Realistic modelling of cortical pyramidal neurons

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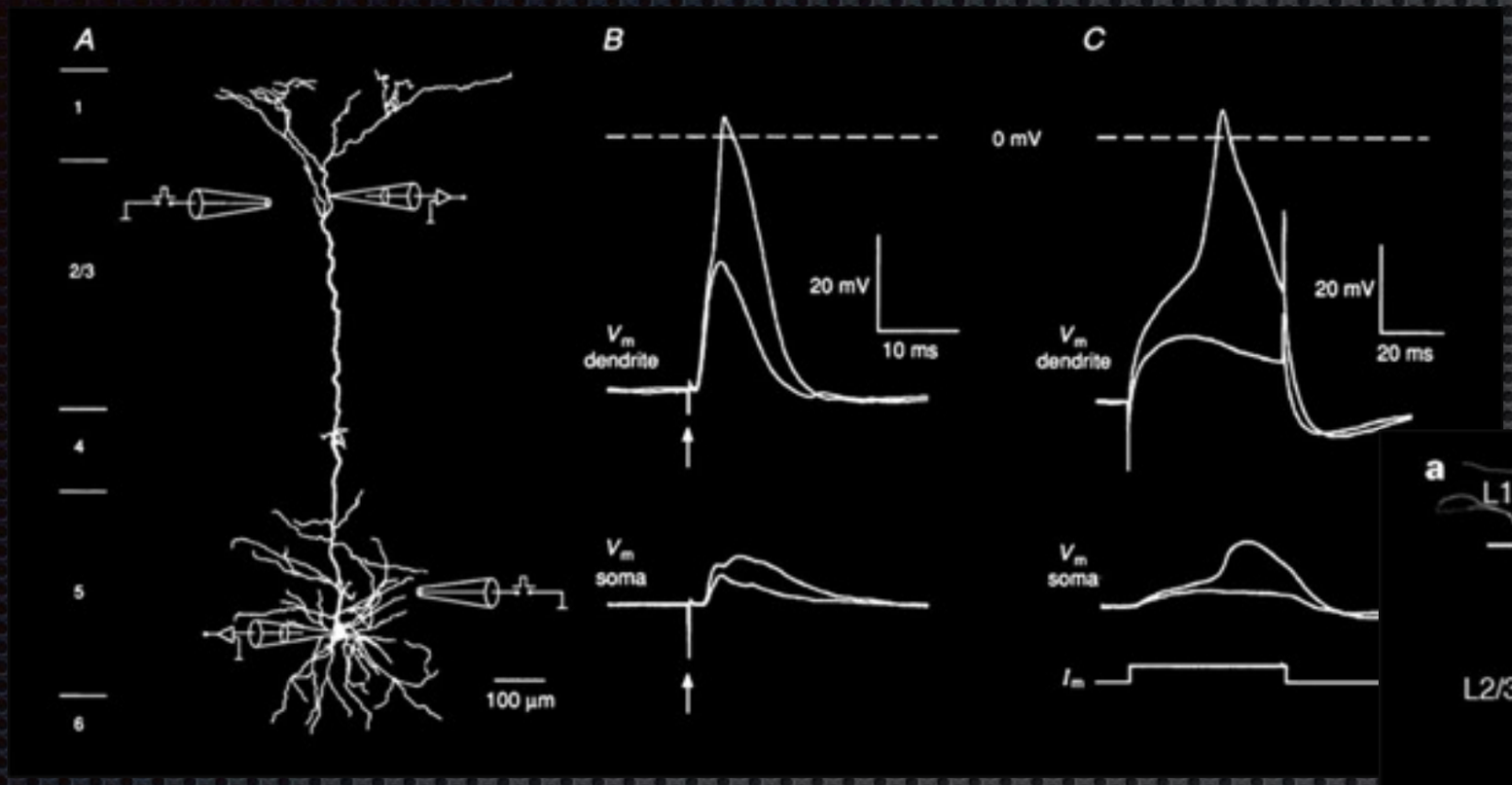
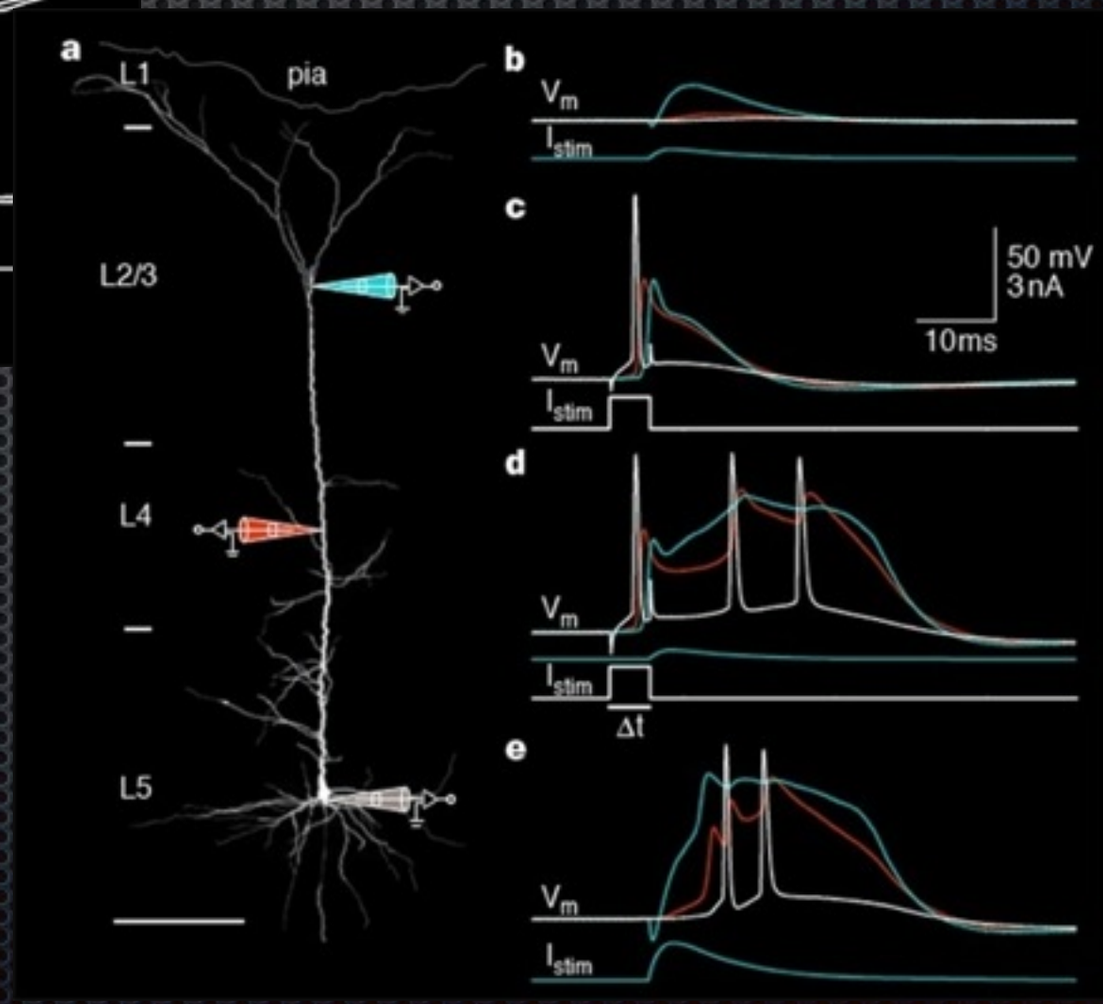
Dendritic calcium spikes

Isolated dendritic spikes



Schiller, Schiller, Stuart and Sakmann, J. Physiol 1997

BAC - Firing



Larkum, Zhu and Sakmann. Nature 1999

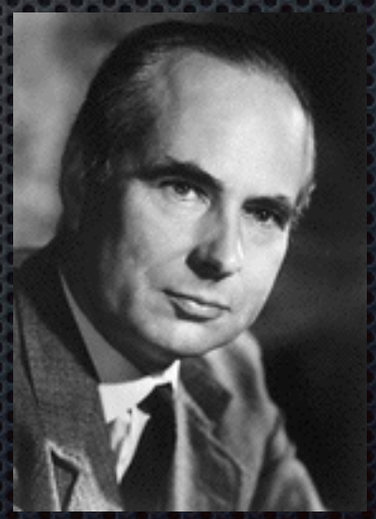
Specific Question:

What is the ionic mechanism of dendritic spikes?

General Question:

What do pyramidal neurons compute?

The obvious(ly naive) approach(?)



Take it apart. Put it back together. Understand.

Is the HH approach naive?

People will tell you, correctly, that……

- Cortical neurons express 10-15 voltage-gated channels.
- Conductance densities are far from homogenous.
- Models have a vast parameter space that is practically impossible to tune.

"Lets design a model reproducing the behaviour."

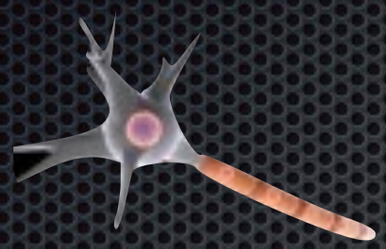
What are we (defeatedly) ignoring?

- That neuronal physiology results from a specific biophysical mechanism.
- That descriptive models capture part of the physiology, not all of it.
- That we will forever doubt the model's ability to perform realistic computations.

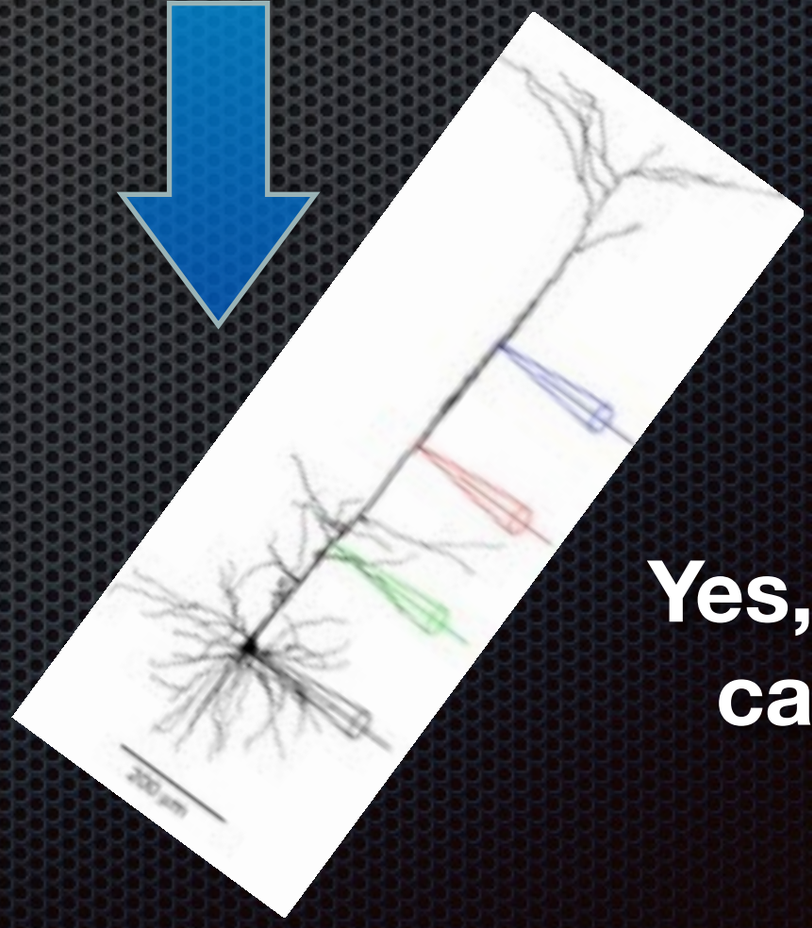
Beginnings (2005)

Is it possible to automatically constrain a model? What is the required data set?

Compartmental neuronal model With unknown parameters



Genetic algorithm & Fit function



Yes, we can!

Keren, Peled and Korngreen, J. Neurophysiol 2005

2004 - 25 CPUs - a.k.a Brain

Conclusions for 2005

- Constraining a model for a dendrite requires fitting dendritic membrane potential recordings.
- Constraining a full model requires also data from the axon initial segment.
- Constraining a model using only somatic data provides only reconstruction of behaviour, not mechanistic insights.
- We need a bigger computer…..

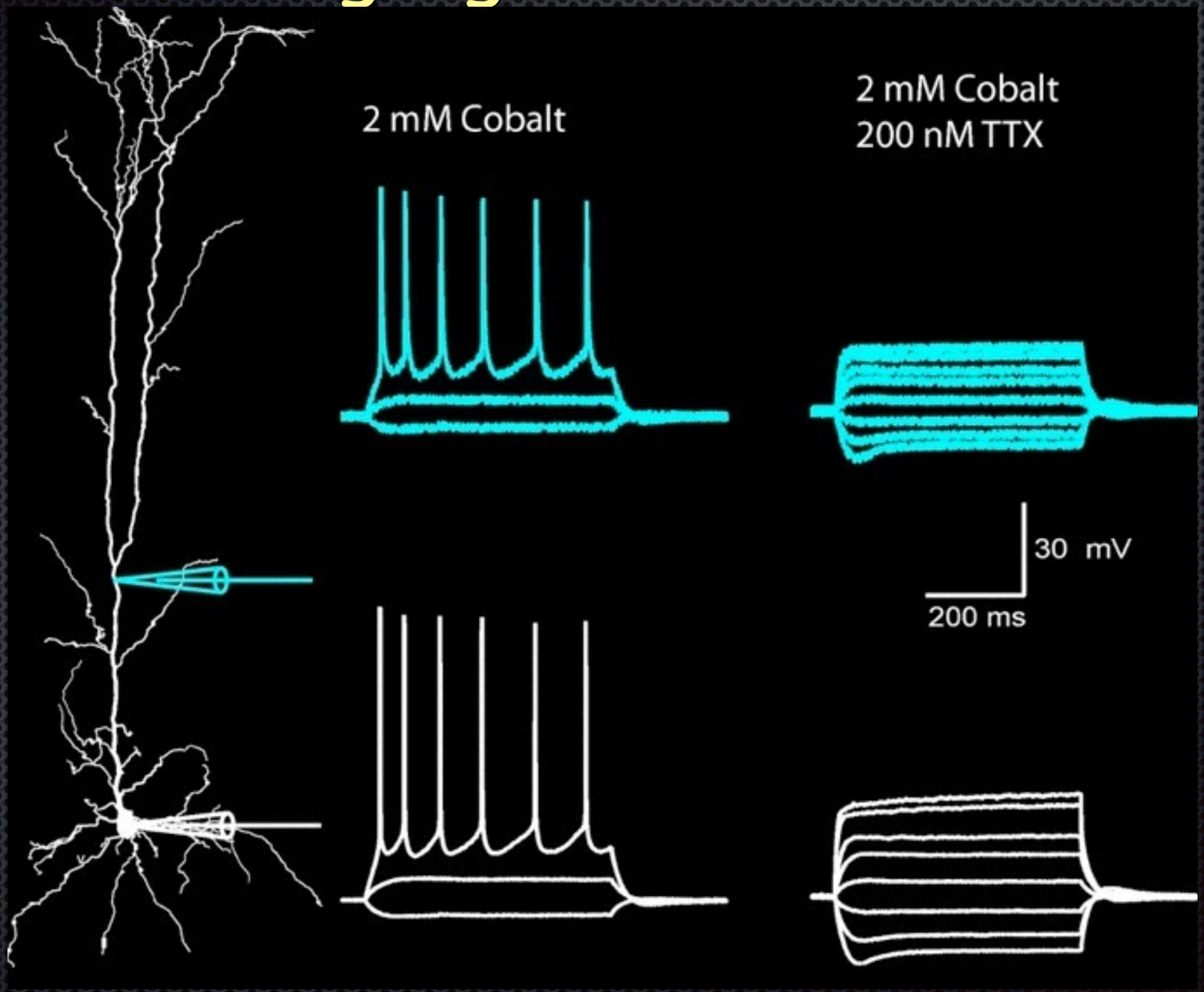
2007 - 168 CPUs - a.k.a Pinky

Recently - GPUs

Experimental parameter peeling

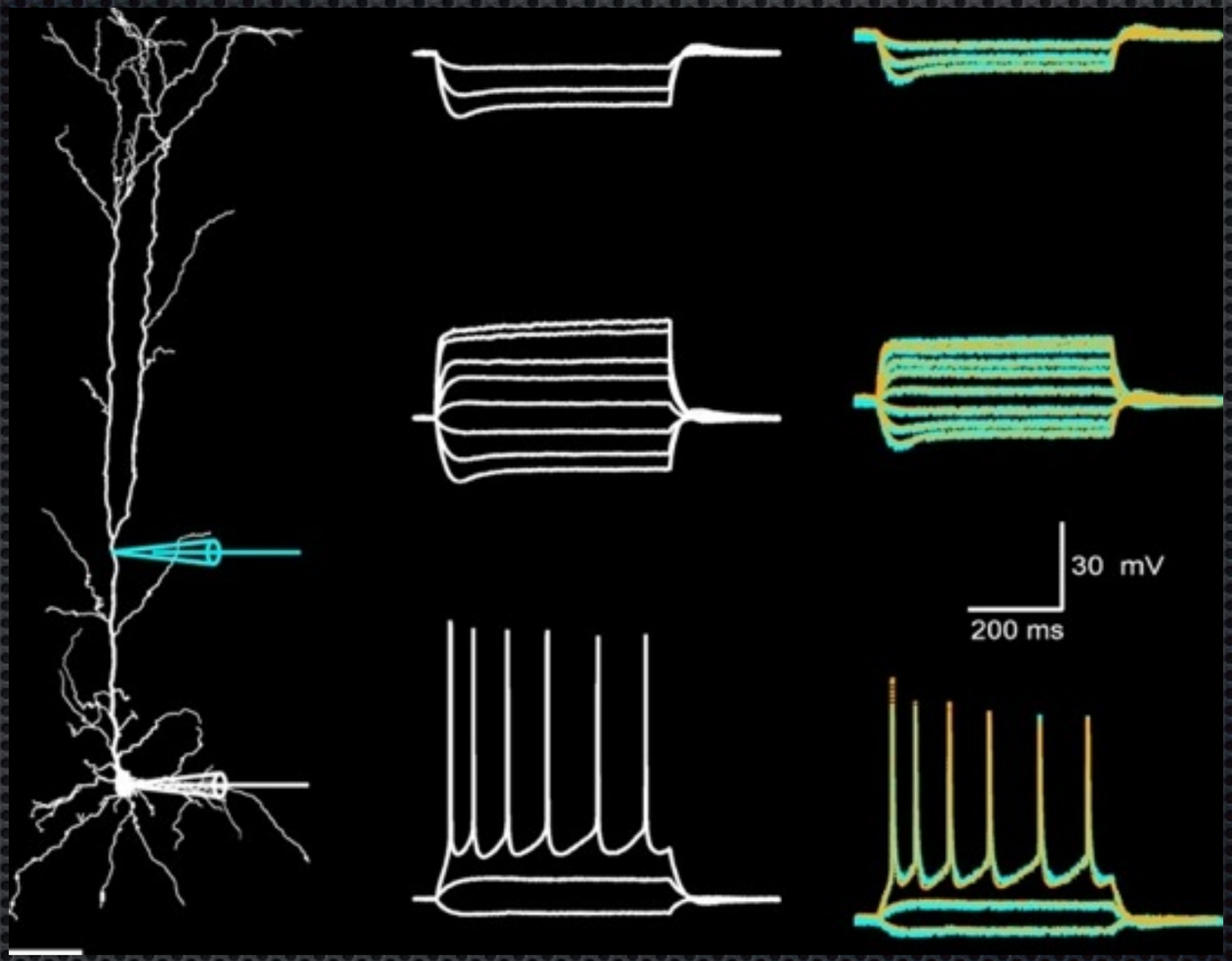
- **Reducing parameter space by blocking ion channel families.**
- **Increase the number of blockers, each time recording from a “simpler” neuron.**
- **Fit the “simplest” recording first, adding only a few parameters in each fitting stage.**

Parameter peeling. Stage 1: Block all voltage-gated calcium channels.



