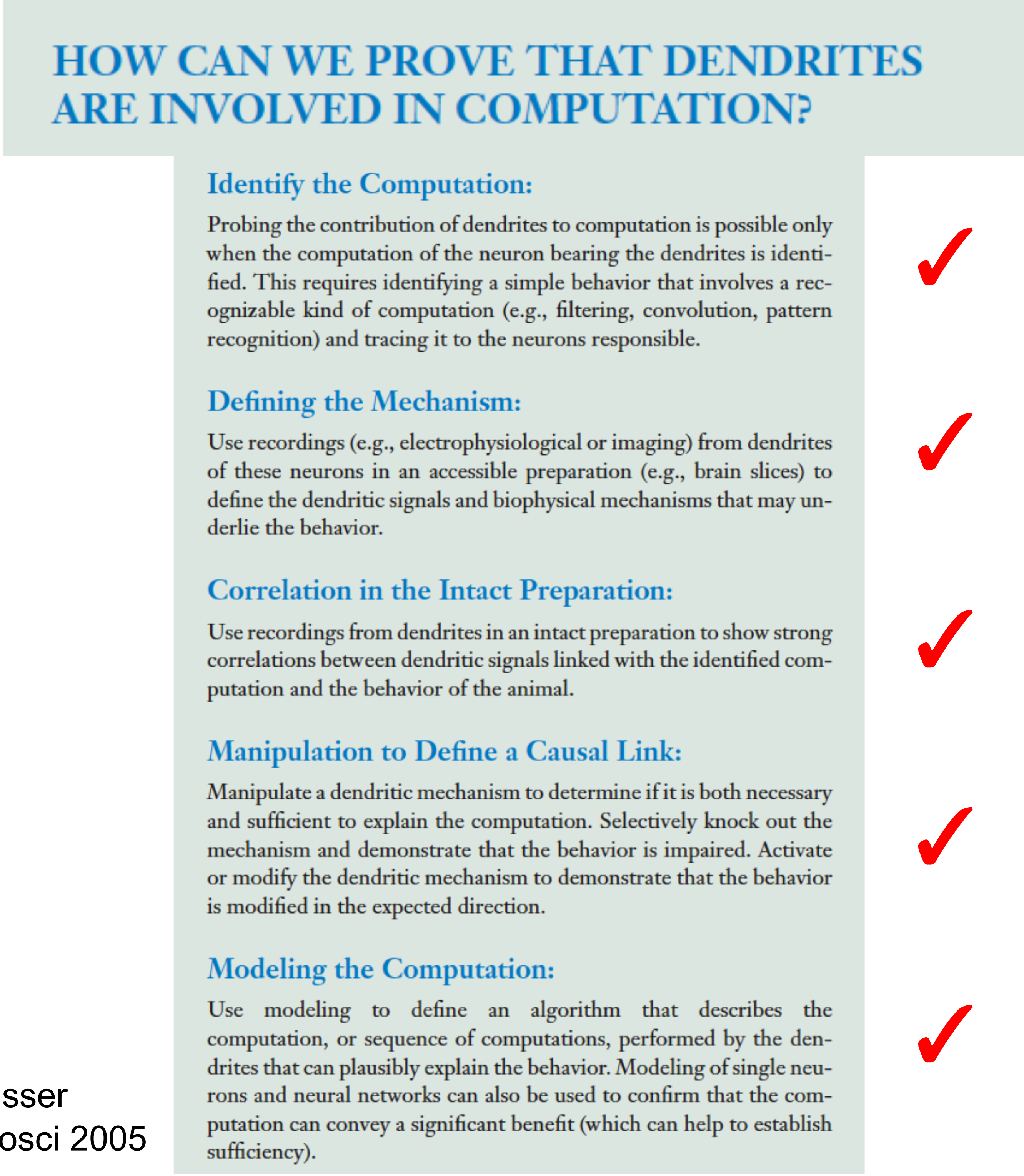








Takahashi…Larkum, Science 2016



HOW CAN WE PROVE THAT DENDRITES ARE INVOLVED IN COMPUTATION?

