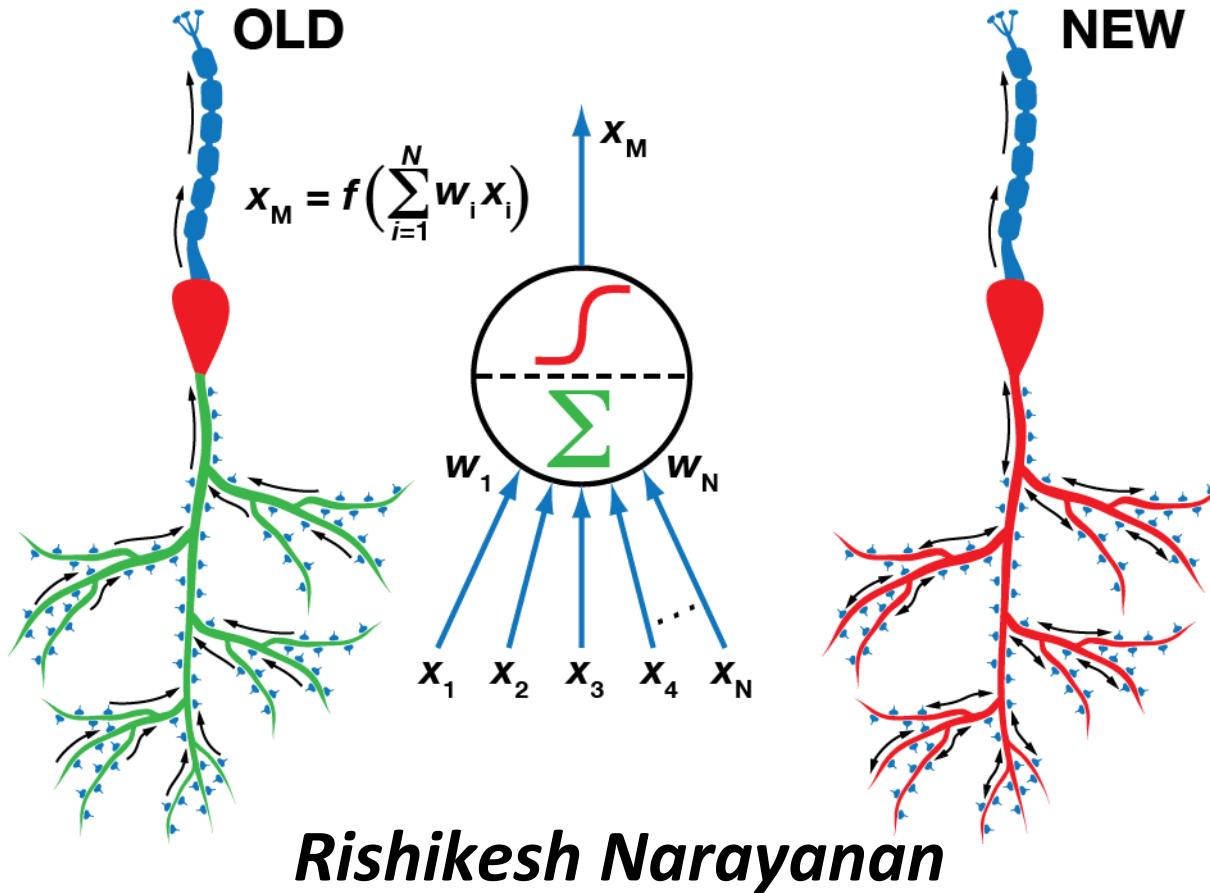


# Dendritic ion channels and intrinsic plasticity



Indian Institute of Science, Bangalore

July 7, 2016: Computational Approaches to Memory and Plasticity  
National Centre for Biological Sciences, Bangalore

# Is LTP Memory?

Neuron, Vol. 20, 1–2, January, 1998, Copyright ©1998 by Cell Press

## A Million Dollar Question: Does LTP = Memory?

### Ubiquitous Plasticity and Memory Storage

Charles F. Stevens

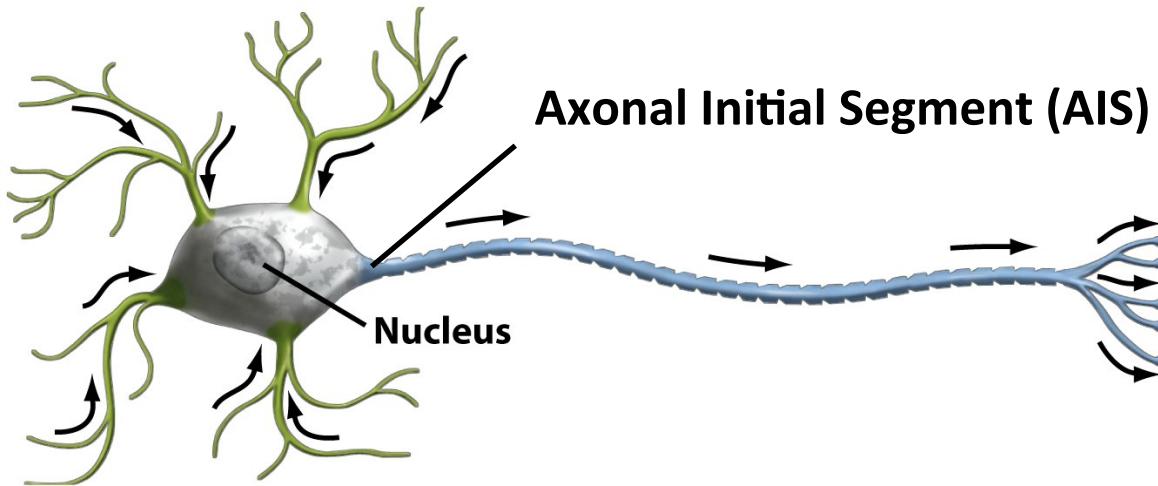
Sang Jeong Kim<sup>1,\*</sup> and David J. Linden<sup>2,\*</sup>

Neuron 56, November 21, 2007

If an extraterrestrial neuroscientist managed to obtain a badge and abstract book and attend the Society for Neuroscience annual meeting, she could be forgiven for concluding that humans believe that memory storage is solely accomplished through LTP/LTD of fast (ionotropic) neurotransmission at excitatory, glutamatergic synapses. Indeed, the vast majority of presentations would support this conclusion.

# Law of dynamic polarization

Proposed by Santiago Ramón y Cajal for how a neuron processes information



**Dendrites**  
Collect electrical signals

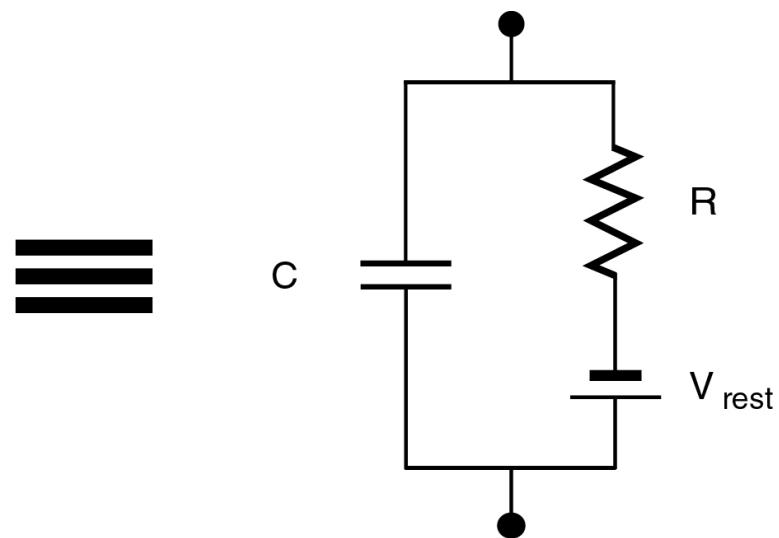
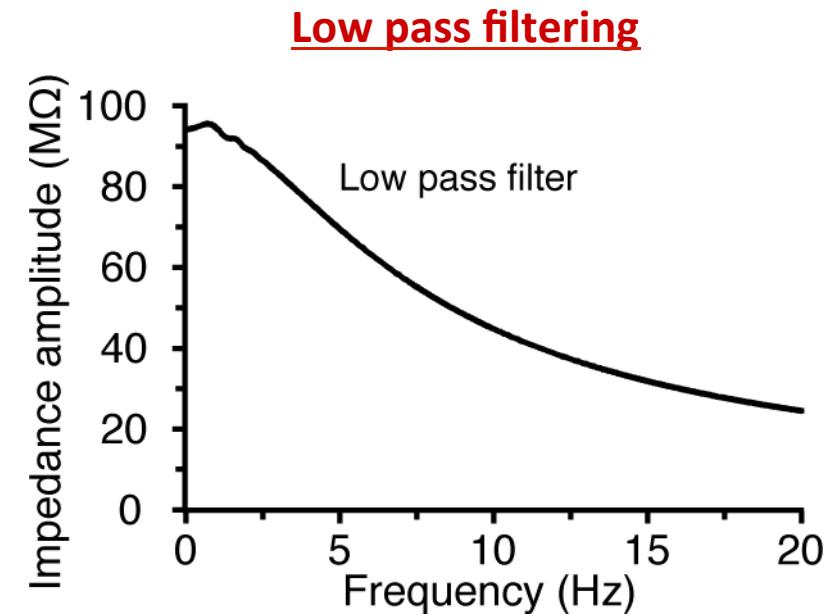
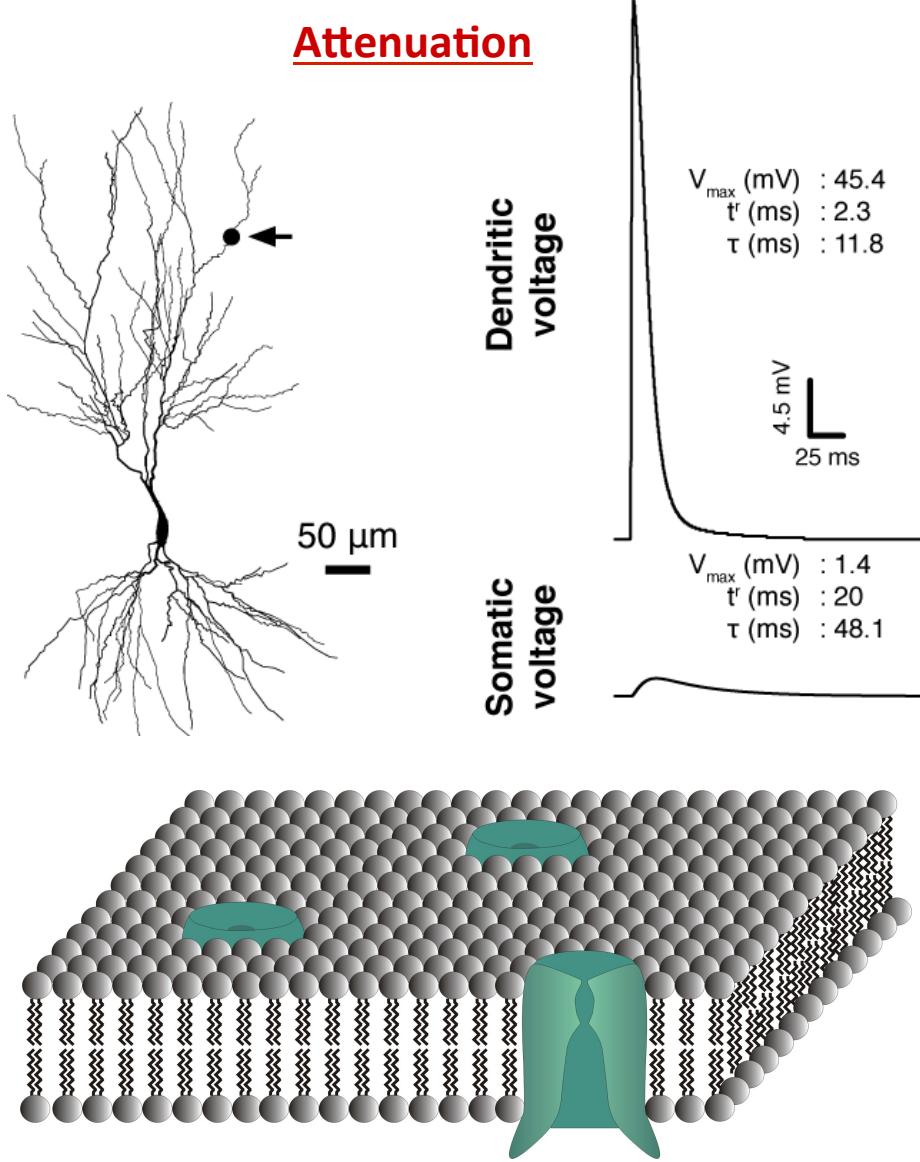
**Cell body**  
Integrates incoming signals and generates outgoing signal to axon

**Axon**  
Passes electrical signals to dendrites of another cell or to an effector cell

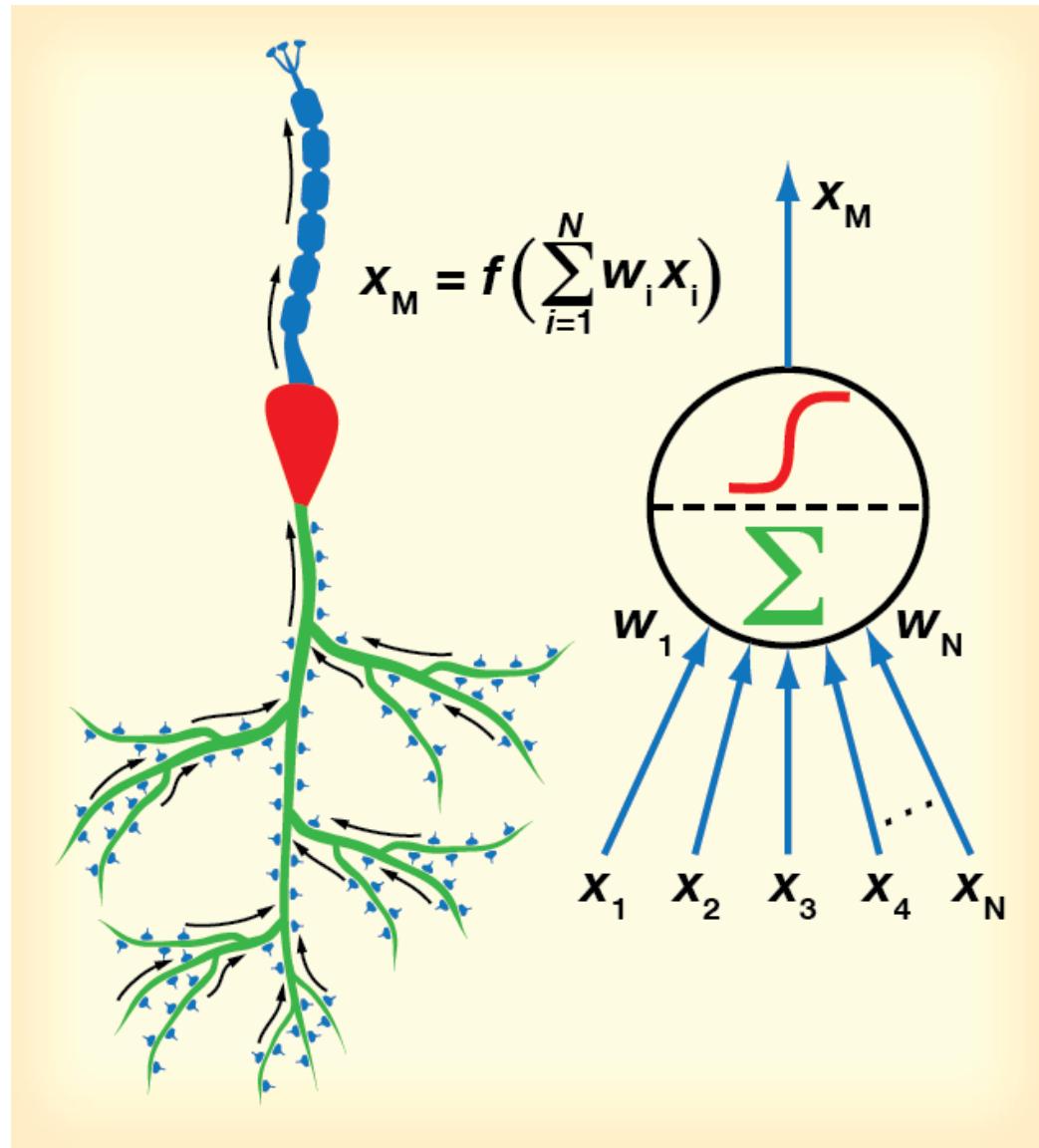
Figure 45-2b Biological Science, 2/e  
© 2005 Pearson Prentice Hall, Inc.



