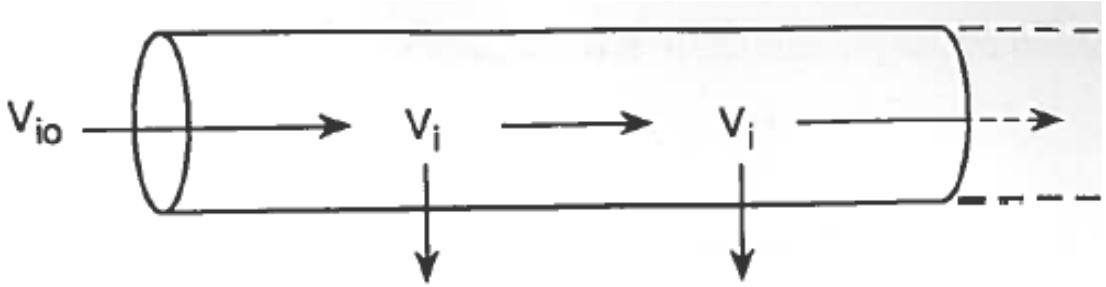
Neuronal Integration:

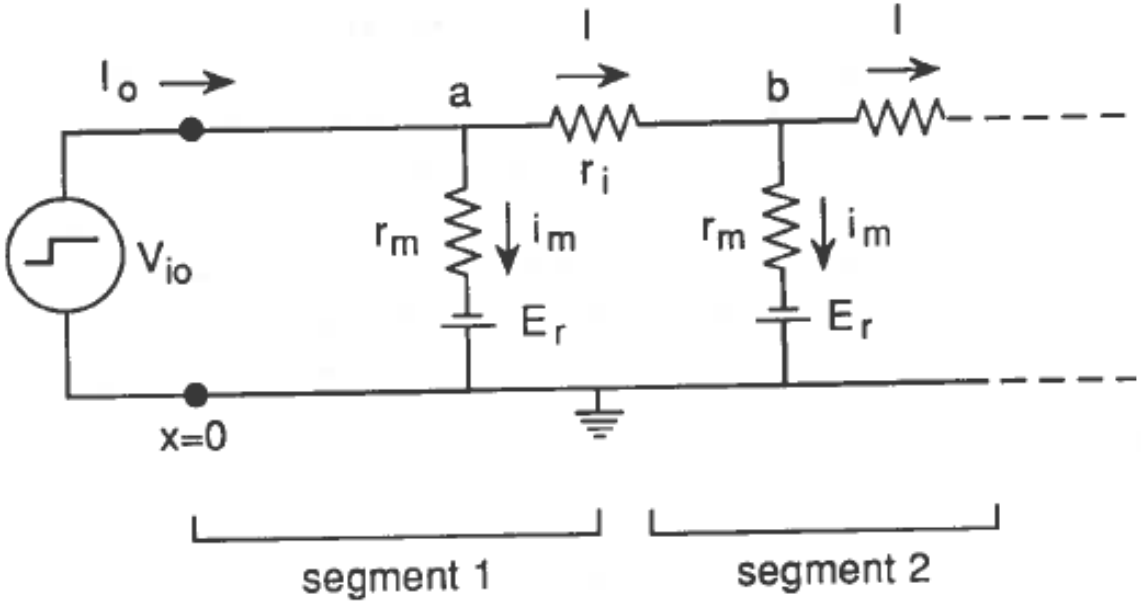
- Cable theory
- Passive integration in dendrites
- Orthodromic and antidromic (bAP) spike propagation
- “Active” properties of dendrites
  - Intrinsic & synaptic mechanisms
- Axonal integration
  - Analog vs. Digital components of AP-evoked release
  - Determinants of AP initiation

Passive spread of voltage along a leaky cable



$$V = \frac{r_m}{r_i} \cdot \frac{d^2V}{dx^2}$$

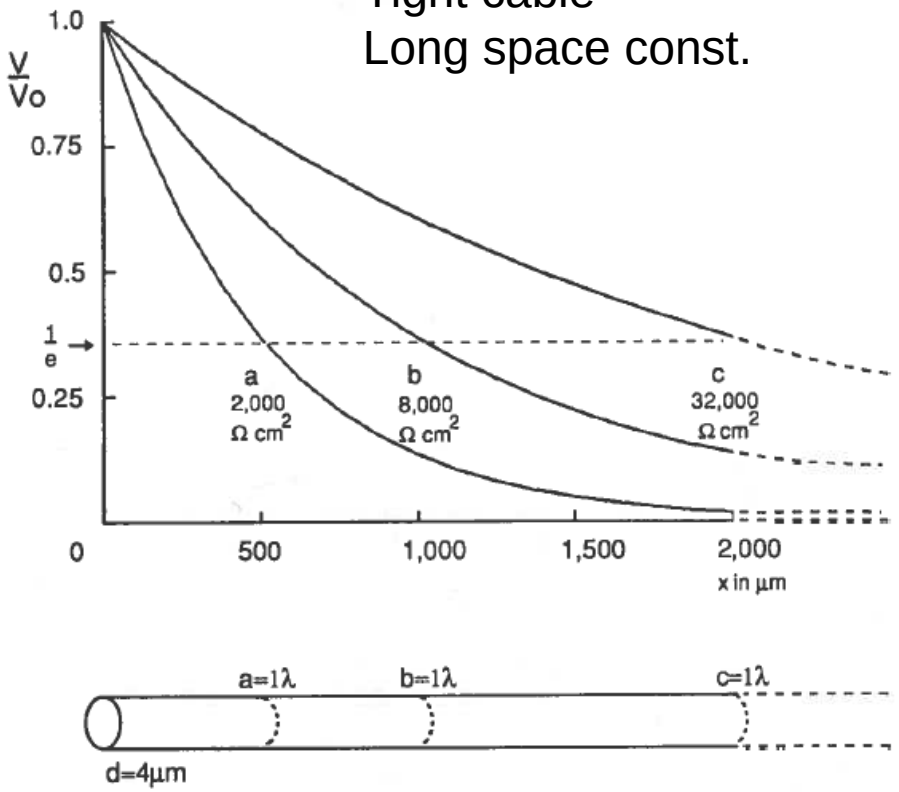
$$\lambda^2\left(\frac{d^2V}{dx^2}\right) - V = 0;\ \lambda = \sqrt{\frac{r_m}{r_i}}$$



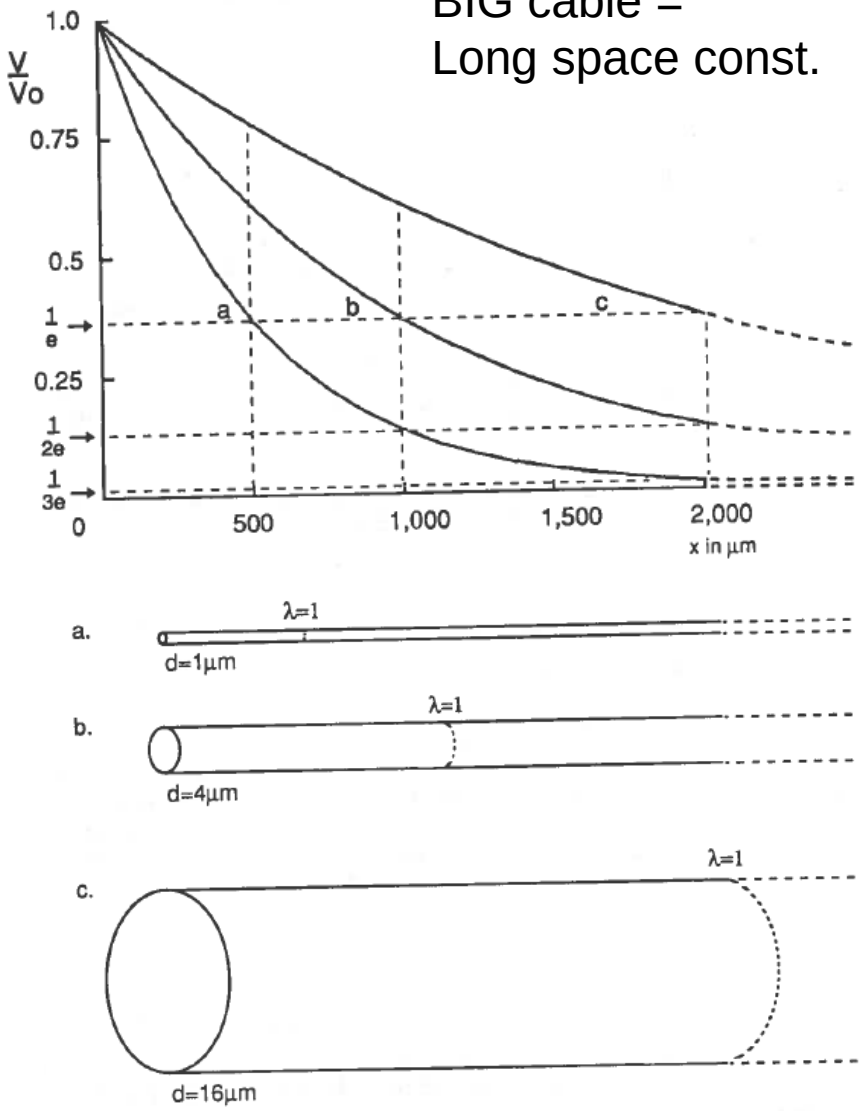
$$\lambda = \sqrt{\frac{r_m}{r_i}} = \sqrt{\frac{R_m}{R_i} \cdot \frac{d}{4}}$$

$$\lambda \propto d, r_m$$

Tight cable =
Long space const.



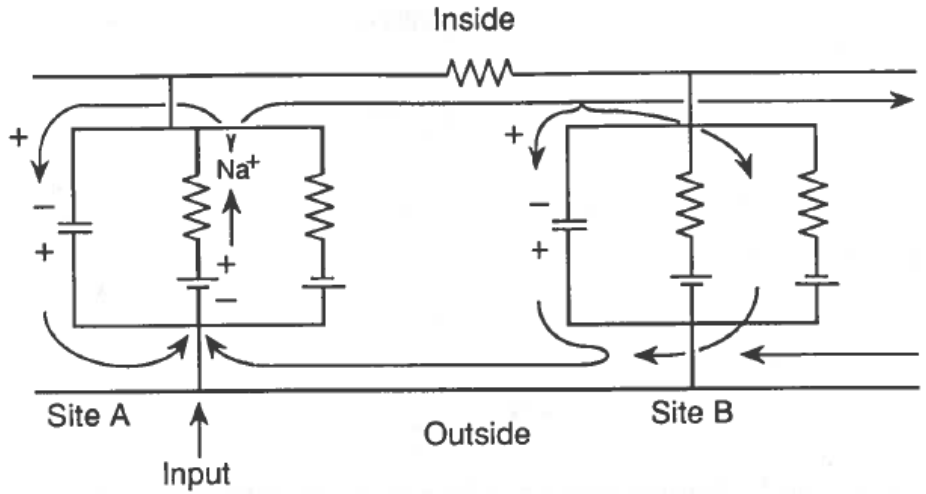
BIG cable =
Long space const.

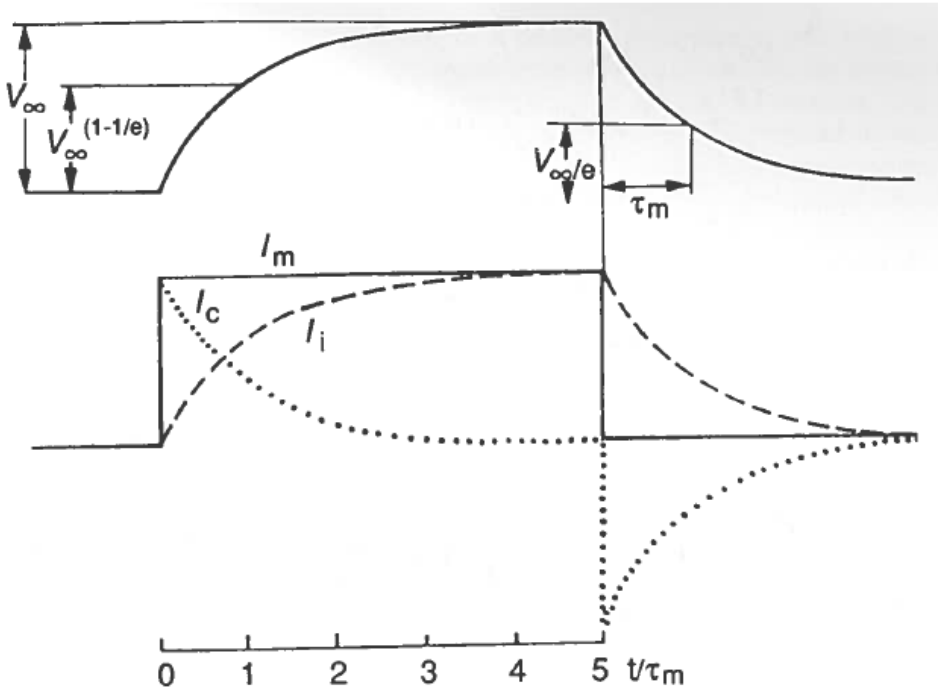


Note: we're currently ignoring membrane capacitance

Let's stop ignoring capacitance:

$$\tau = r_m c_m$$

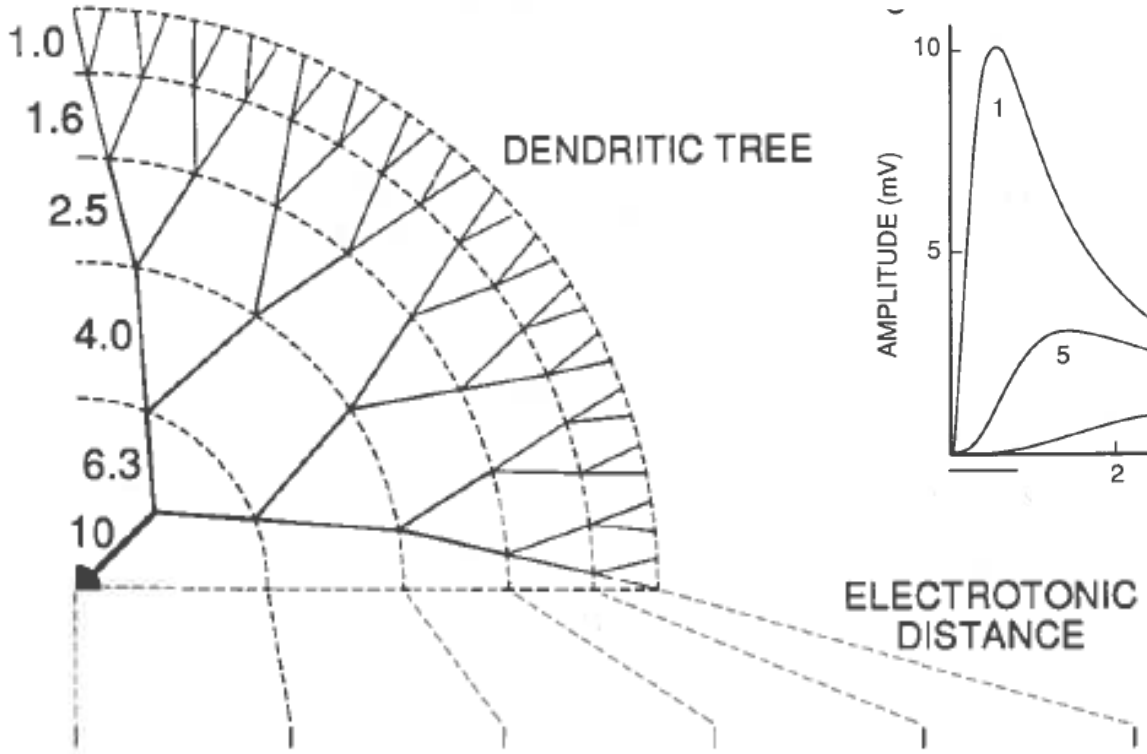


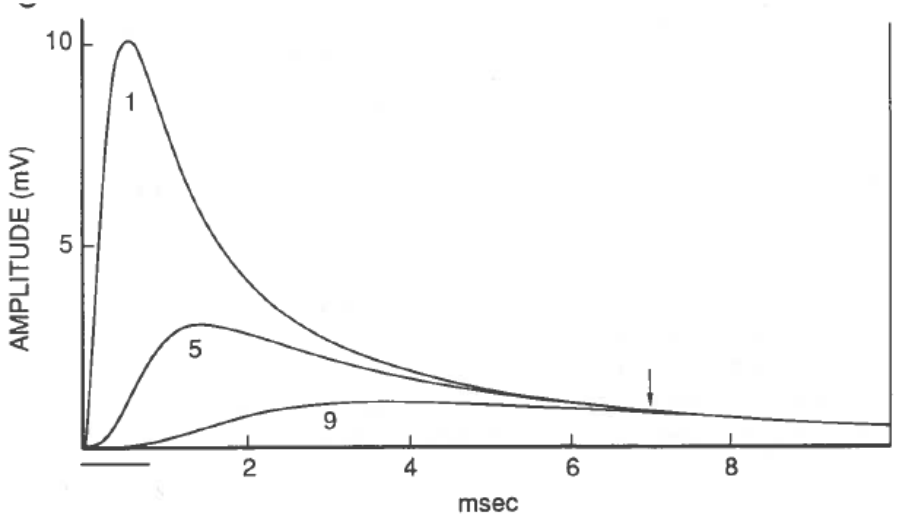


Membranes take time to charge.

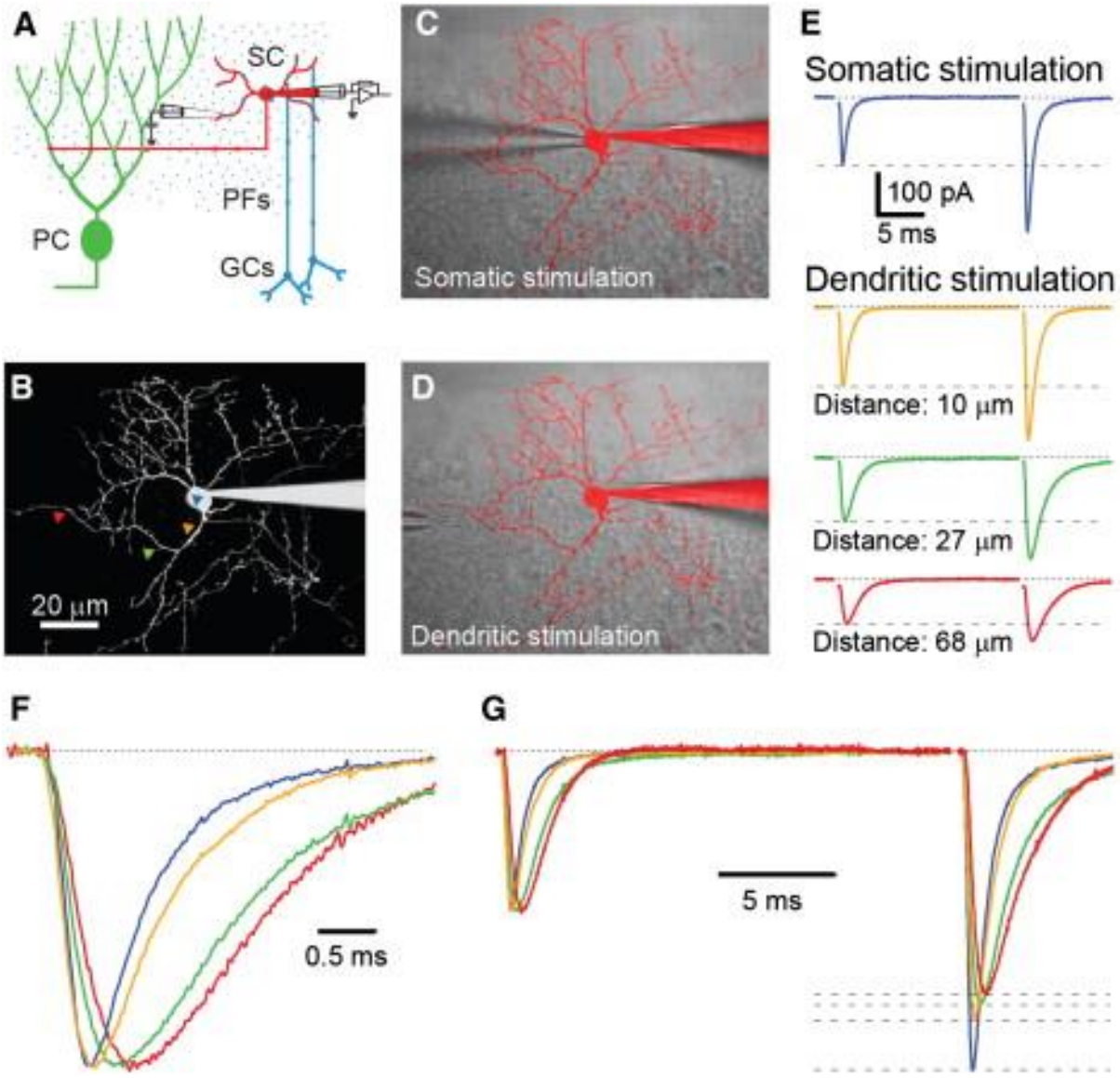
Distal synaptic inputs appear slower at the soma.