Identify the Computation:

Probing the contribution of dendrites to computation is possible only when the computation of the neuron bearing the dendrites is identified. This requires identifying a simple behavior that involves a recognizable kind of computation (e.g., filtering, convolution, pattern recognition) and tracing it to the neurons responsible. ✓

Defining the Mechanism:

Use recordings (e.g., electrophysiological or imaging) from dendrites of these neurons in an accessible preparation (e.g., brain slices) to define the dendritic signals and biophysical mechanisms that may underlie the behavior. ✓

Correlation in the Intact Preparation:

Use recordings from dendrites in an intact preparation to show strong correlations between dendritic signals linked with the identified computation and the behavior of the animal. ✓

Manipulation to Define a Causal Link:

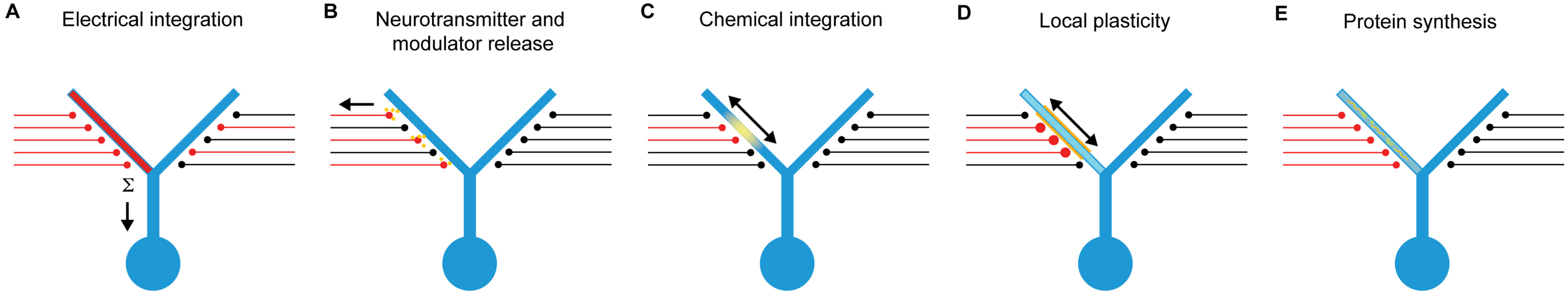
Manipulate a dendritic mechanism to determine if it is both necessary and sufficient to explain the computation. Selectively knock out the mechanism and demonstrate that the behavior is impaired. Activate or modify the dendritic mechanism to demonstrate that the behavior is modified in the expected direction. ✓

Modeling the Computation:

Use modeling to define an algorithm that describes the computation, or sequence of computations, performed by the dendrites that can plausibly explain the behavior. Modeling of single neurons and neural networks can also be used to confirm that the computation can convey a significant benefit (which can help to establish sufficiency). ✓