# Law of dynamic polarization: integrate and fire neurons



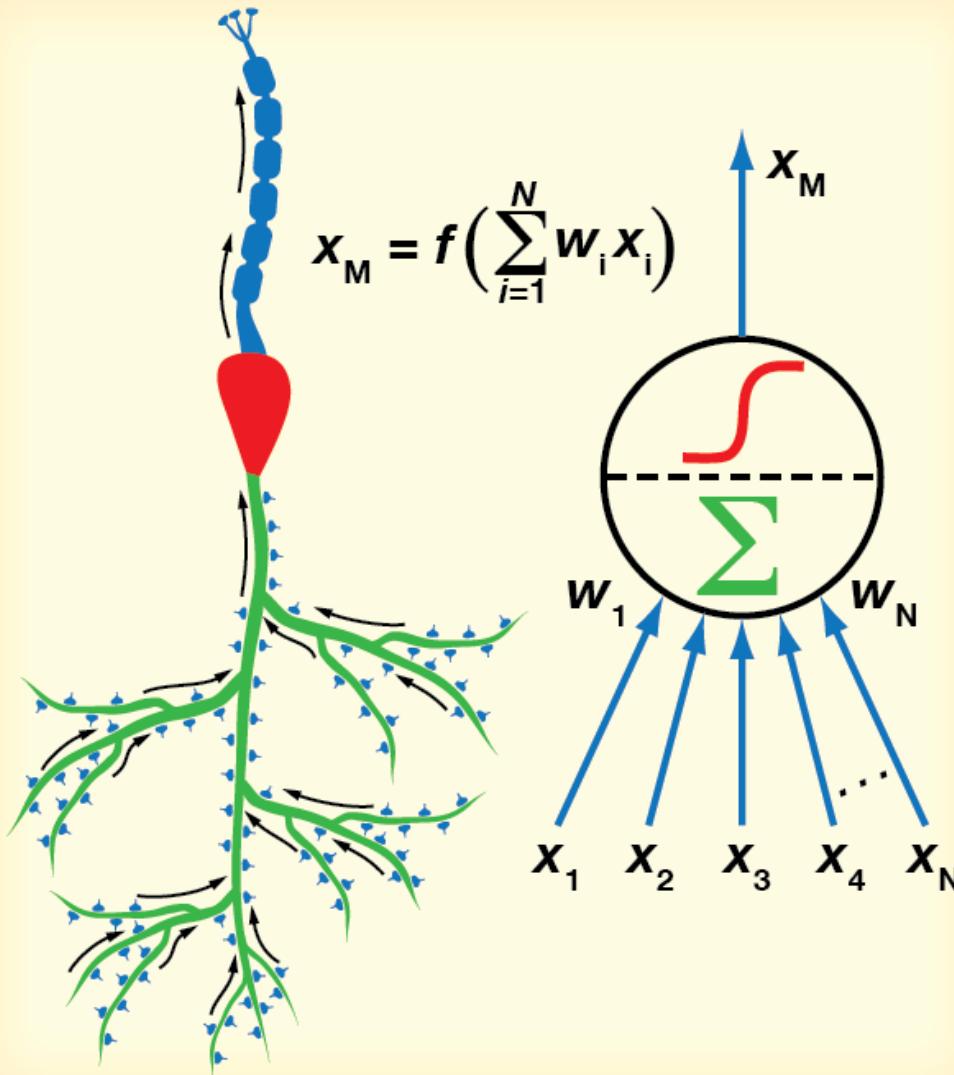
# Simple model of single neuronal function



**As we saw in yesterday's lecture ...**

**In this simple model, the cellular basis for learning  
and memory was postulated to be rooted in  
synaptic changes**

# Synaptic learning theory



Neurons are simple algebraic summation units

Synapses change in response to learning and form a putative cellular substrate for learning and memory

# Various learning rules have been proposed to understand learning based on synaptic plasticity

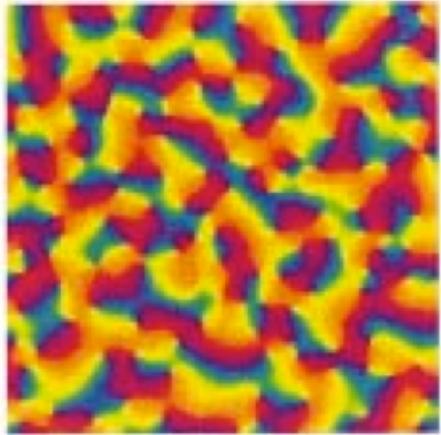
The Hebb Rule  
for Synaptic Plasticity:  
Algorithms and  
Implementations

Terrence J. Sejnowski and Gerald Tesauro

Covariance  
Rule

$$\Delta T_{BA} = \epsilon V_A V_B$$

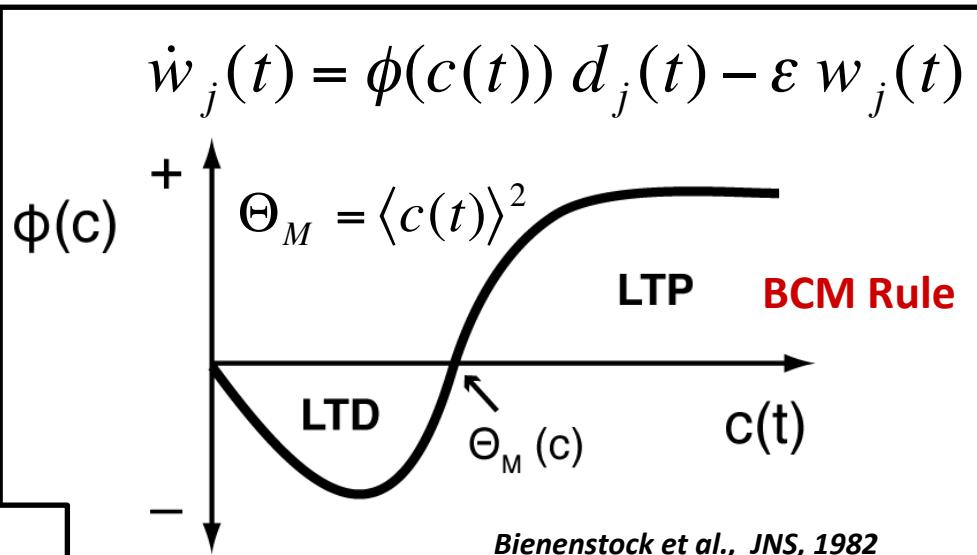
Orientation



Kohonen's  
Rule

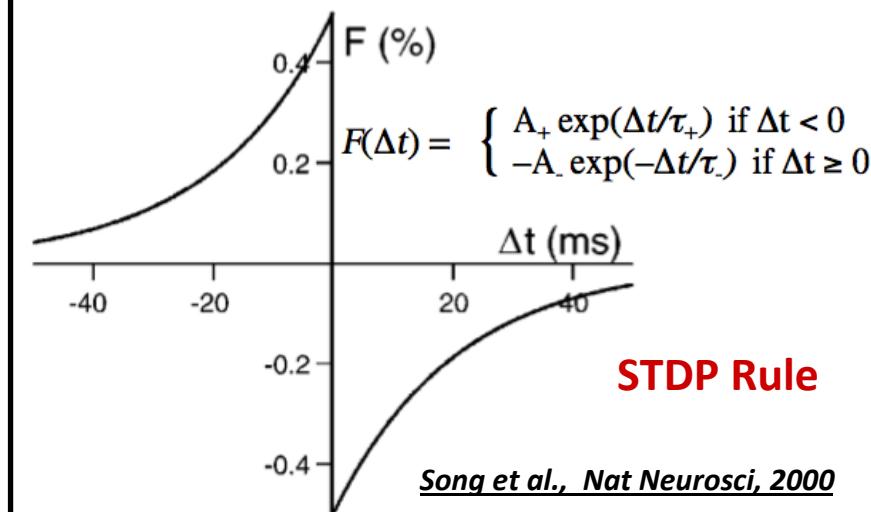
$$\Delta w_j = \epsilon h(j, j^*) (v - w_j)$$

Swindale and Bauer, PRSL, 1998; also see Goodhill, Neuron, 2007



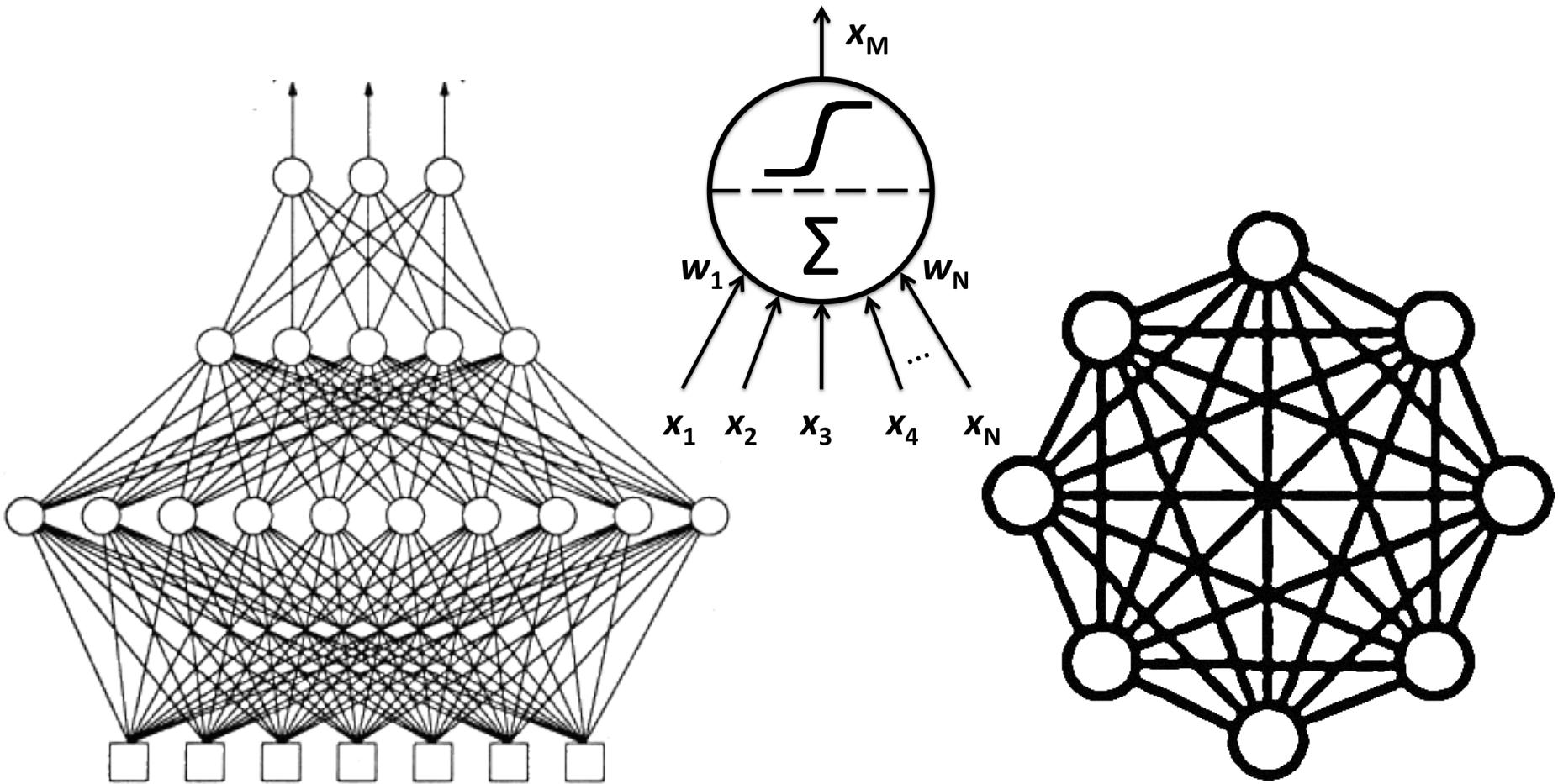
Bienenstock et al., JNS, 1982

STDP Rule



Song et al., Nat Neurosci, 2000

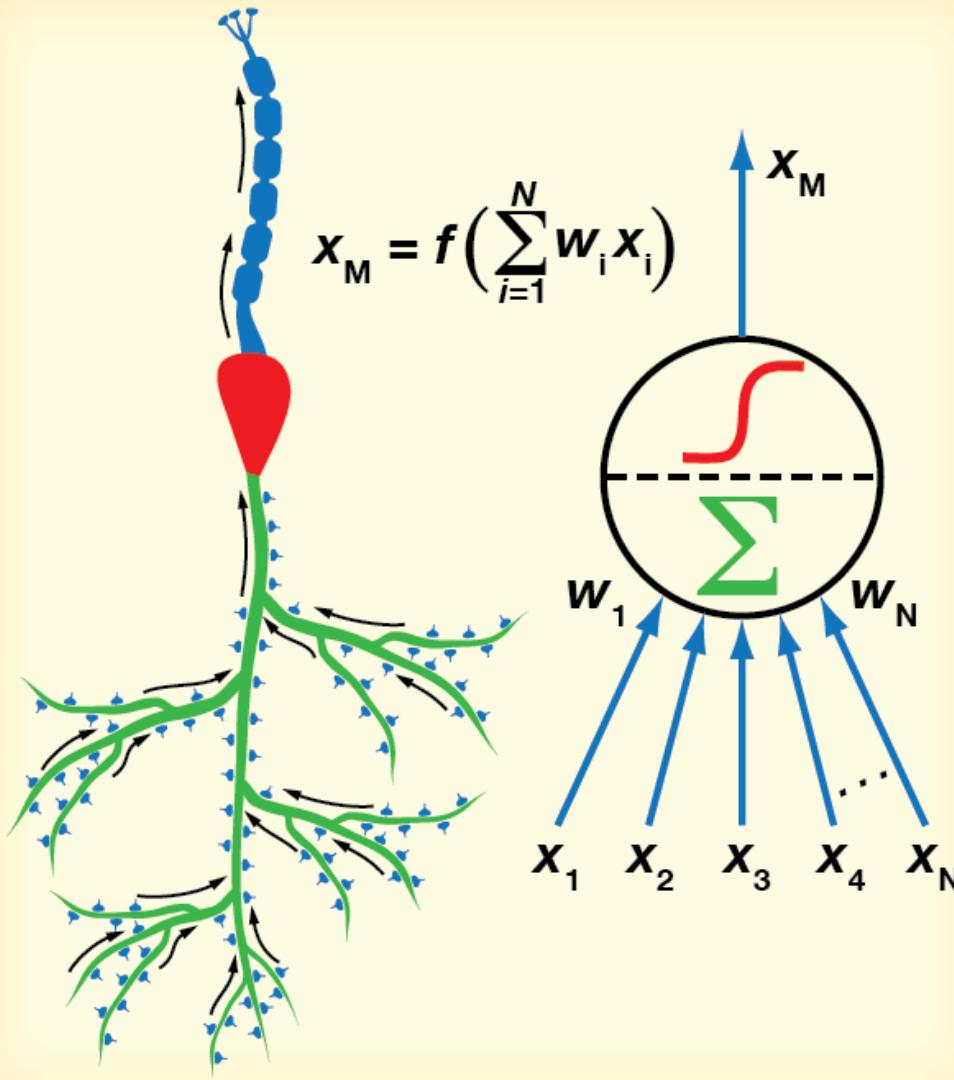
**Using synaptic plasticity as a substrate, artificial neural network architectures and algorithms for learning have been created**