EPSPs are spatiotemporally filtered





Real life example: cerebellar stellate interneurons

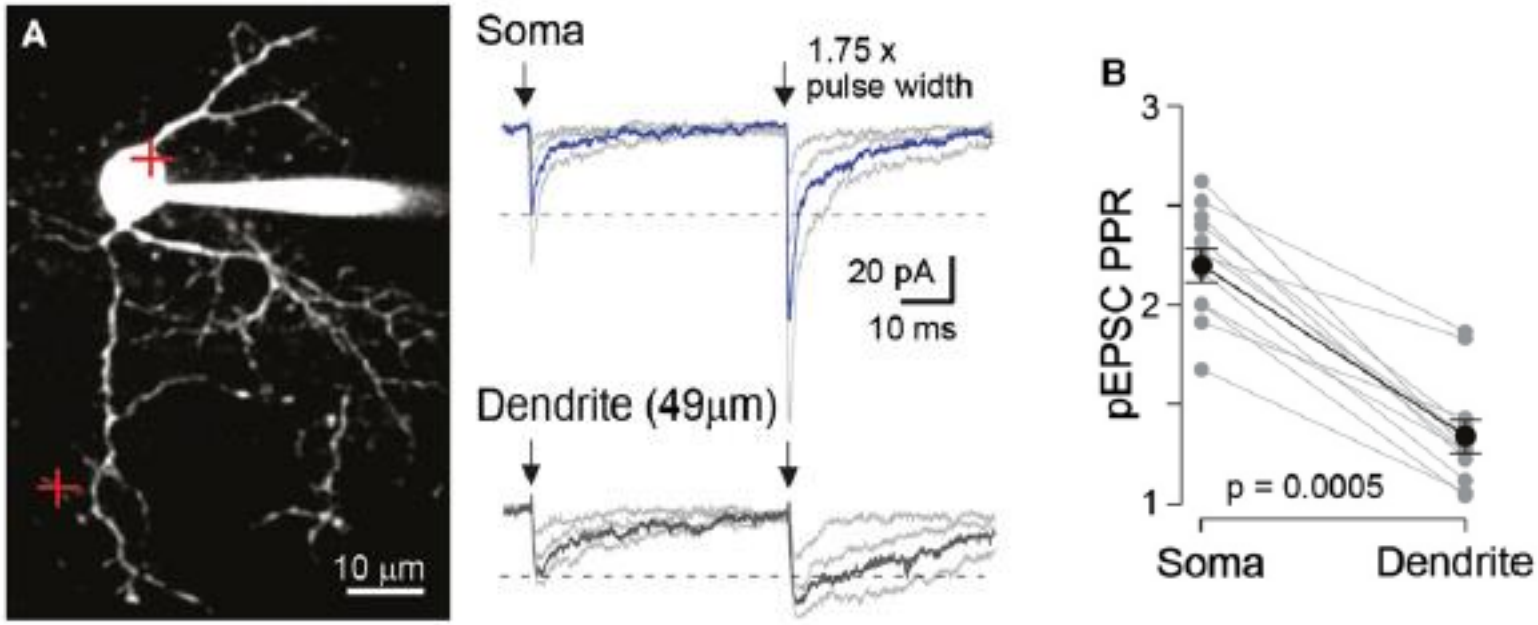


PPR changing with distance?

Is this a pre- or postsynaptic effect?

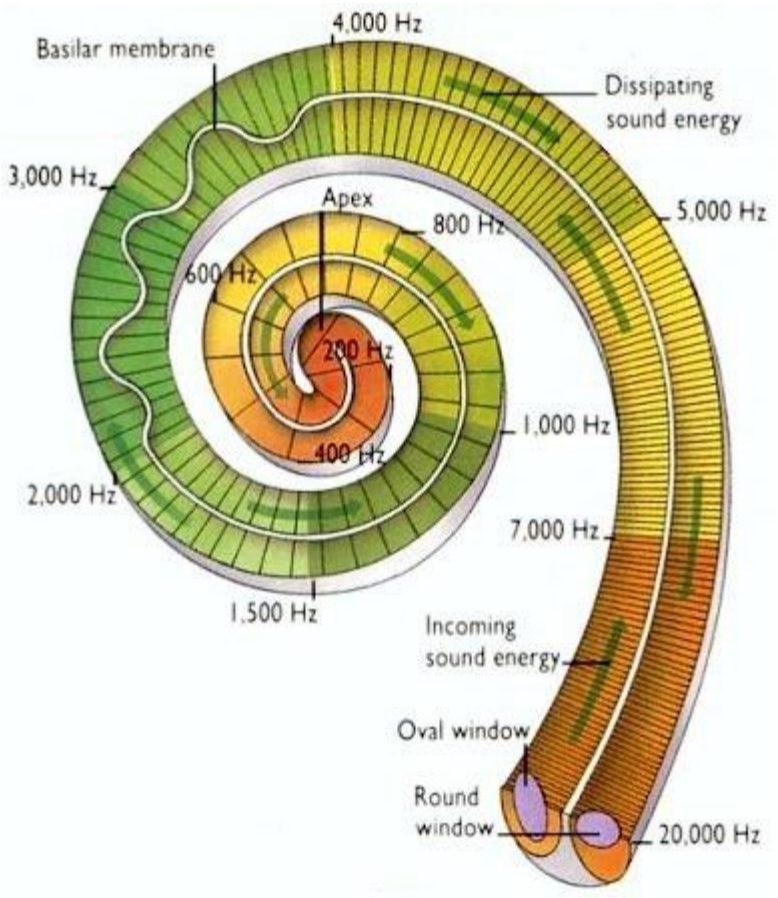
Abrahamsson et al., 2012
PMID: 22445343

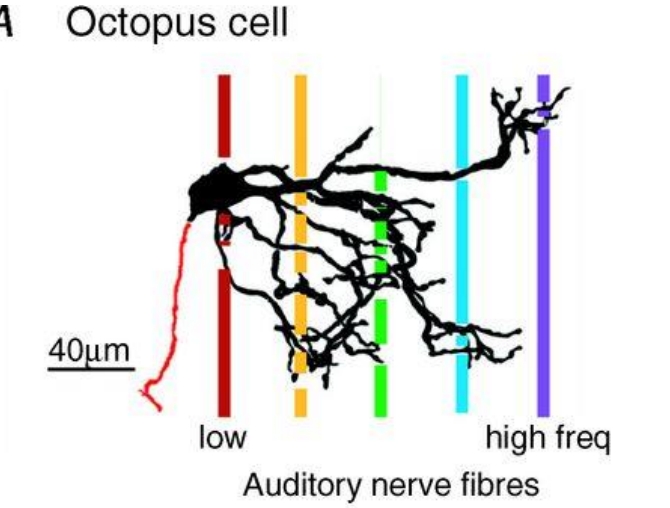
If they uncage, they see the same PPR differences

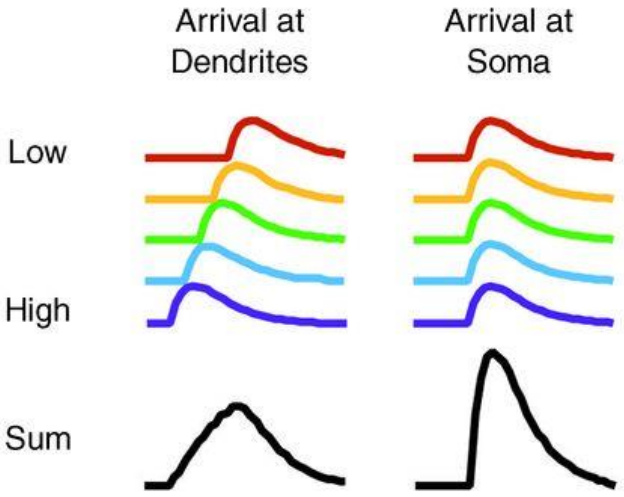


Abrahamsson et al., 2012
PMID: 22445343

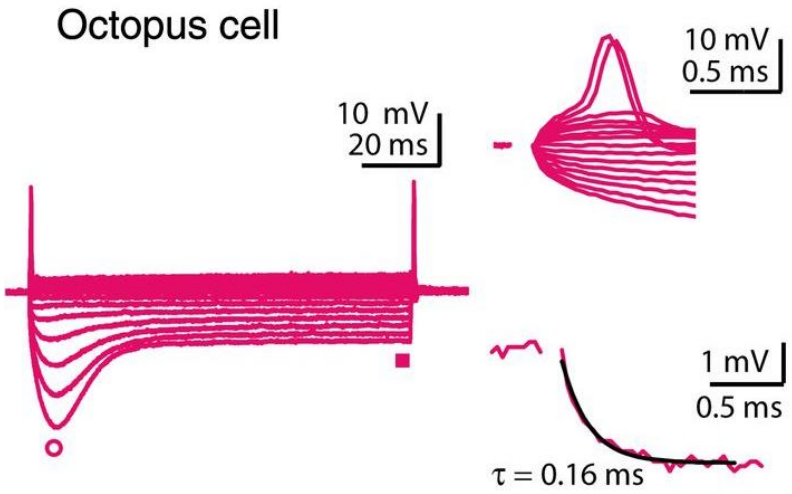
Neuronal "exploitations" of passive cable properties
Exploit #1: encoding broadband auditory chirps

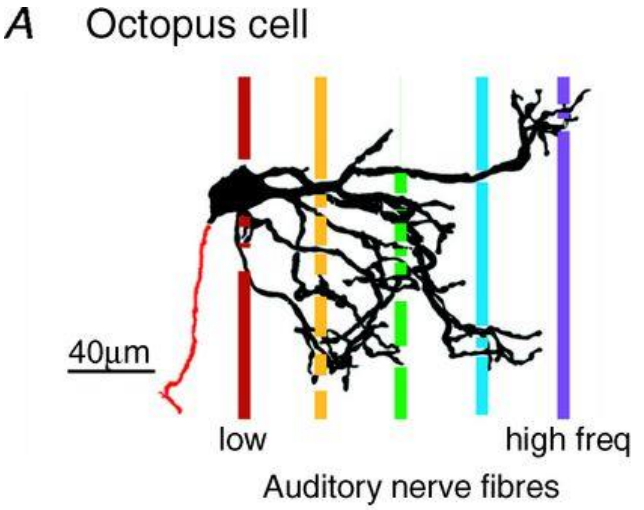


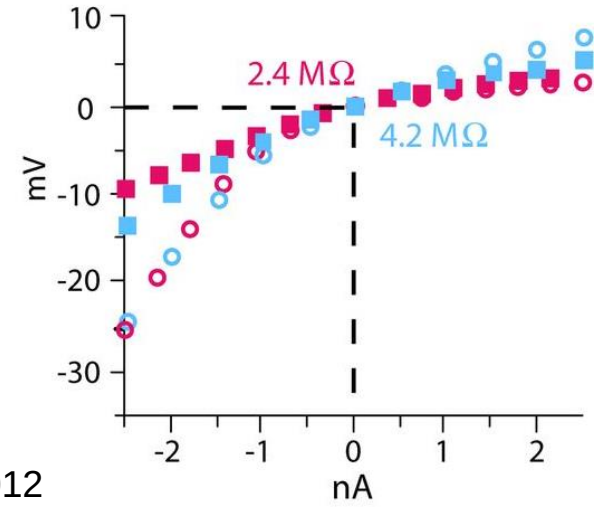


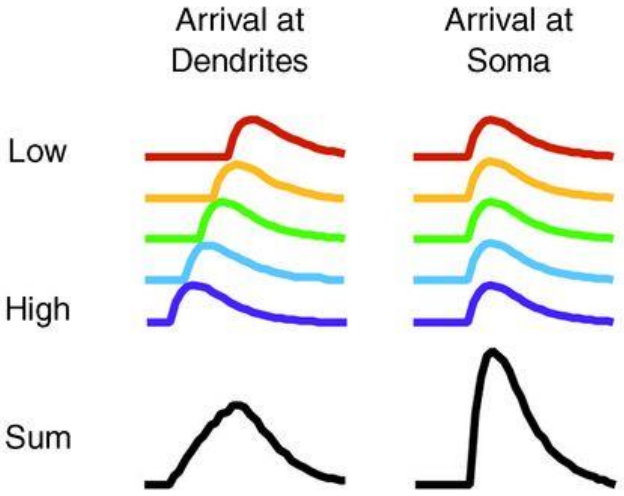


Octopus cells need to be extremely fast integrators. Therefore, *very low* time constant. Mechanism?



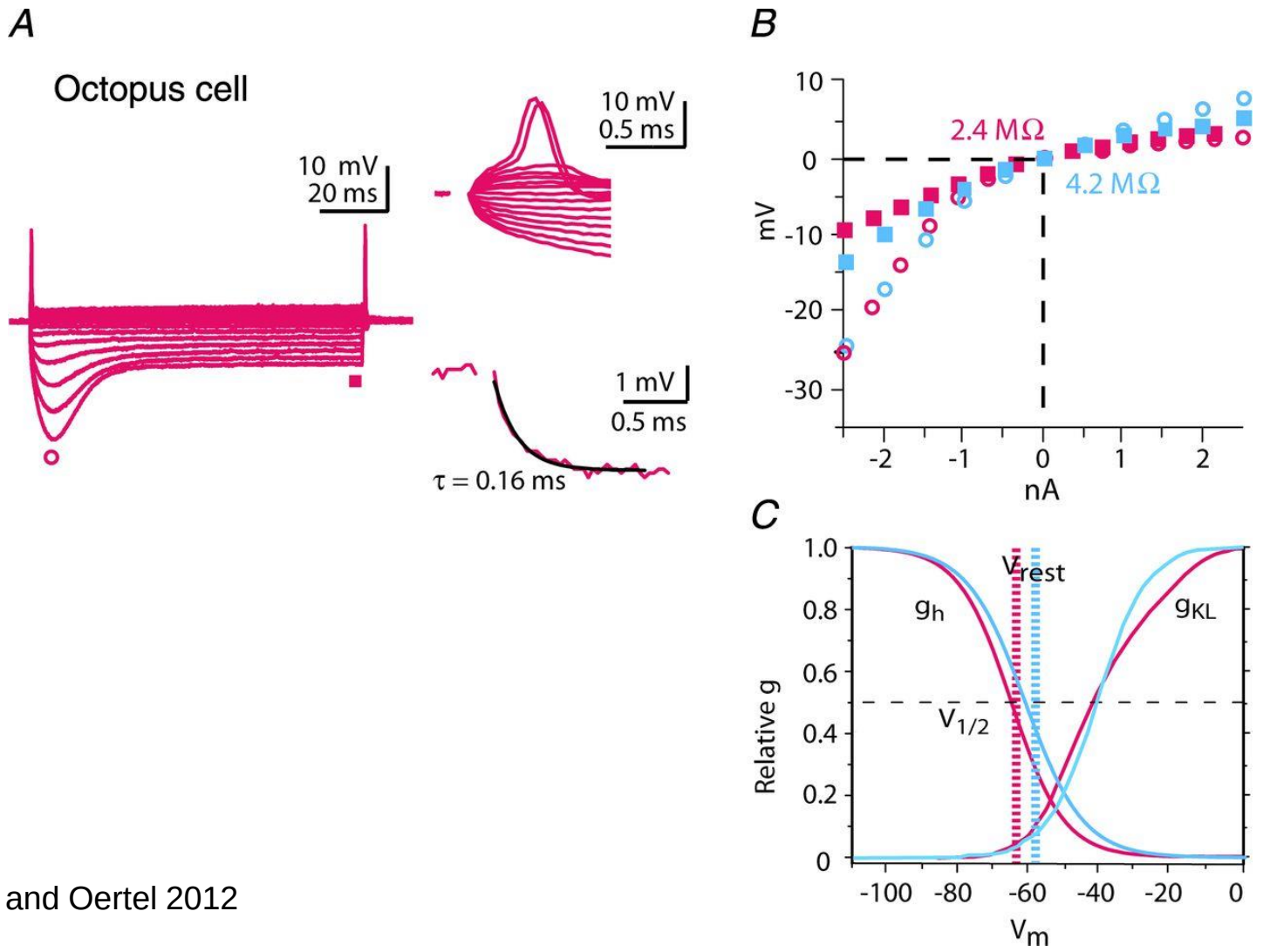






Golding and Oertel 2012

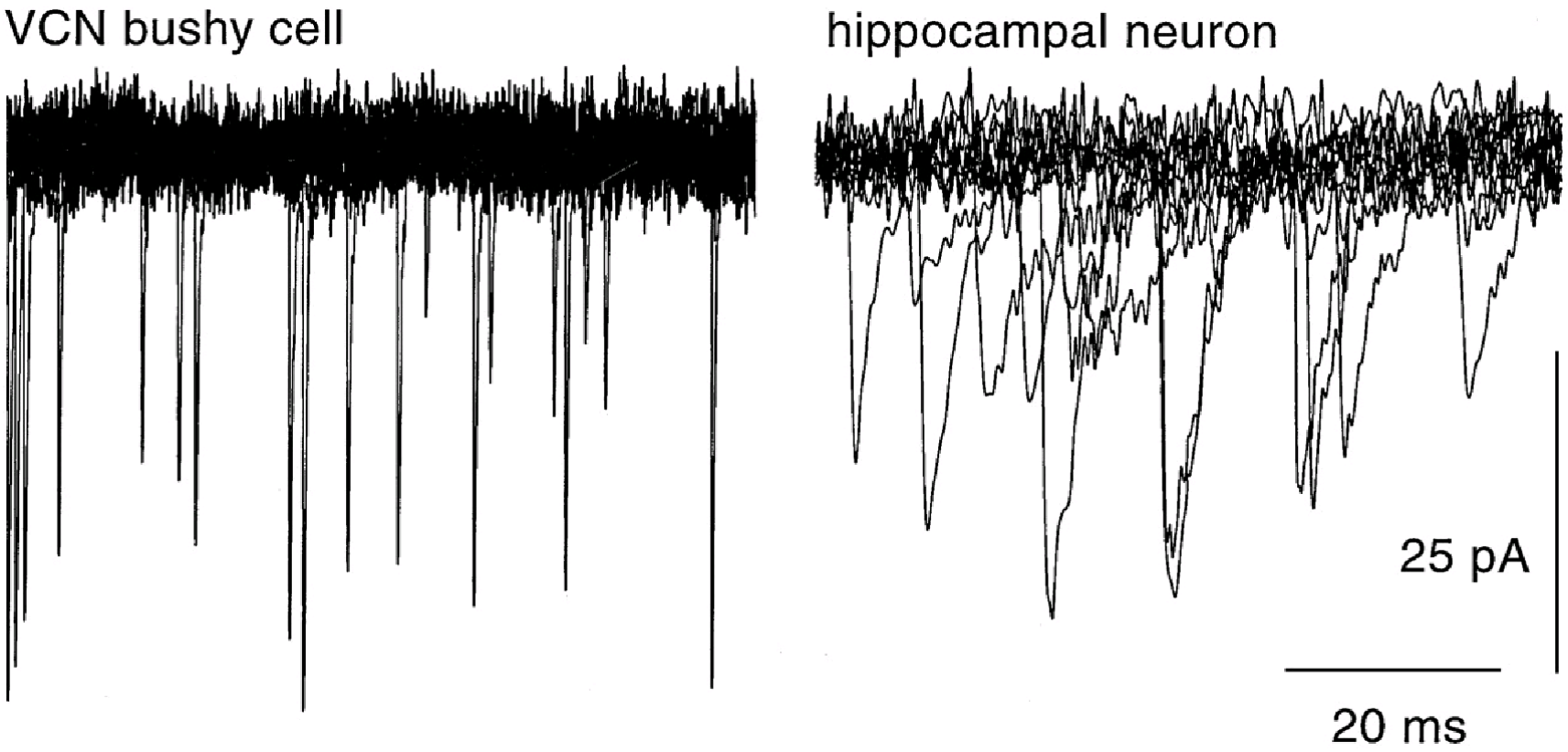
Octopus cells need to be extremely fast integrators. Therefore, *very low* time constant. Mechanism?