Keren, Bar-Yehuda and Korngreen, J. Physiol 2009

Peel parameter groups to fit model to the data

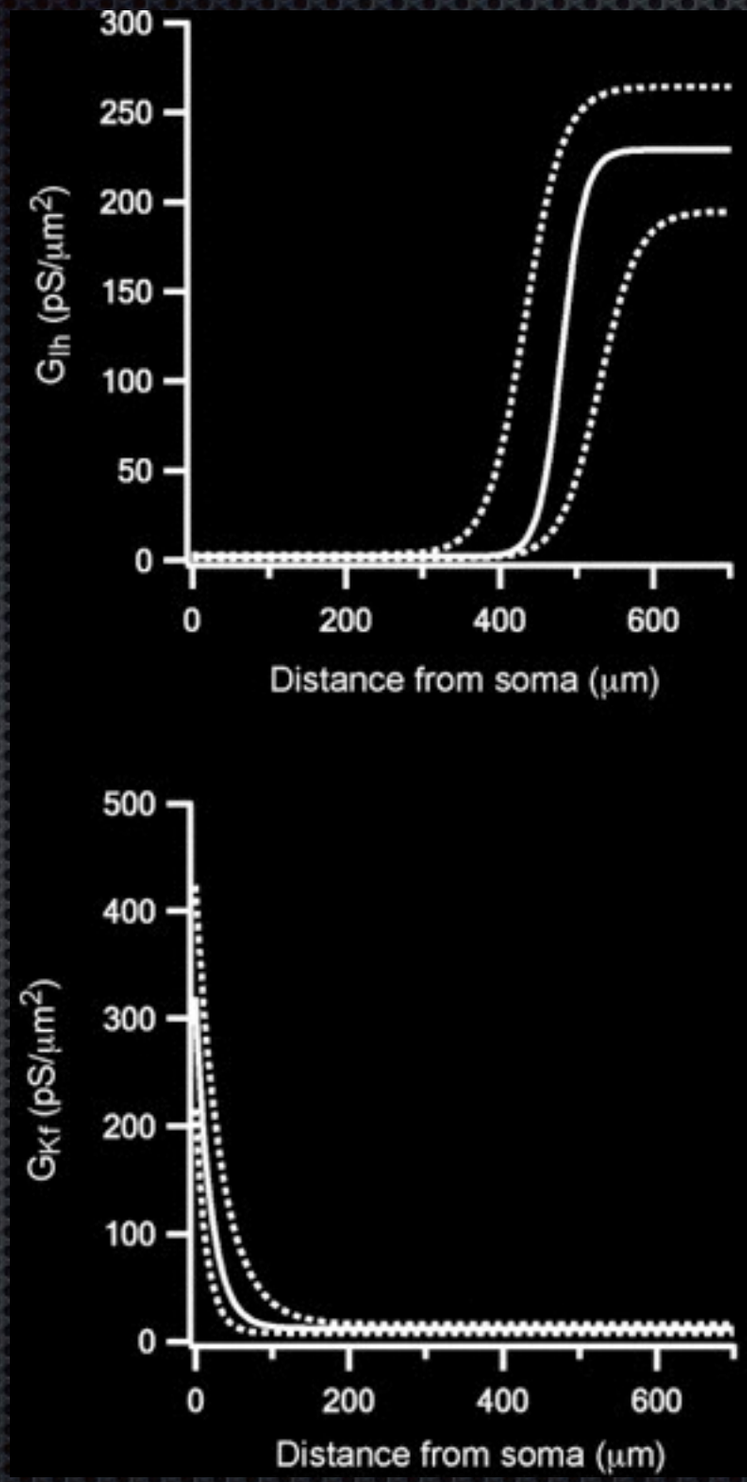


Use somatic action potentials as voltage-clamp commands and constrain the model using only the dendritic recording

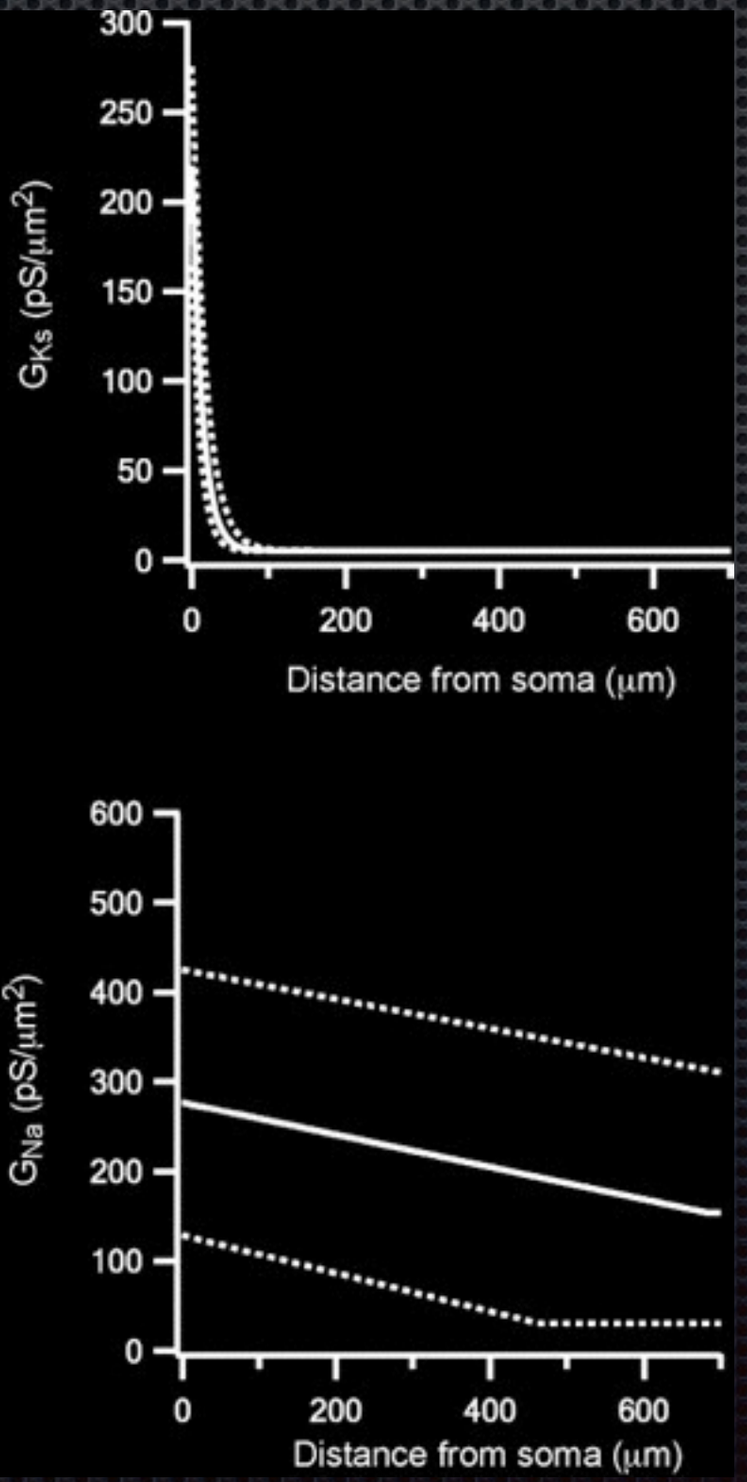
Keren, Bar-Yehuda and Korngreen, J. Physiol 2009

Stage 1: reduced model

I_H



K_S

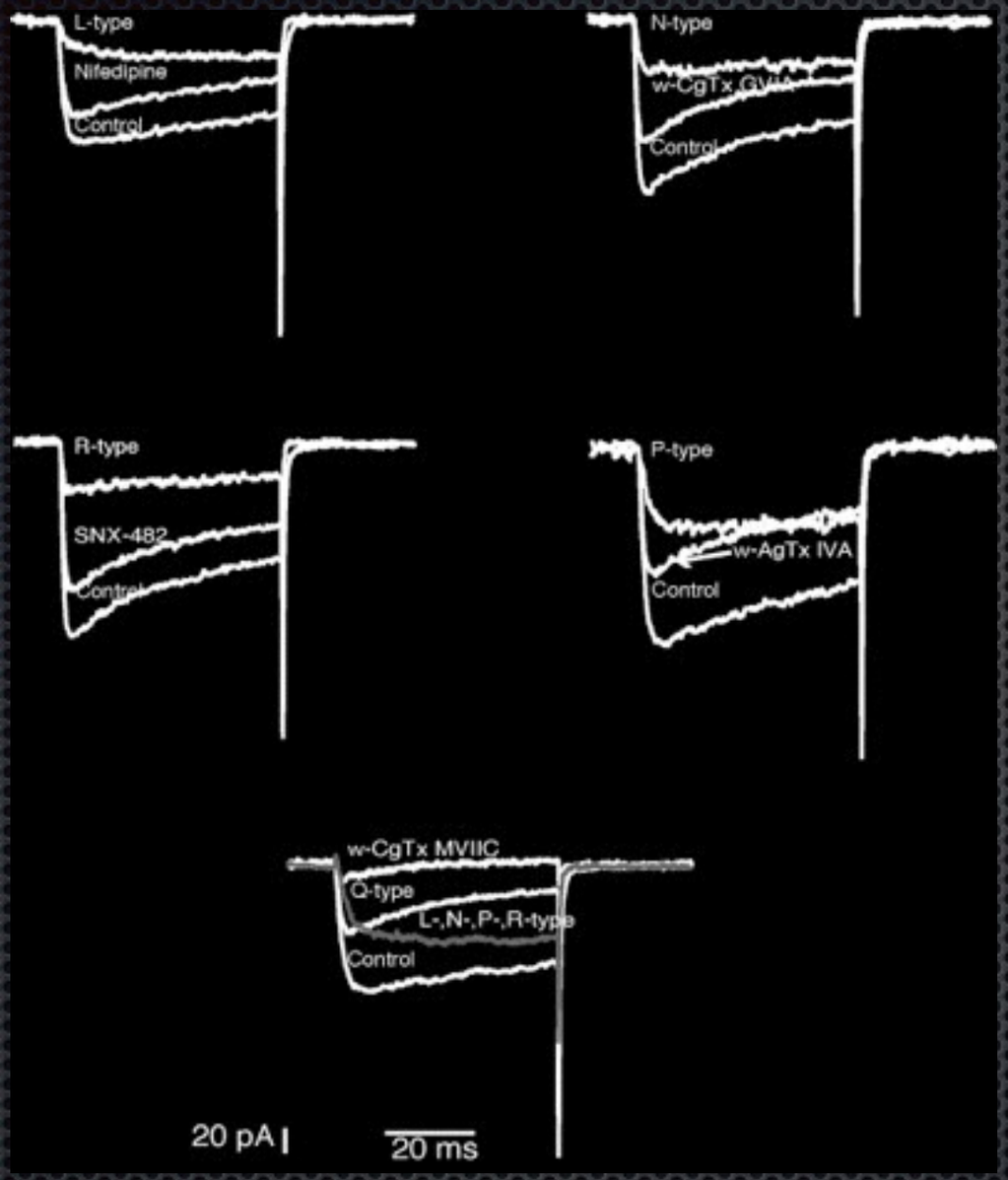


K_f

Na

Keren, Bar-Yehuda and Korngreen, J. Physiol 2009

Stage 2 - Isolation of voltage-gated calcium currents in nucleated patches.

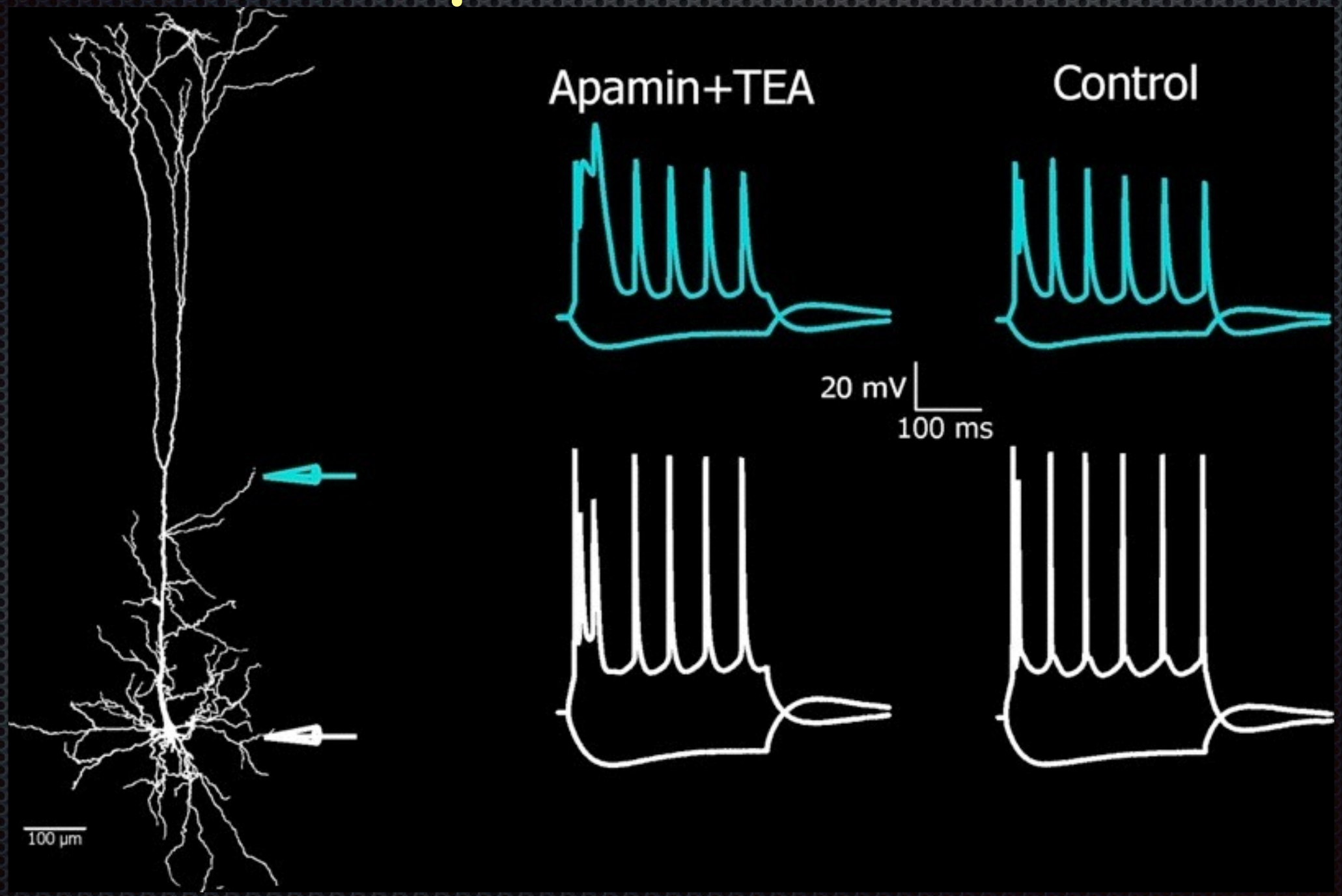


No t-type in somatic recordings

Reduce the five conductances to two Hodgkin-Huxley like kinetic models - HVA and MVA