**Hopfield network, Multi-layer perceptron, Support vector machines, Boltzmann machine, etc.**

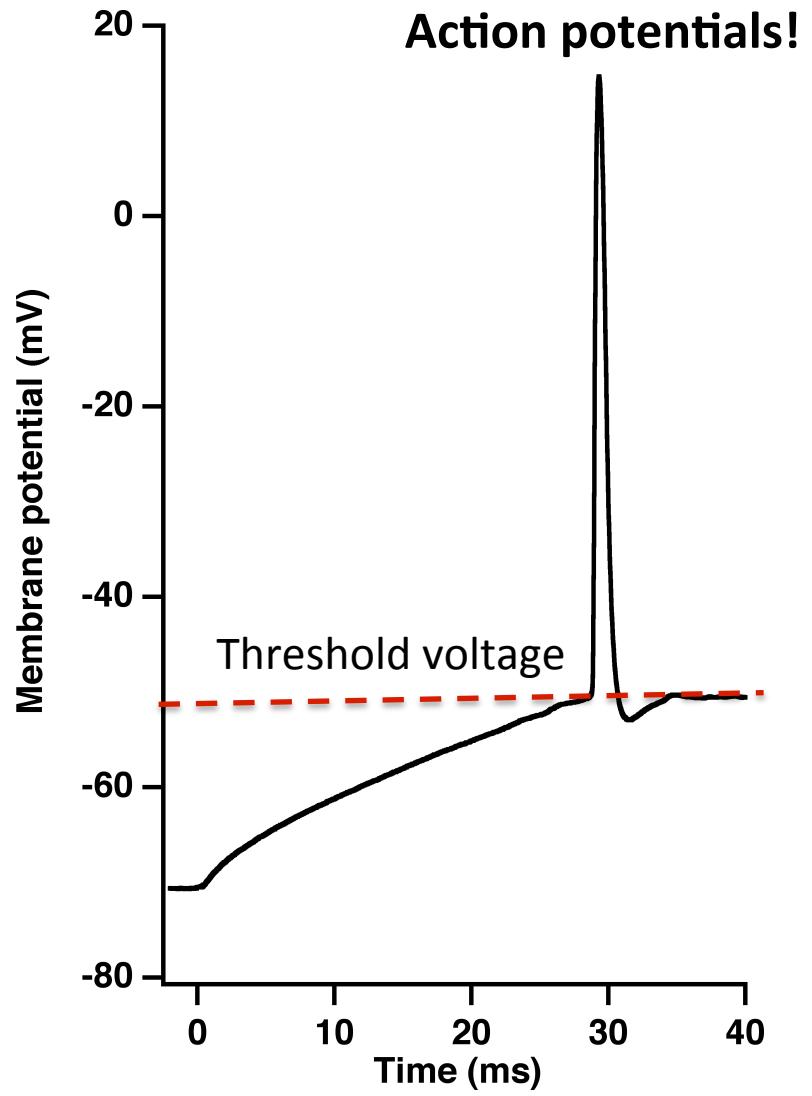
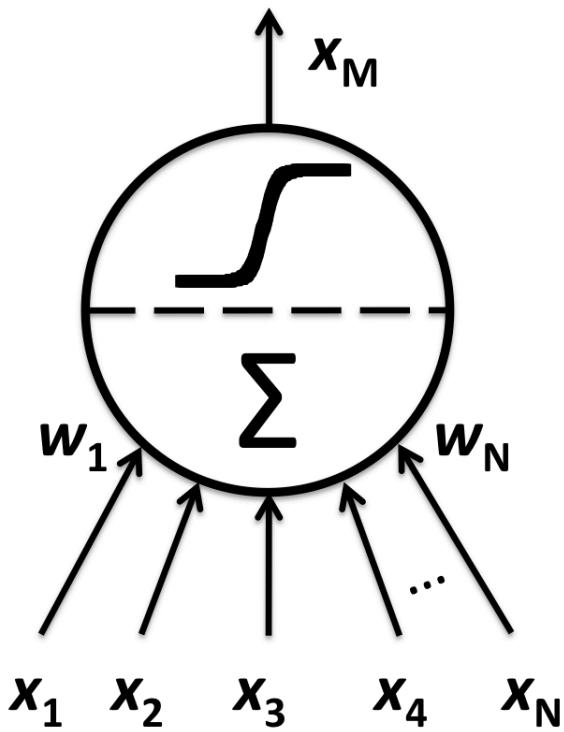
**In that narrative, it turned out later, we were  
driven by multiple oversimplifications!**

# Oversimplification #1



The “nonlinearity” resides only in the cell body, and the rest of it just computes an algebraic sum of incoming inputs and propagates it towards the cell body

# So, what is this “nonlinearity”?

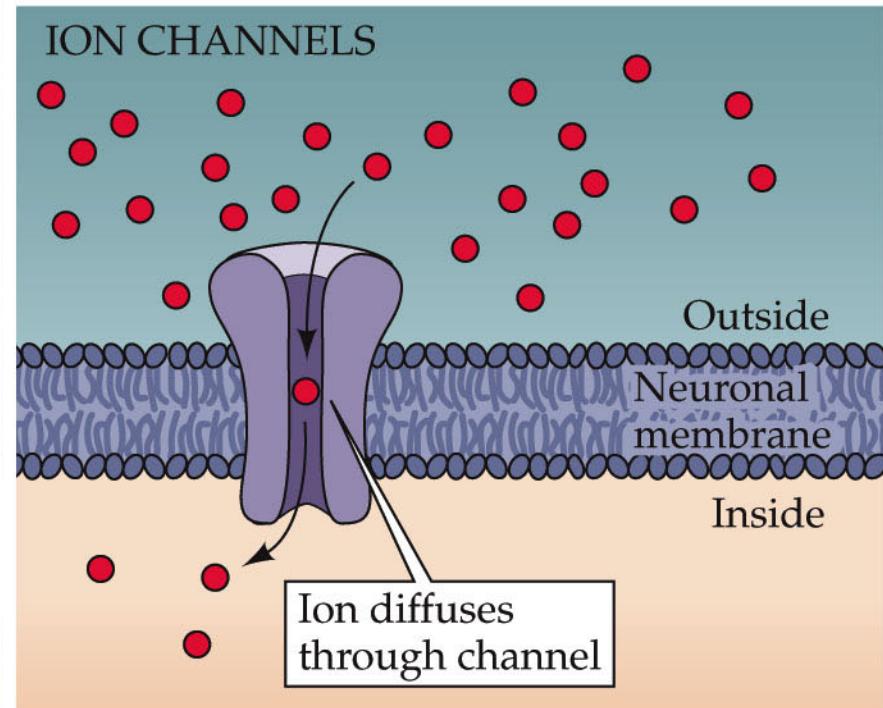


Current injected = 250 pA

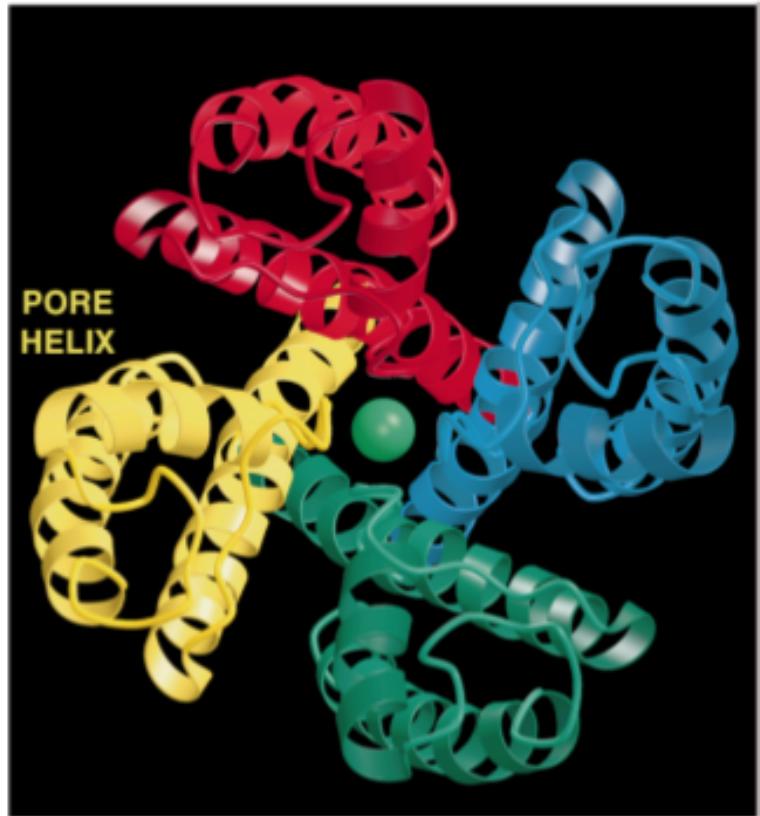
# What mediates this “nonlinearity”?

Action potential generation is mediated by complex interactions between sodium-specific and potassium-specific ion channels.

The “nonlinearity” is brought about by the voltage-dependence of these channels.

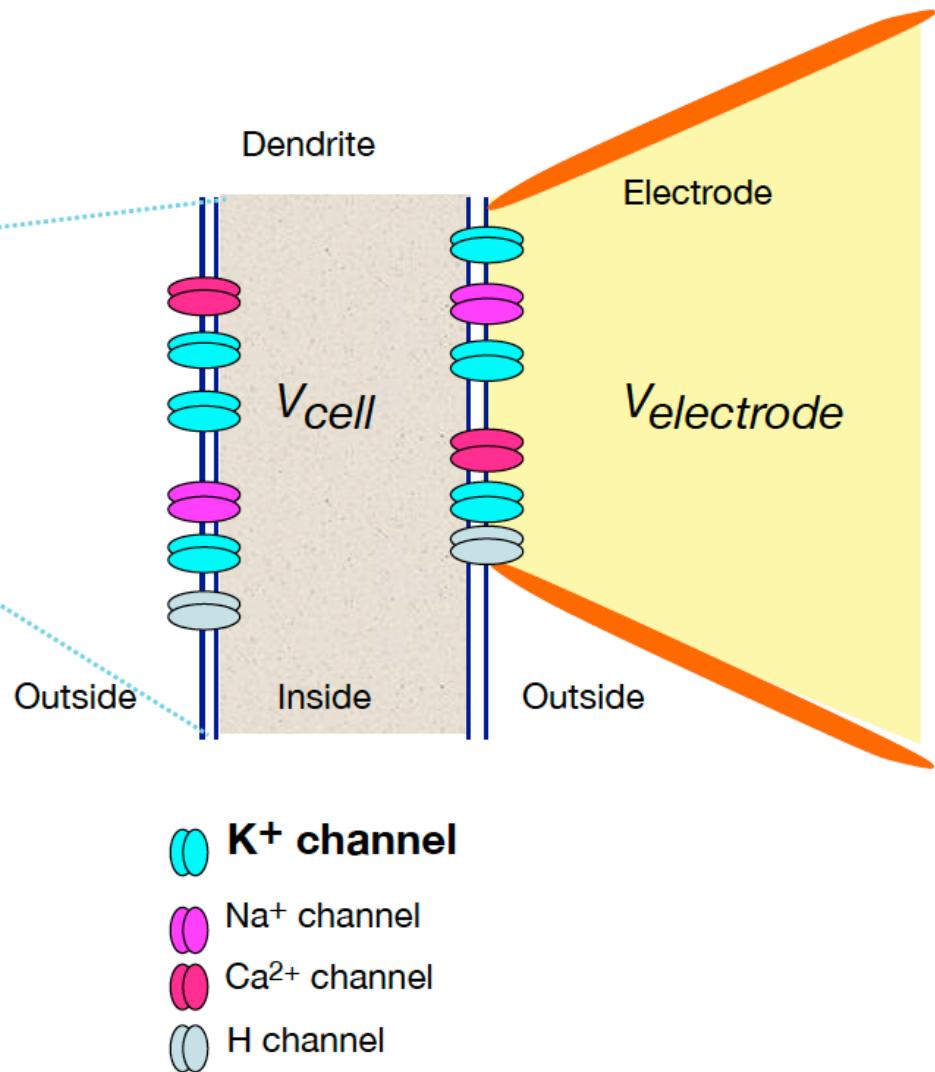
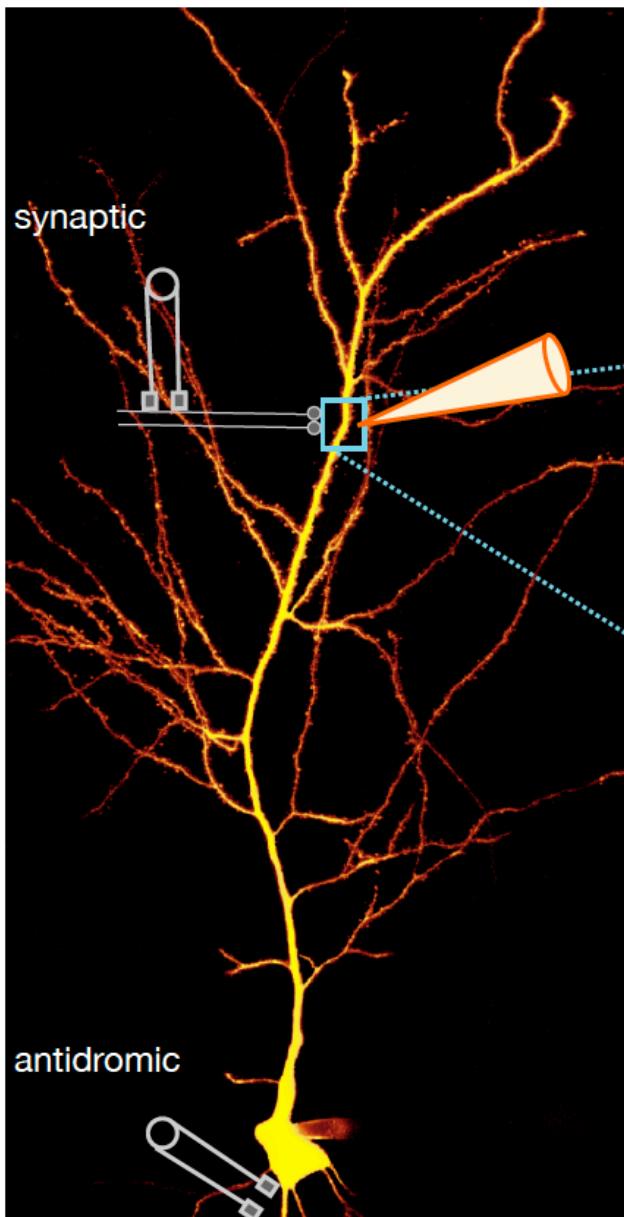