Golding and Oertel 2012

There is a synaptic component to coincidence detection, too

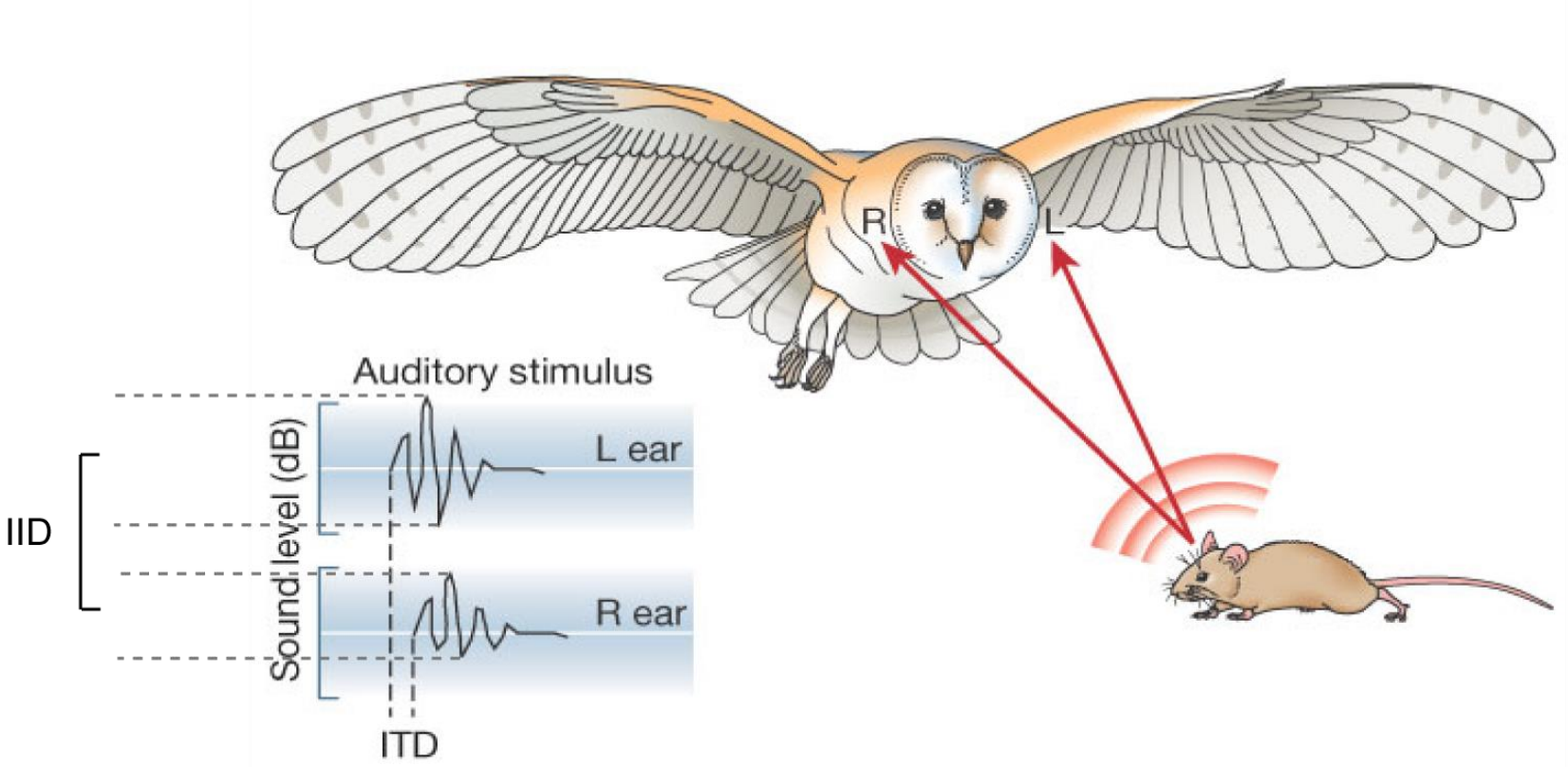
Synaptic currents are unusually brief in auditory brainstem



In part due to channel properties (AMPA subunit $GluR4_{flop}$ desensitize quickly)

What other mechanisms could speed PSPs in auditory brainstem?

Exploit #2: Interaural timing difference coding (nucleus laminaris in birds, medial superior olive in mammals)



ITD: Interaural timing difference
IID: Interaural intensity difference

Knudsen 2002

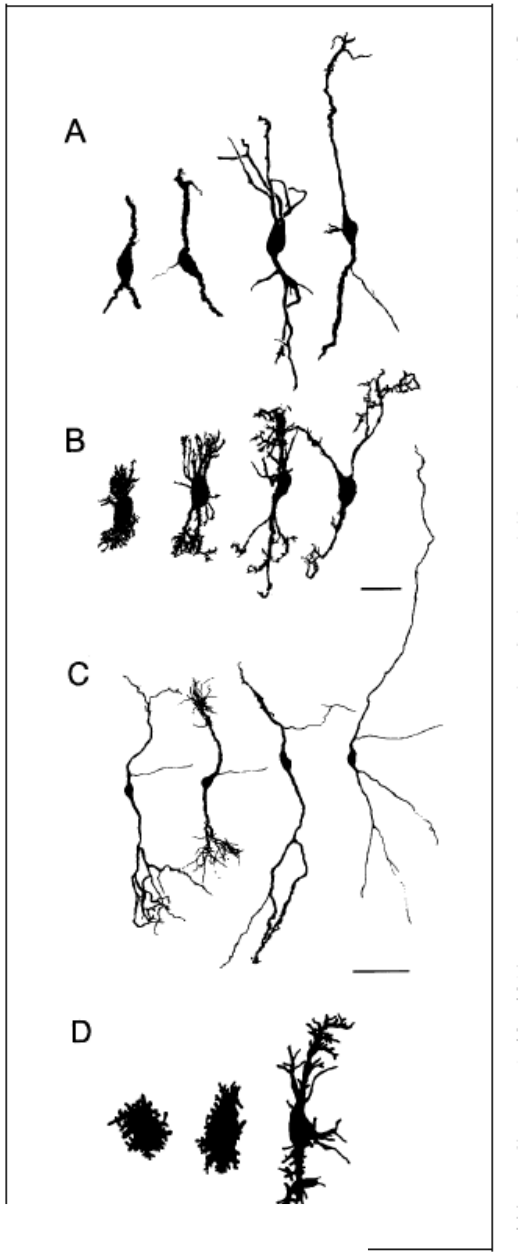
Auditory coincidence detection is done by convergence of binaural signals onto bipolar neurons

Alligator

Chick

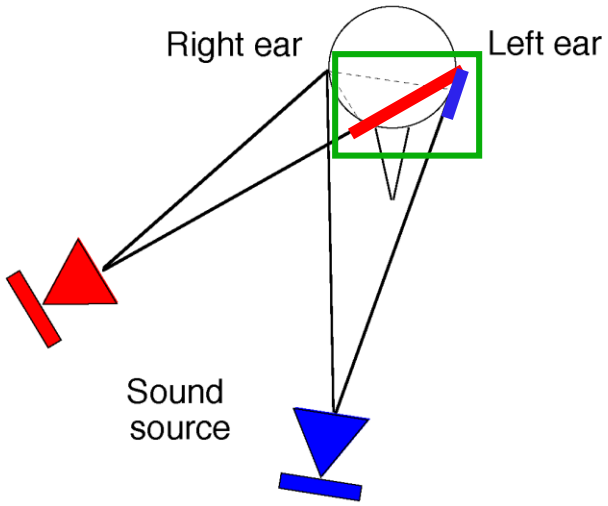
Guinea pig

Owl

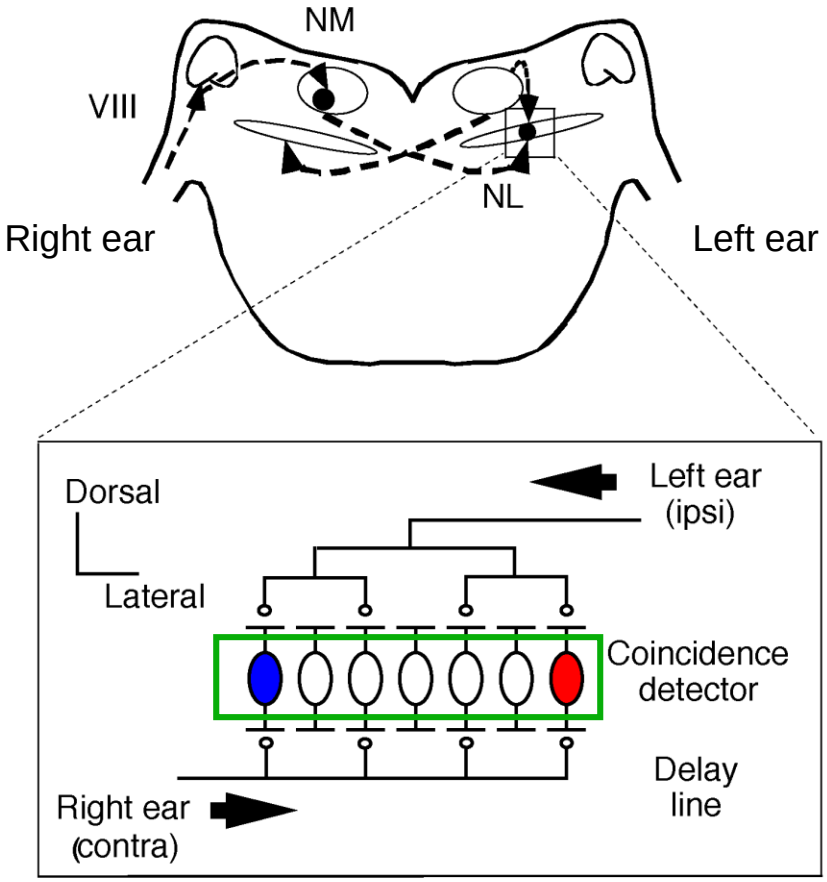


ITD detection in chick nucleus laminaris (NL)

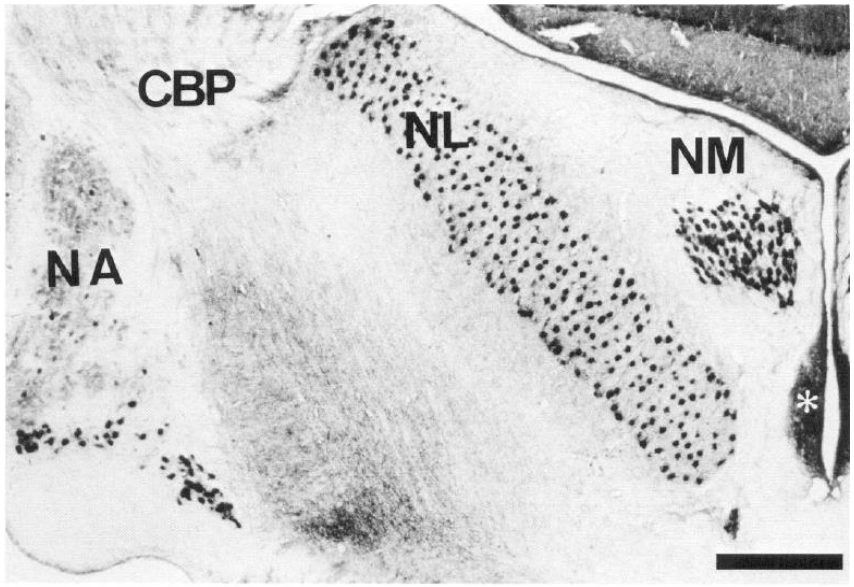
Interaural time difference (ITD)



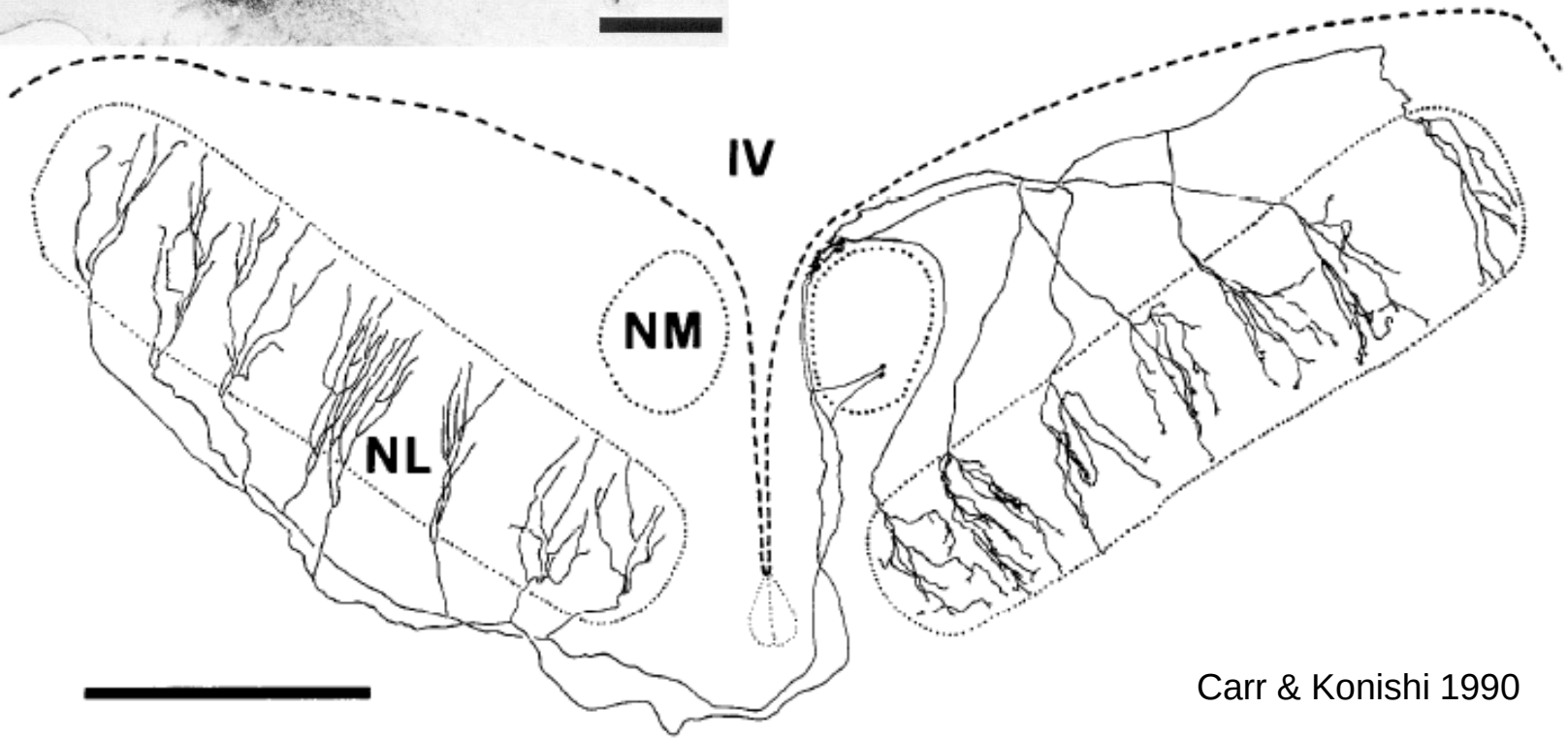
Axonal conduction delay



Jeffress model for ITD coincidence detection (1948)

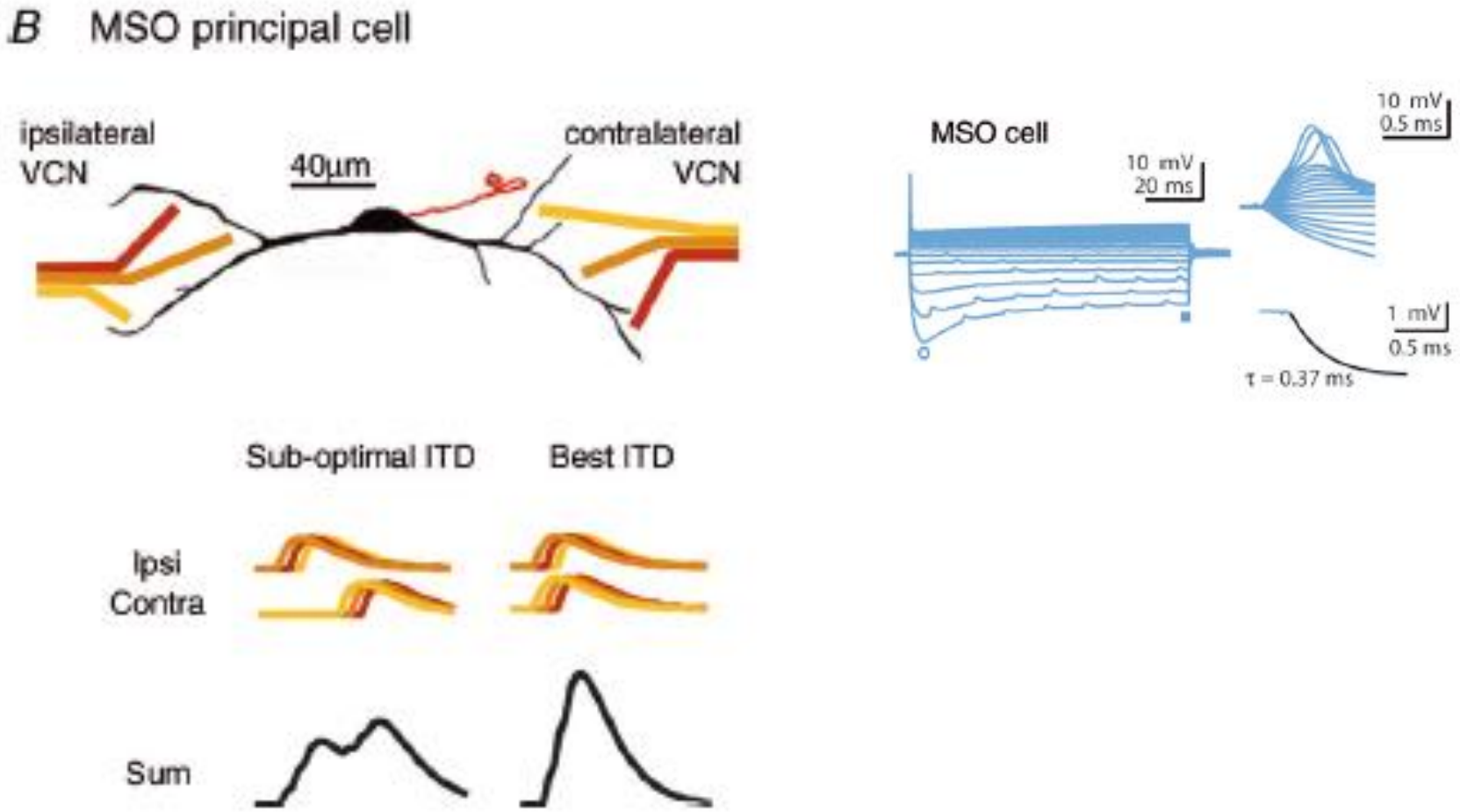


Evidence for axonal delay lines in owl.