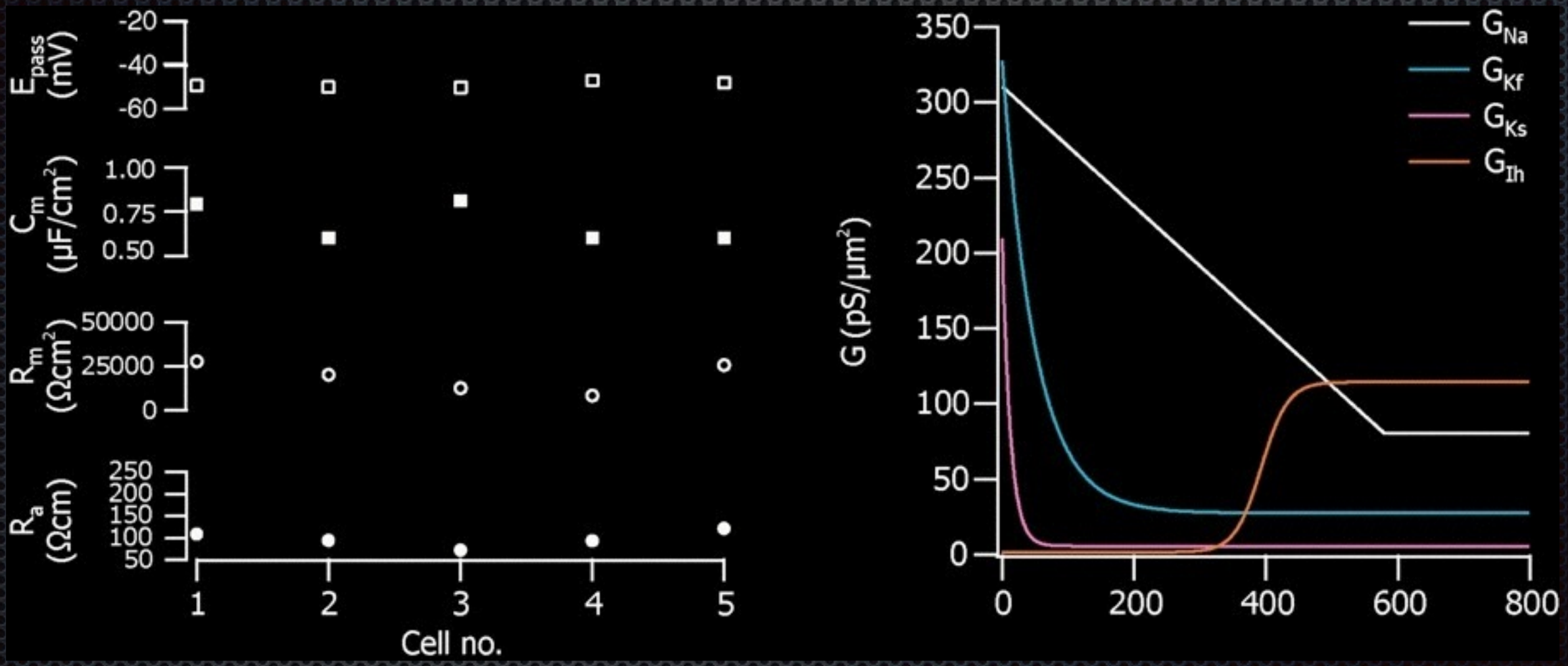
Almog and Korngreen, PLoS ONE, 2009

Stage 2: block calcium activated potassium channels



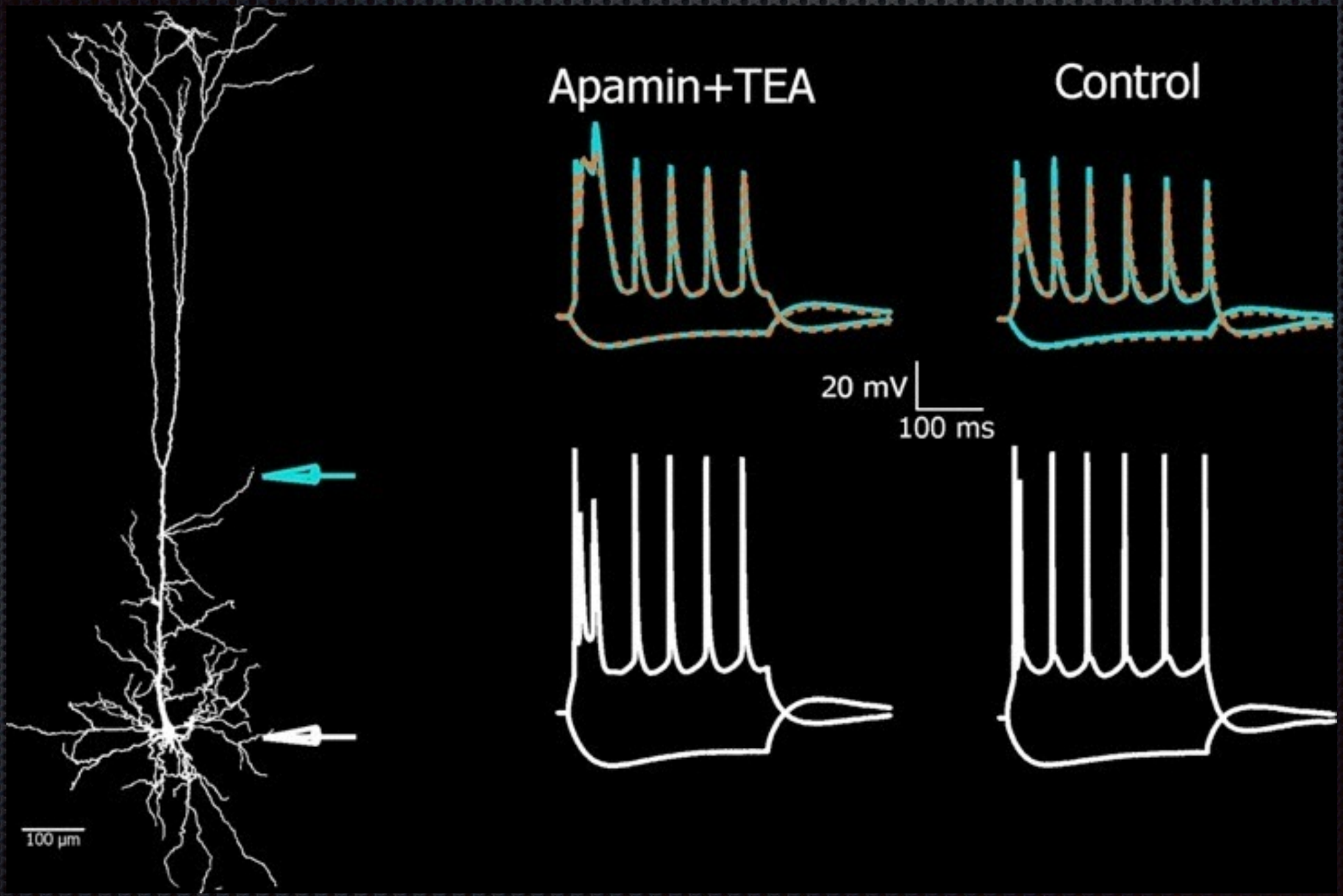
Almog and Korngreen, Journal of Neurosci. 2014

Use stage 1 model as the backbone of stage 2



Almog and Korngreen, Journal of Neurosci. 2014

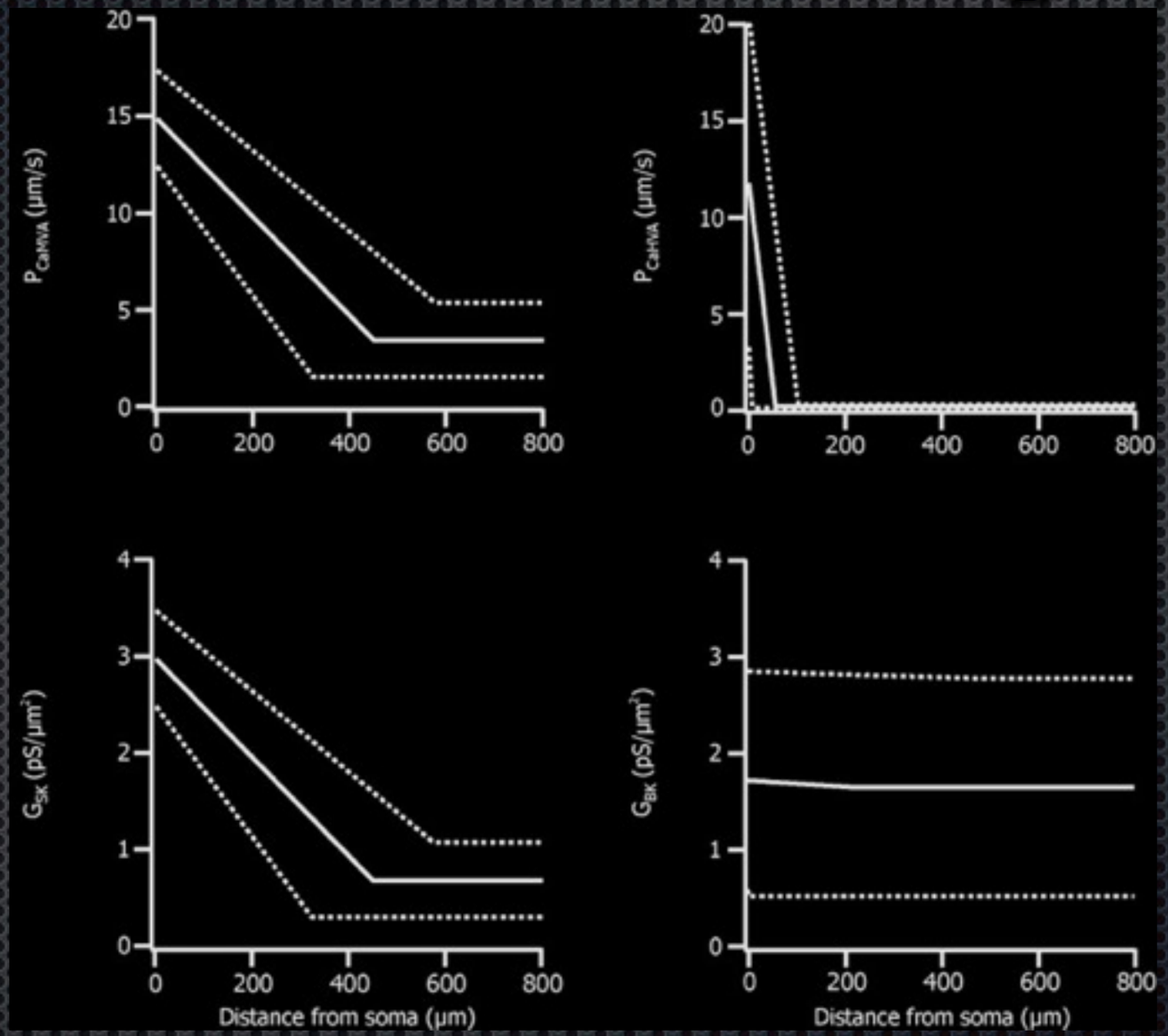
THE FIT



Almog and Korngreen, Journal of Neurosci. 2014

Four new conductances constrained in stage 2

MVA Ca



HVA Ca

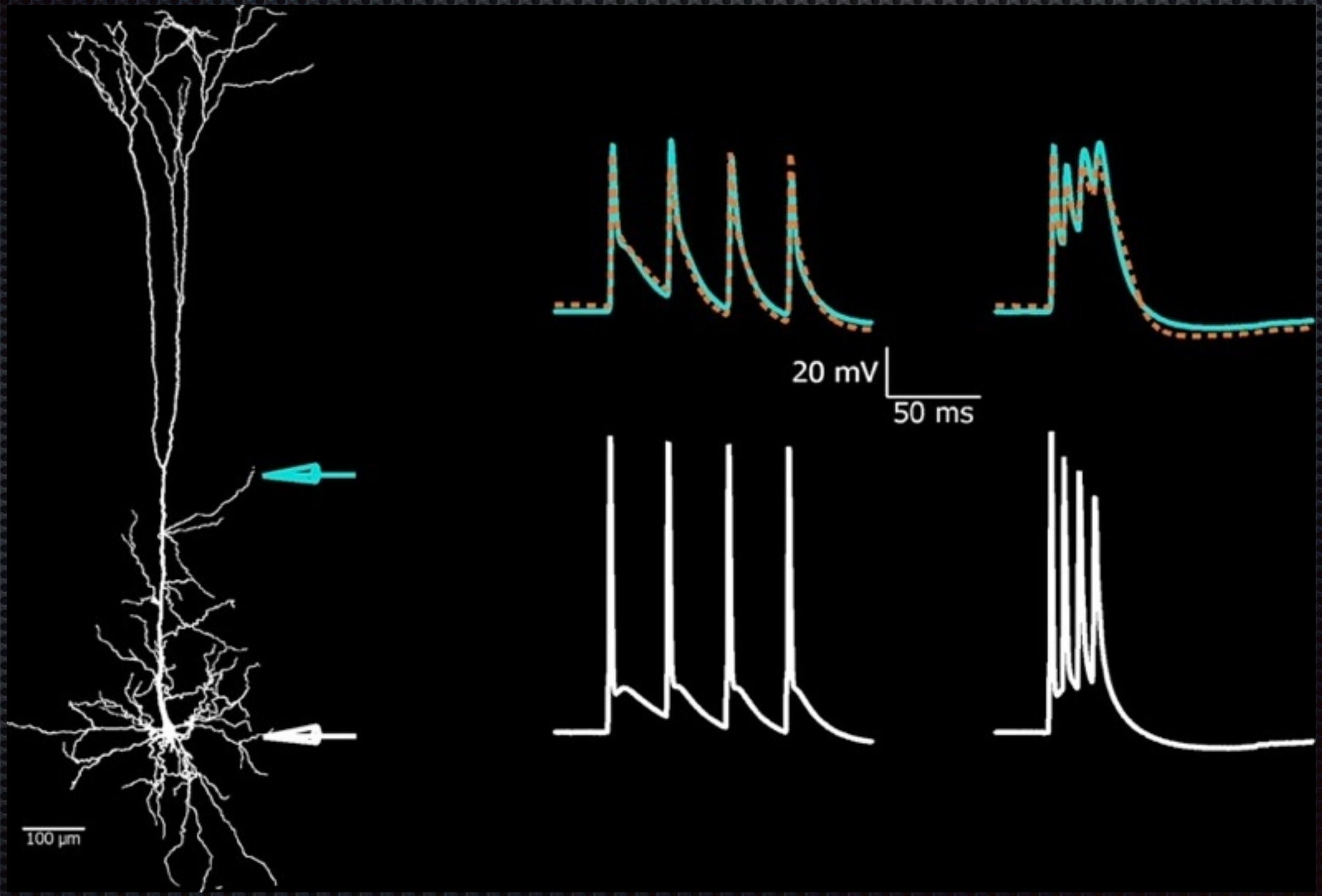
SK

BK

No distal calcium hot zone!

Almog and Korngreen, Journal of Neurosci. 2014

Testing the model using a different set of data.

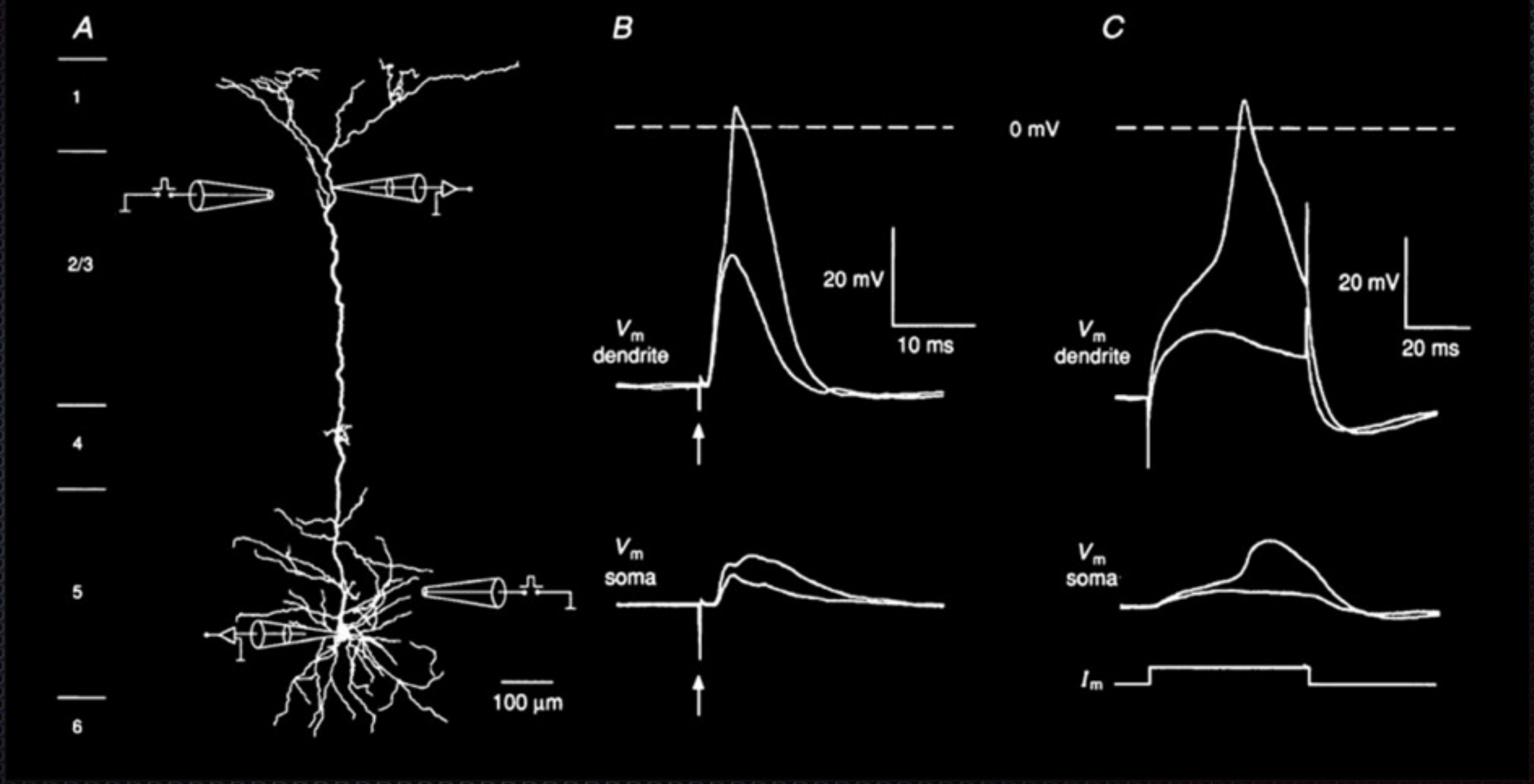


Almog and Korngreen, Journal of Neurosci. 2014

Journal of Physiology (1997), **505.3**, *pp.*605–616

Calcium action potentials restricted to distal apical dendrites of rat neocortical pyramidal neurons