# Channel structure



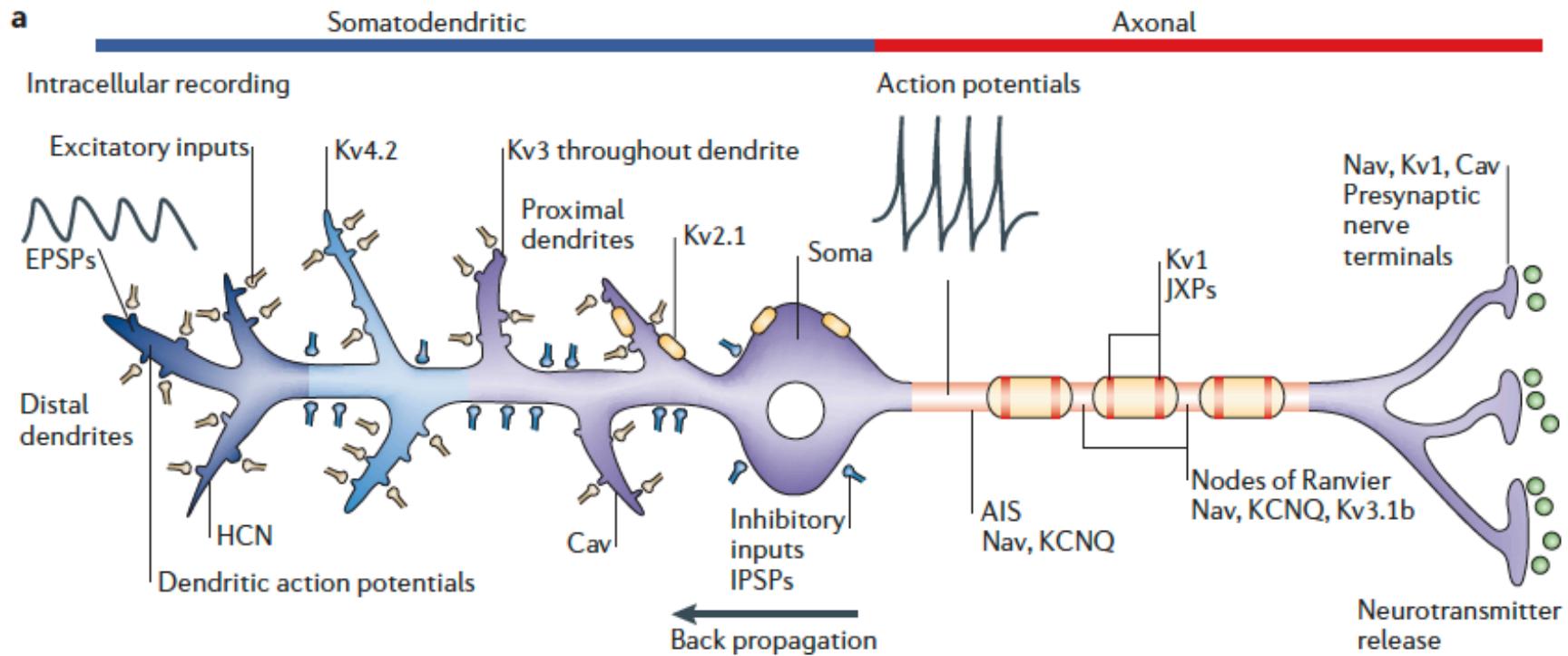
Doyle et al., Science, 1998

# Measuring these channels currents: cell-attached recordings

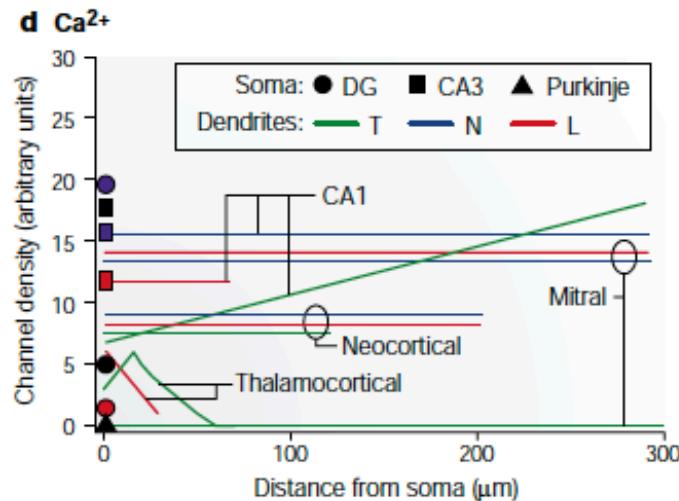
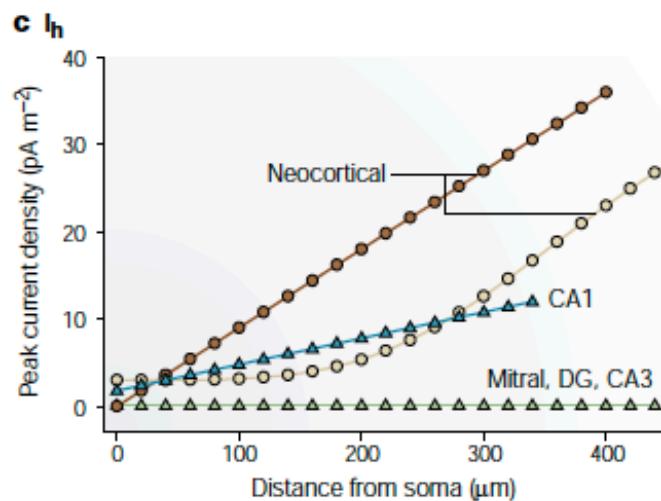
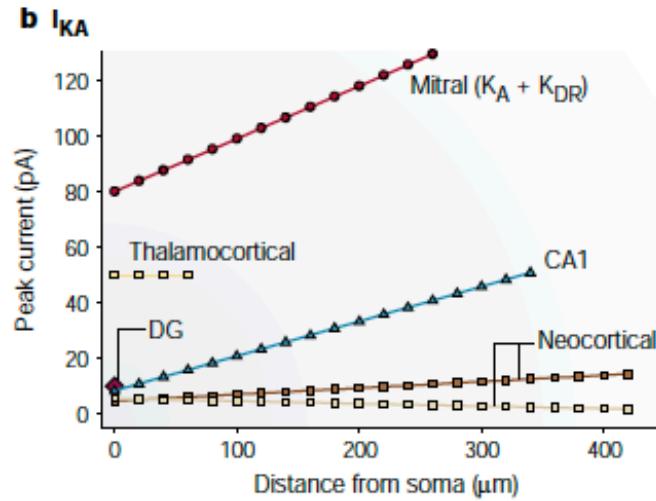
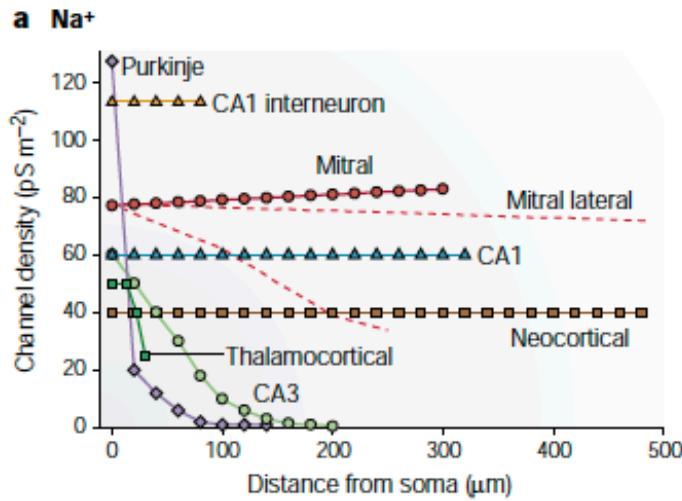


# Research over the past two decades has shown...

**Ion channels are present all throughout the neuron, with different channels present at different locations with different densities!**



# Every neuron is unique in terms of properties and distribution of channels!



# Neurons break the law of dynamic polarization

The power of active dendrites!

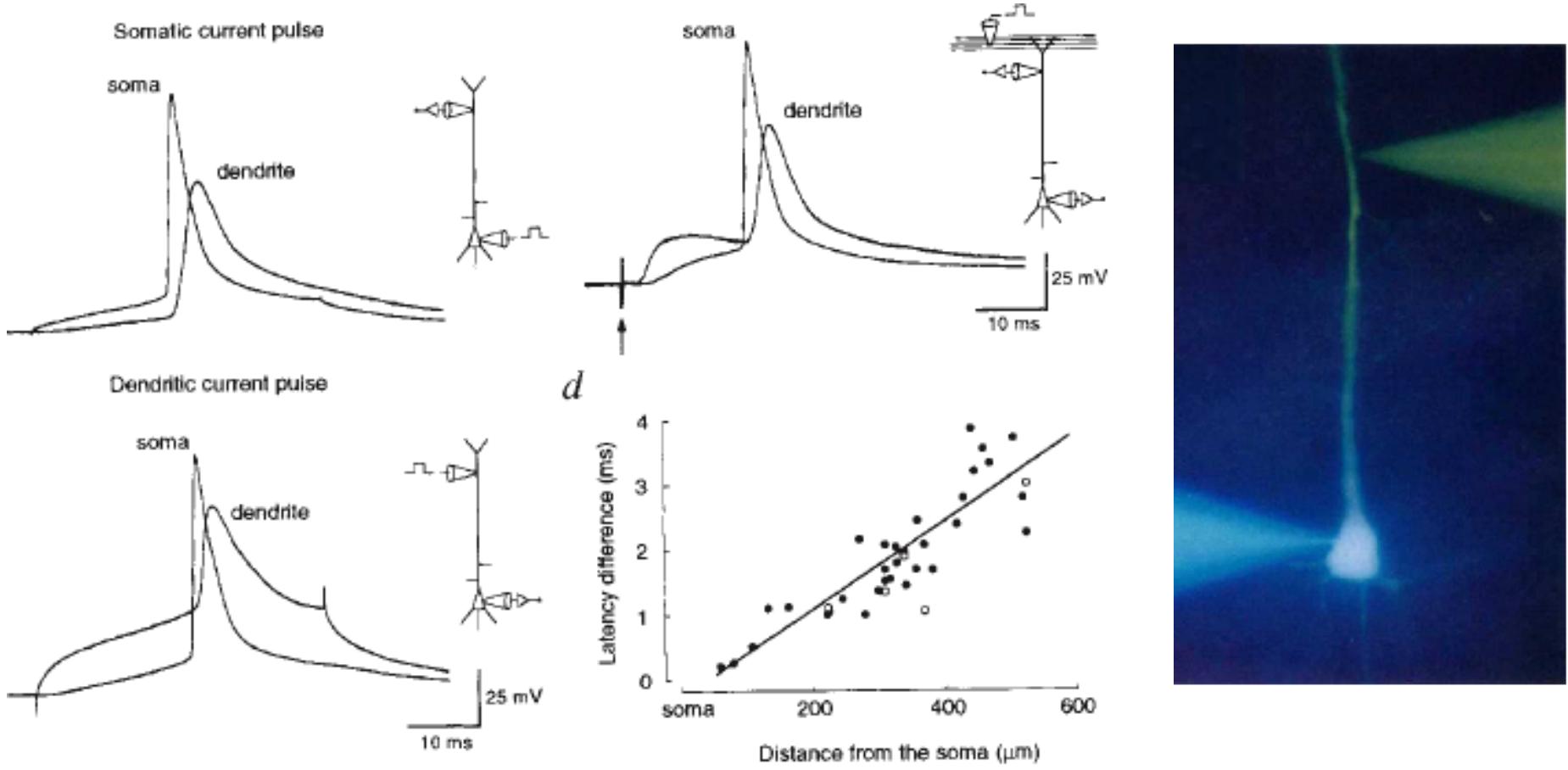


Action potentials can propagate back into the dendrites!!

Spikes can initiate at dendritic sites!!!

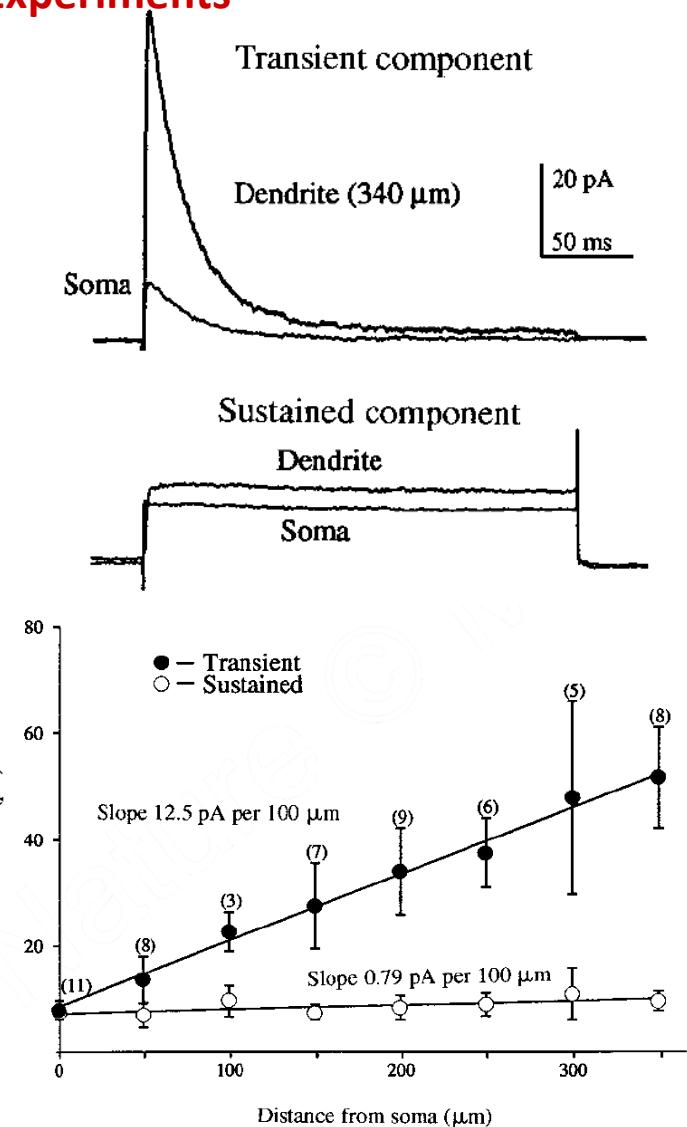
Neurons cease to be simple integrate-and-fire low pass units

# Backpropagation of action potentials

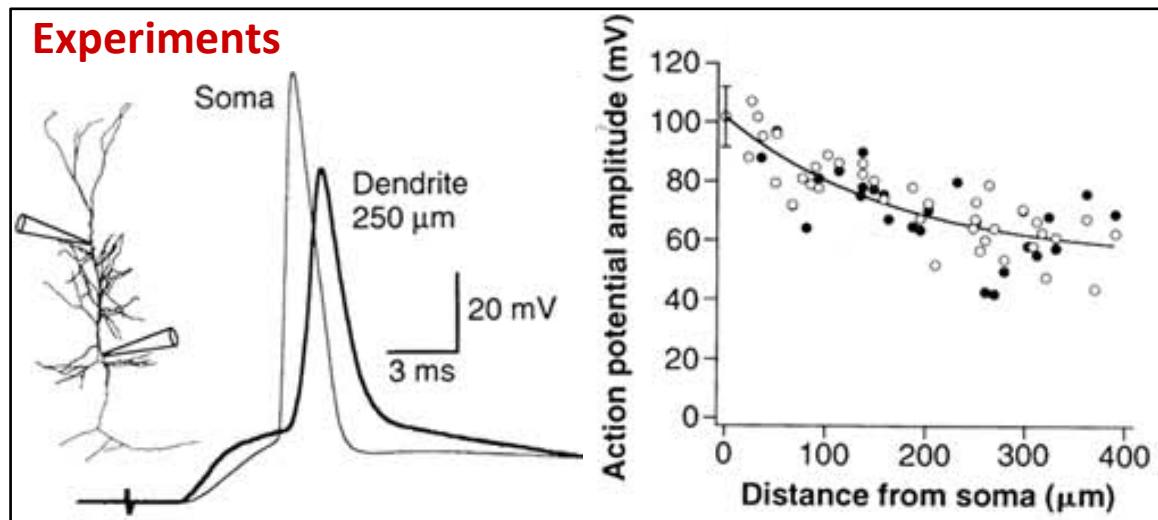


# Backpropagation of action potentials depends on ion channels

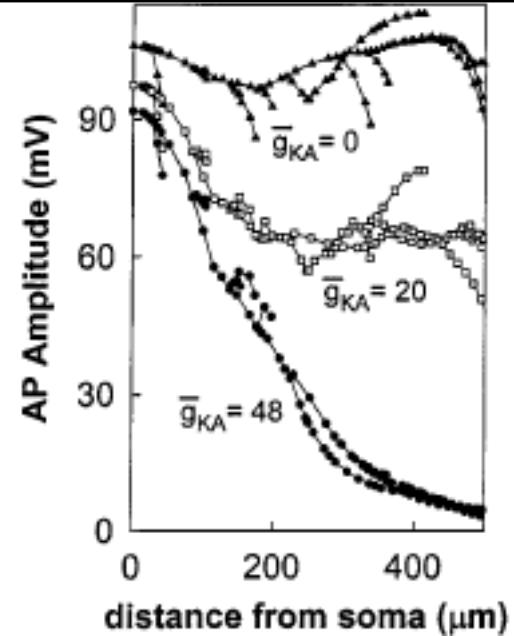
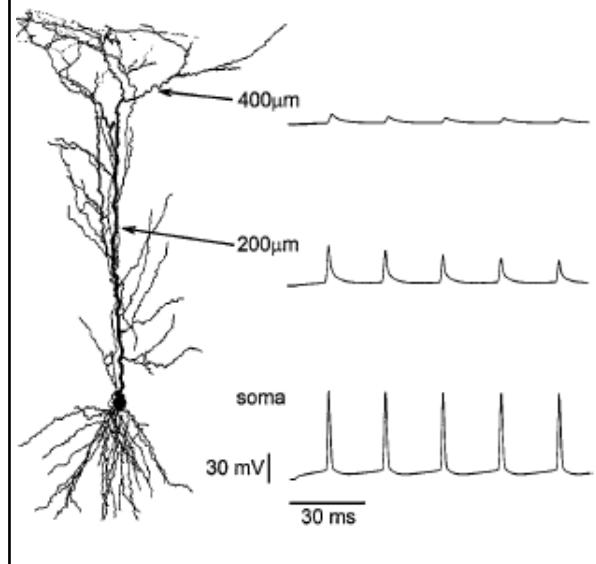
## Experiments