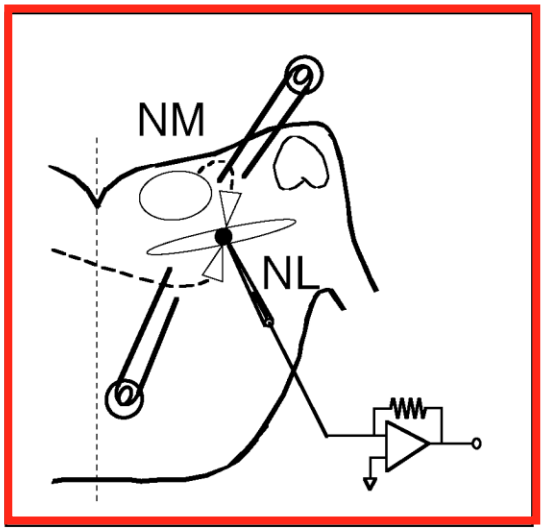


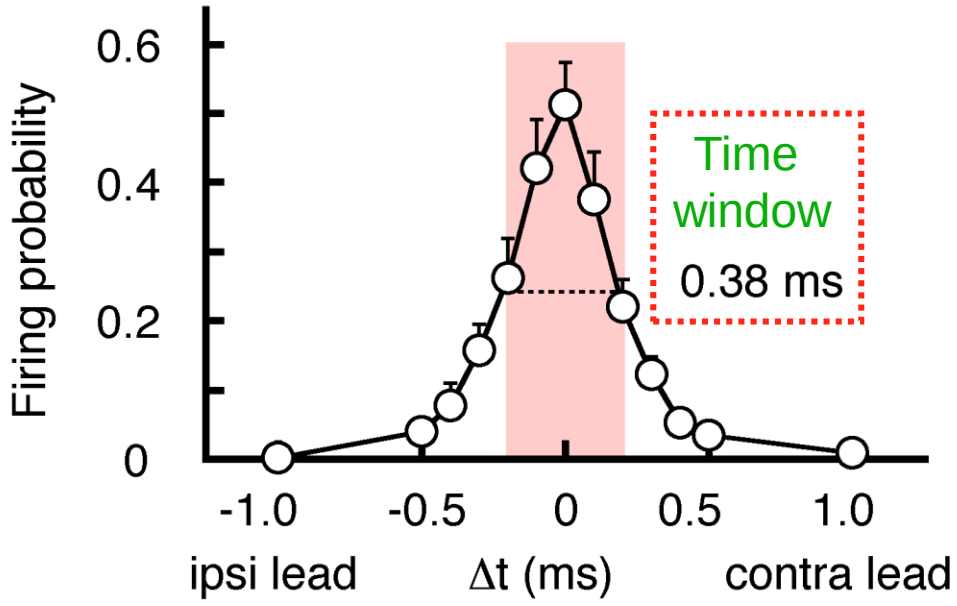
Carr & Konishi 1990

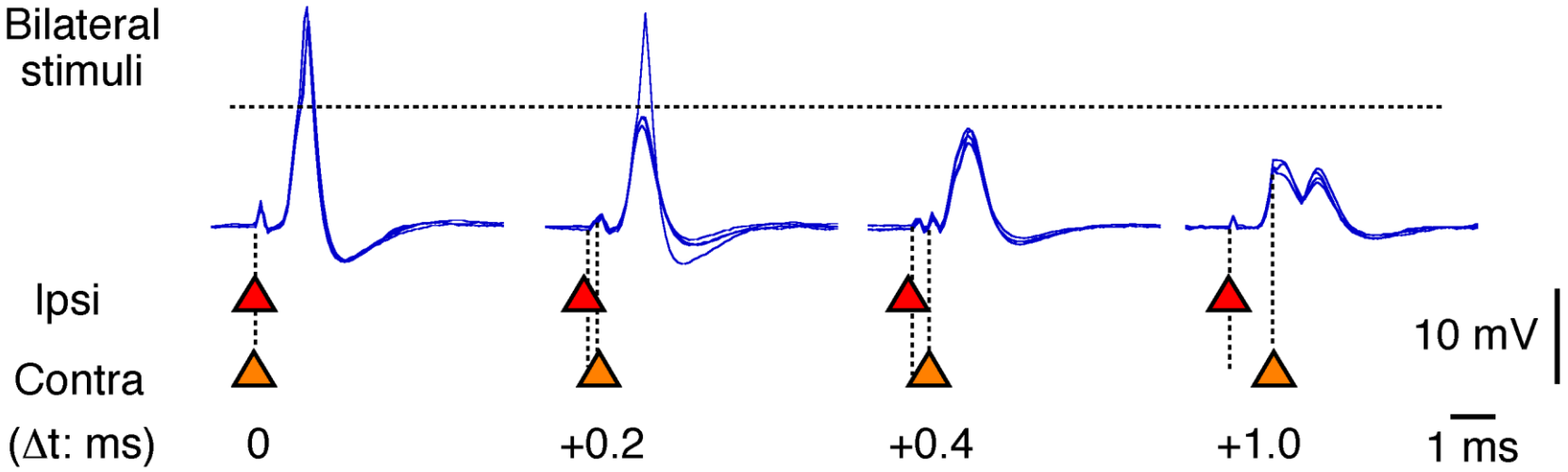
Properties of bipolar coincidence detector cells



Accurate coincidence detection in post-hatch chick (40˚C)

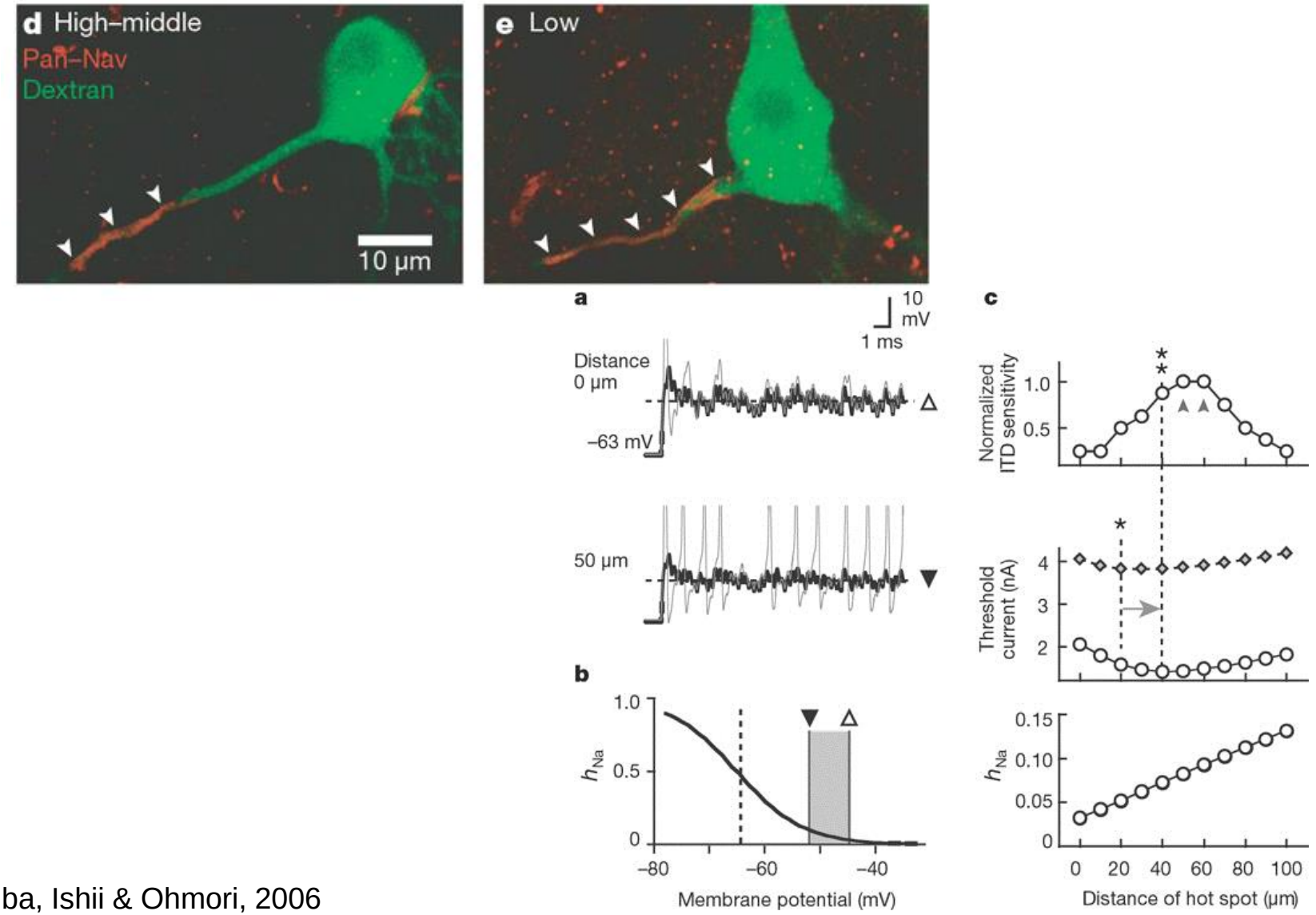






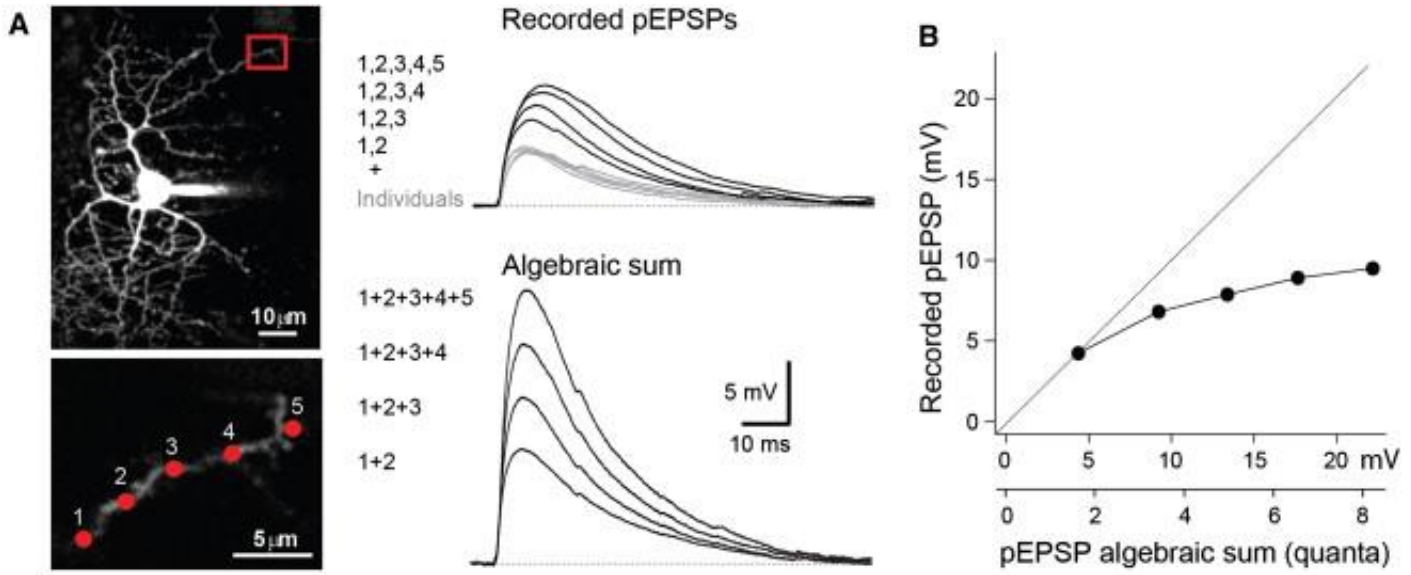
Kuba et al., 2003

It’s not just dendrites. Position of spike initiation zone in axon also contributes to proper ITD processing.

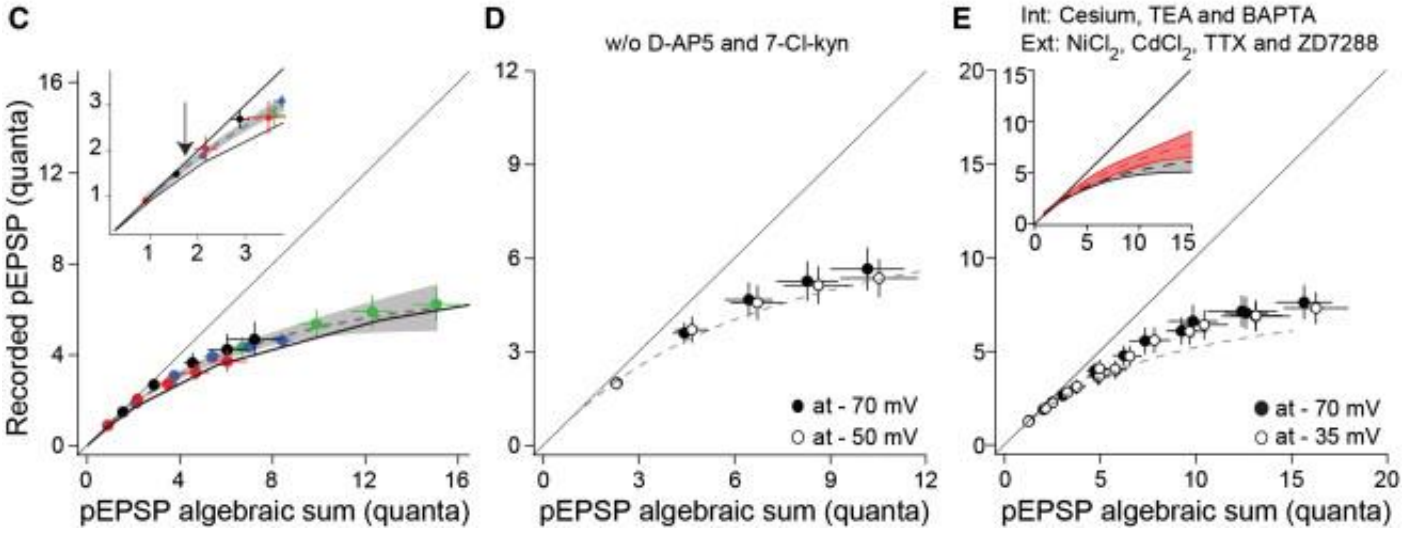


Kuba, Ishii & Ohmori, 2006

Exploit #3? Sublinear integration of neighboring inputs in cerebellar stellates.

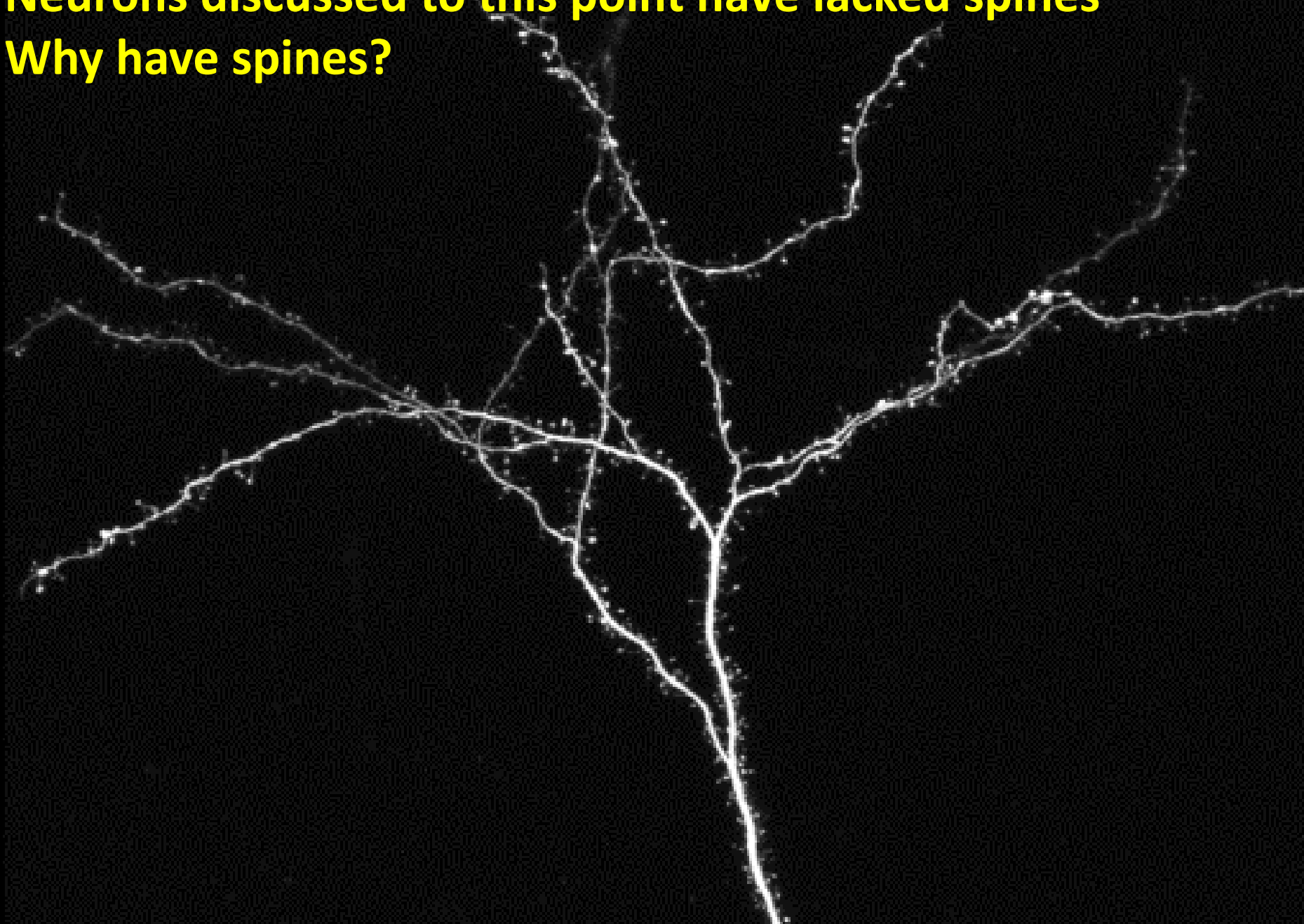


NB: r_{input} = 1 GΩ !

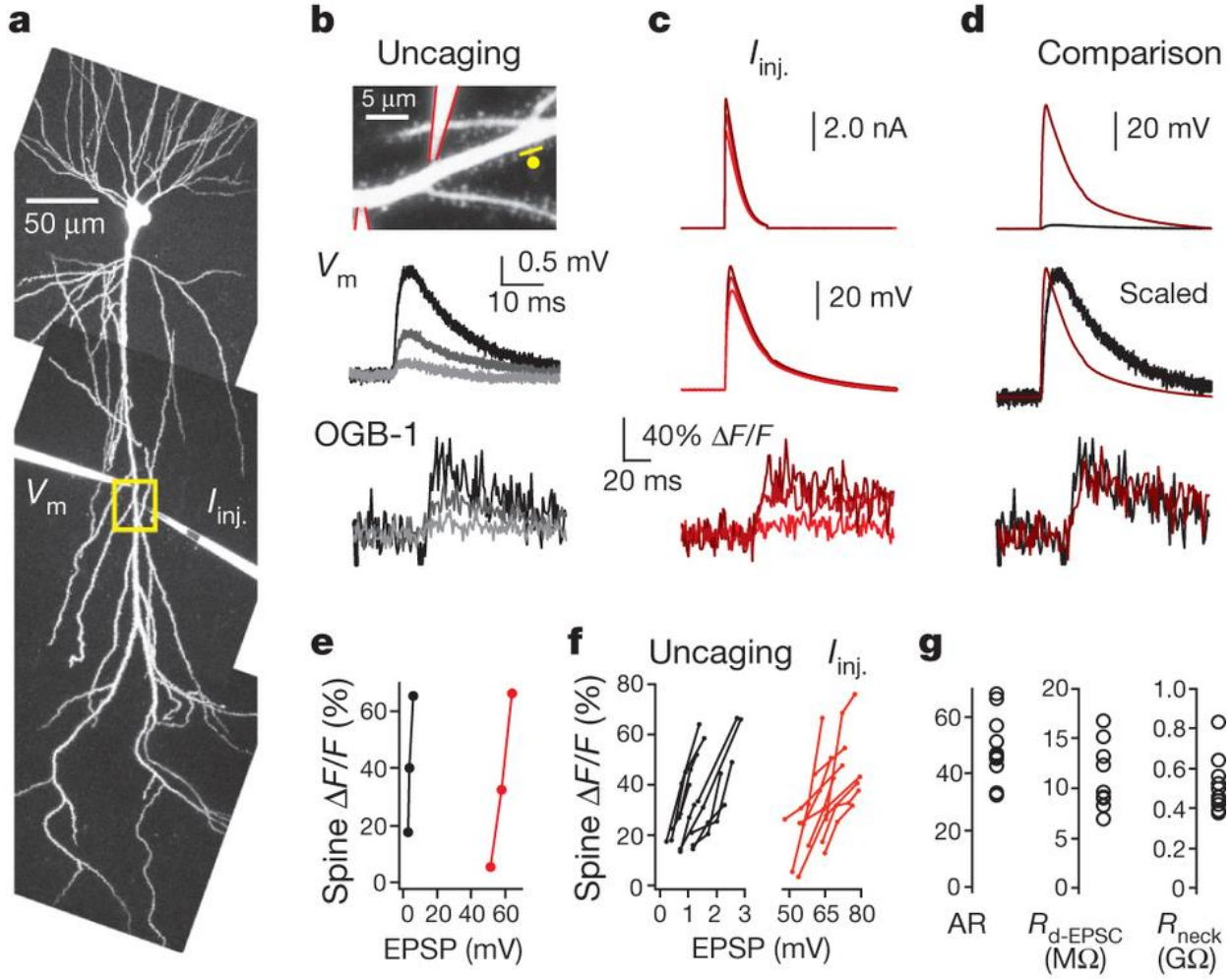


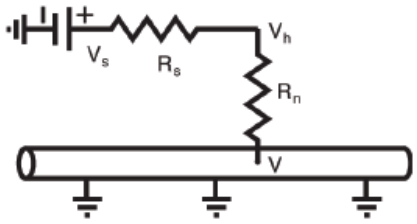
What's the implication here?

Neurons discussed to this point have lacked spines
Why have spines?



How electrically compartmentalized are spines?