Jackie Schiller, Yitzhak Schiller, Greg Stuart and Bert Sakmann



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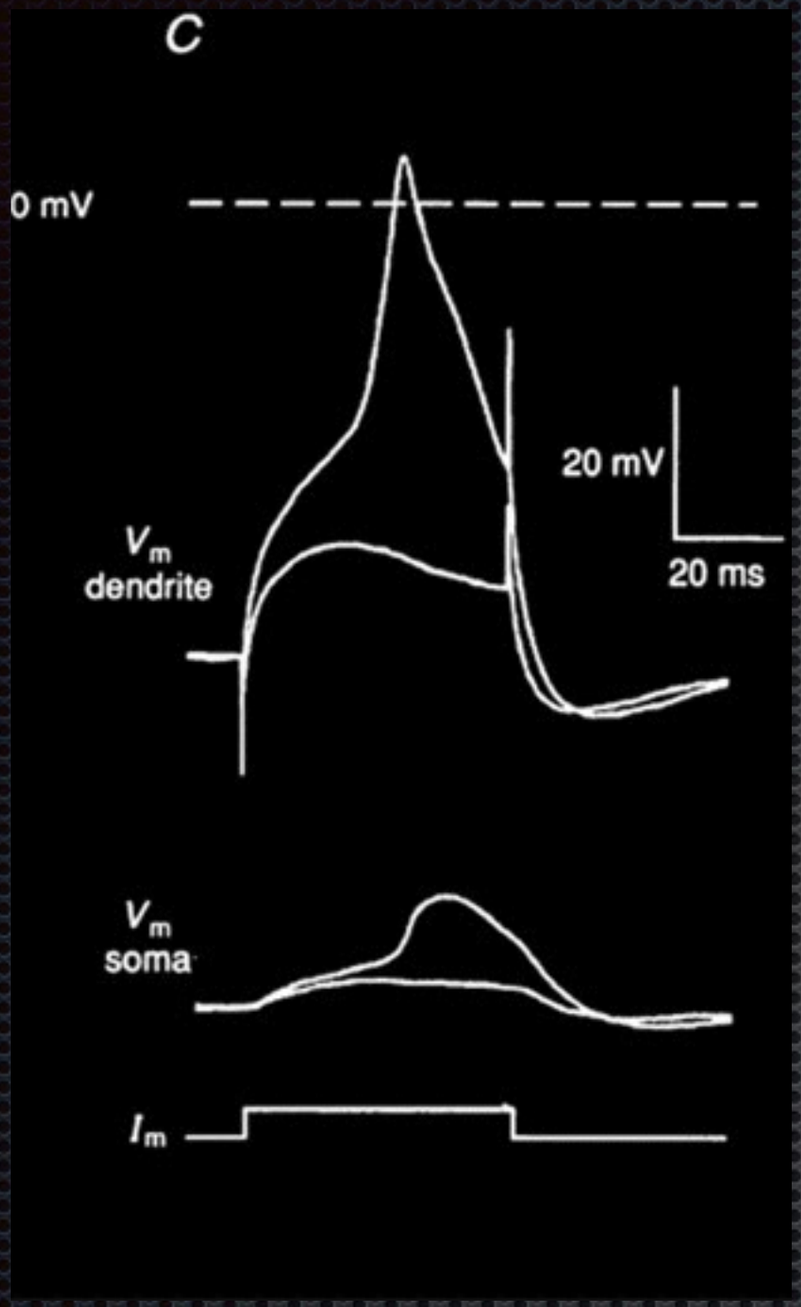
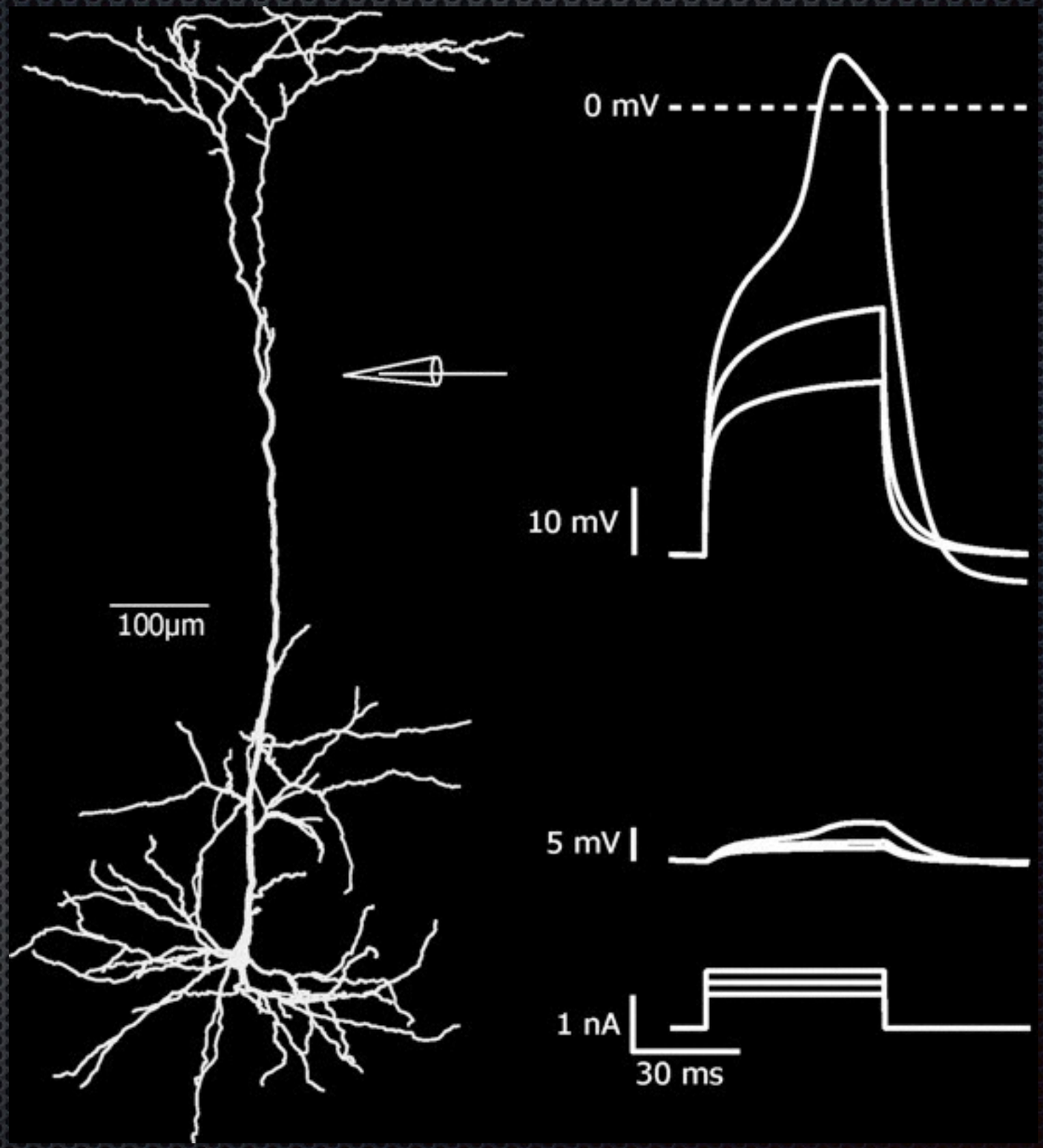
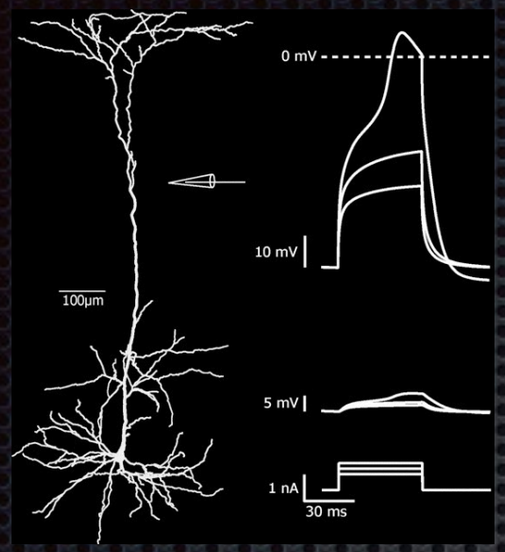
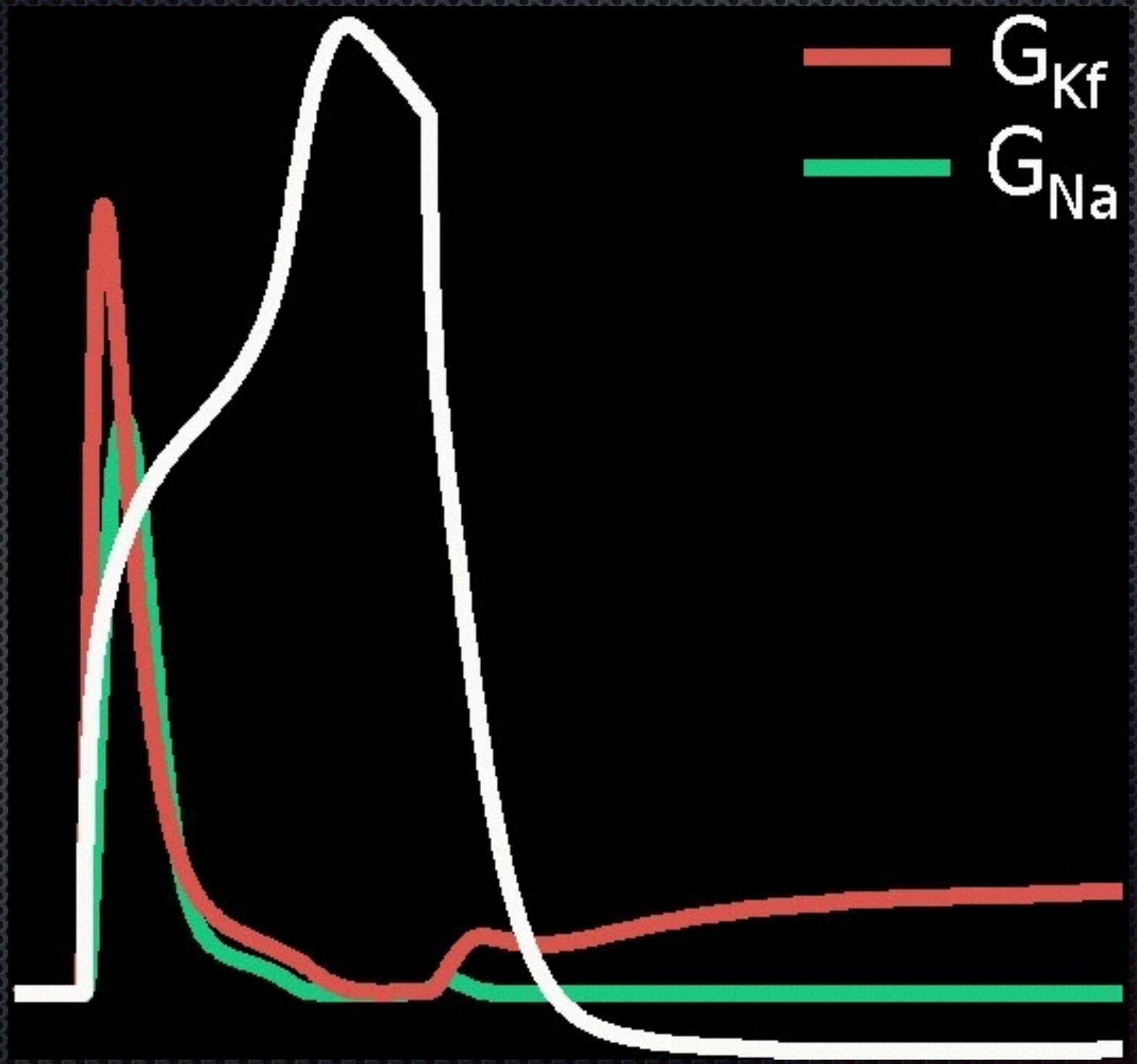




Almog and Korngreen, Journal of Neurosci. 2014

Initiation of an isolated spike





Almog and Korngreen, Journal of Neurosci. 2014

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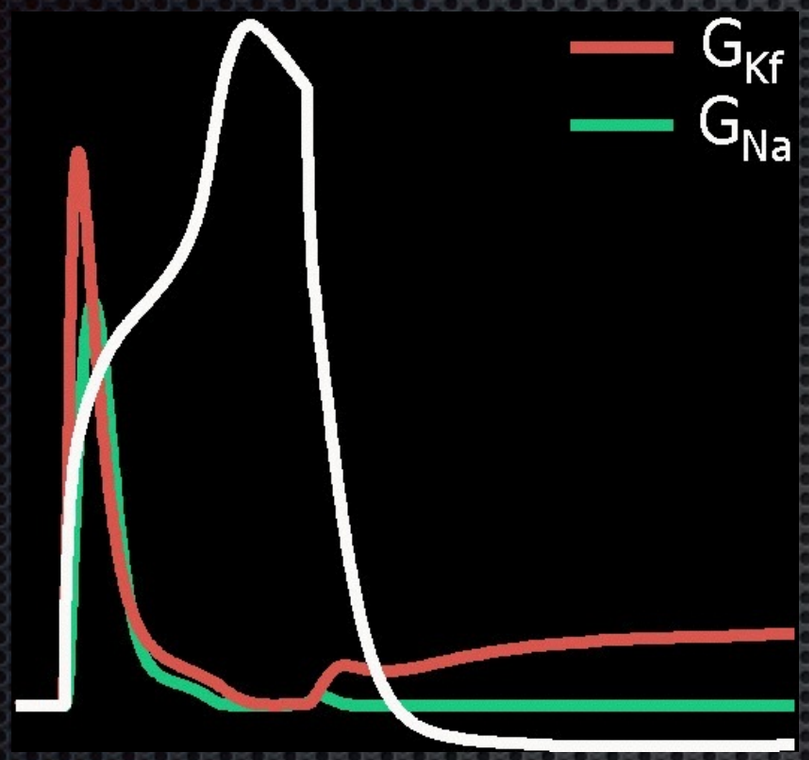

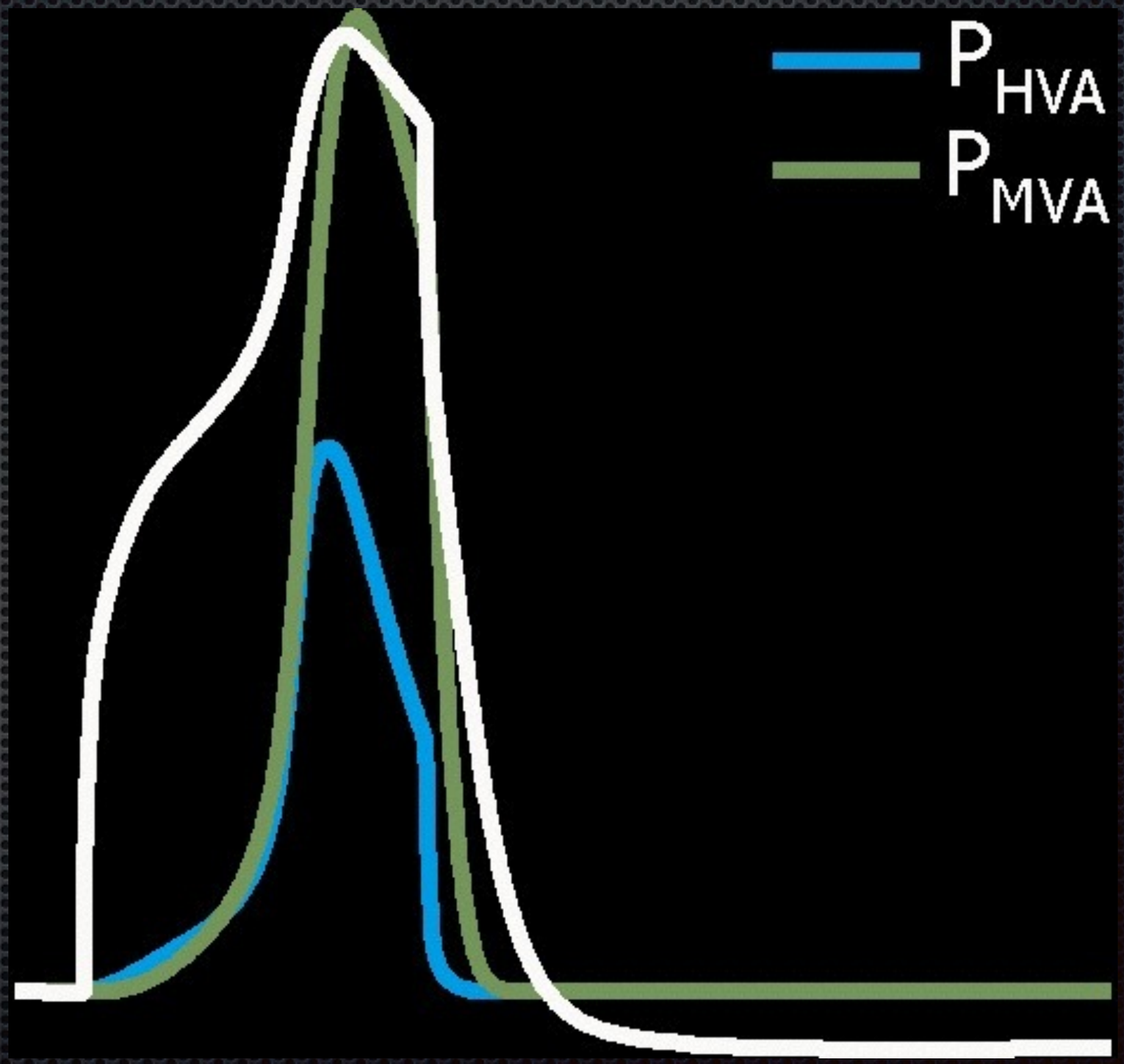

Almog and Korngreen, Journal of Neurosci. 2014

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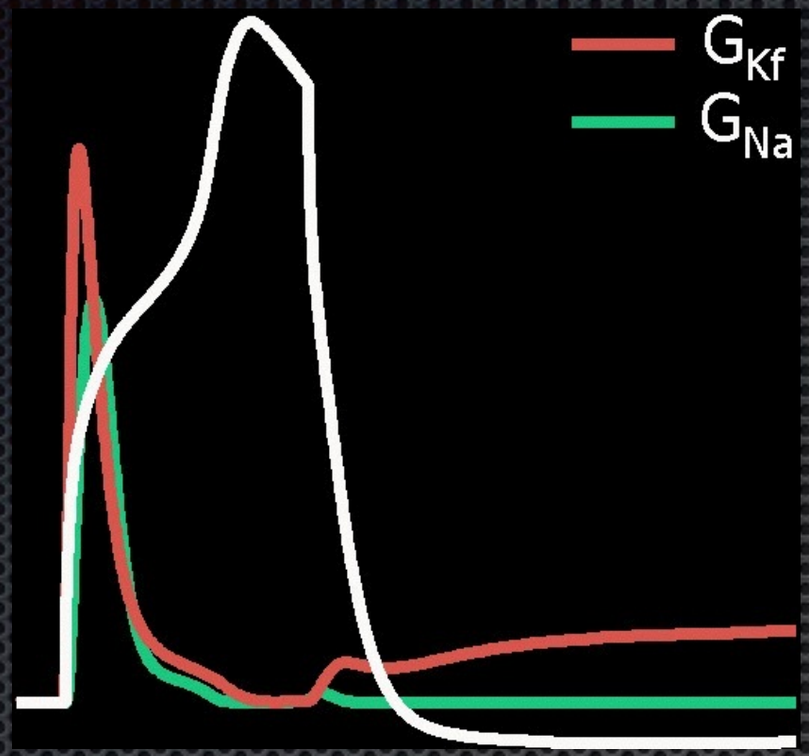
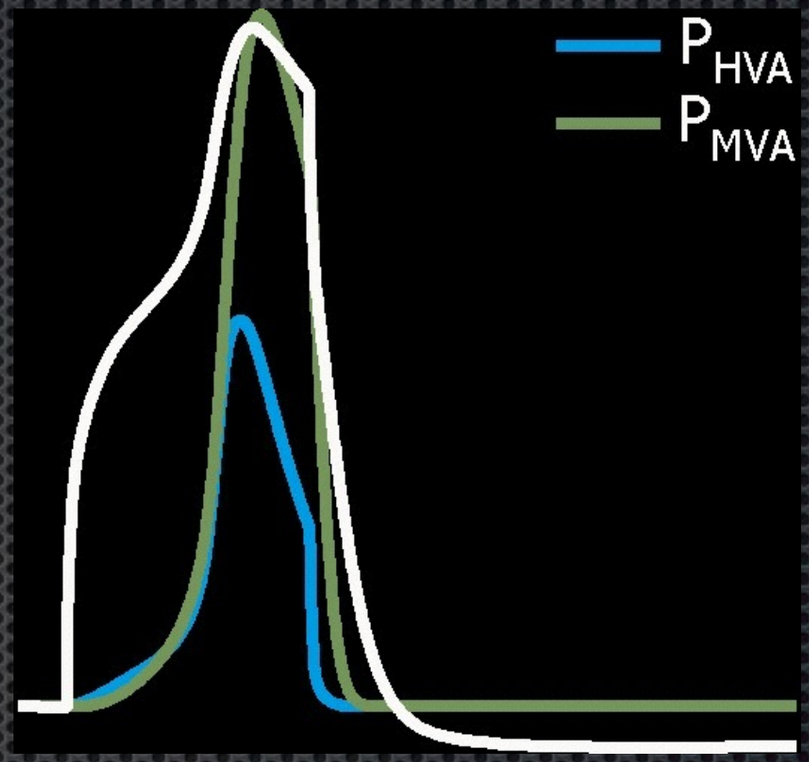
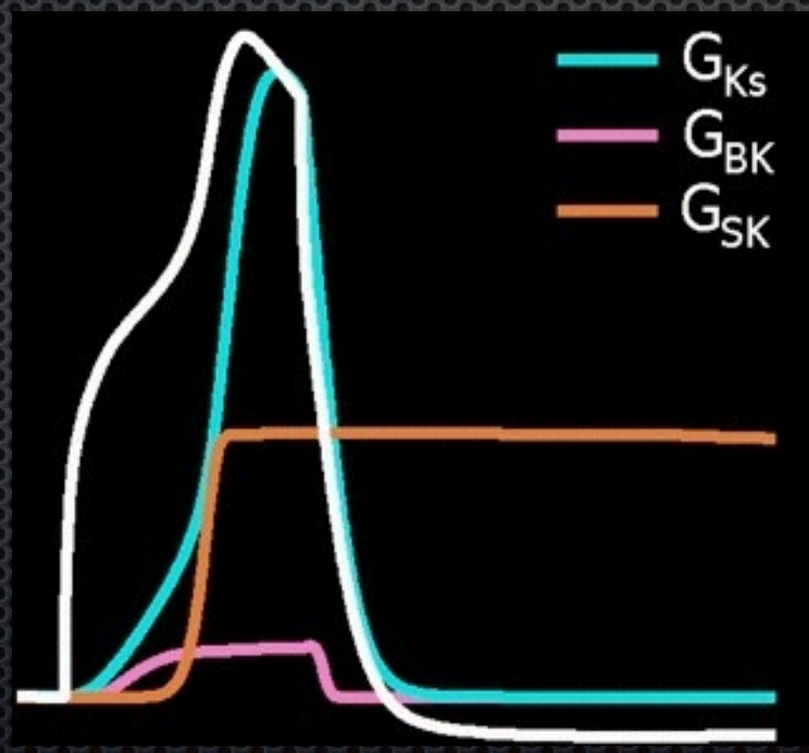
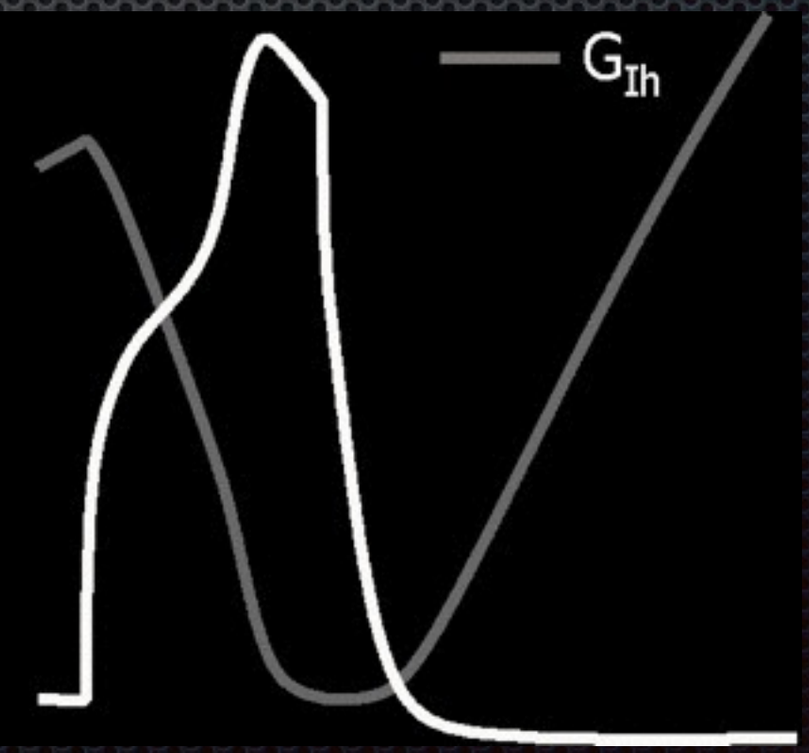