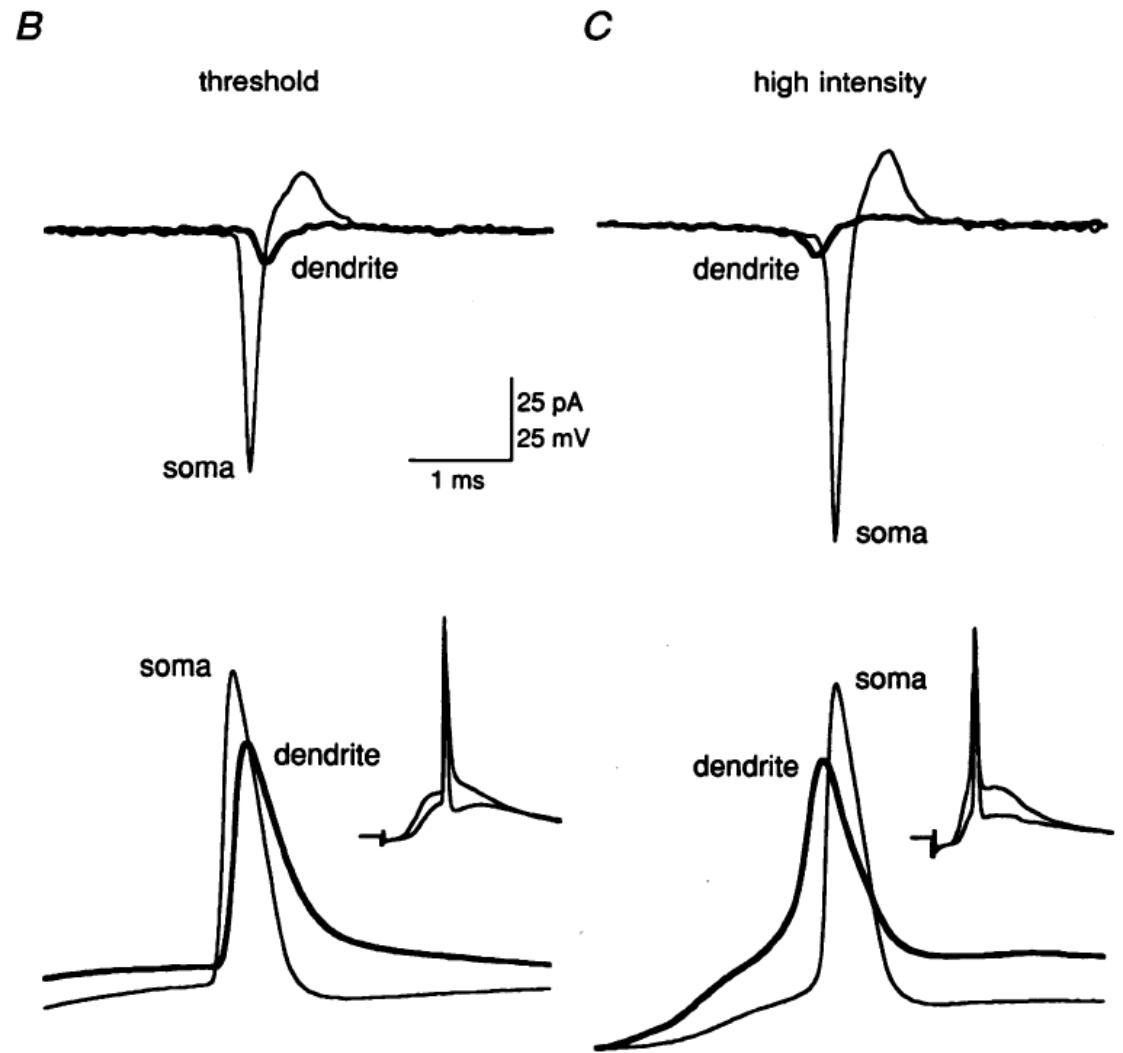
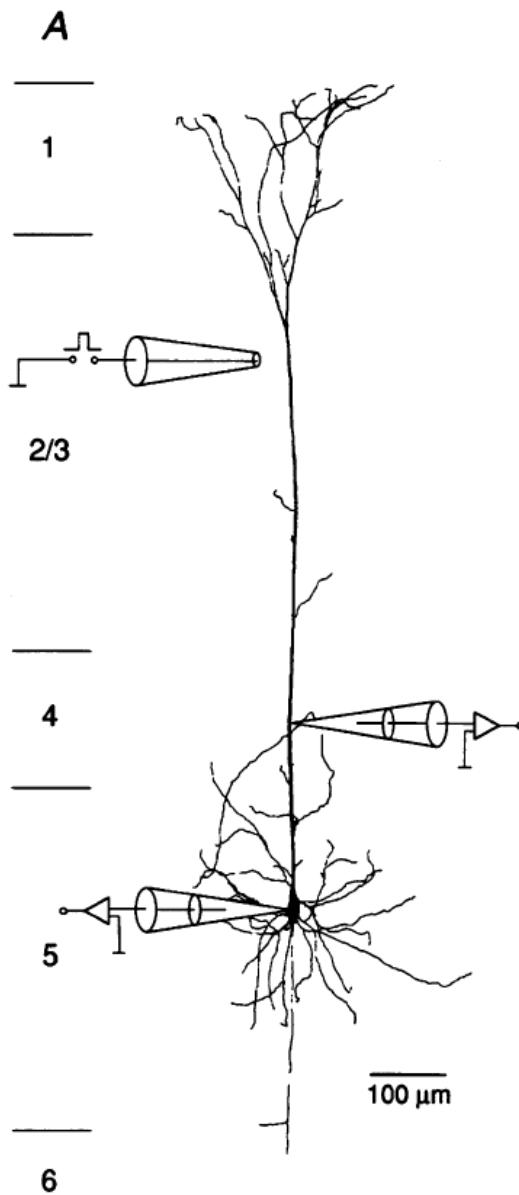
## Experiments



## Simulations



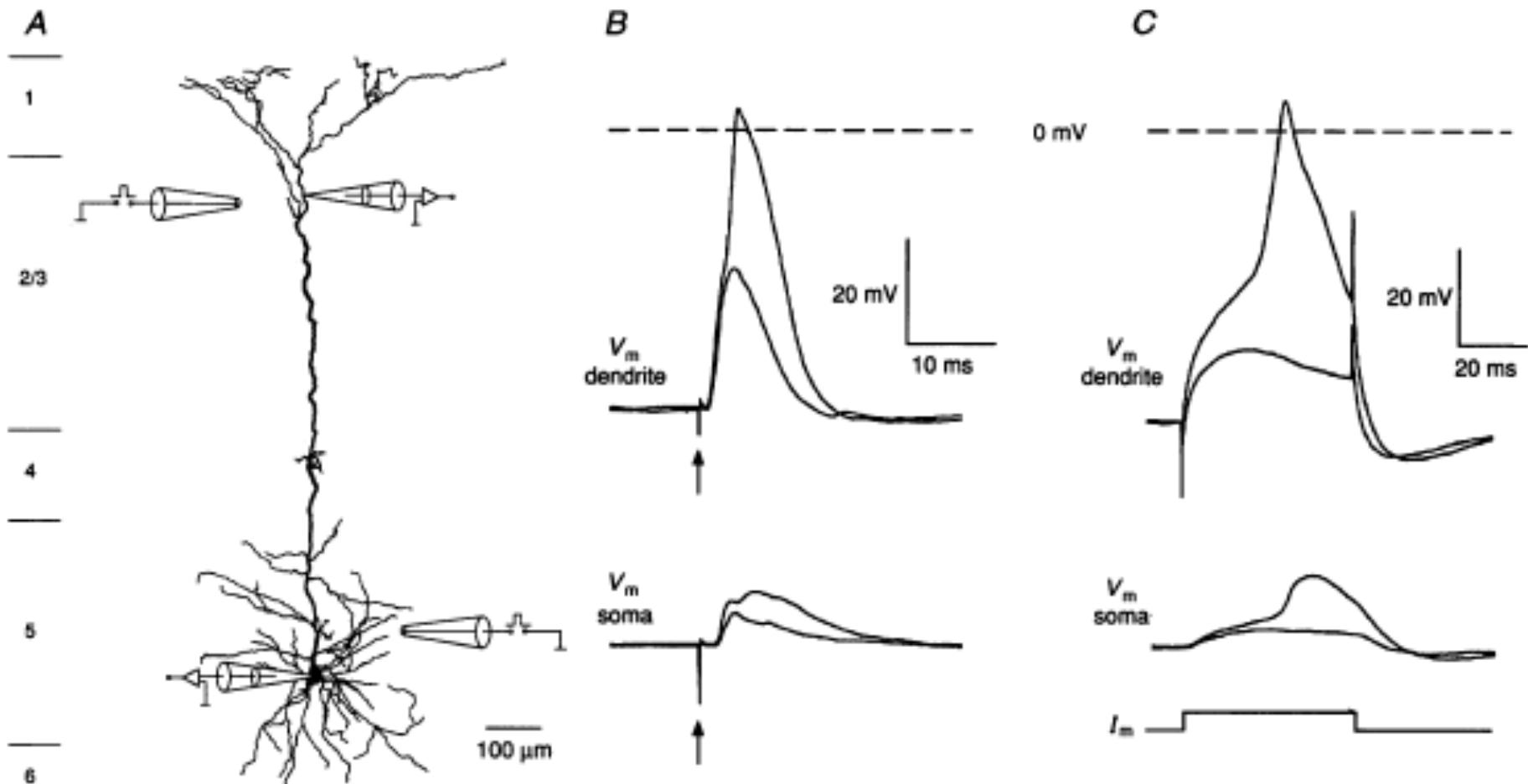
# Dendritically initiated spikes: Sodium spikes



*Stuart et al., J. Phys., 1997*

These spikes are blocked by TTX

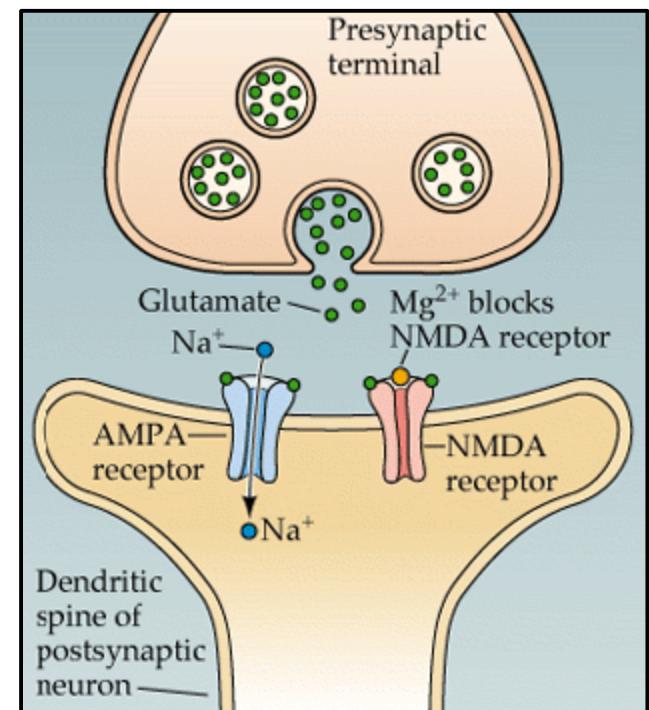
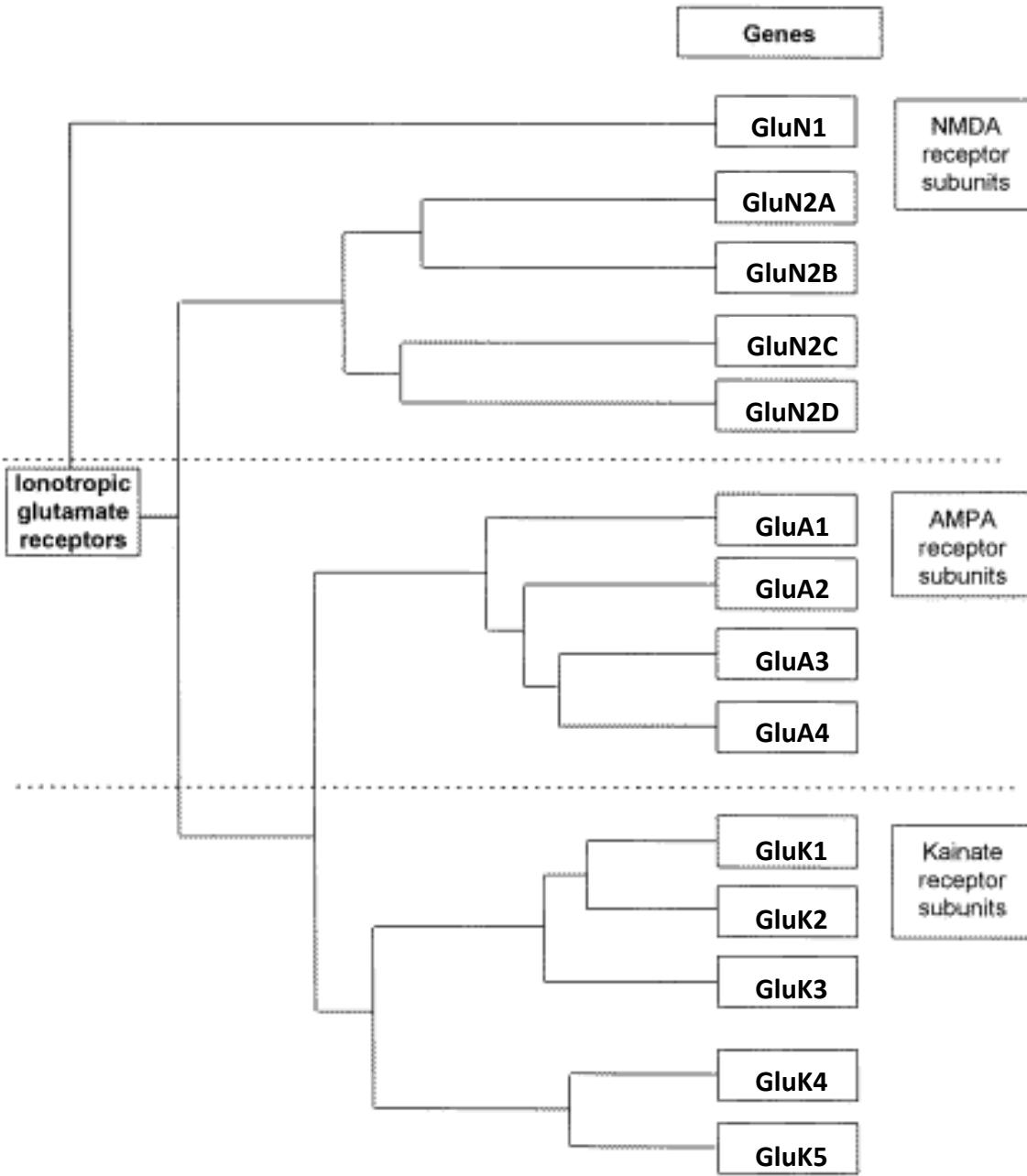
# Dendritically initiated spikes: Calcium spikes