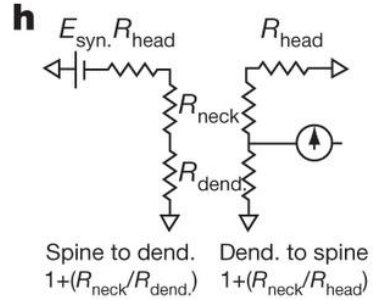




$$V_{head} = E_{syn.} \frac{R_{neck} + R_{dend.}}{1/G_{syn.} + R_{neck} + R_{dend.}}$$

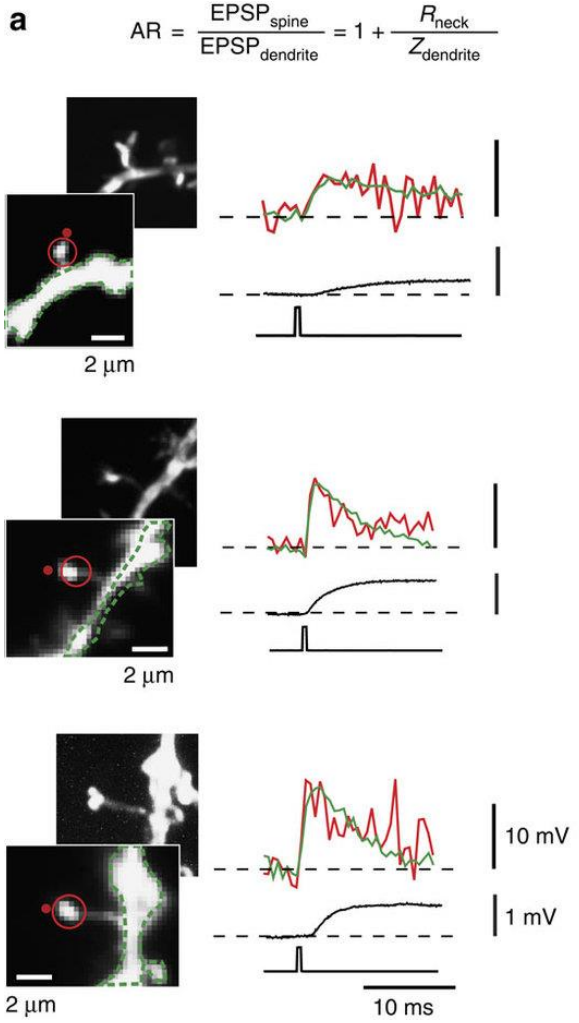
$$V_{dend.} = E_{syn.} \frac{R_{dend.}}{1/G_{syn.} + R_{neck} + R_{dend.}}$$

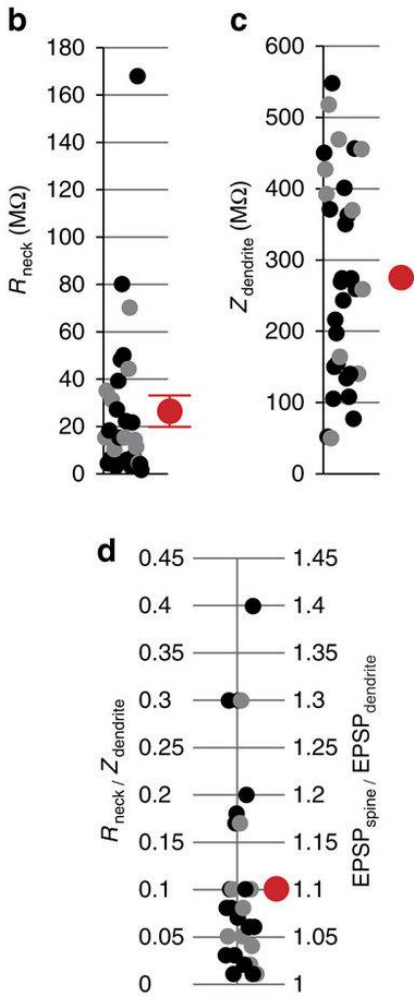
$$AR = \frac{R_{neck} + R_{dend.}}{R_{dend.}} = 1 + \frac{R_{neck}}{R_{dend.}}$$

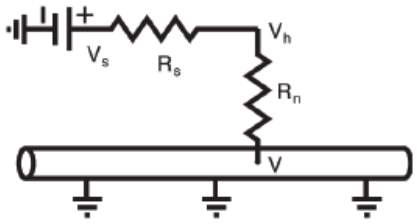


Harnett et al., 2012 In TTX and D-AP5, all Ca influx through VGCCs

How electrically compartmentalized are spines?







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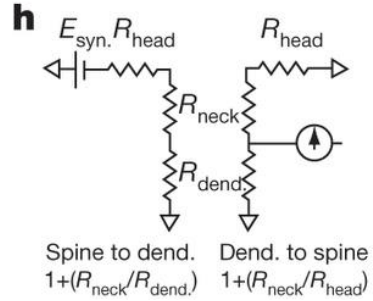
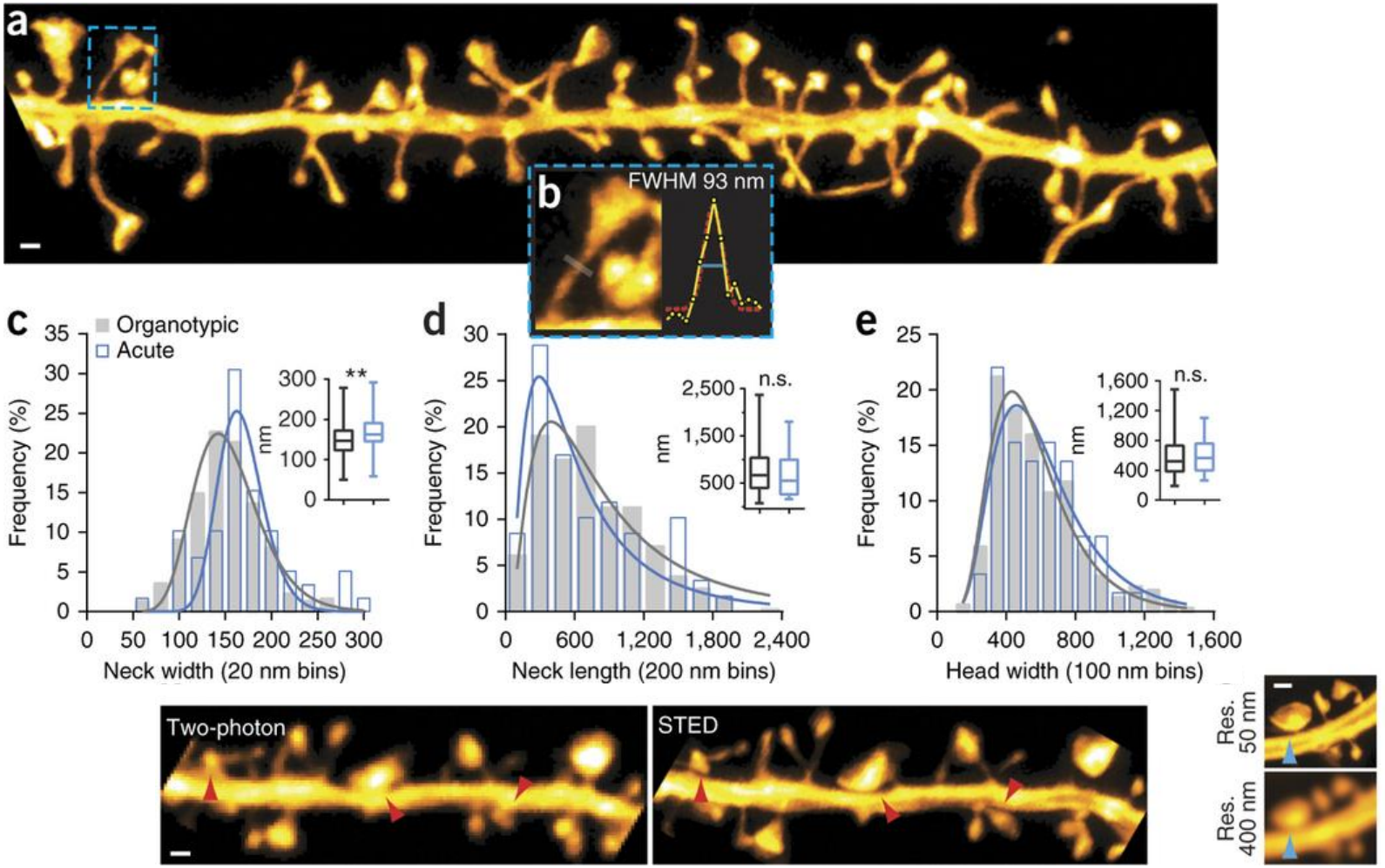


VDS have improved… why not just image the voltage in the spine?
Popovic et al., 2025

How electrically compartmentalized are spines?

wow… light microscopes have improved…



Tønnesen et al., 2014

How electrically compartmentalized are spines?
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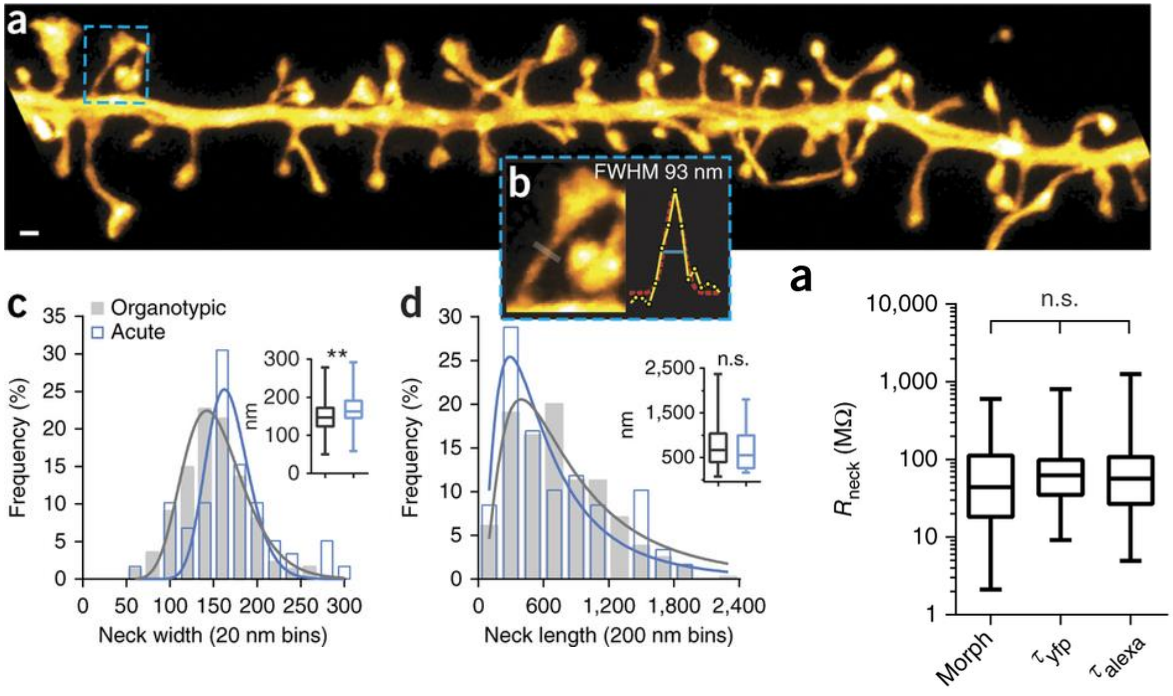
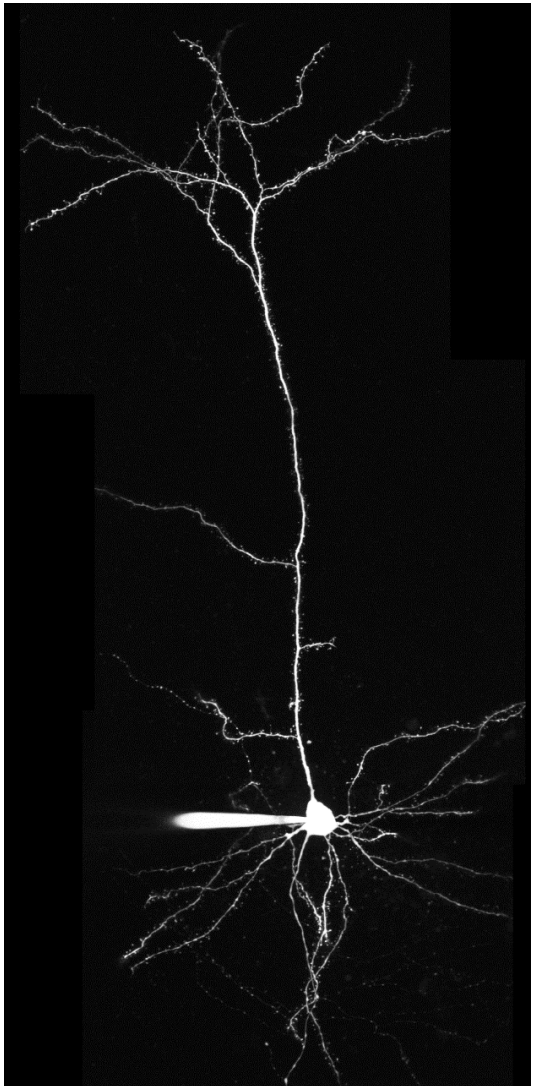
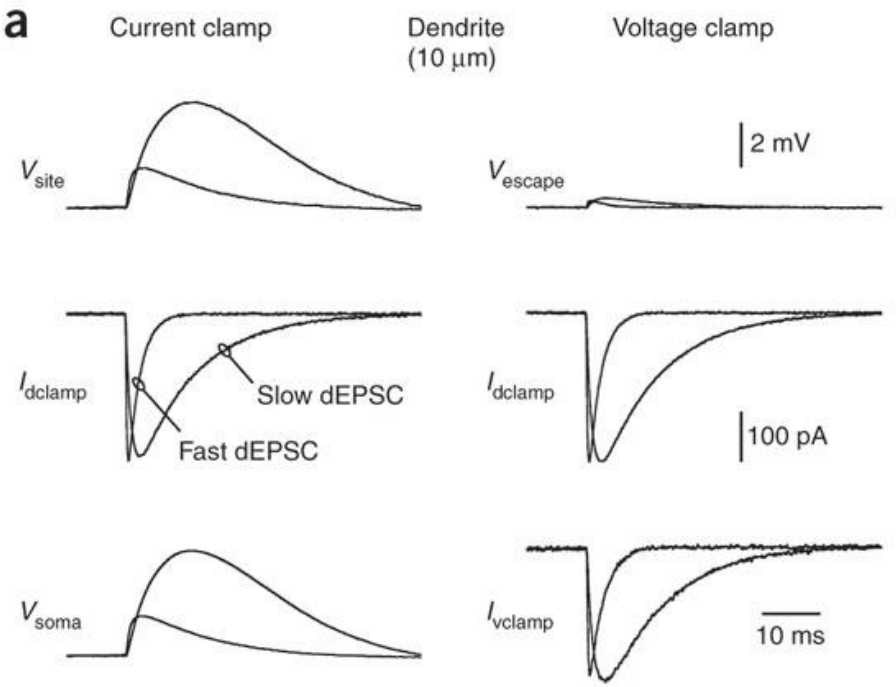


Tønnesen et al., 2014

Passive properties make voltage clamp difficult in dendritic cells
Active properties make voltage clamp a nightmare



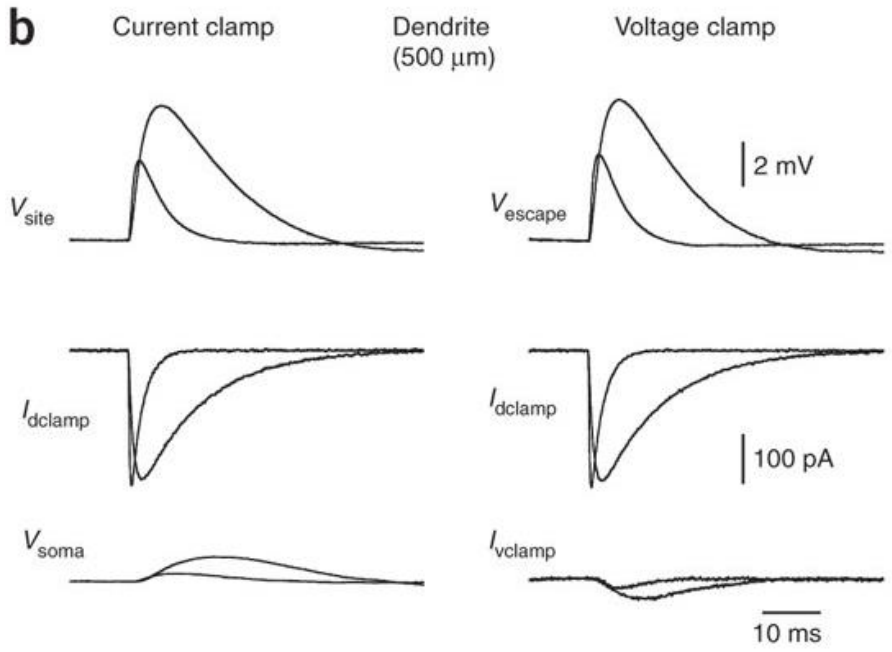
Voltage clamp is really good for local currents