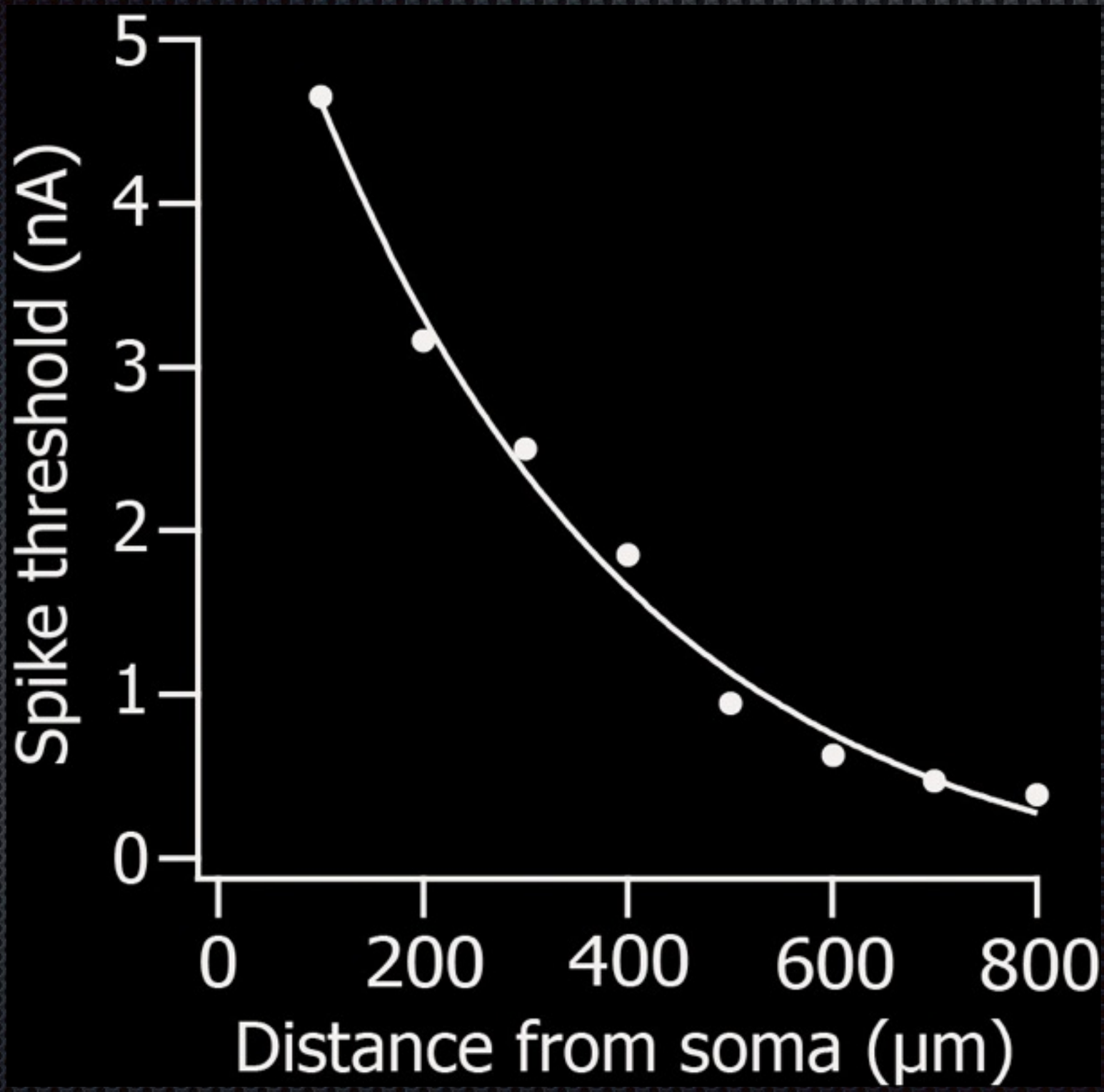






Almog and Korngreen, Journal of Neurosci. 2014

Dendritic spike threshold

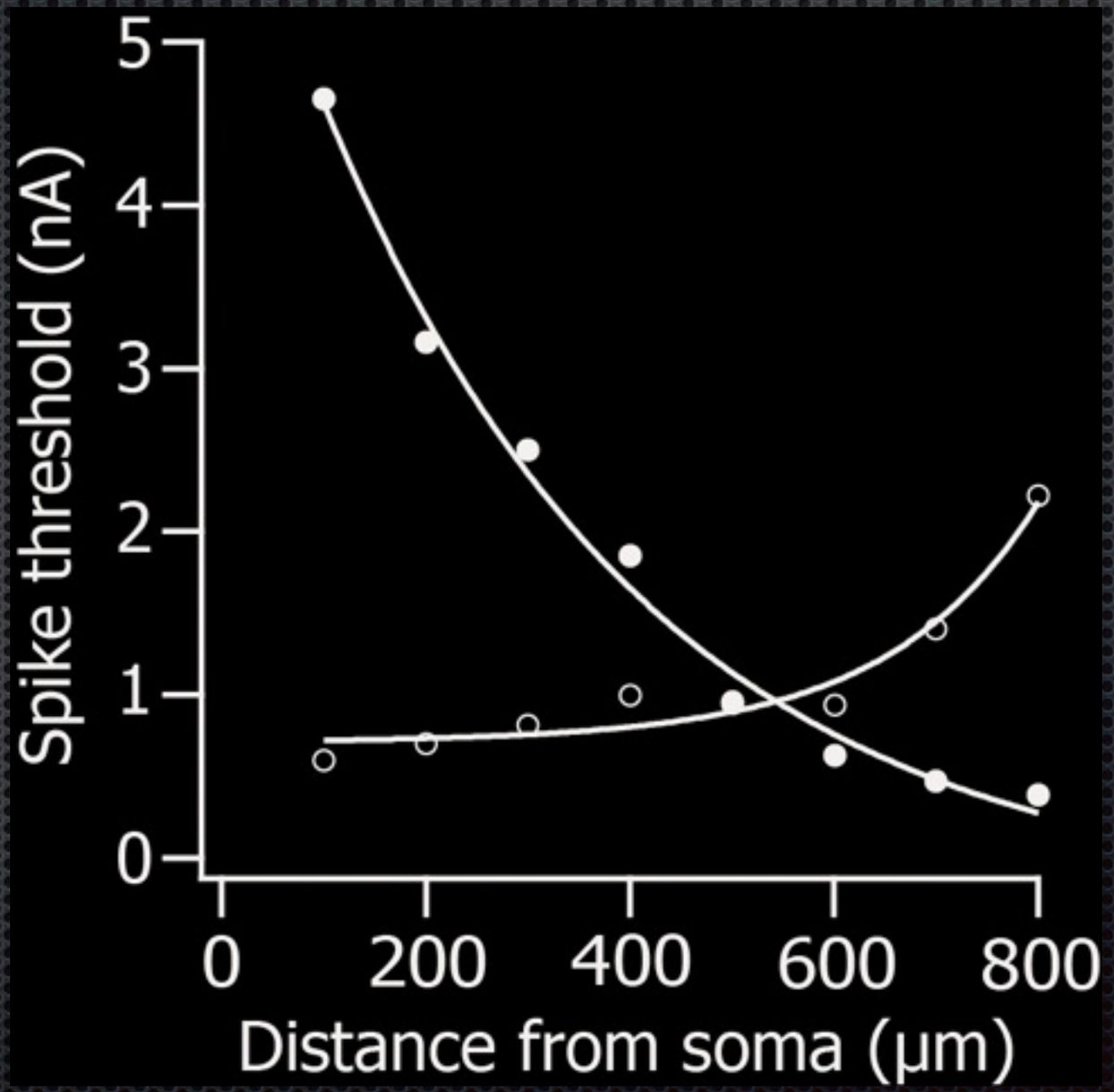


Almog and Korngreen, Journal of Neurosci. 2014

Our model was constrained without an axon.....

- So we added an artificial axon
- The axon we added is based on the venerable Mainen 1996 axon.
- It is a horrible axon.
- **Seriously folks, it is a horrible axon - generating action potentials not resembling the data .....**

Threshold for an axonal action potential when current is injected at the dendrite



Almog and Korngreen, Journal of Neurosci. 2014

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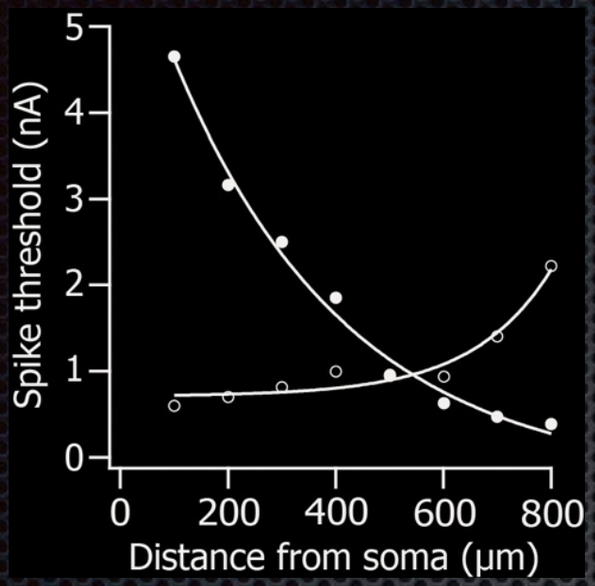
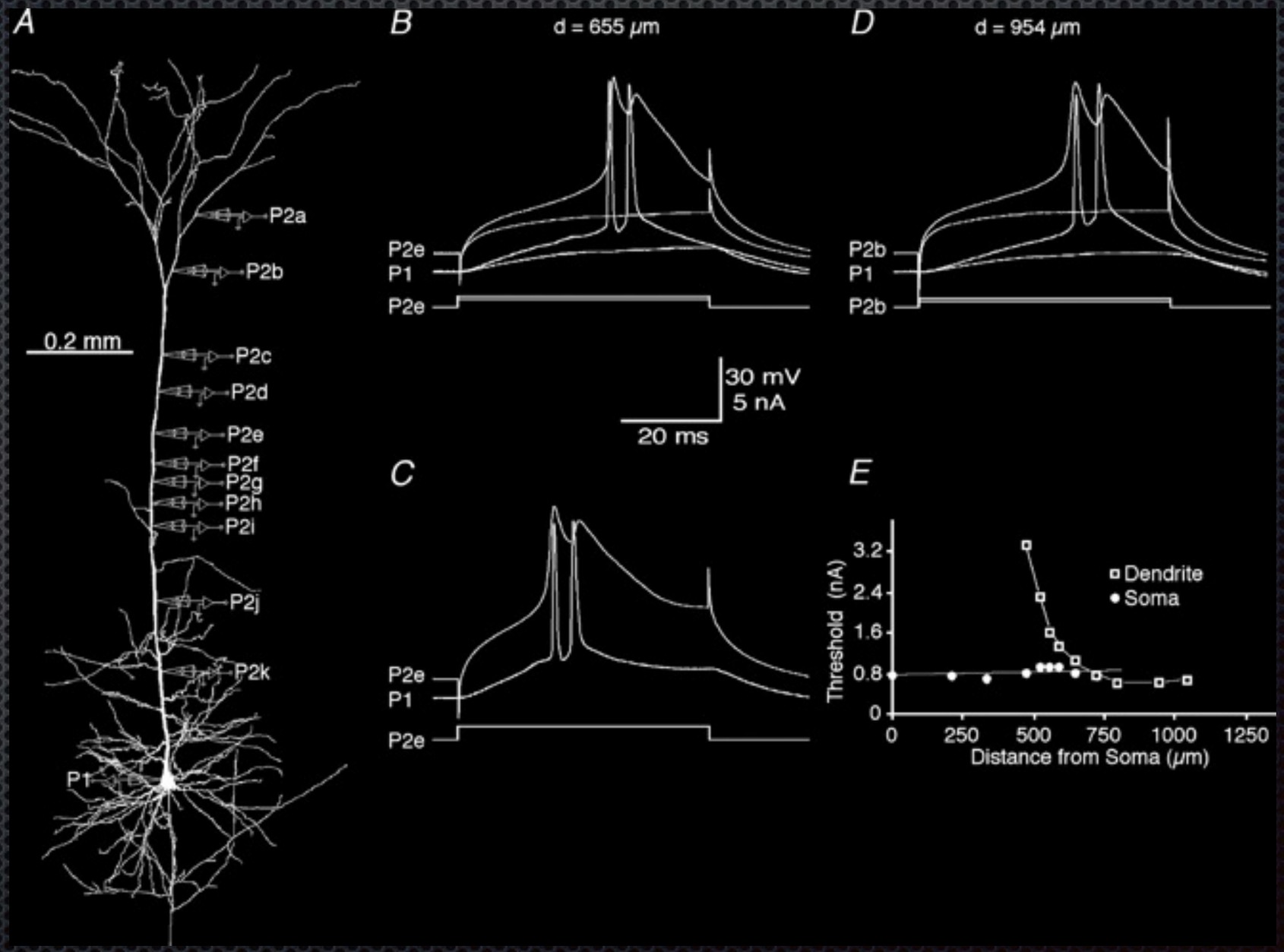
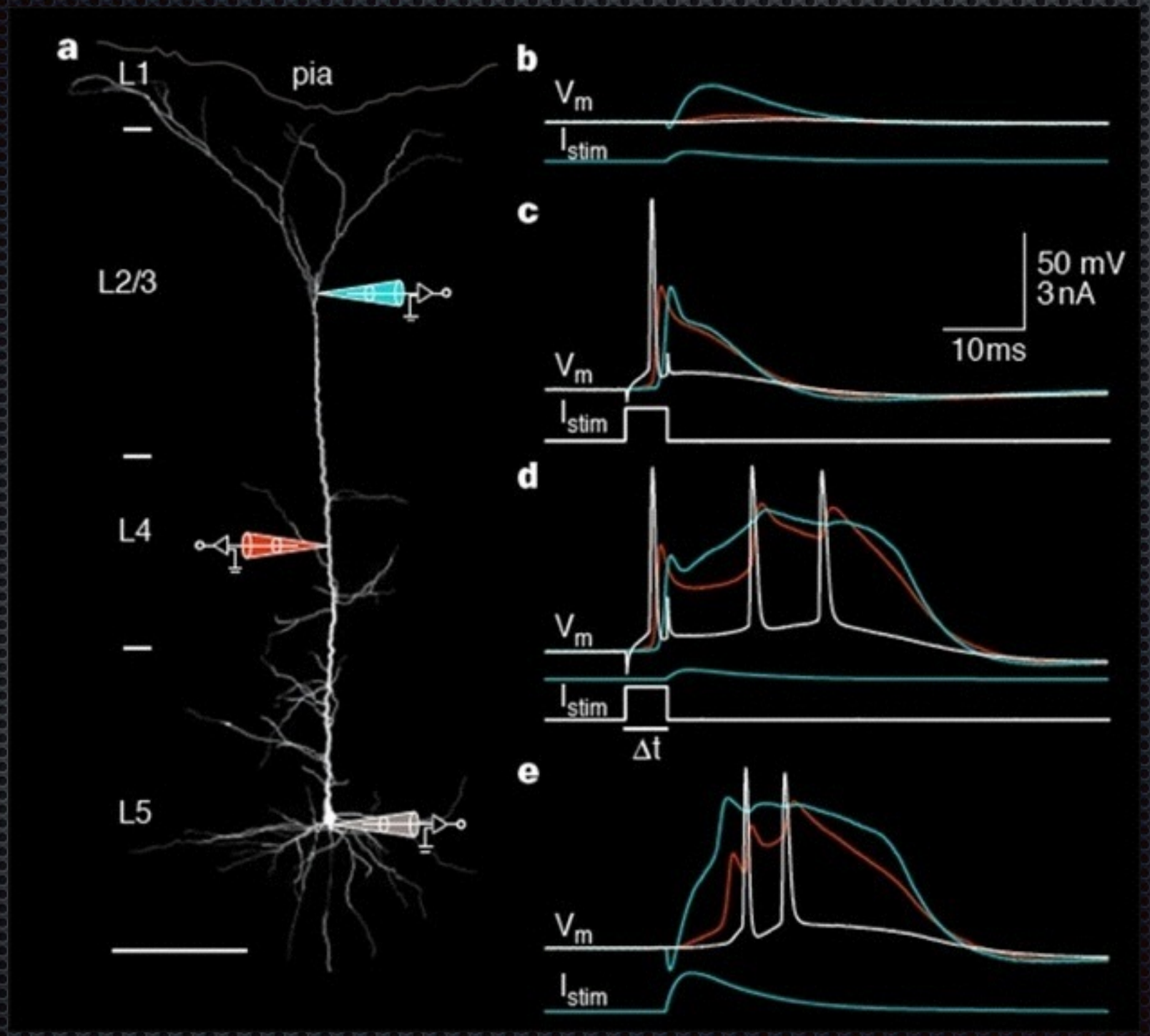