These spikes are blocked by cadmium

Schiller et al., J. Phys., 1997

# Glutamate receptors



## AMPAR, KAR

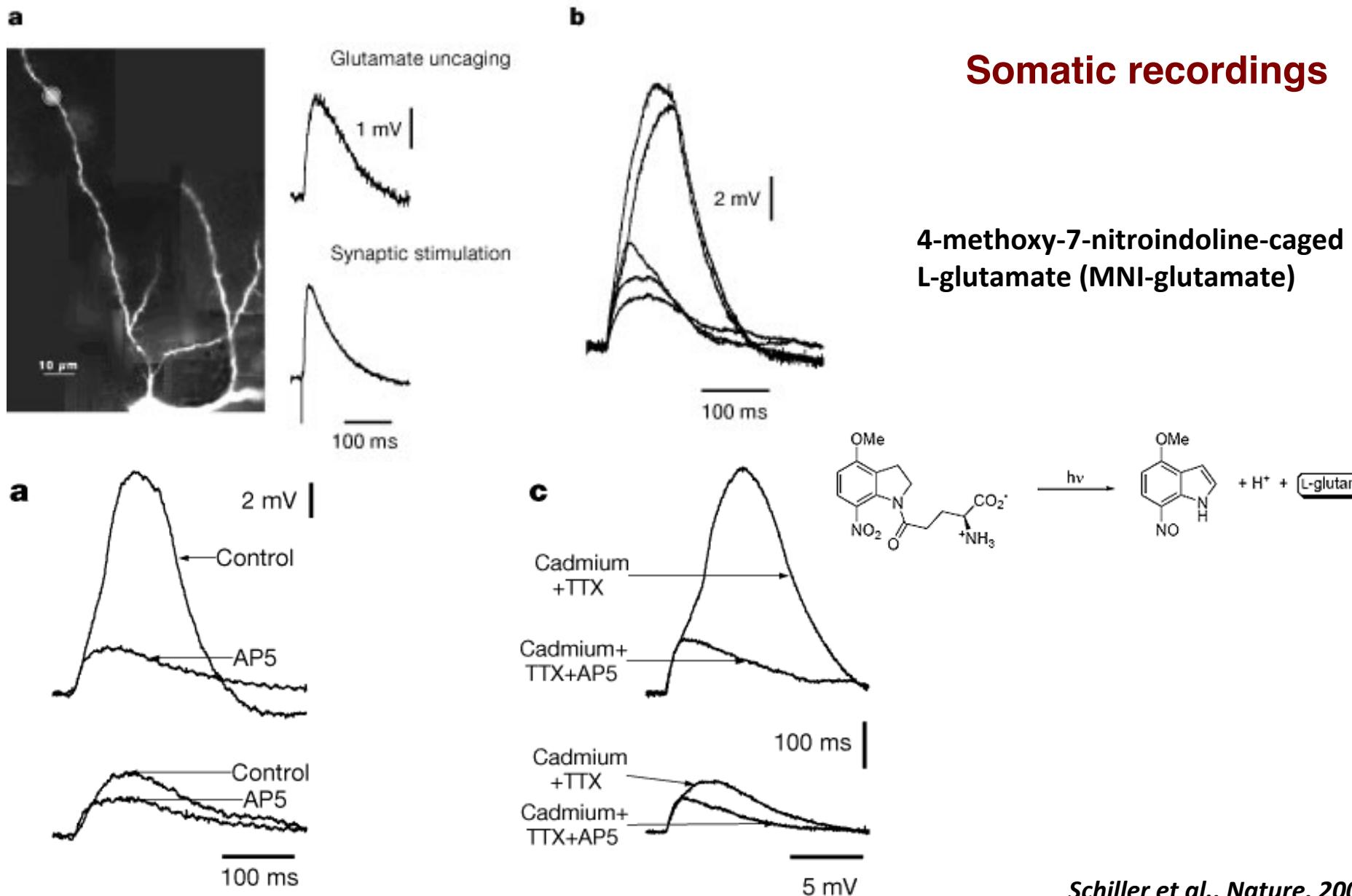
→ Na<sup>+</sup>, K<sup>+</sup>, (Ca<sup>2+</sup>) permeant

## NMDAR

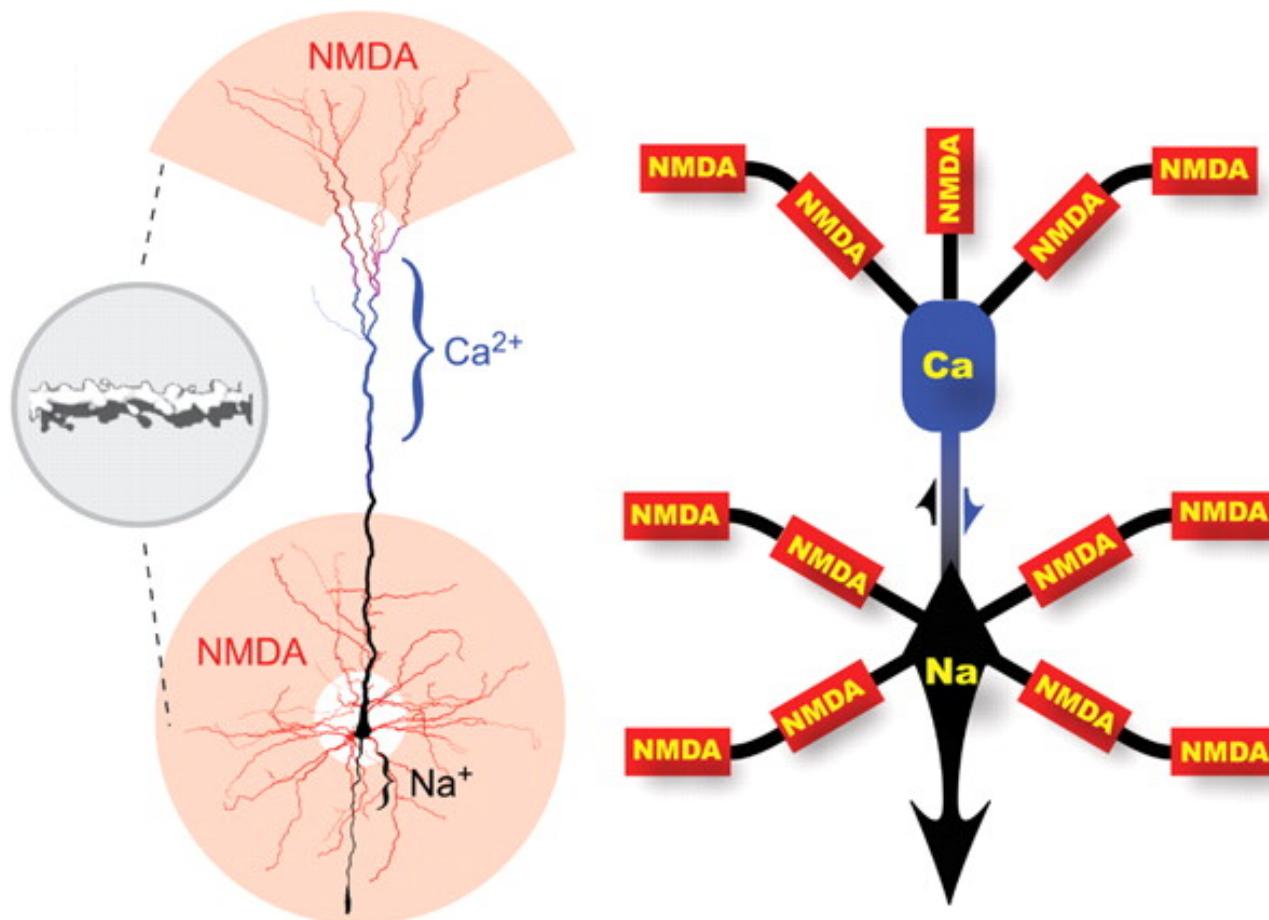
→ Na<sup>+</sup>, K<sup>+</sup>, Ca<sup>2+</sup> permeant

→ Voltage dependent (Mg<sup>2+</sup>)

# Dendritically initiated spikes: NMDA spikes

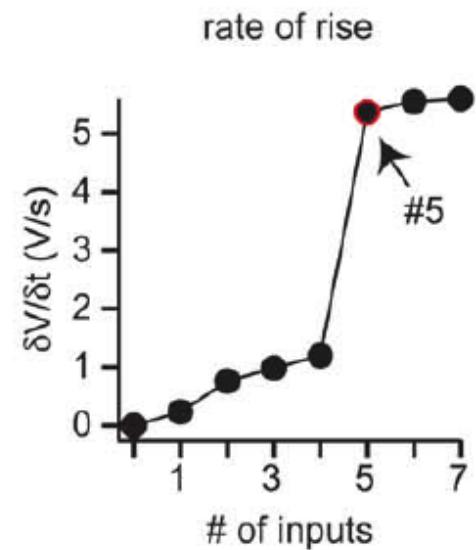
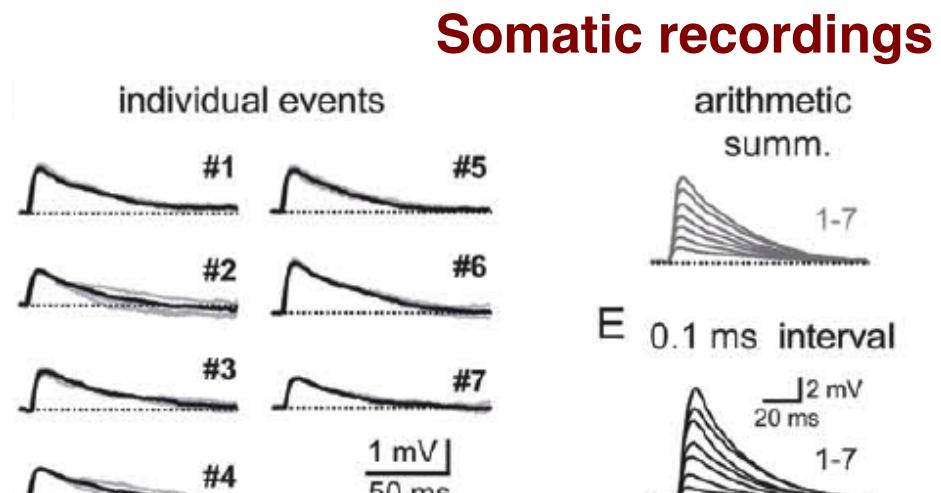
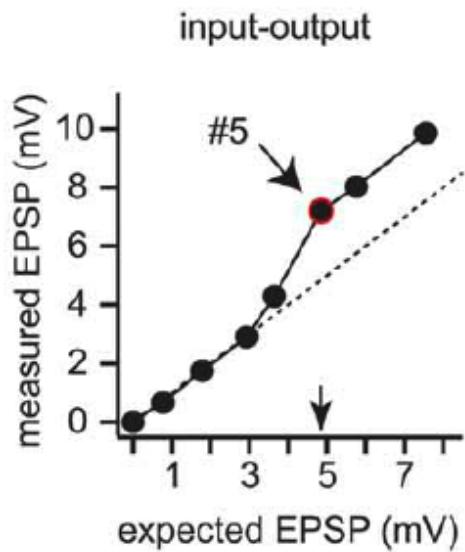
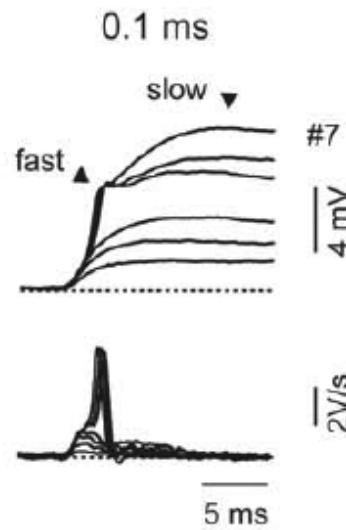
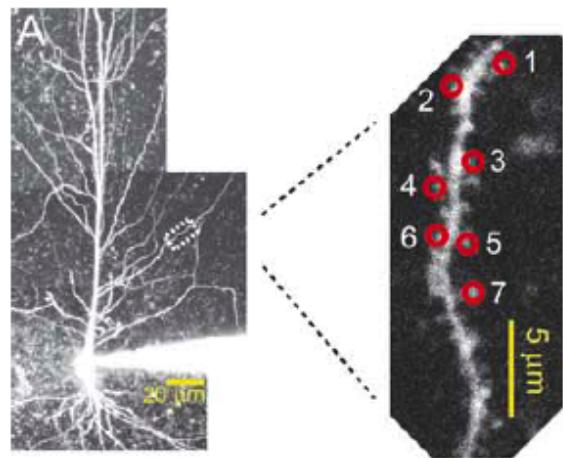


# Cortical neurons: Different regions, different spikes

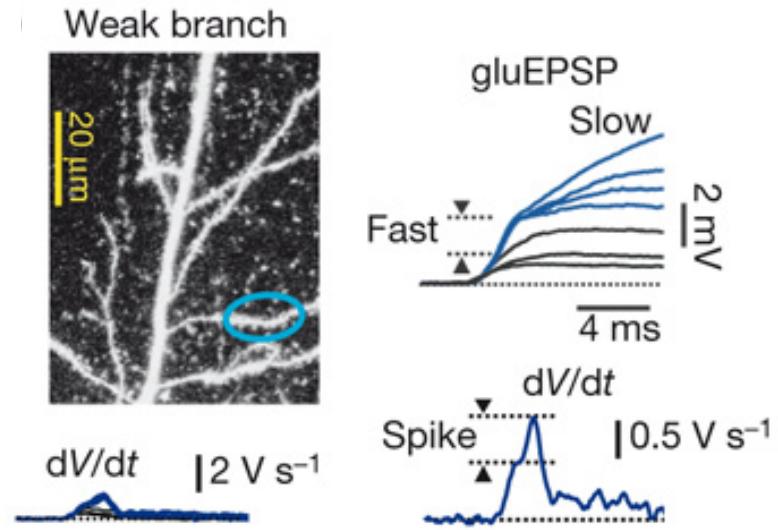
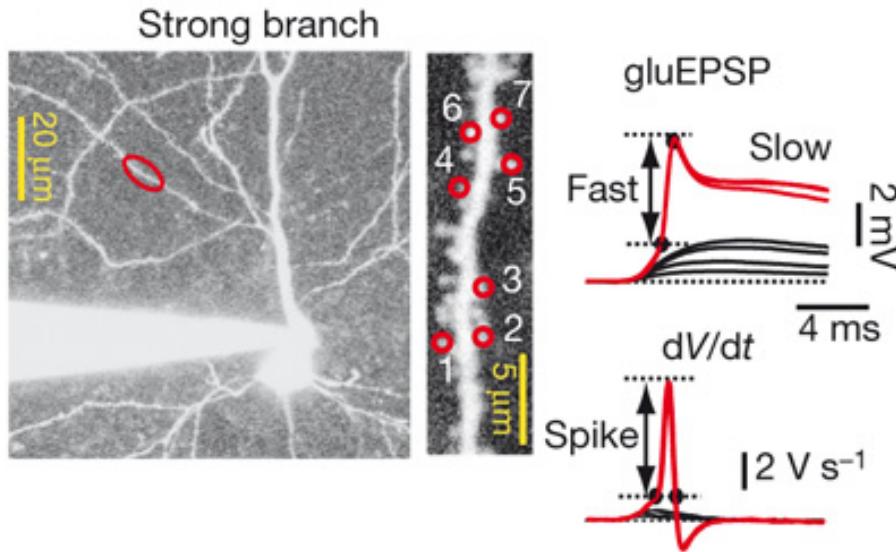