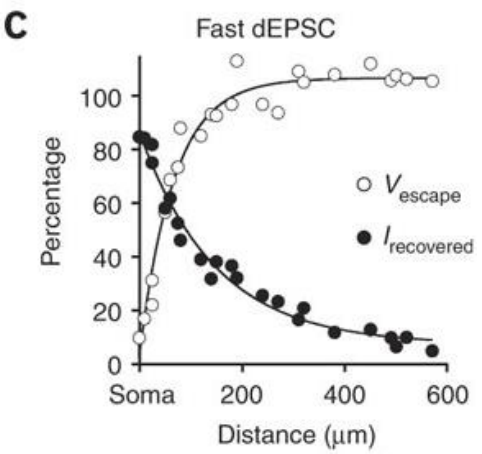


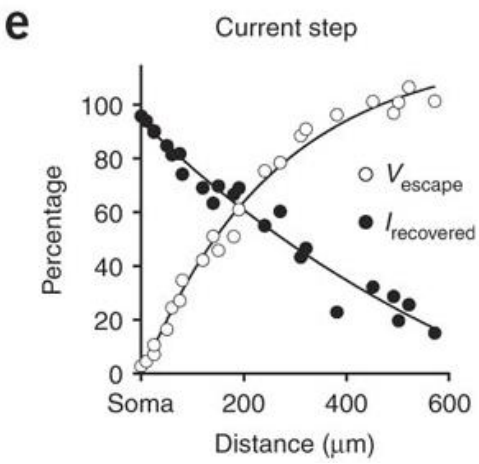
Williams &
Wozny 2008

Practical consideration for interpreting somatic voltage-clamp data

Voltage clamp is really bad for distal currents

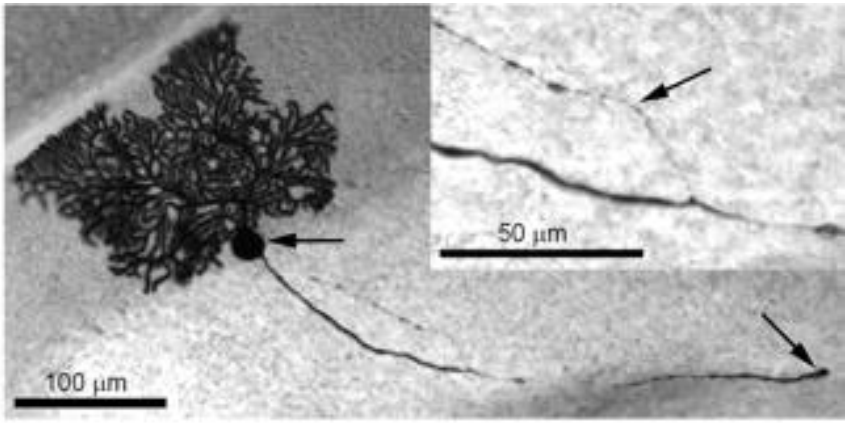


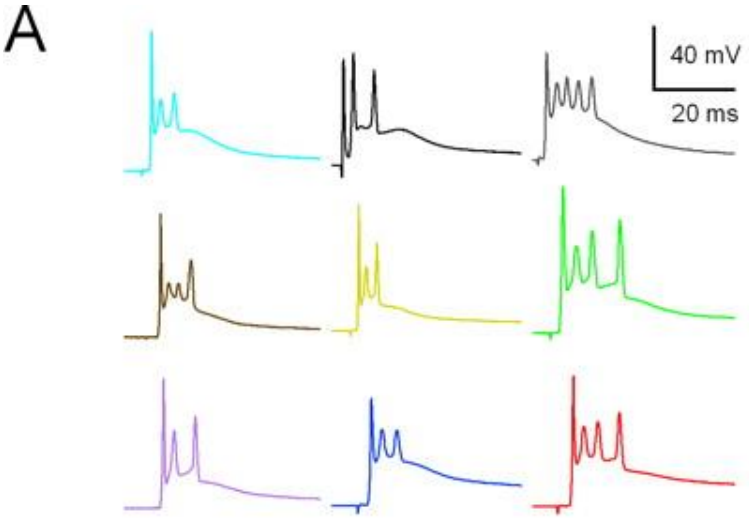


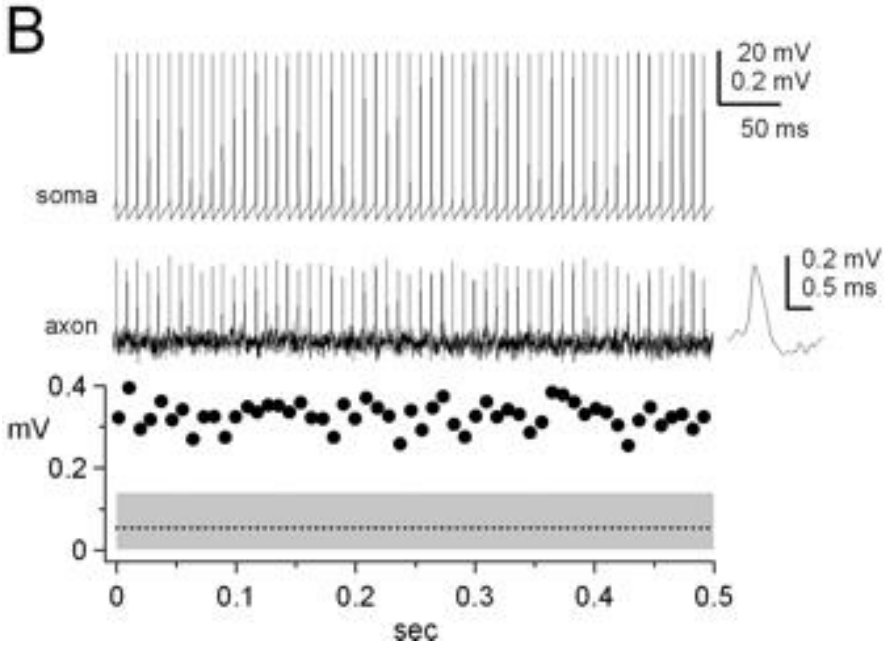


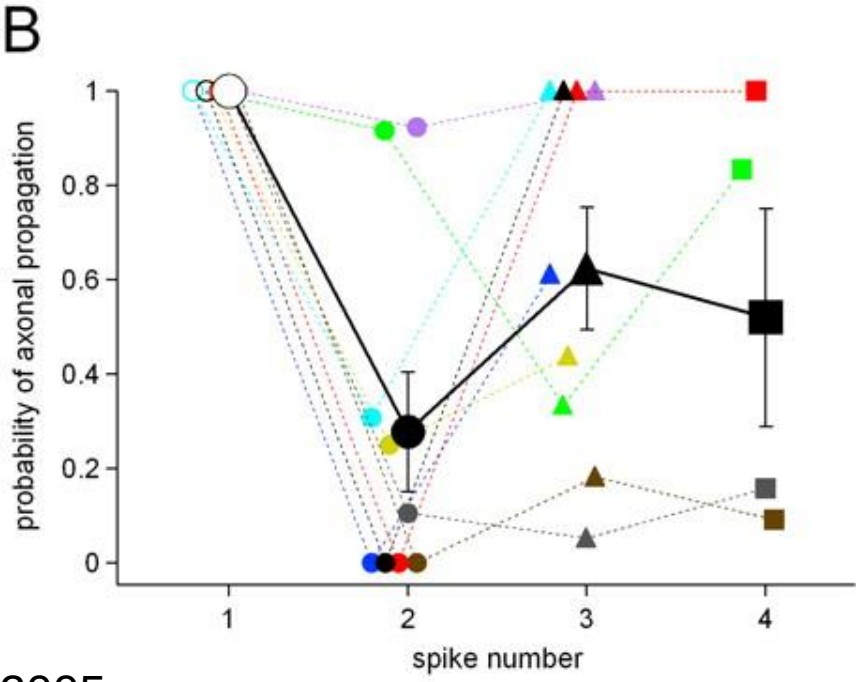
Williams & Wozny 2008

AP propagation down axon is *generally* reliable



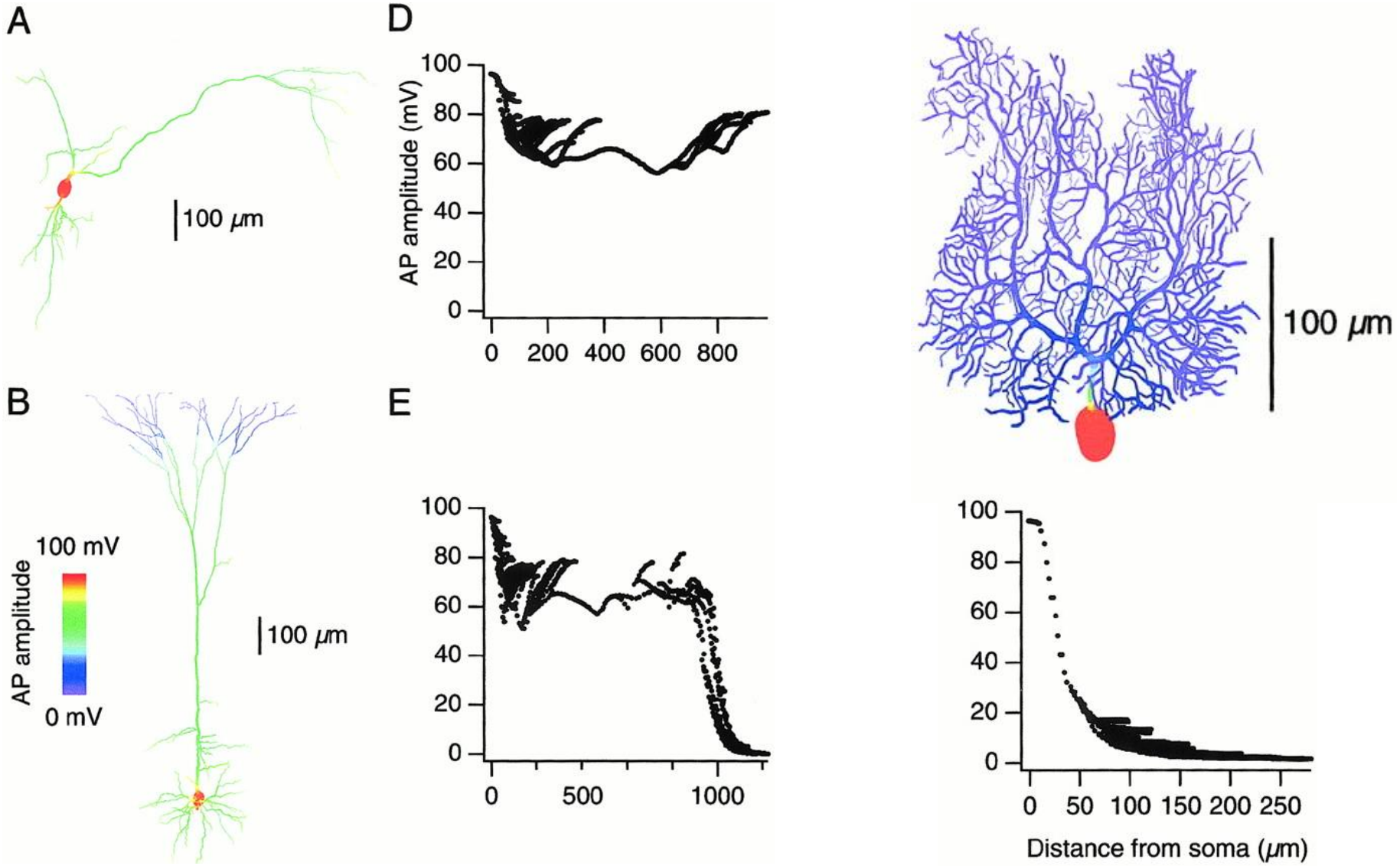






Khaliq and Raman, 2005

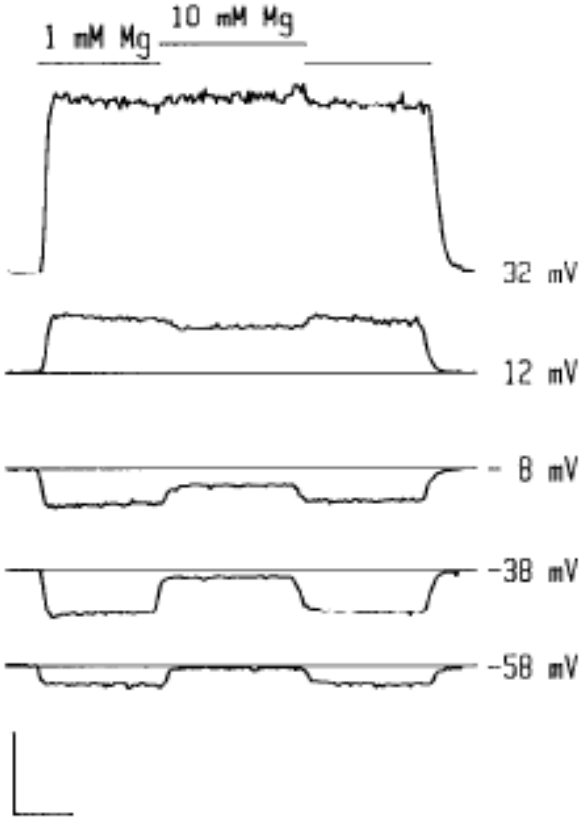
Dendritic backpropagation is quite variable

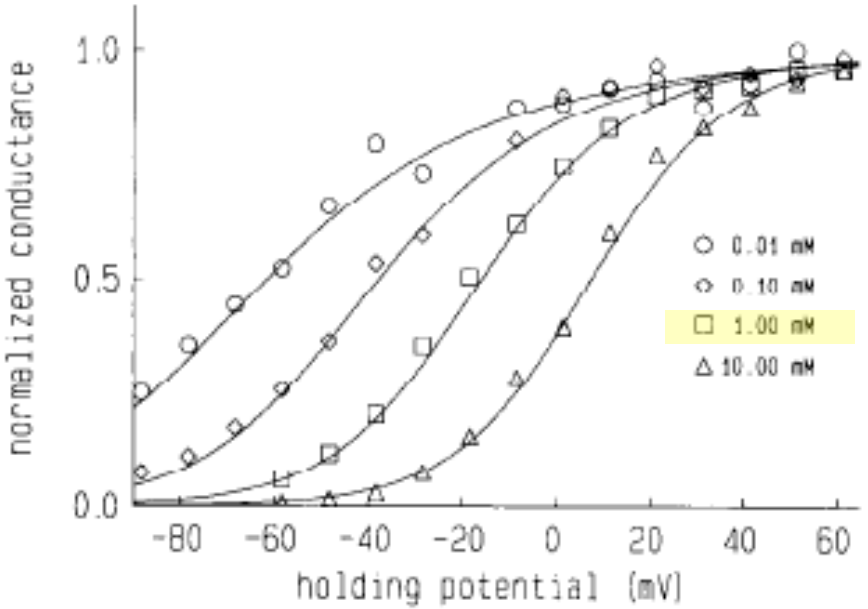


Vetter, Roth, Hausser, 2005

Now on to active properties:

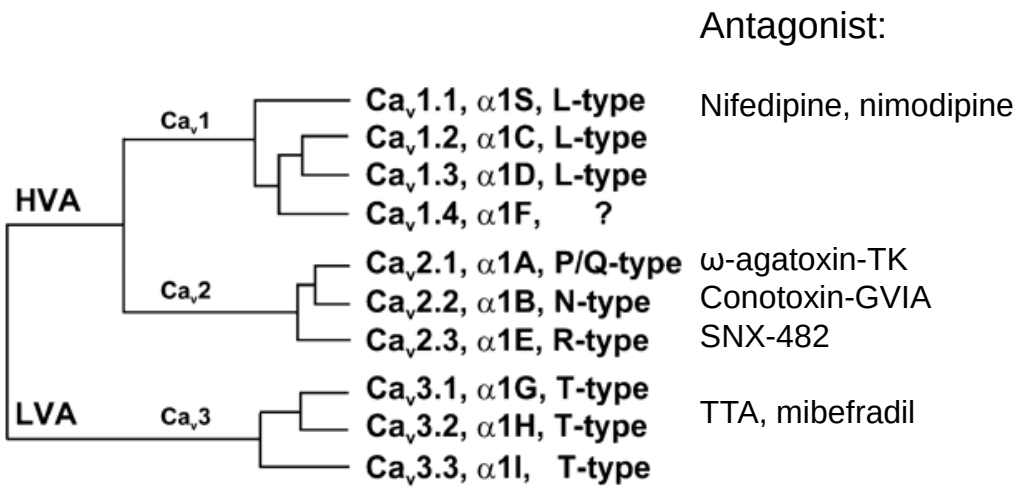
Recruitment/inactivation of channels and receptors

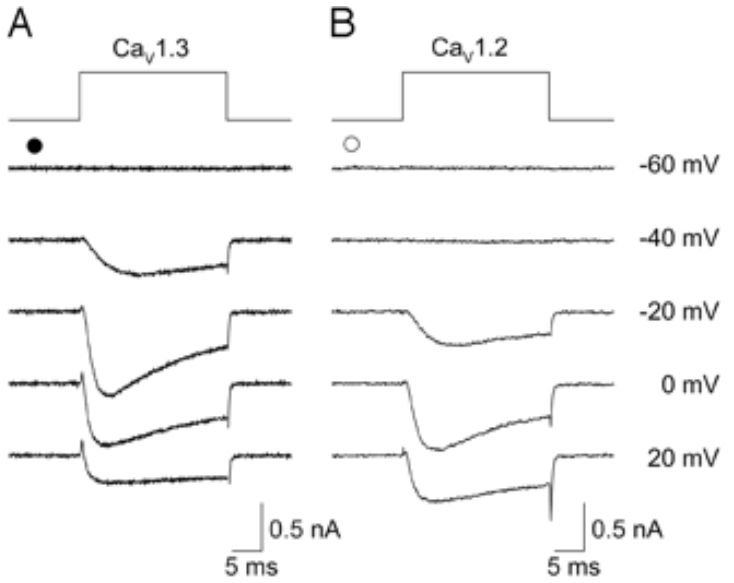




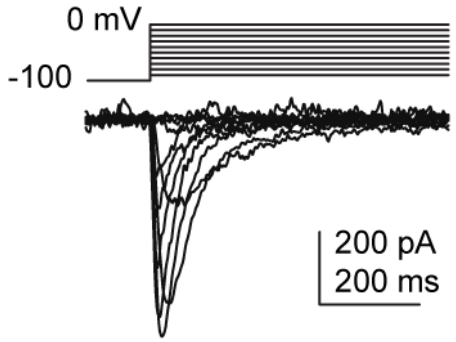
NDMAR: Jahr and Stevens,1990

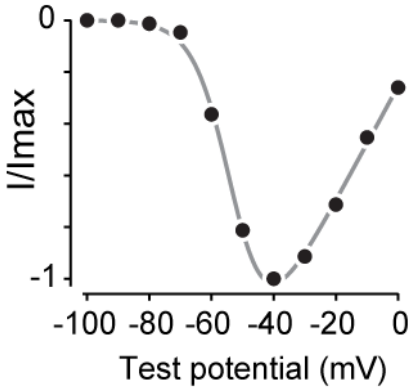
Ca^{2+} channel types respond differentially to depolarization

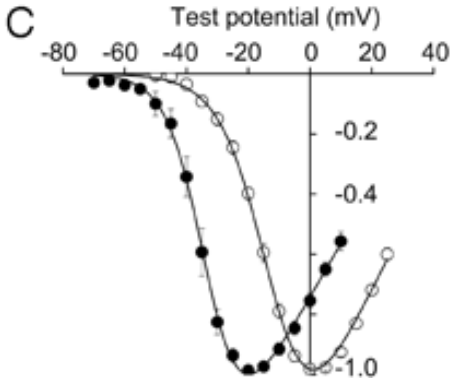




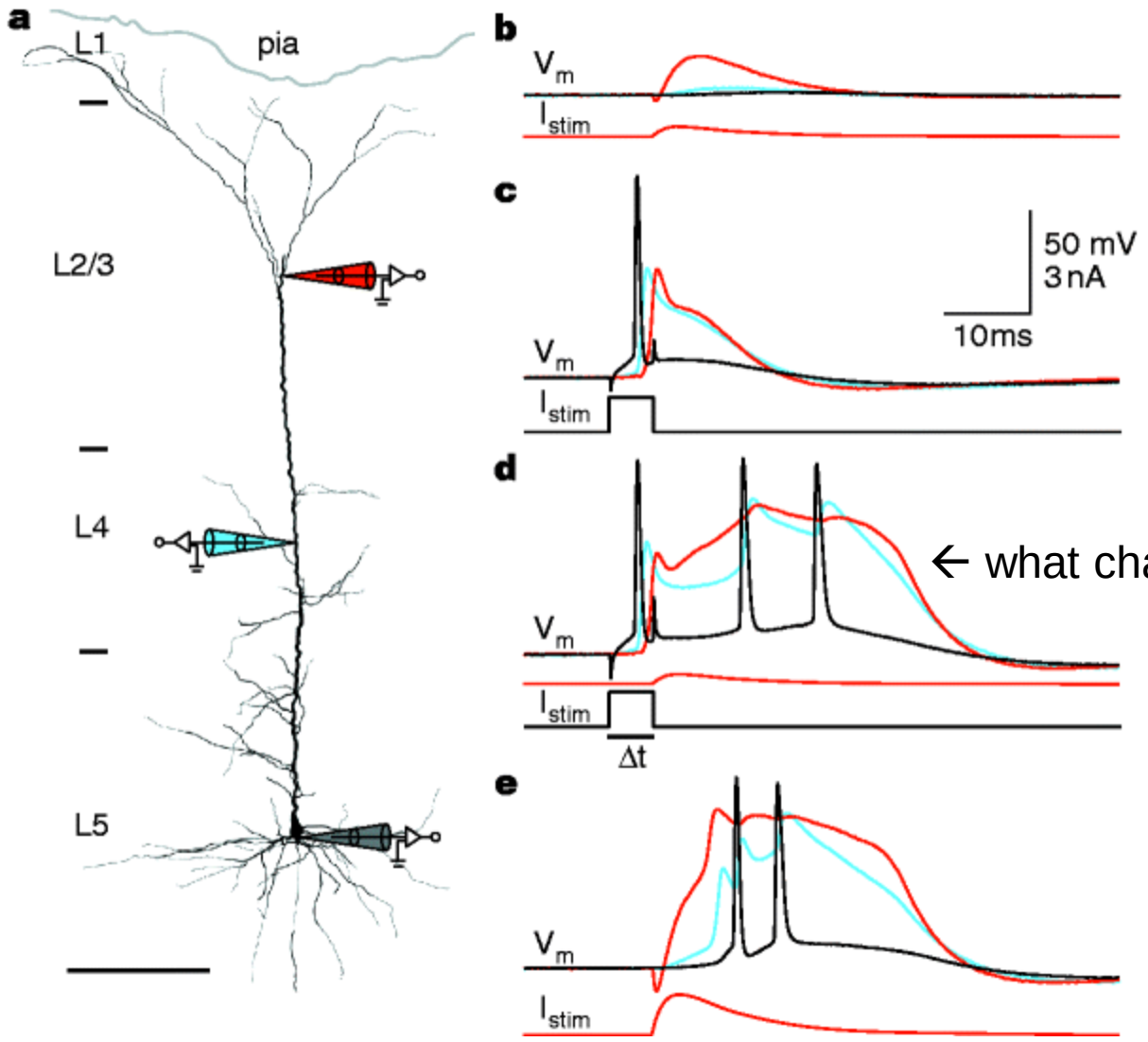
Ca$_V$3.2 (T-type)







Dendritic spike trigger zones in cortical pyramidal cells



Tuft PSP alone

bAP alone

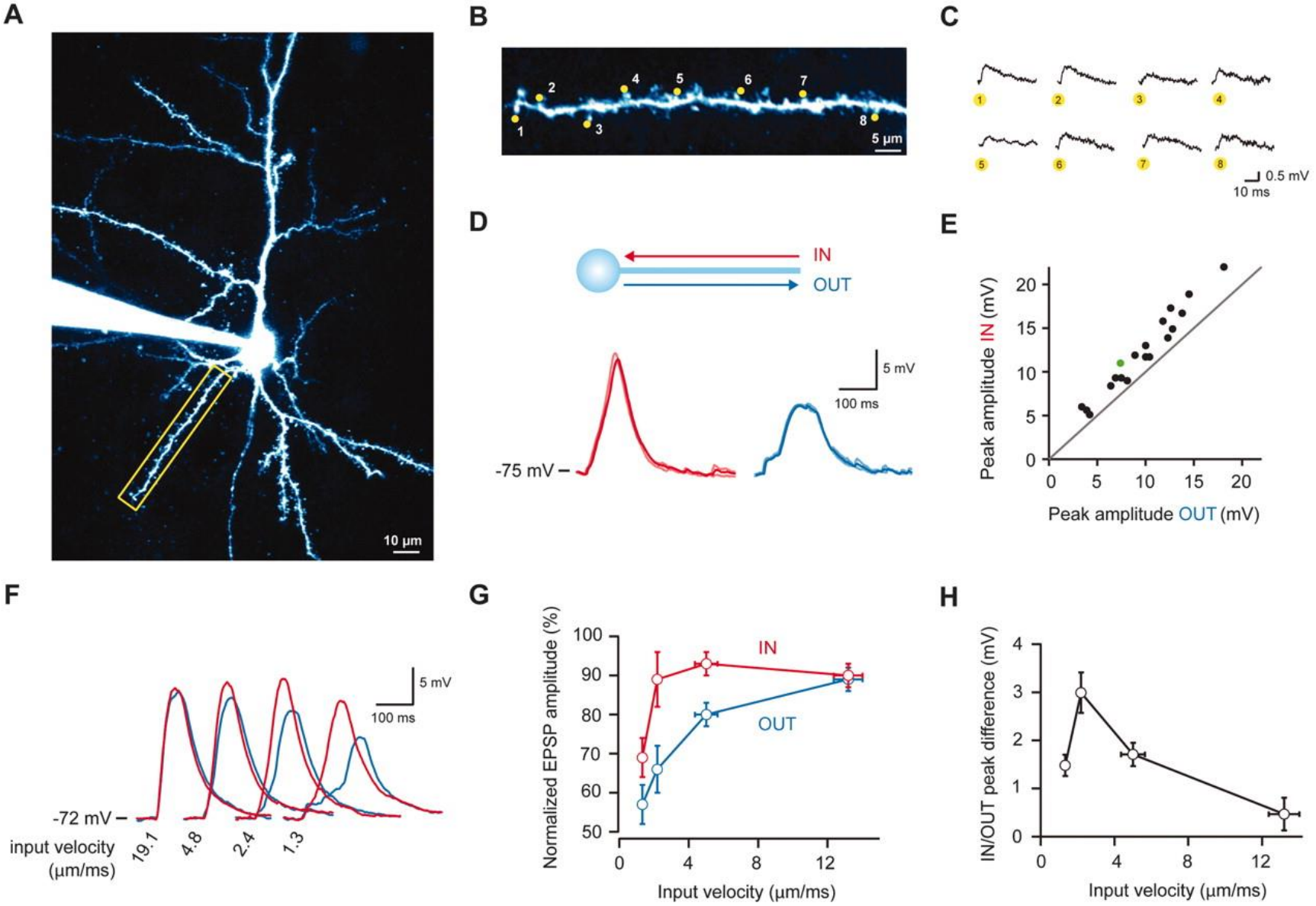
← what channels?