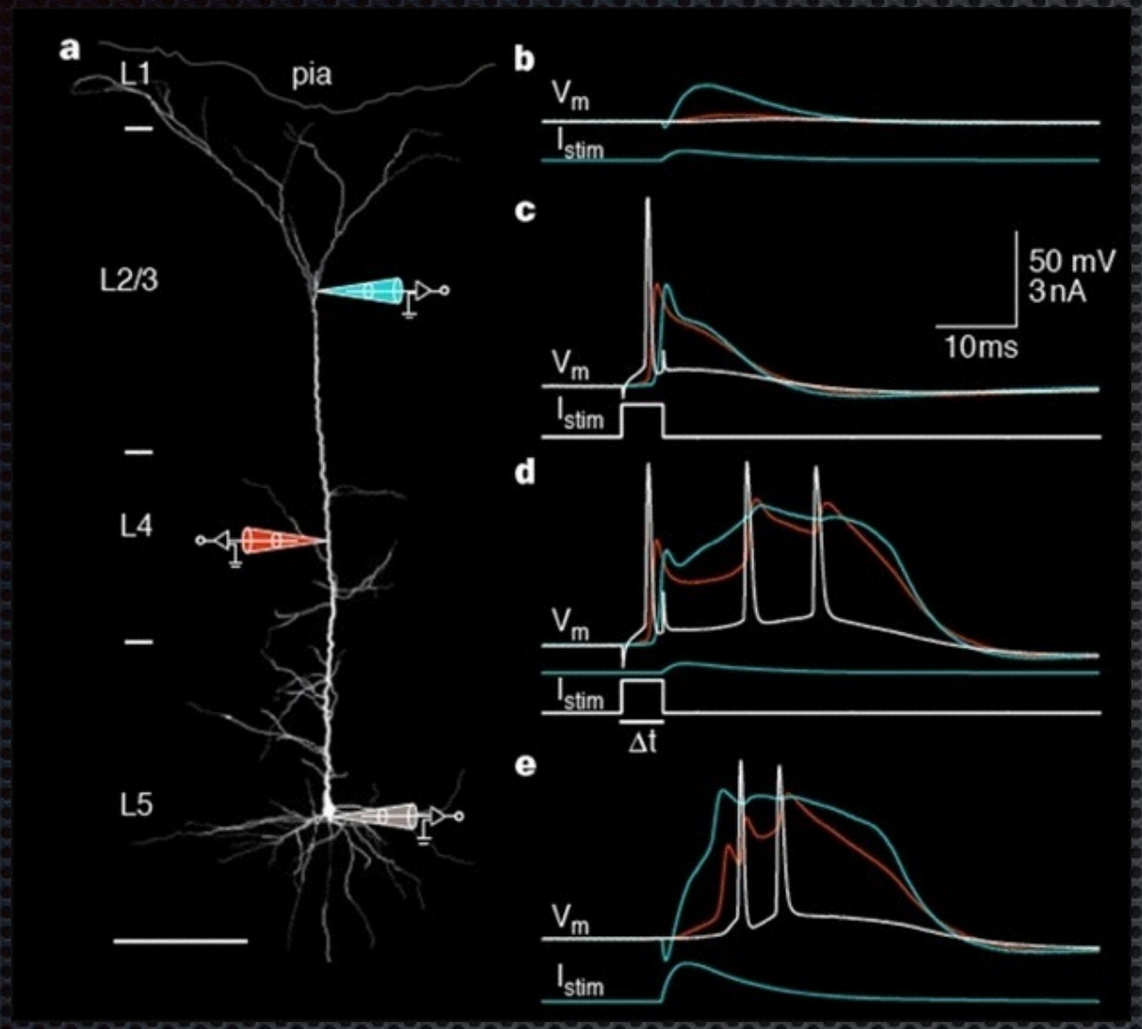
Larkum and Zhu,The Journal of Neuroscience, 2002, 22(16): 6991-7005

BAC-Firing

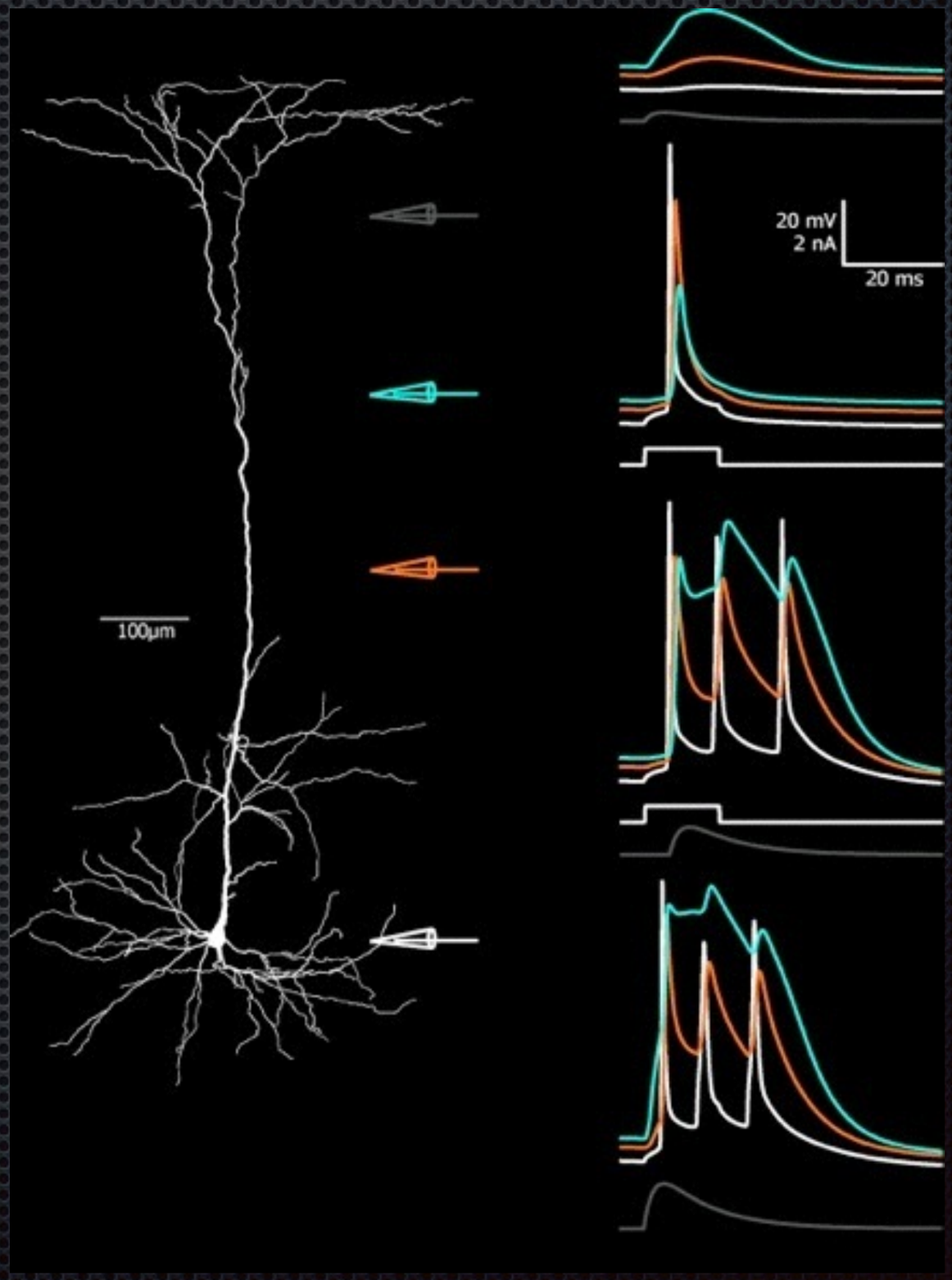


Larkum, Zhu and Sakmann. Nature 1999

BAC-Firing (artificial axon)

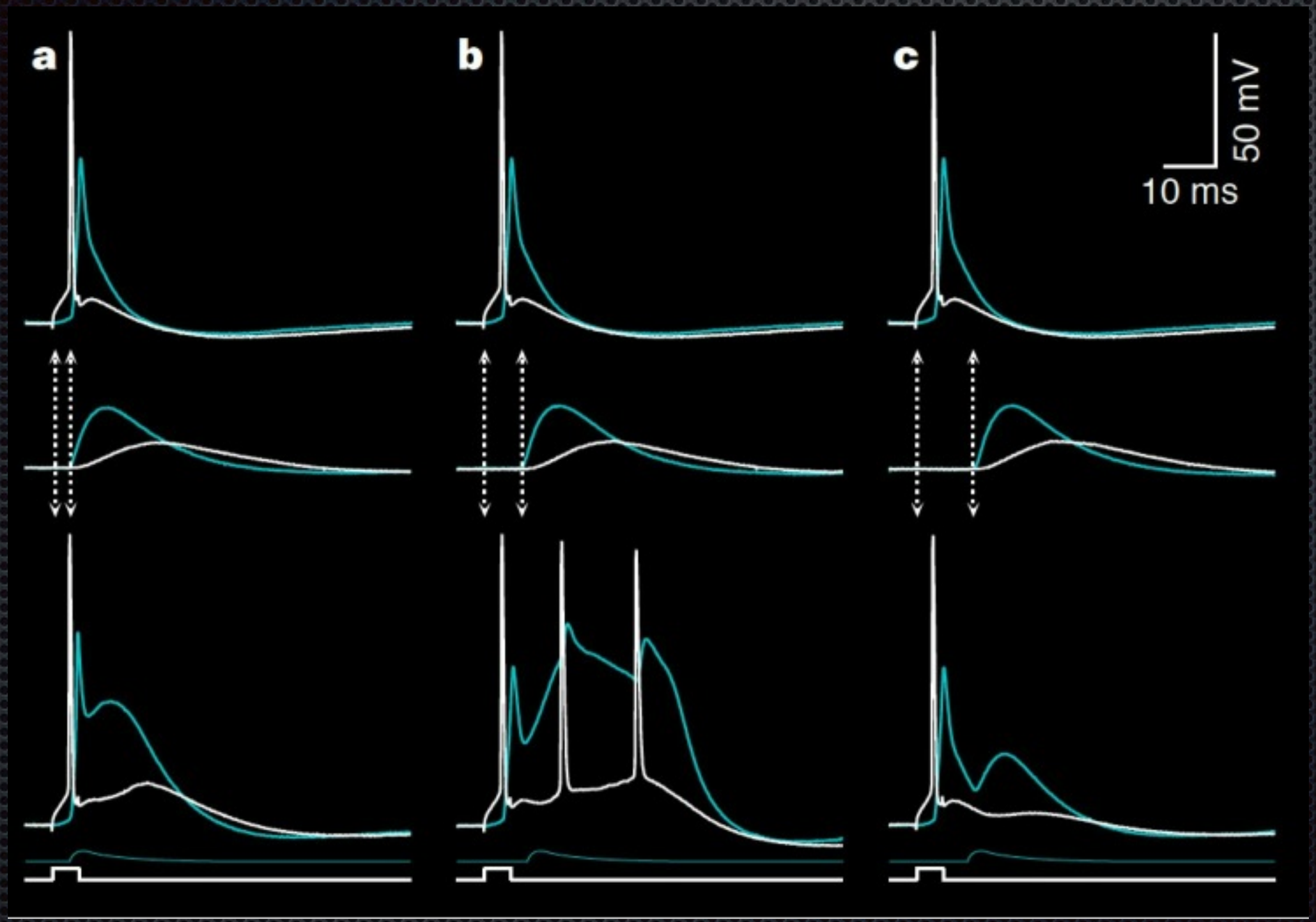


Larkum, Zhu and Sakmann. Nature 1999



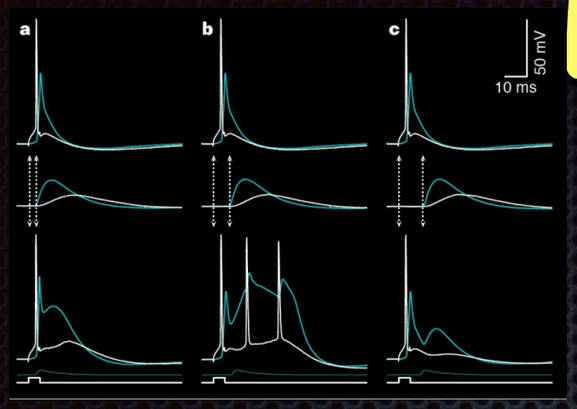
Almog and Korngreen, Journal of Neurosci. 2014

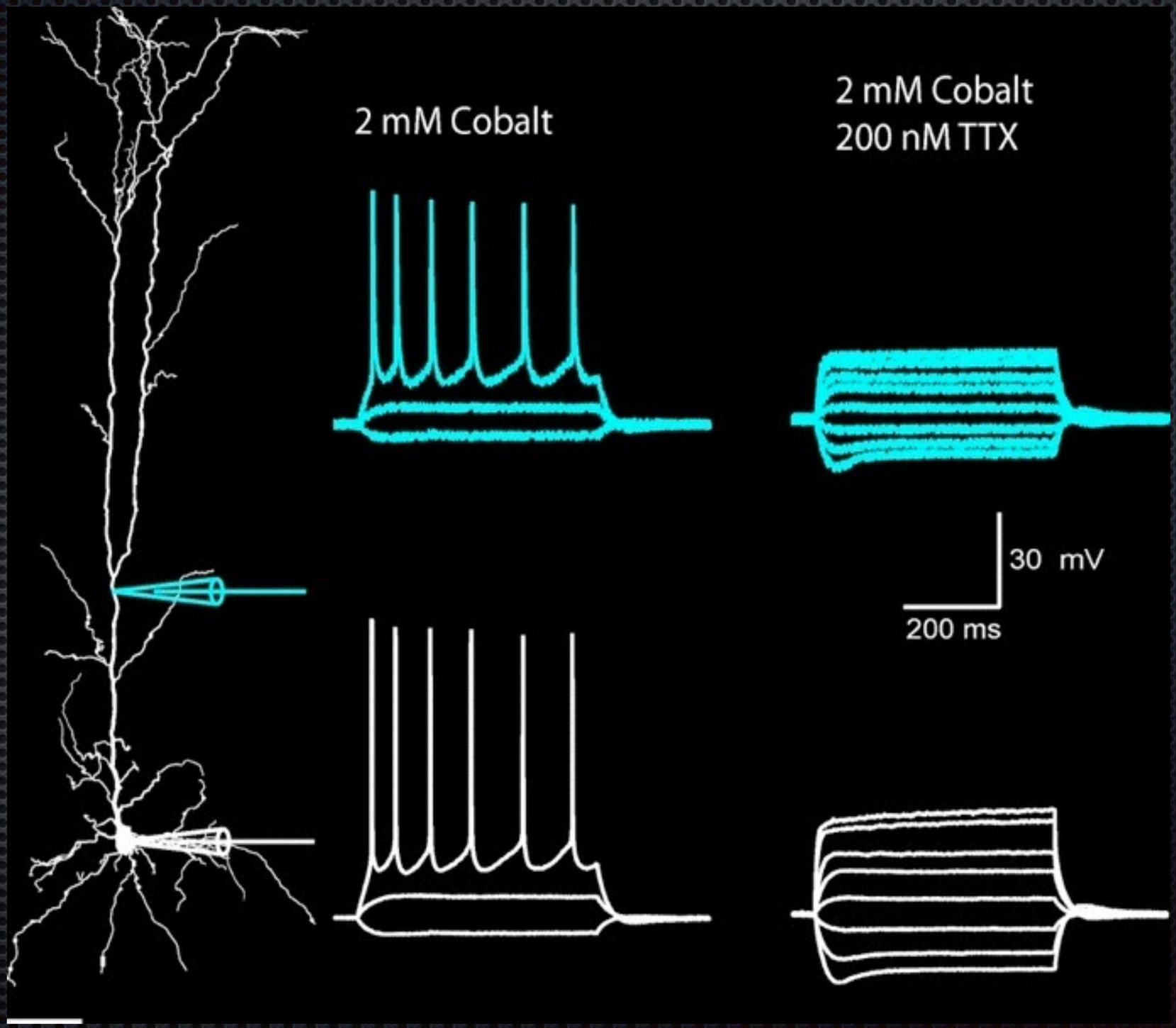
BAC-firing timing



Larkum, Zhu and Sakmann, Nature, 398, 1999

BAC-firing timing

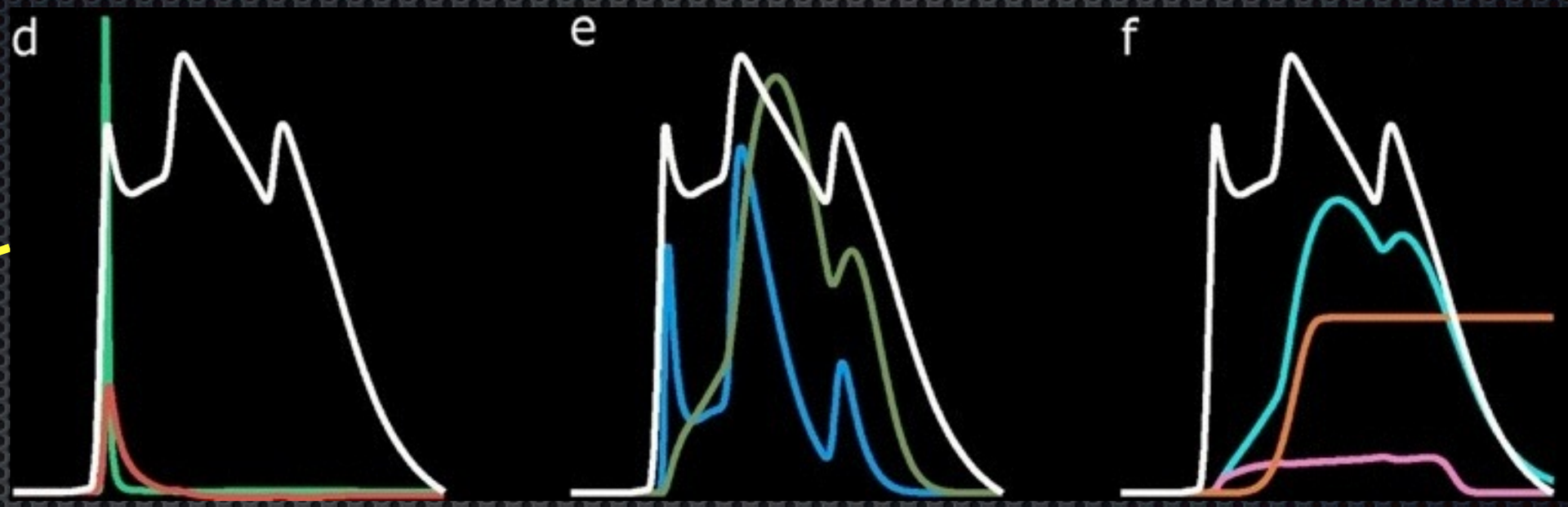




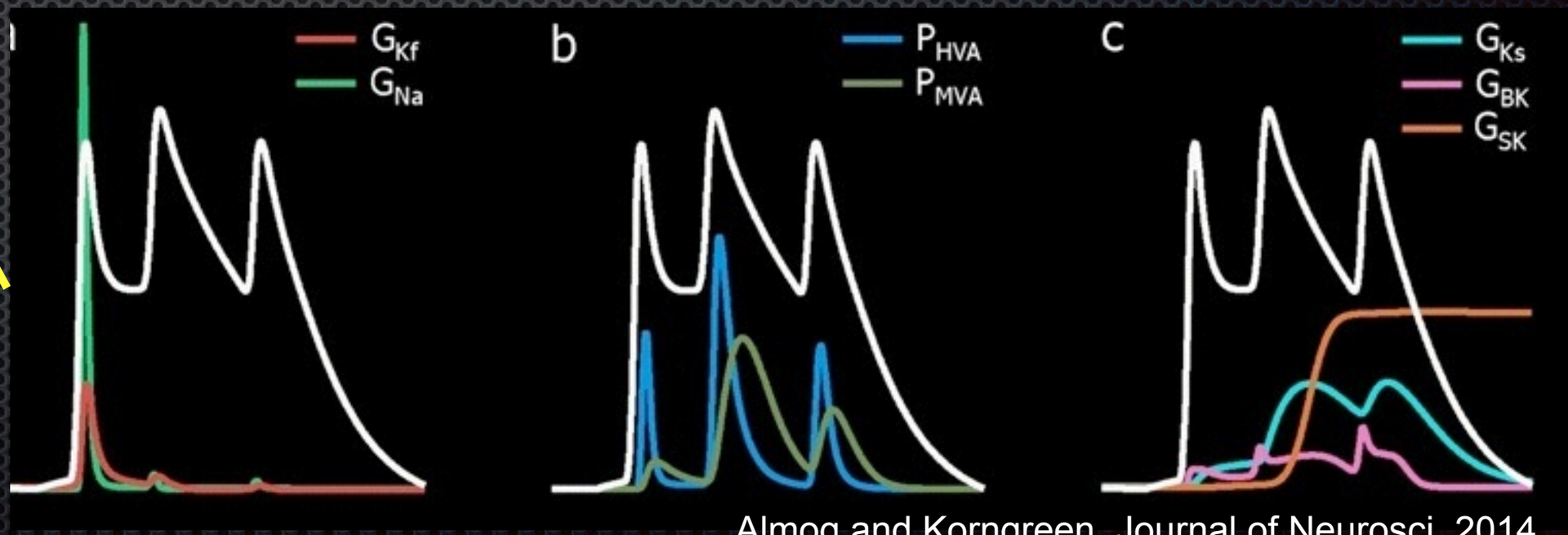
Almog and Korngreen, Journal of Neurosci. 2014