*Larkum et al., Nature, 2009*

# Dendritically initiated sodium spikes in CA1 oblique dendrites

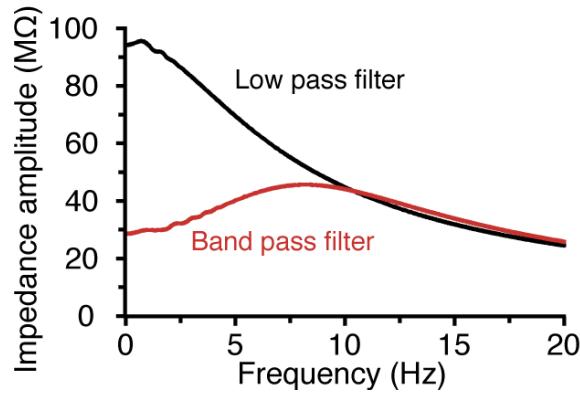
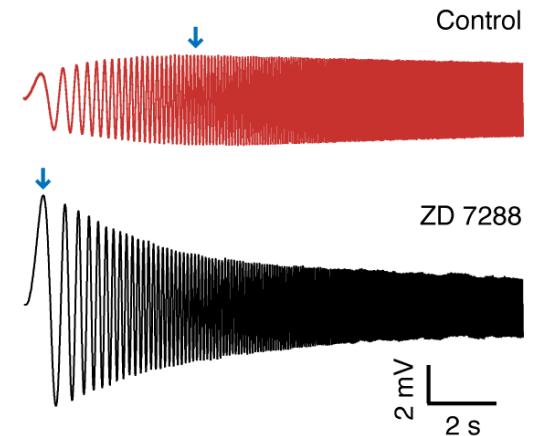


# Branches have differing strengths in terms of initiation of dendritic spikes

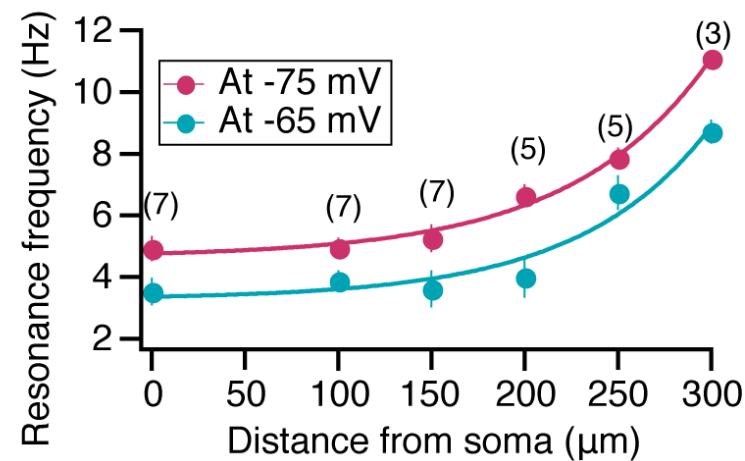
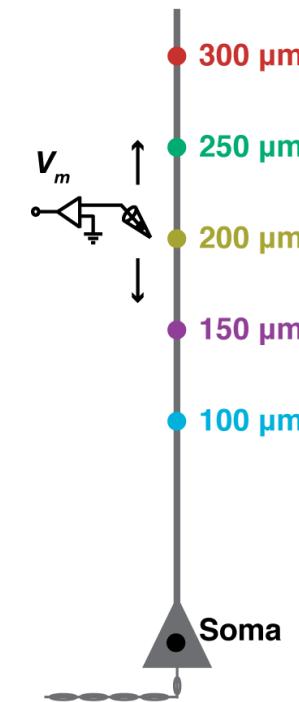
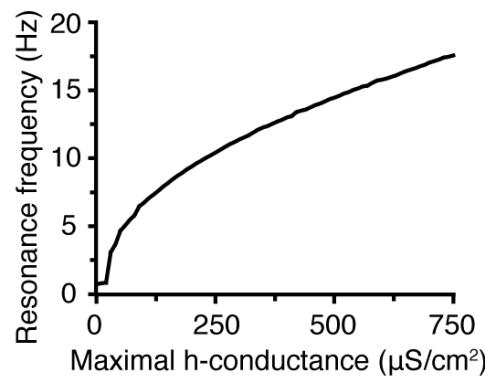
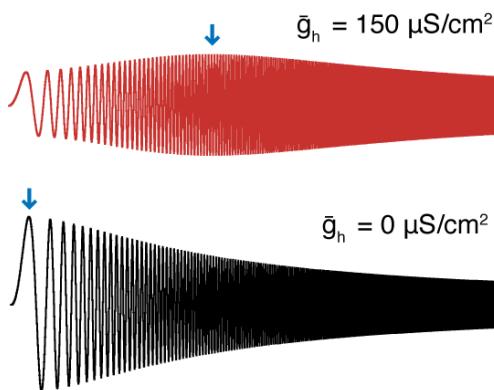


# Neurons cease to be low-pass integrators: The *h* (HCN) channel heavily alters neuronal response characteristics

## Experiments

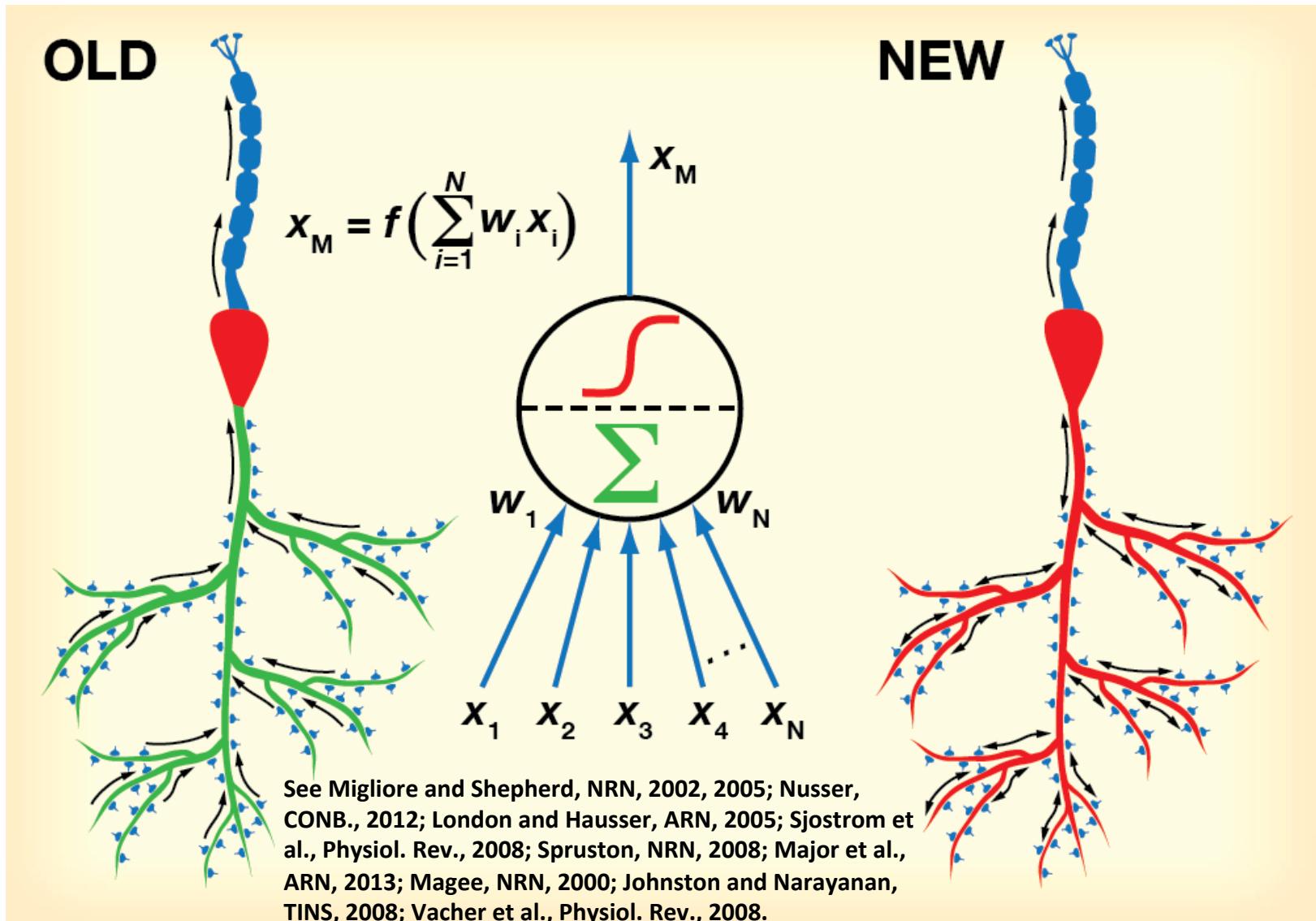


## Simulations

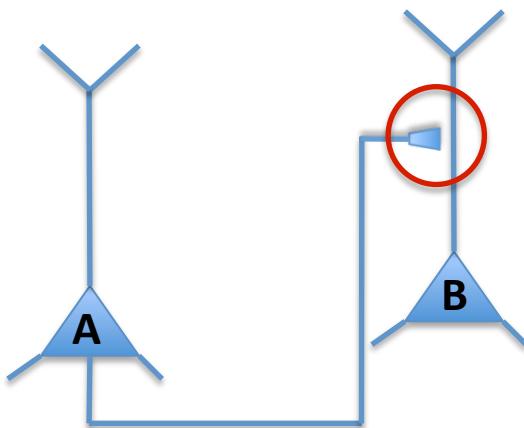


Also changes the input resistance of the neuron

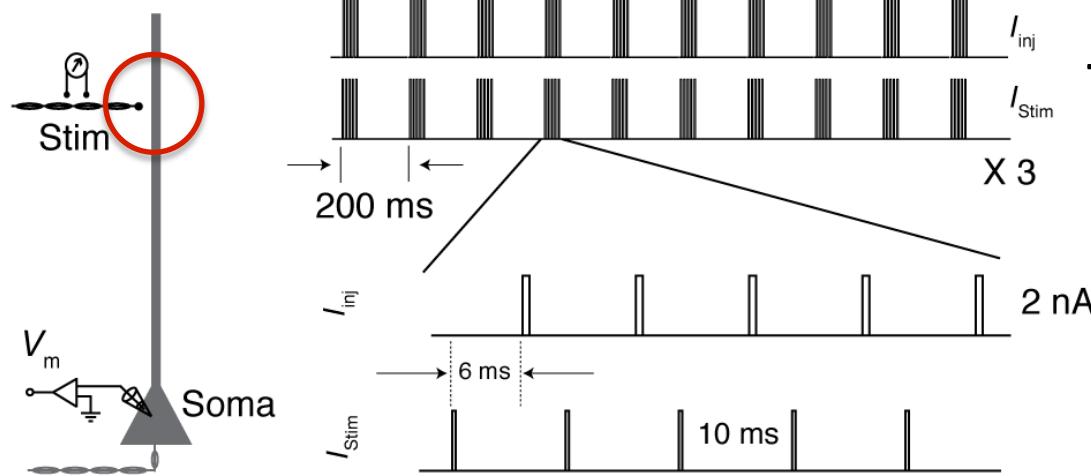
# Summary of oversimplification #1: Processing is nonlinear and information flow is bidirectional in active dendrites



# Oversimplification #2



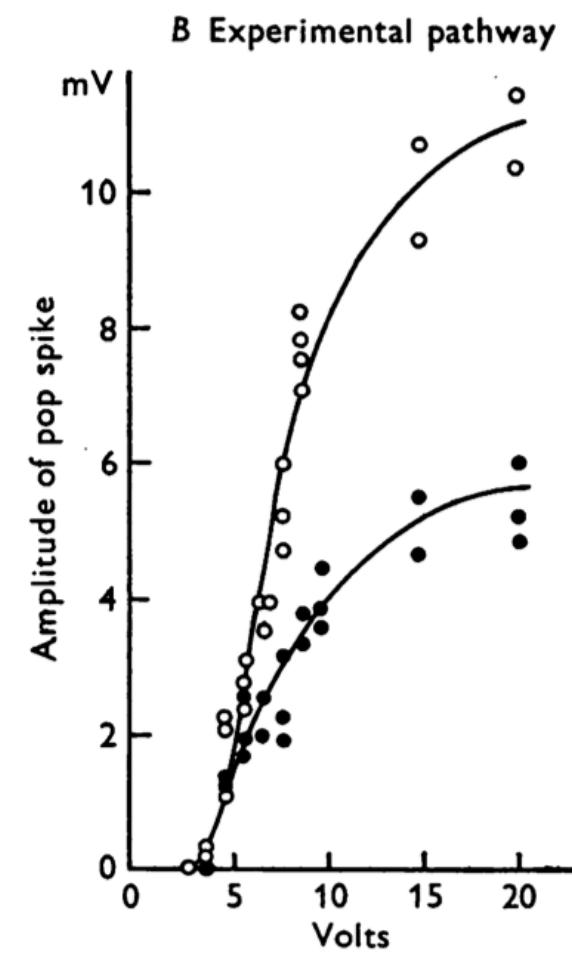
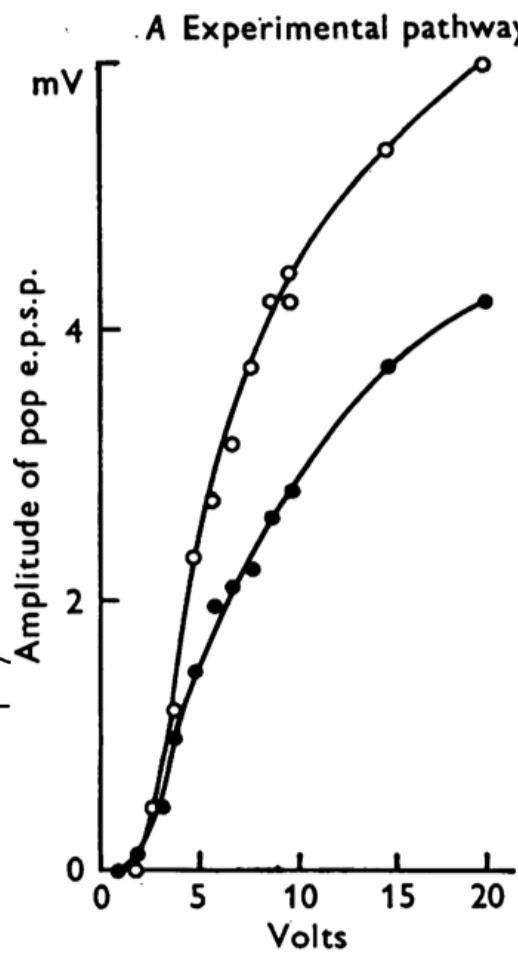
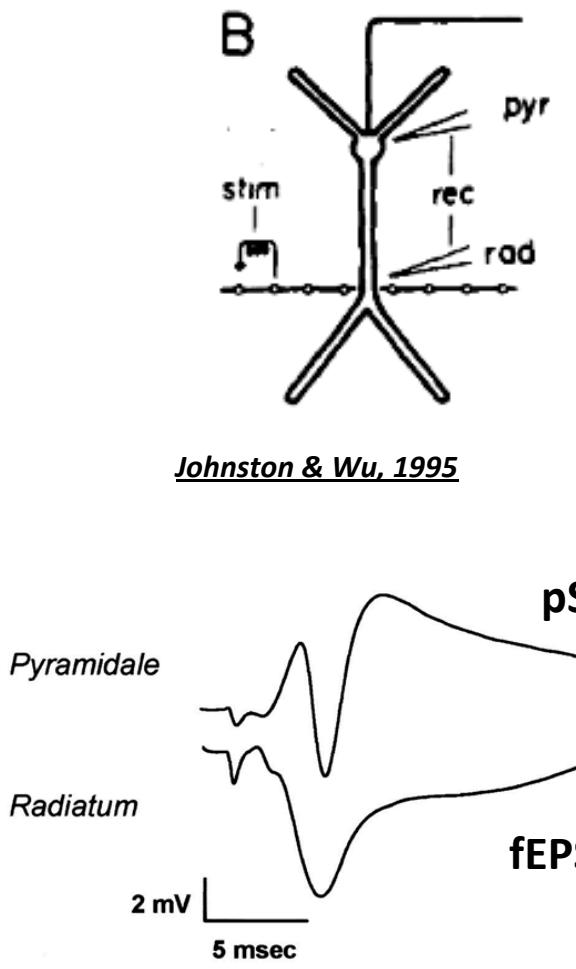
Repeated pairing, as postulated by Hebb, specifically leads to changes only in the appropriate synapses