Pair the two

Big tuft PSP is enough
(and at times, a bAP burst)

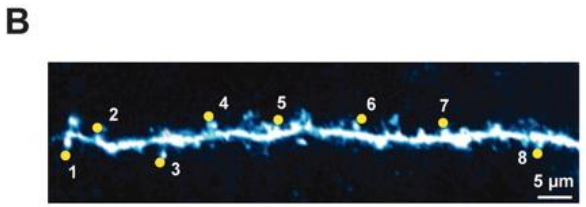
Larkum Sakmann, 1999

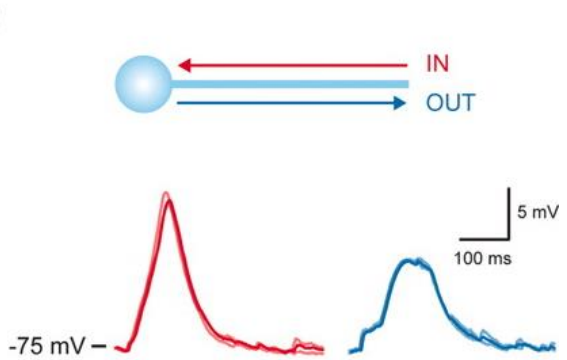
Active properties of dendritic branches

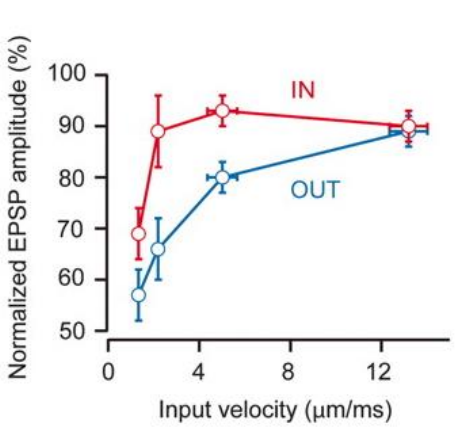


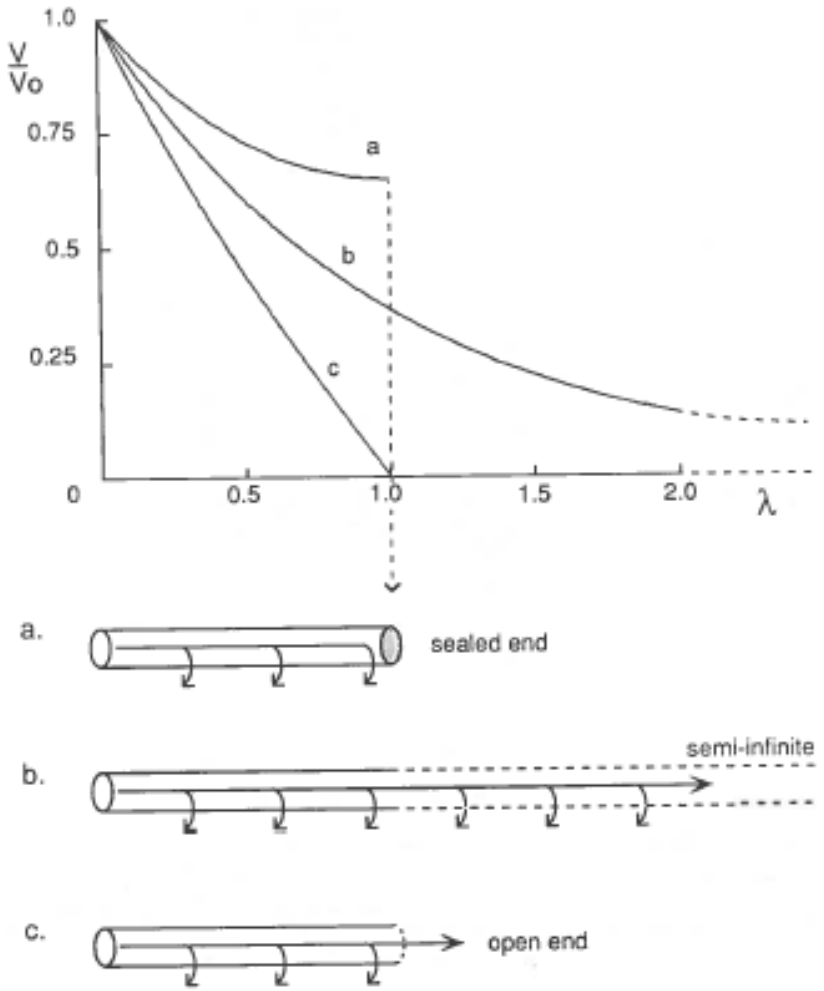
Branco Hausser 2010

Why is “in” better than “out”?



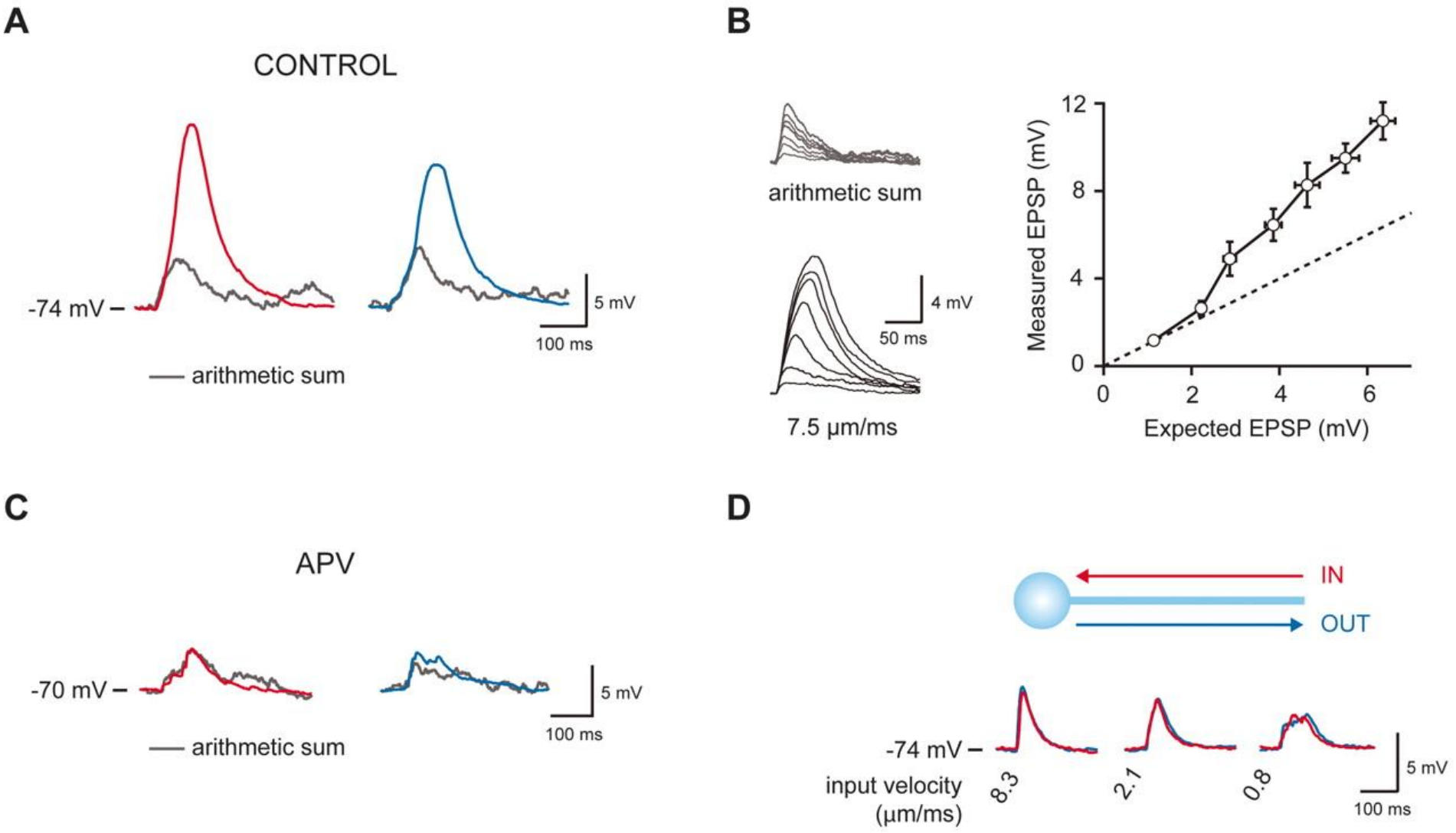






Branco Hausser 2010

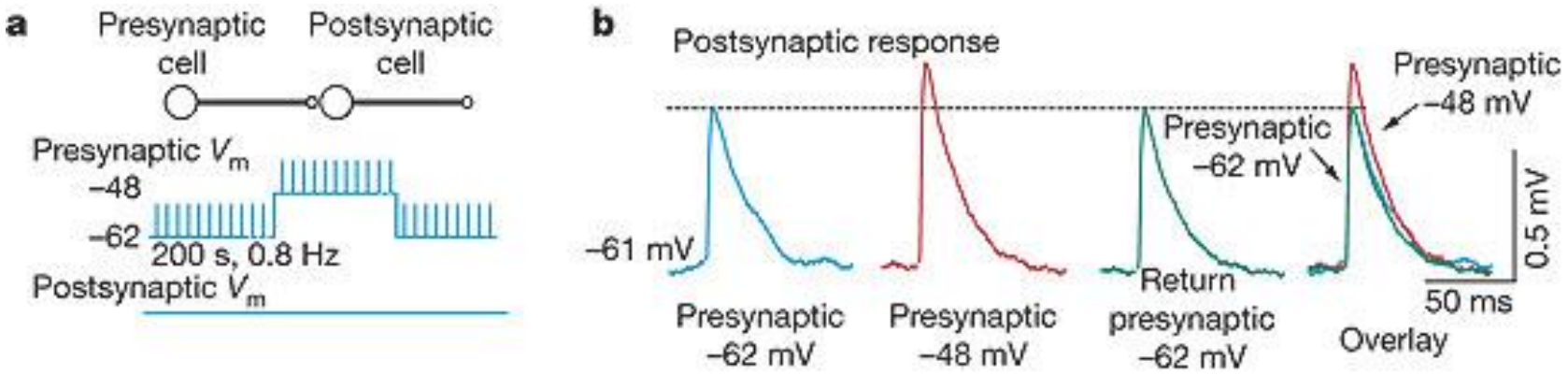
Mechanism here: boosting by NMDAR activation



what other mechanisms could support dendritic supralinearities?

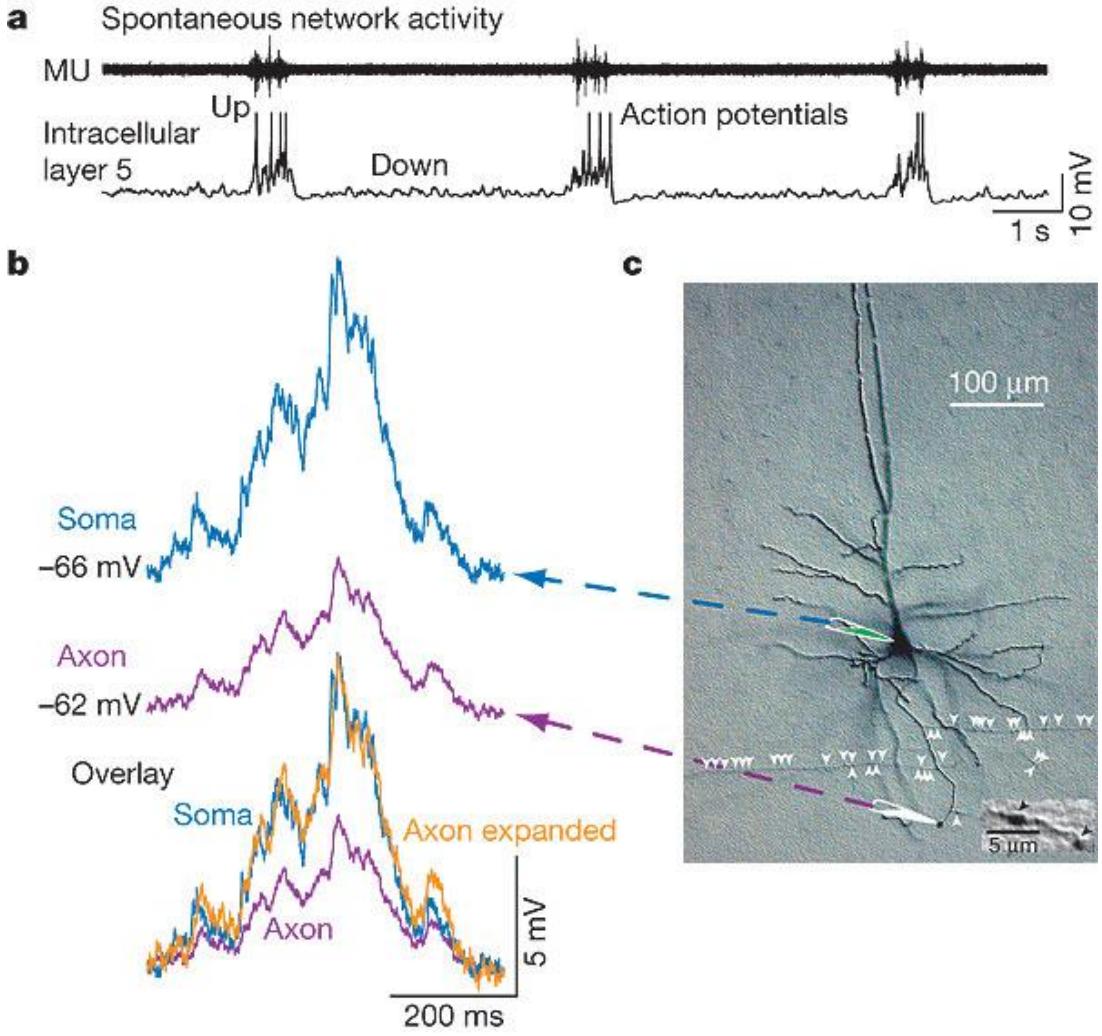
Integration in axons—

Postsynaptic EPSP amp can increase if presynaptic soma is depolarized. Why?



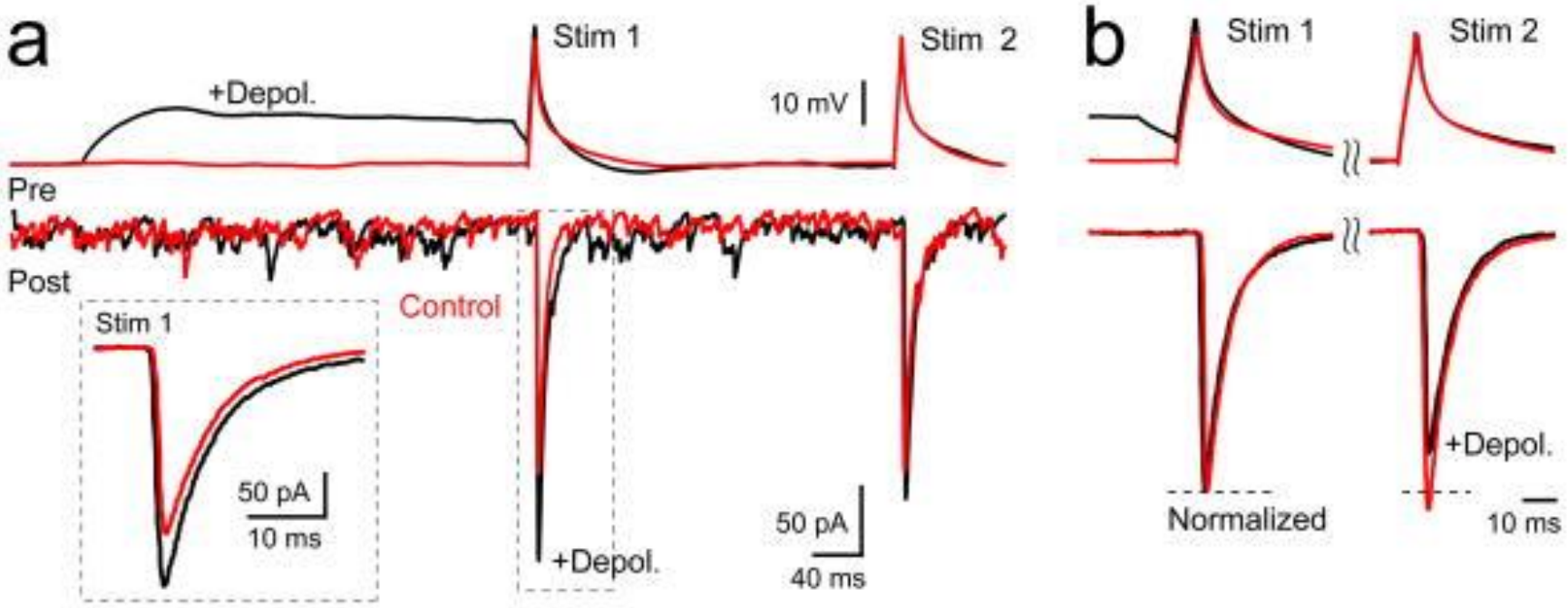
Shu, Hasenstaub, McCormick 2006

Potential mechanism #1: subthreshold depolarizations propagate down axon (aka, analog axonal signaling)



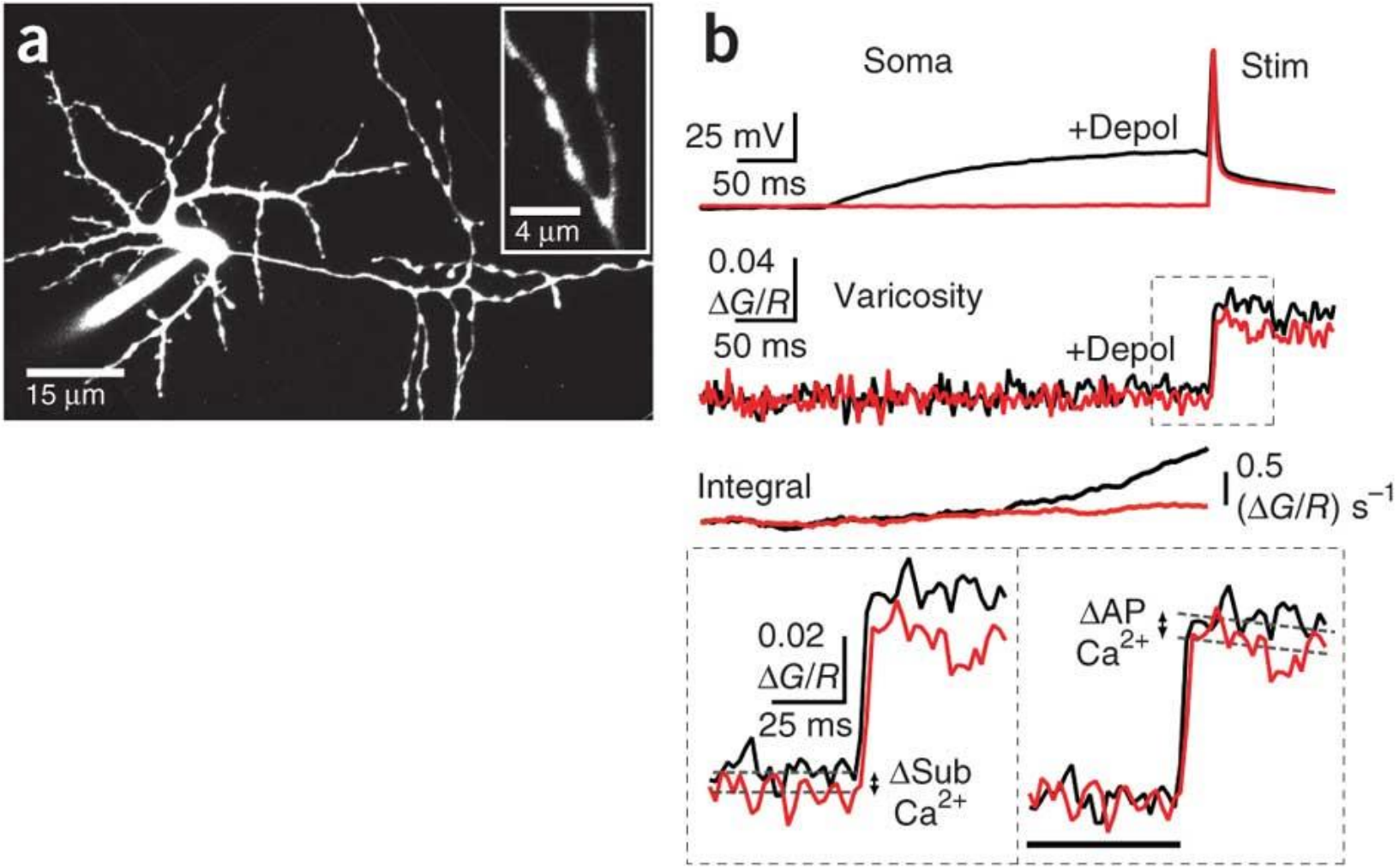
Shu, Hasenstaub, McCormick 2006

What's that depolarization doing in the axon?
1st IPSP amplitude increases, PPR decreases.