BAC-firing mechanism

~600 micrometer from the soma

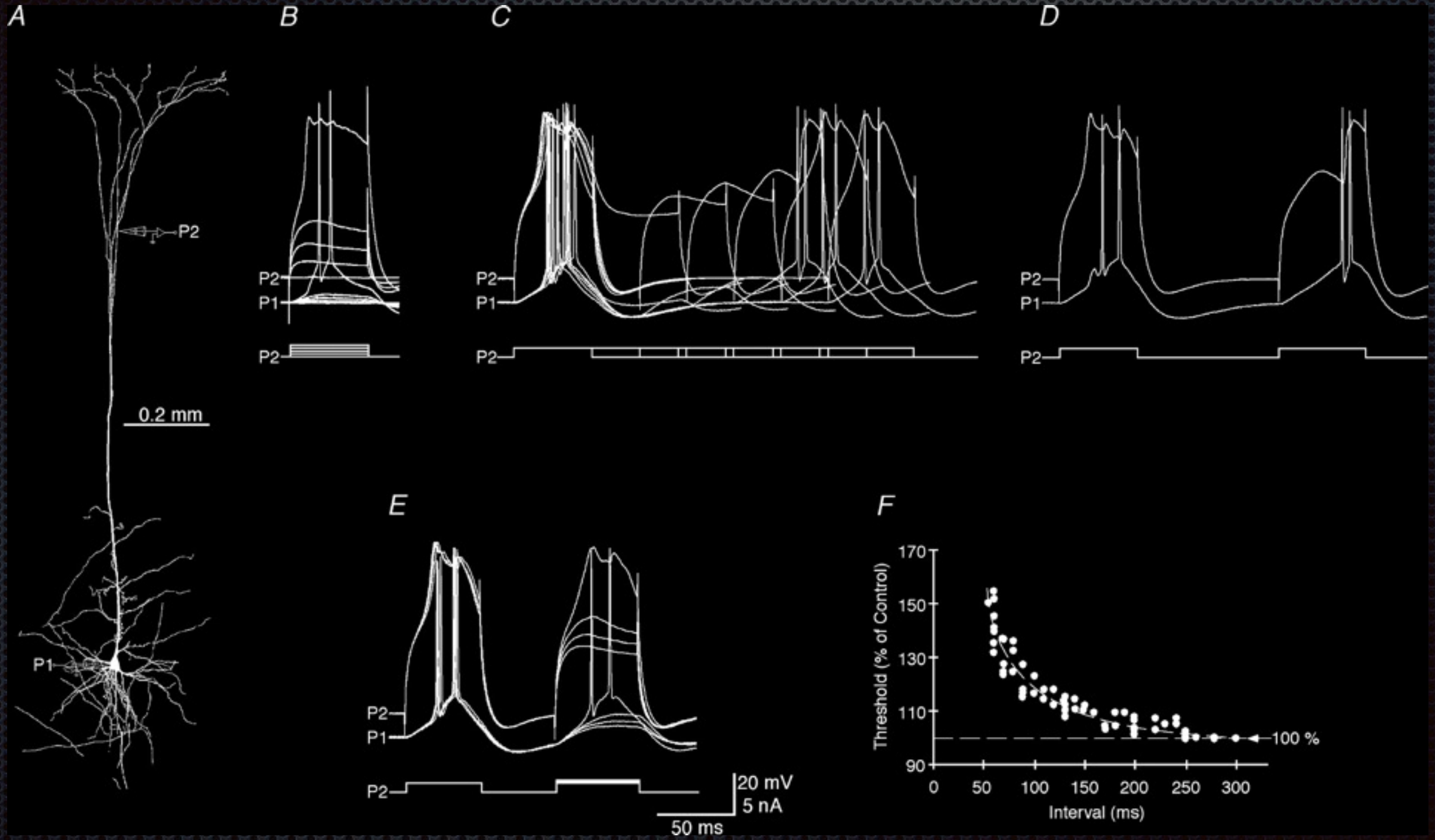


~450 micrometer from the soma



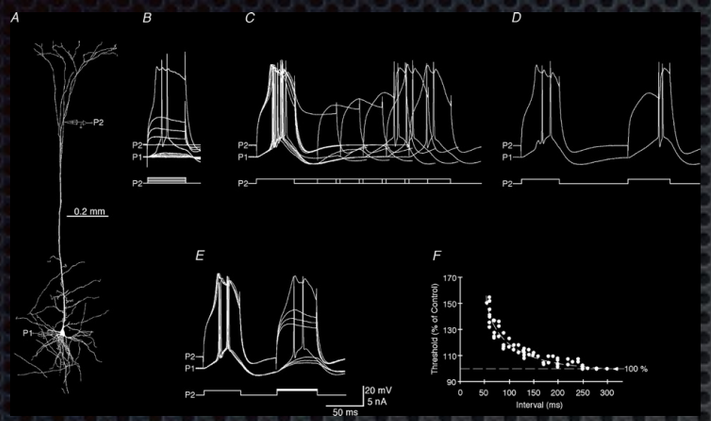
Almog and Korngreen, Journal of Neurosci. 2014

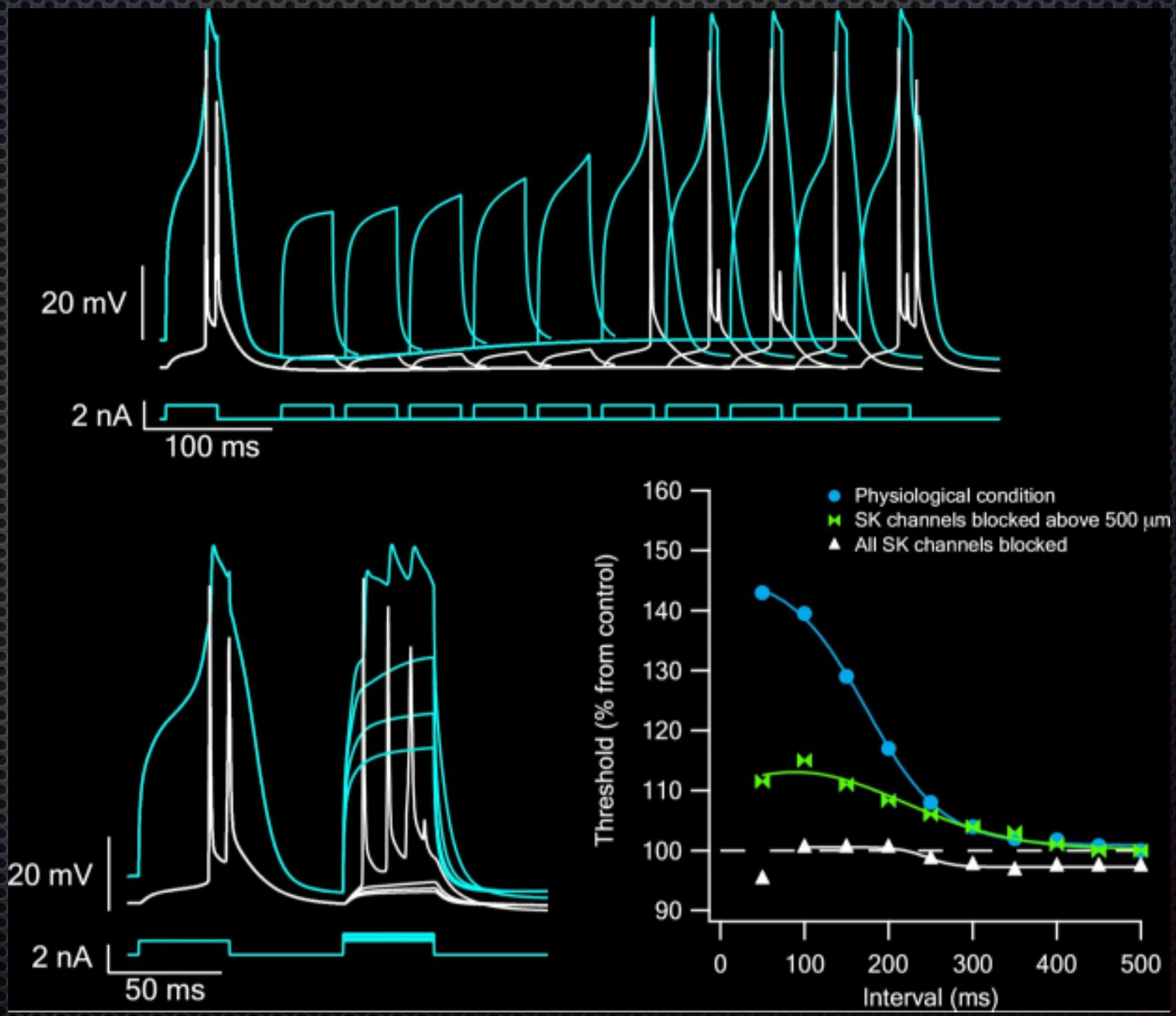
BAC-firing refractory period



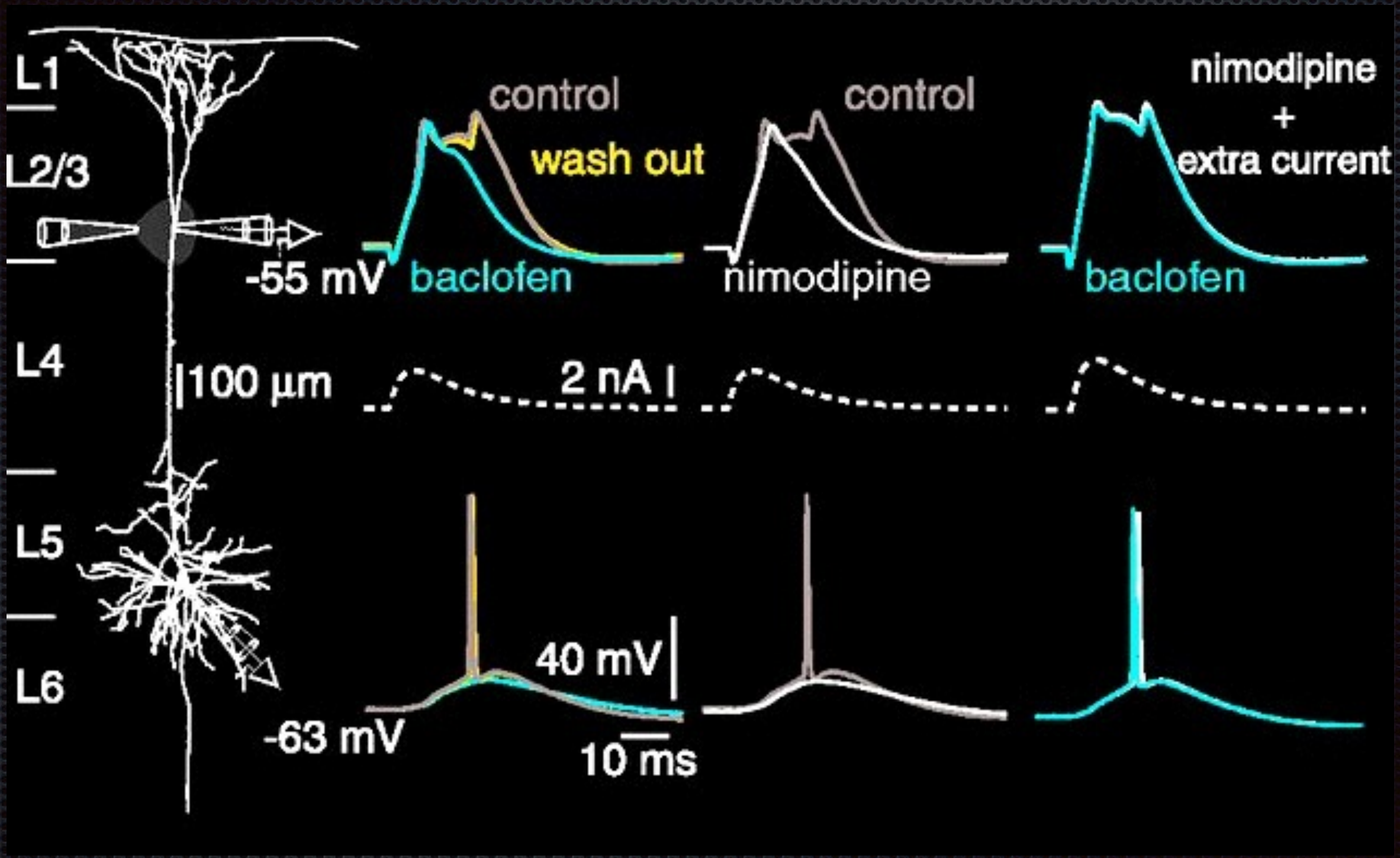
Larkum and Zhu,The Journal of Neuroscience, 2002, 22(16): 6991-7005

BAC-firing refractory period mechanism



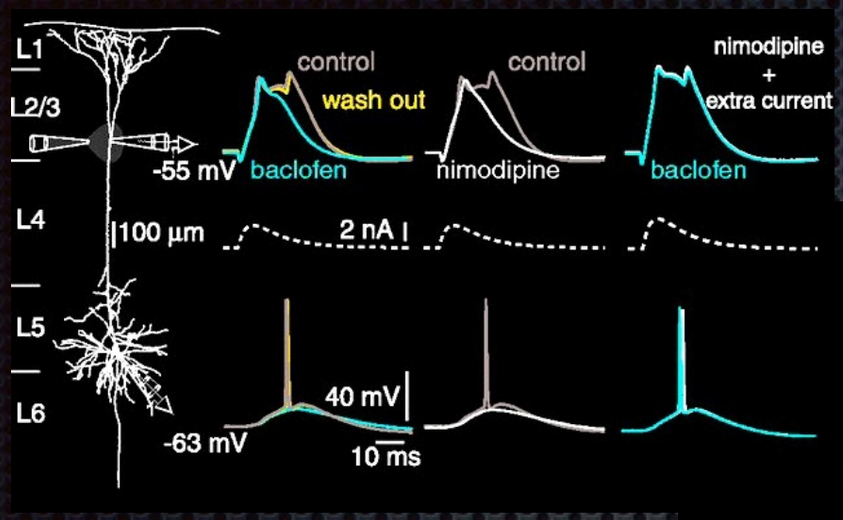


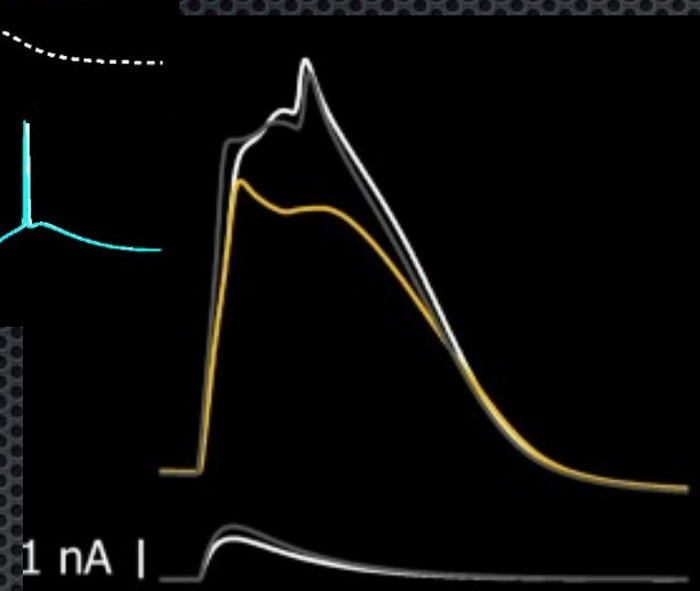
Calcium spike robustness

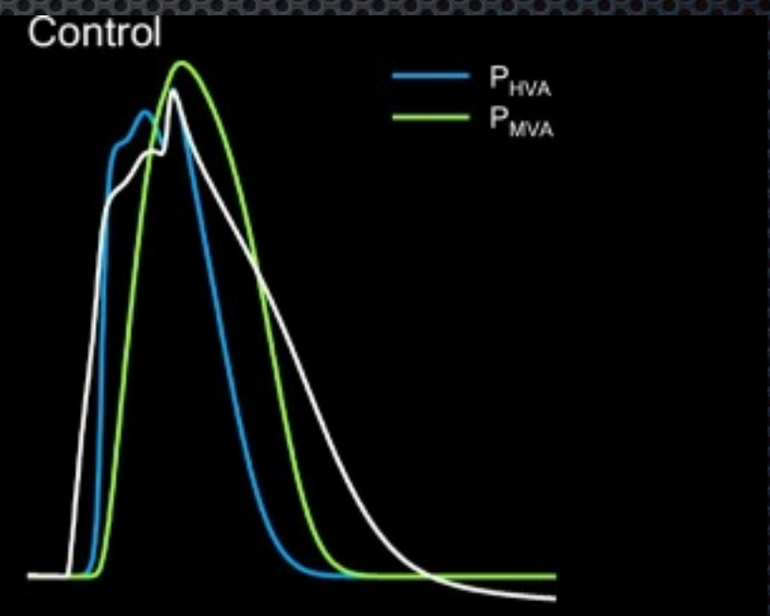


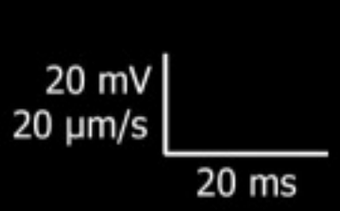
Pérez-Garci, Larkum and Nevian, The Journal of Physiology, 591, 1599-1612, 2012