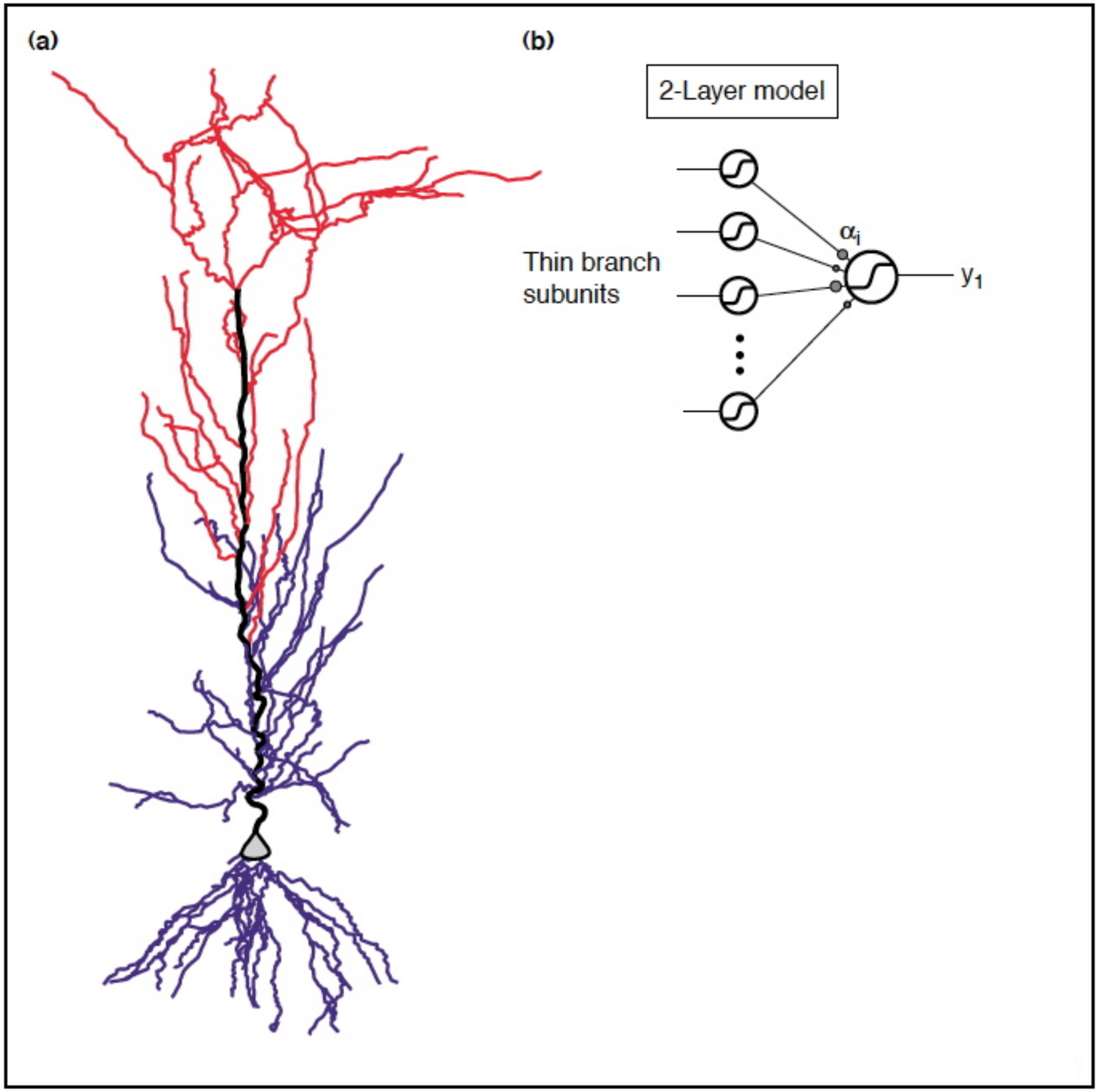
London & Häusser
Ann Rev Neurosci 2005

Single dendritic branches as fundamental functional units in the CNS

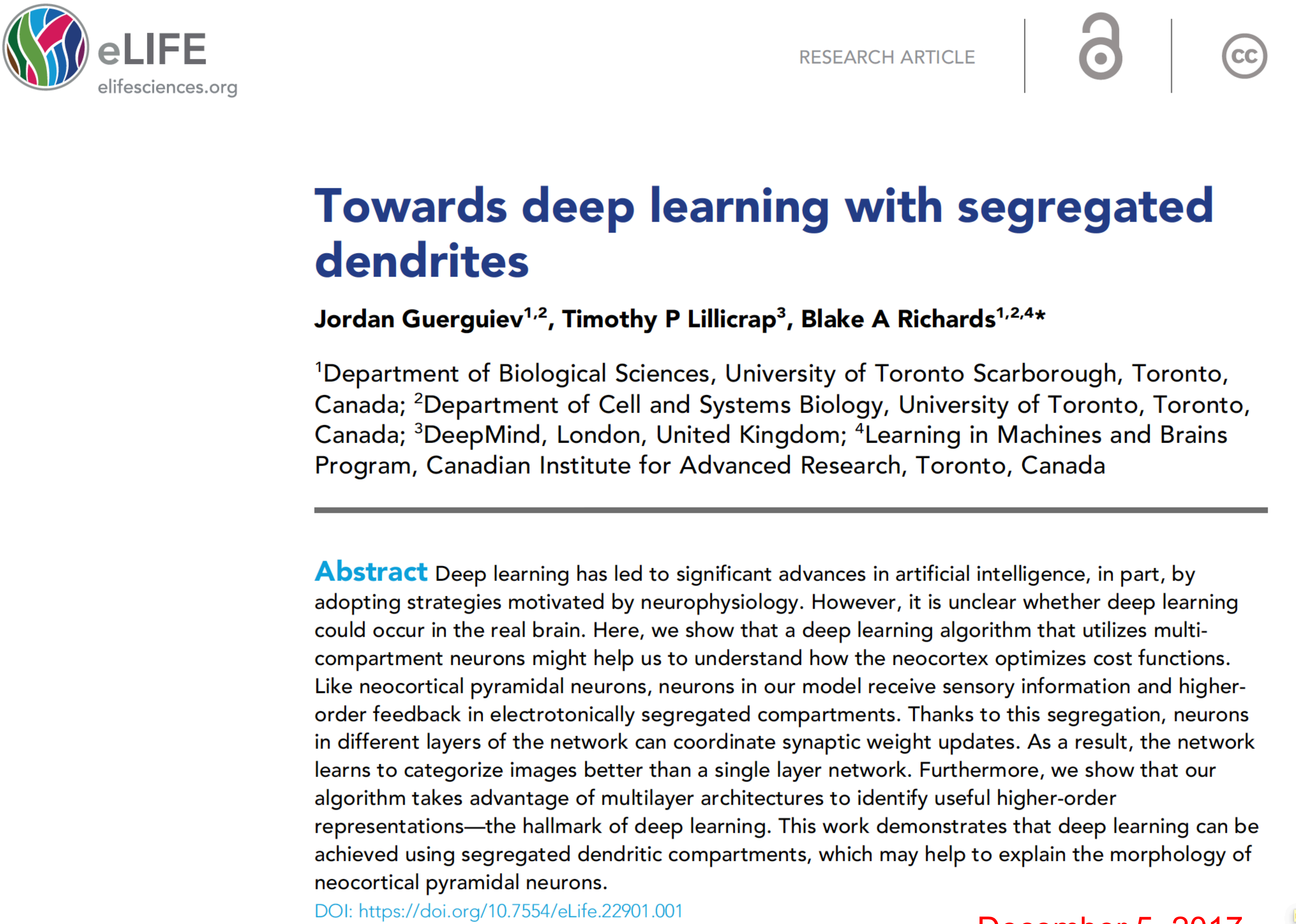


Branco & Häusser, Current Opinion in Neurobiology, 2010

The pyramidal cell as a multi-layered network



Häusser & Mel, 2003



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RESEARCH ARTICLE

Towards deep learning with segregated dendrites

Jordan Guerguiev[1,2], Timothy P Lillicrap[3], Blake A Richards[1,2,4]*

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Abstract Deep learning has led to significant advances in artificial intelligence, in part, by adopting strategies motivated by neurophysiology. However, it is unclear whether deep learning could occur in the real brain. Here, we show that a deep learning algorithm that utilizes multi-compartment neurons might help us to understand how the neocortex optimizes cost functions. Like neocortical pyramidal neurons, neurons in our model receive sensory information and higher-order feedback in electrotonically segregated compartments. Thanks to this segregation, neurons in different layers of the network can coordinate synaptic weight updates. As a result, the network learns to categorize images better than a single layer network. Furthermore, we show that our algorithm takes advantage of multilayer architectures to identify useful higher-order representations—the hallmark of deep learning. This work demonstrates that deep learning can be achieved using segregated dendritic compartments, which may help to explain the morphology of neocortical pyramidal neurons.

DOI: https://doi.org/10.7554/eLife.22901.001

December 5, 2017

Take-home messages

1. Synaptic integration is the way inputs are combined to generate output

2. The temporal and spatial pattern of inputs is critical to synaptic summation

3. Dendrites express voltage-gated channels which can promote spike backpropagation or trigger local spikes

4. Active dendrites generate functional subcompartments in the neuron

5. Synaptic integration in real neurons is more complex - and more powerful - than in simple, linear-summing units