Christie Jahr 2011

Depolarizations activate VGCCs in boutons?



note that this is in 1 GOhm stellate cells.

What would you expect in leakier cells?

What about cells with much longer axons?

Christie Jahr 2011

Modulatory mechanisms that alter integration

Too many to list, really. But some are:

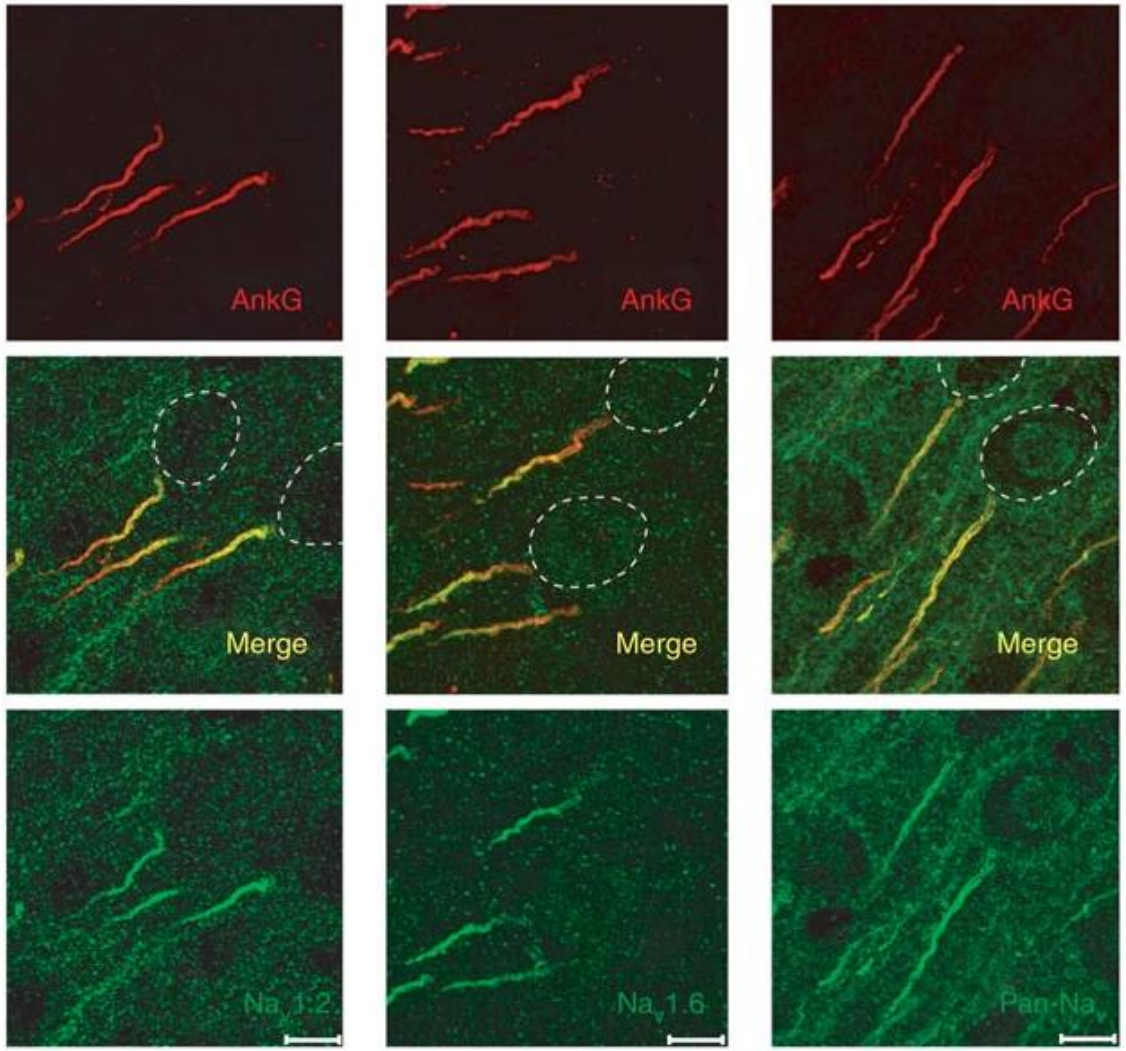
—modulation of membrane resistivity near V_{rest}
- HCN channels
- K channels

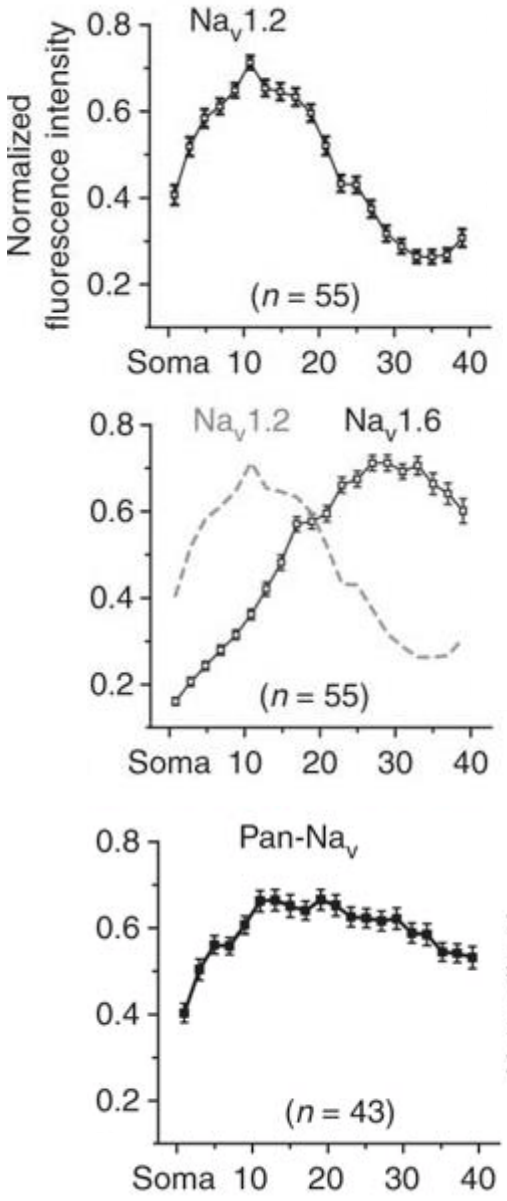
—modulation of channels that contribute to dendritic nonlinearities
- Ca channels
- K channels
- NMDA receptors

—modulation of spike initiation
- K channel inactivation in AIS
- Na channel inactivation
- “supporting” channels in AIS: KCNQ, VGCCs
- Position and length of AIS relative to soma

—modulation of plasticity (a.k.a., plasticity of plasticity: metaplasticity)

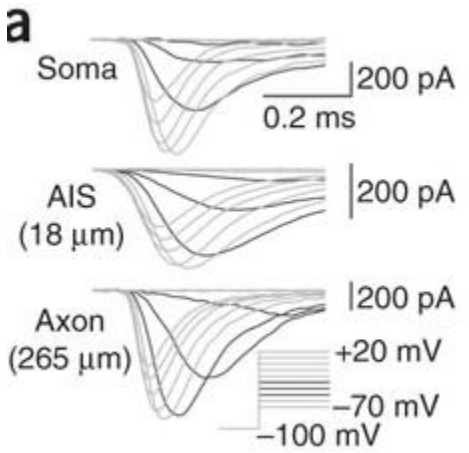
Spike initiation zone has 2 Na_V isoforms — $Na_V1.2$ proximal, 1.6 distal

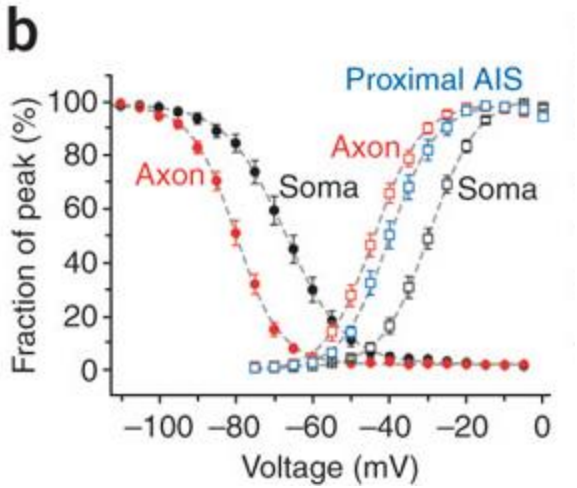


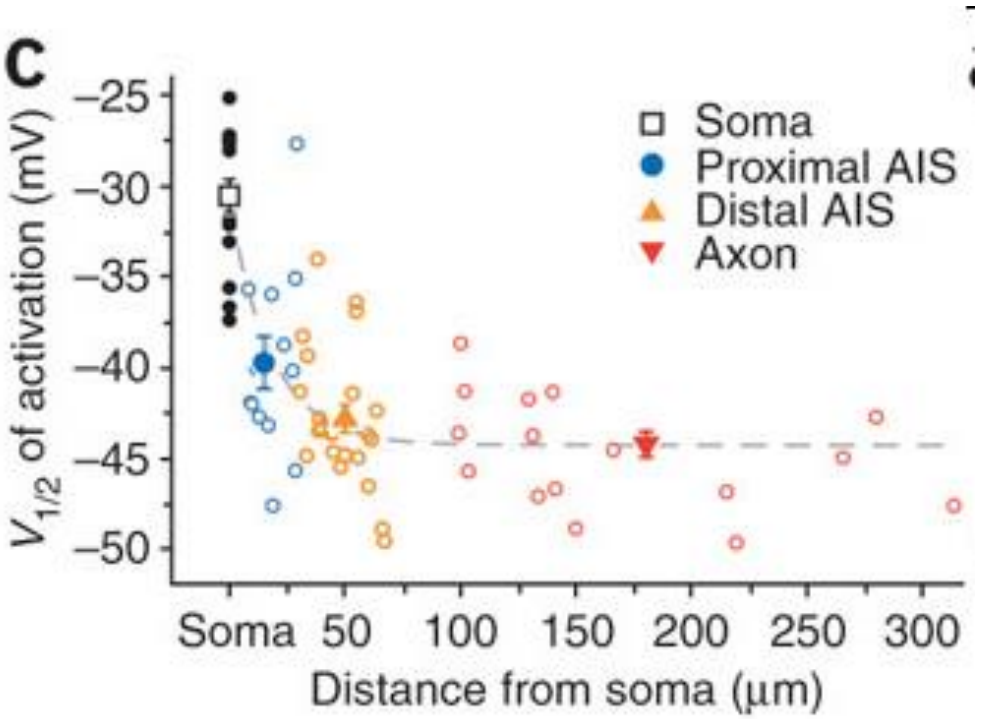


Hu Shu 2009

Na_V activation kinetics differ by location
—What does this mean for spike initiation?

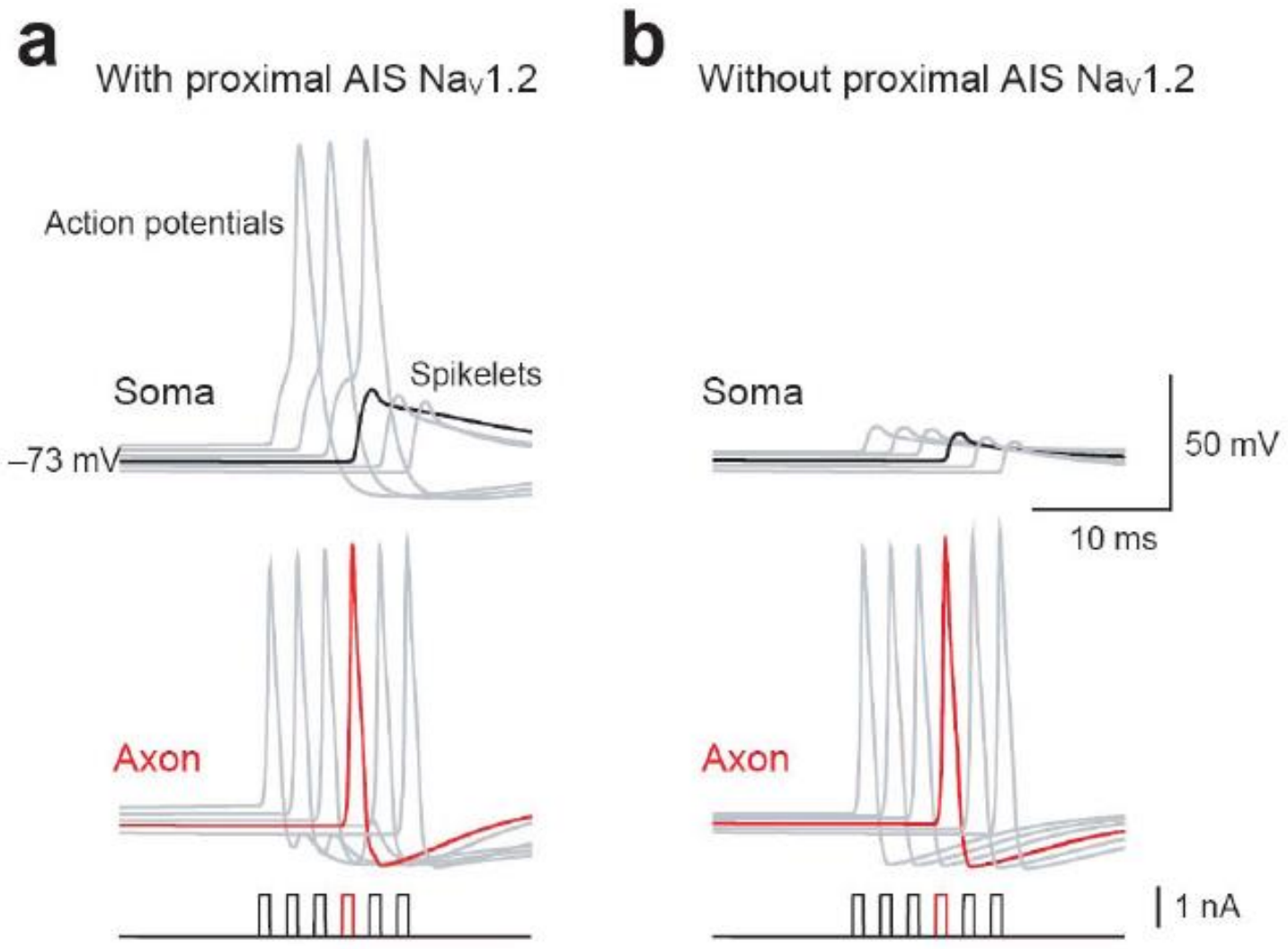






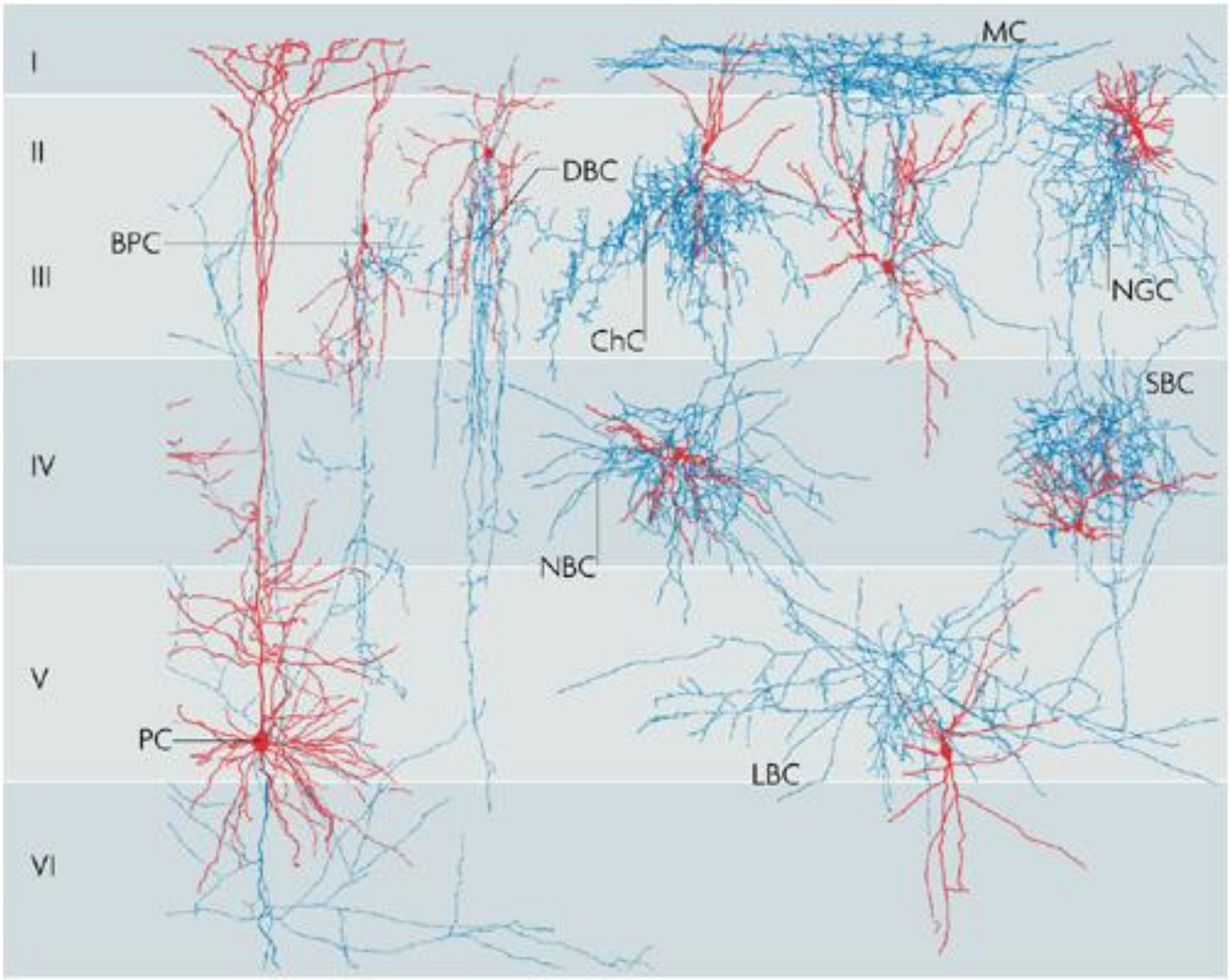
Hu Shu 2009

Remove prox 1.2's, no backpropagation



Hu Shu 2009

Integration is controlled by compartment-specific inhibition



Integration is controlled by compartment-specific inhibition