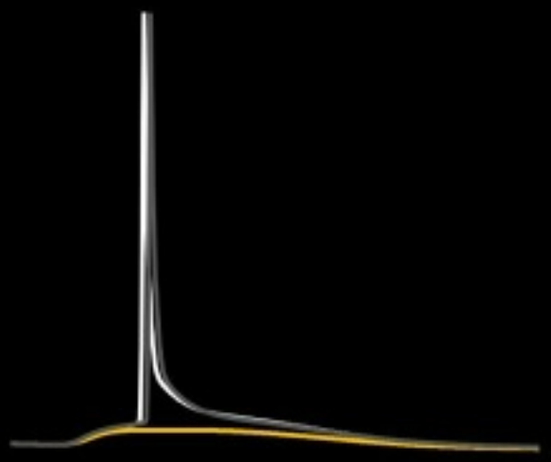
Calcium spike robustness

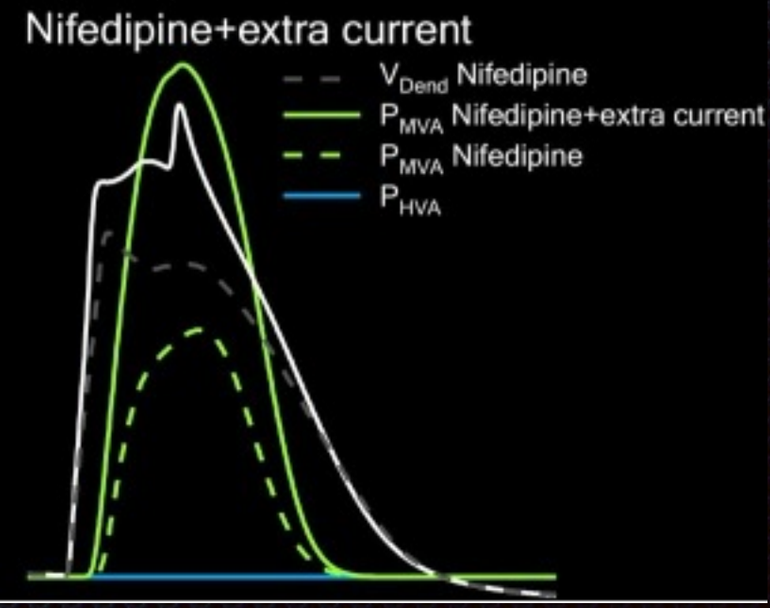






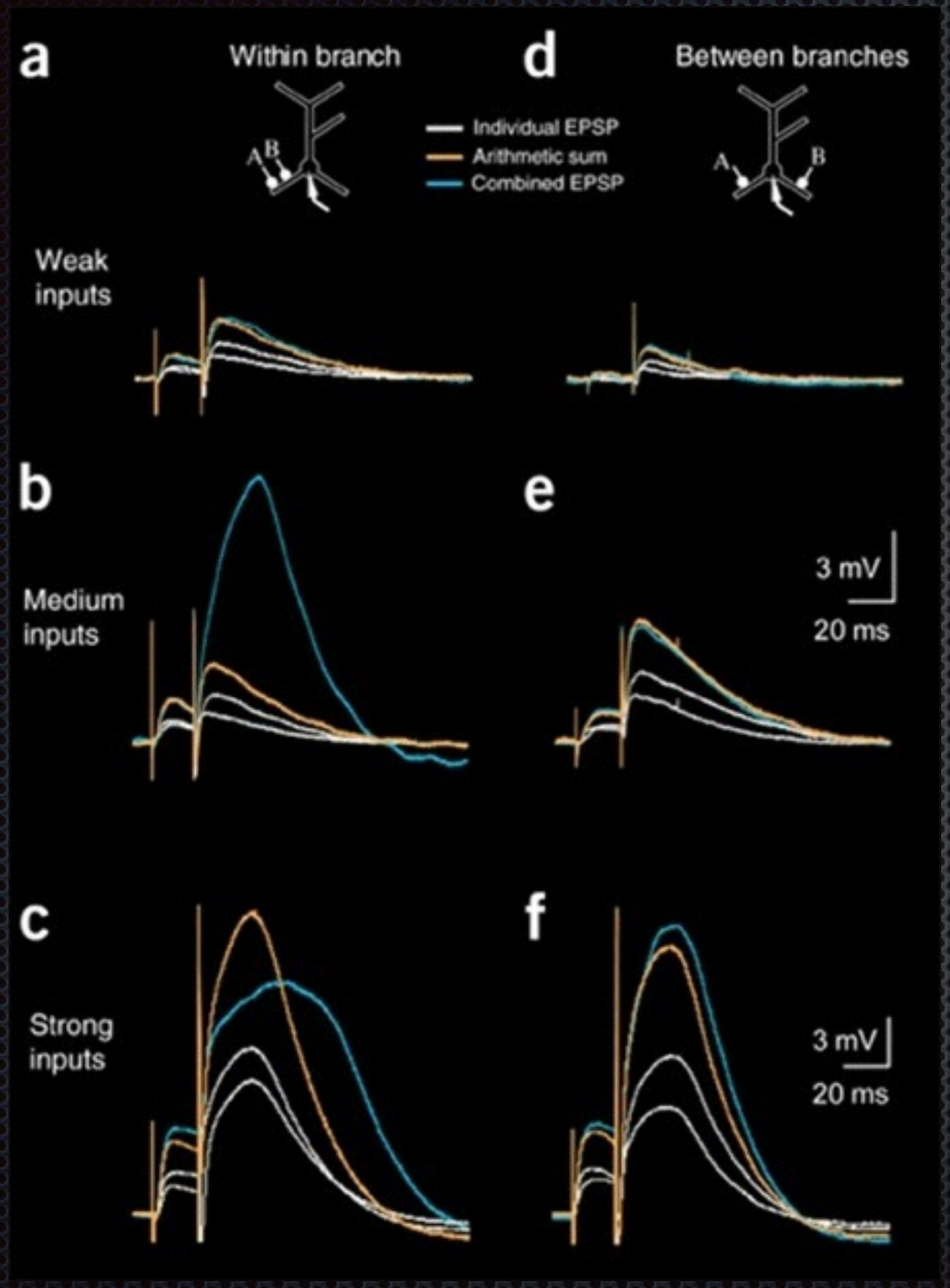




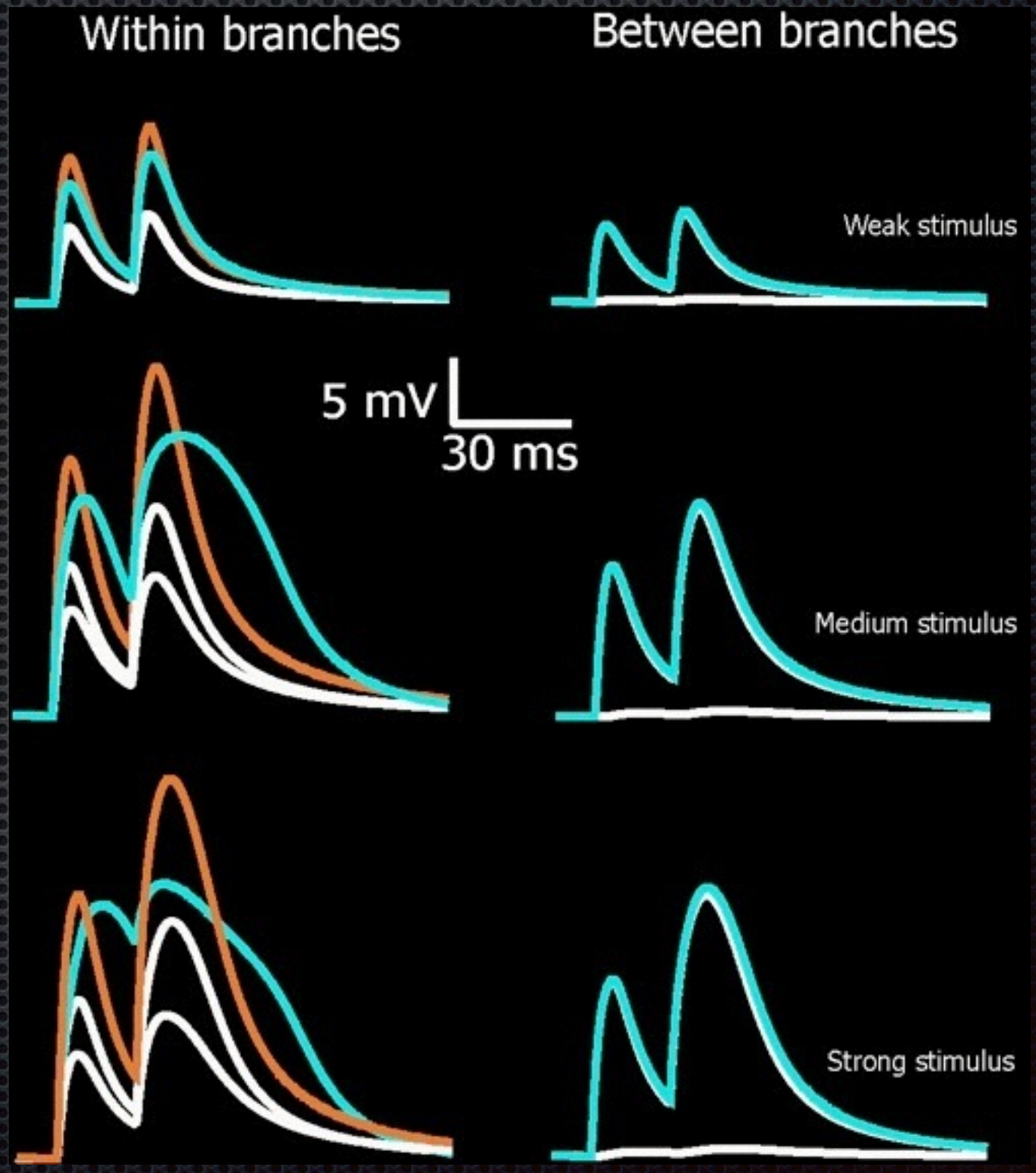


Pérez-Garci, Larkum and Nevian, The Journal of Physiology, 591, 1599–1612, 2012

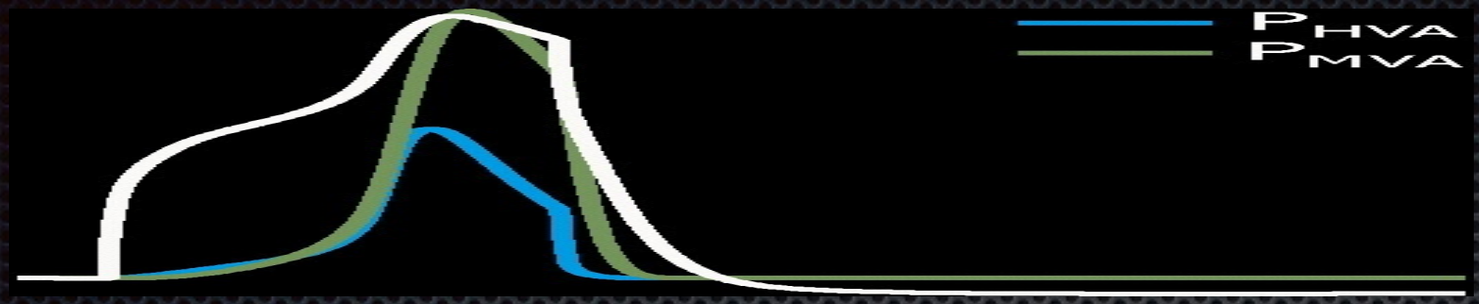
NMDA Spikes....

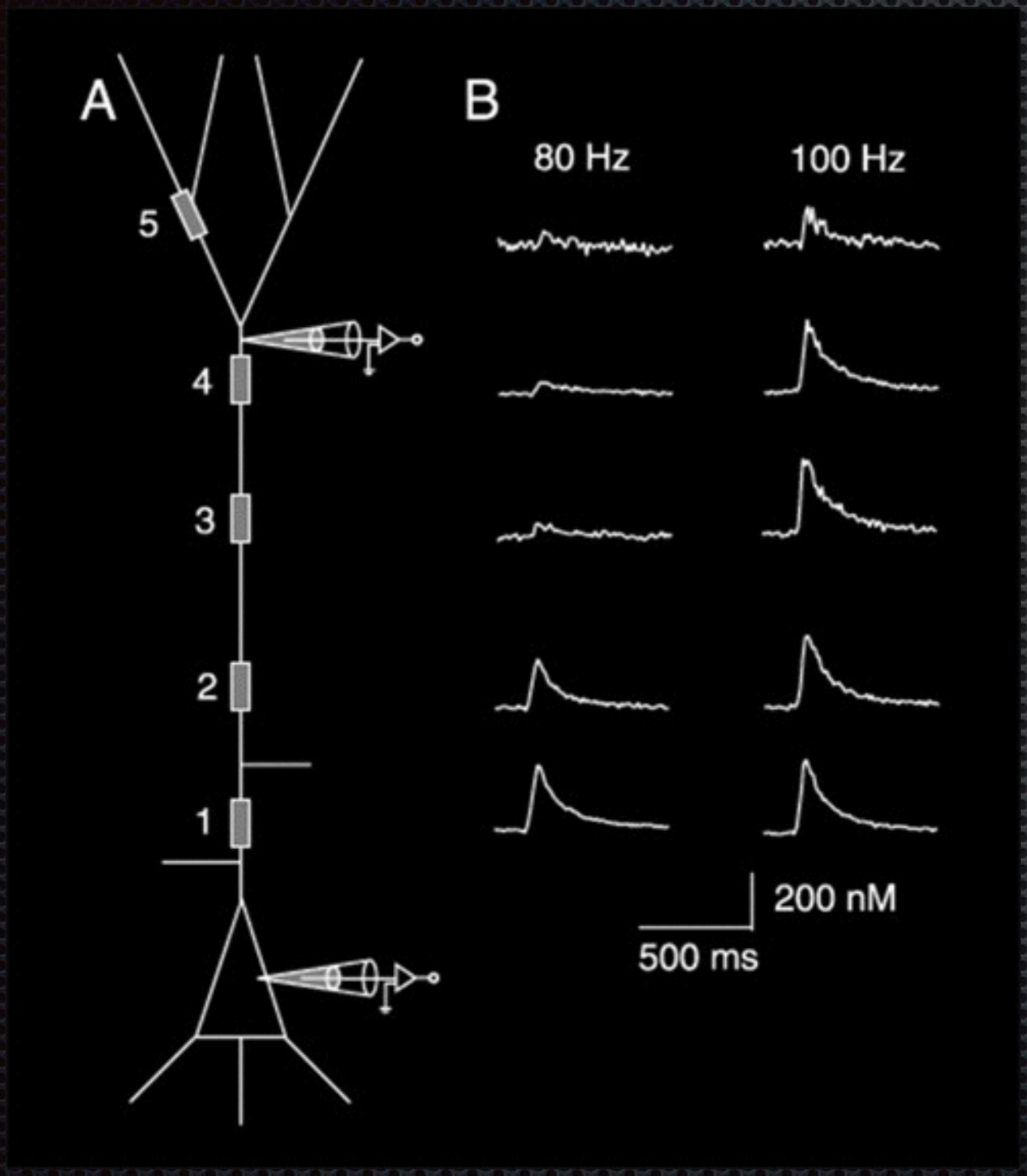


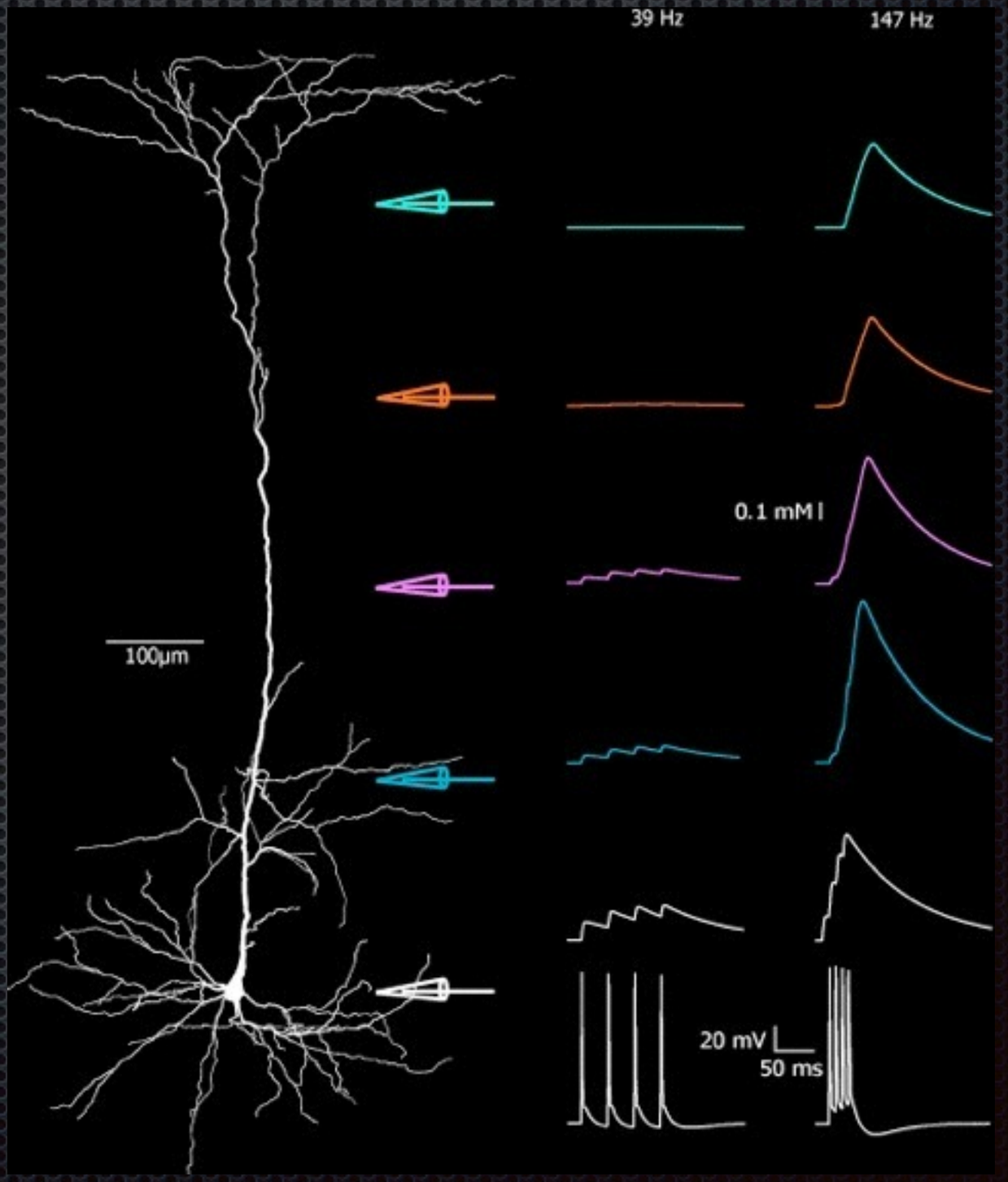
Polsky, Mel and Schiller Nat. Neurosci, 2004



Almog and Korngreen, Journal of Neurosci. 2014


PHVA
PMVA


A
B
80 Hz
100 Hz
5
4
3
2
1
200 nM
500 ms


39 Hz
147 Hz
0.1 mM I
100µm
20 mV
50 ms

Summary

- We constrained a functional model for the apical dendrite of L5 pyramidal neurons using experimental data.
- We propose a mechanism for the generation and propagation of dendritic spikes in L5 pyramidal neurons.
- The model does not require a distal dendritic conductance “hot-zone” or “apical band”.
- The model reproduces “ALL” experimental results.
- The model provides biophysical mechanism for many physiological observations.
- **We highlight the need for more intimate link between data design and numerical simulations**.

What is wrong?

1. I_H - subthreshold EPSP summation not realistic; need to change model.
2. We reduced the number of calcium channels from five to two….
3. SK temperature dependence is wrong.
4. Na - Hodgkin-Huxley model too simple; need to change model (NaP?)
5. Basal dendrites are a crude guess.
6. The axon fits like a left glove to a right foot.

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