# **Activity-dependent intrinsic plasticity**

# Intrinsic changes accompanying synaptic plasticity is as old as LTP itself!

## EPSP-Spike (ES) potentiation



LONG-LASTING POTENTIATION  
OF SYNAPTIC TRANSMISSION IN THE DENTATE AREA  
OF THE ANAESTHETIZED RABBIT FOLLOWING  
STIMULATION OF THE PERFORANT PATH

BY T. V. P. BLISS AND T. LØMO

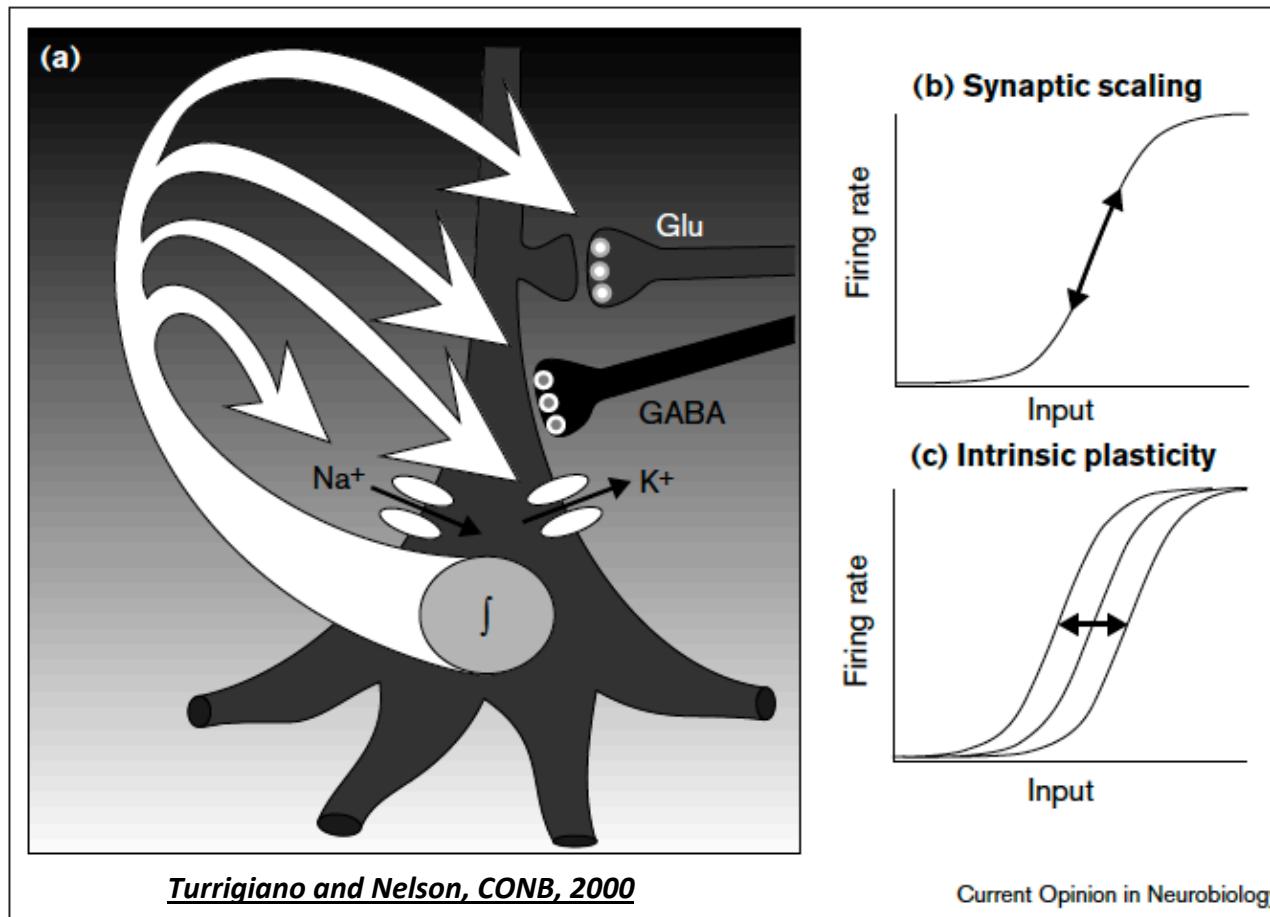
*J. Physiol.* (1973), 232, pp. 331–356

6. The results suggest that two independent mechanisms are responsible for long-lasting potentiation: (a) an increase in the efficiency of synaptic transmission at the perforant path synapses; (b) an increase in the excitability of the granule cell population.

The amplitude of the population spike reflects the number and synchrony of granule cell discharges (Andersen *et al.* 1971a). For a given synaptic input, the number of granule cells discharged will depend on the excitability of the population, and this could be controlled either by intrinsic factors, such as those which determine threshold, or by the extrinsic modulation of tonic excitatory and inhibitory afferent activity.

# Activity-dependent plasticity in ionic conductances

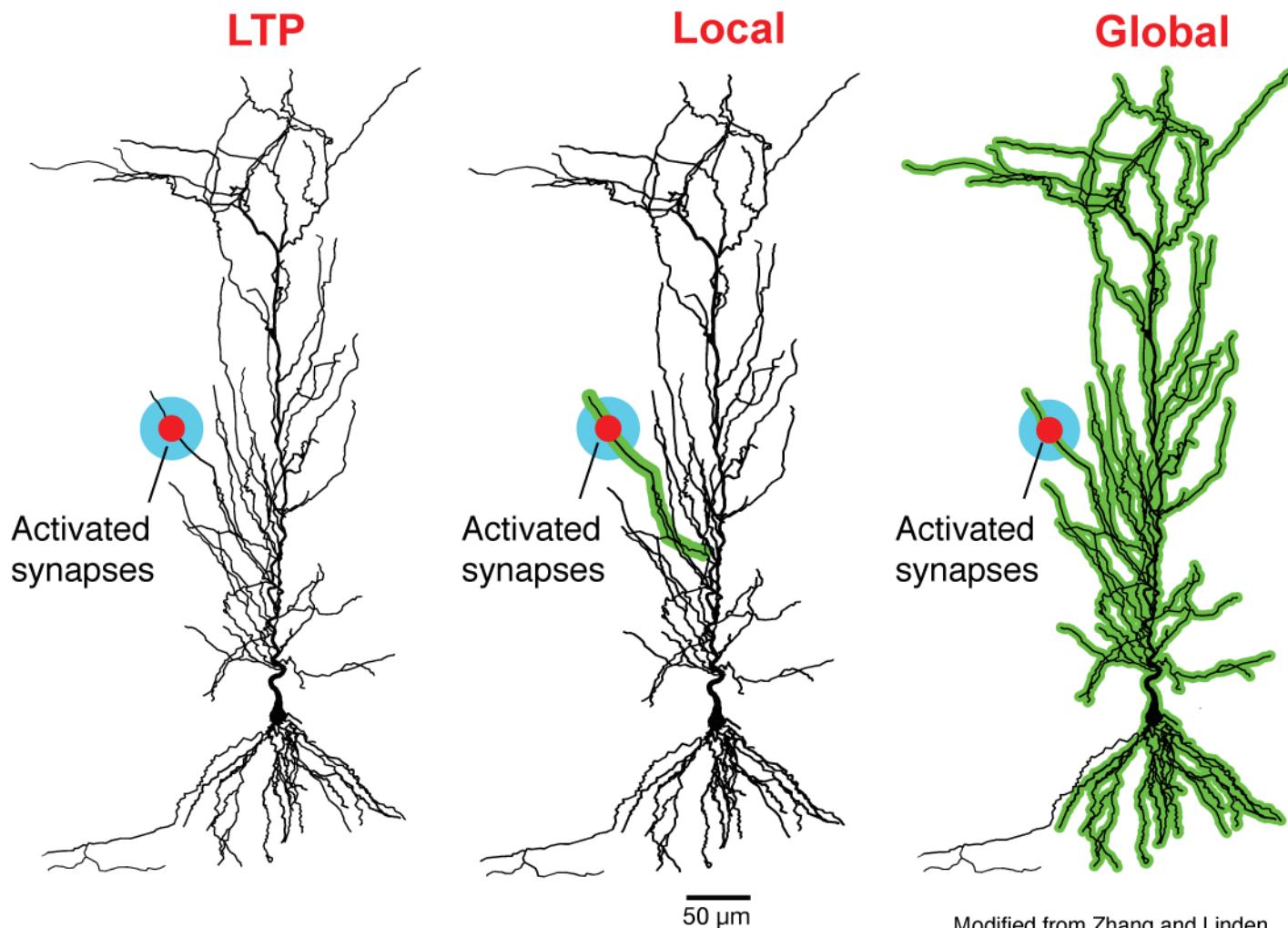
Reboot in 1990s with Eve Marder's laboratory working on ion channel plasticity, and by the discovery of dendritic voltage-gated ion channels



Also see Turriano et al., Science, 1993 and other Marder lab papers that time!

# Voltage-gated ion channels undergo plasticity too!

Multiple functional maps (mediated by voltage gated ion channels) undergo changes in response to the same protocols that are employed for inducing synaptic plasticity!



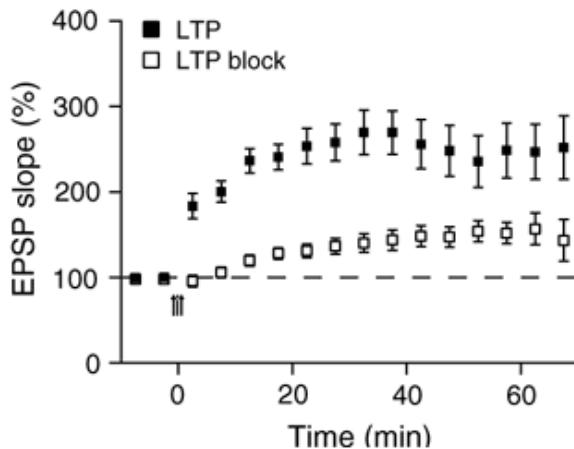
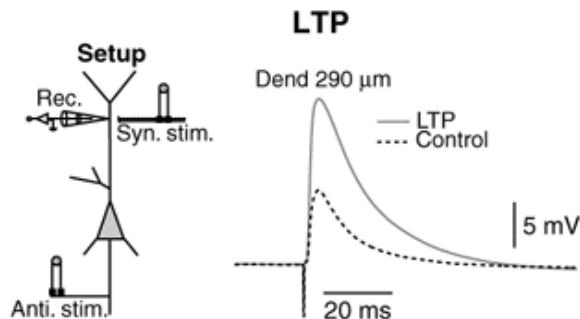
Modified from Zhang and Linden,  
Nature Reviews Neuroscience, 2002

# Local intrinsic plasticity accompanying synaptic plasticity

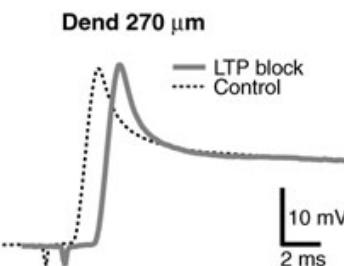
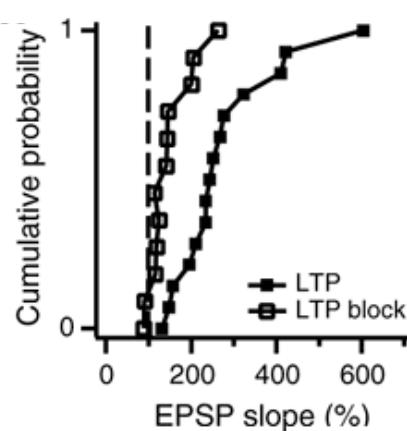
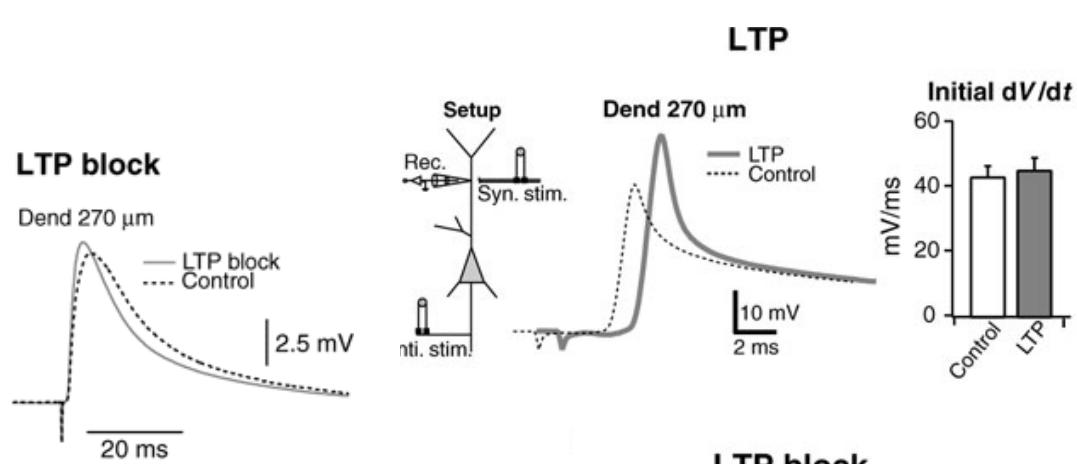
Synaptic weight



A current



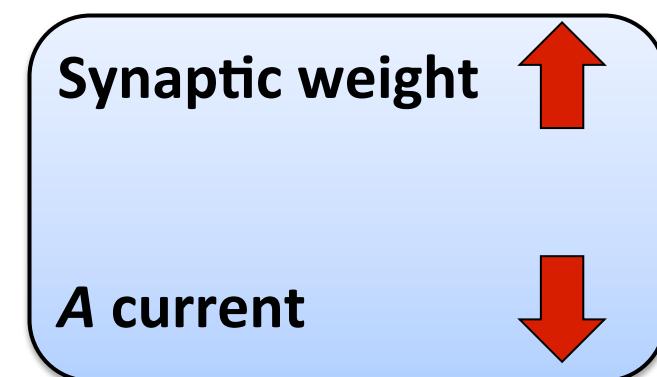
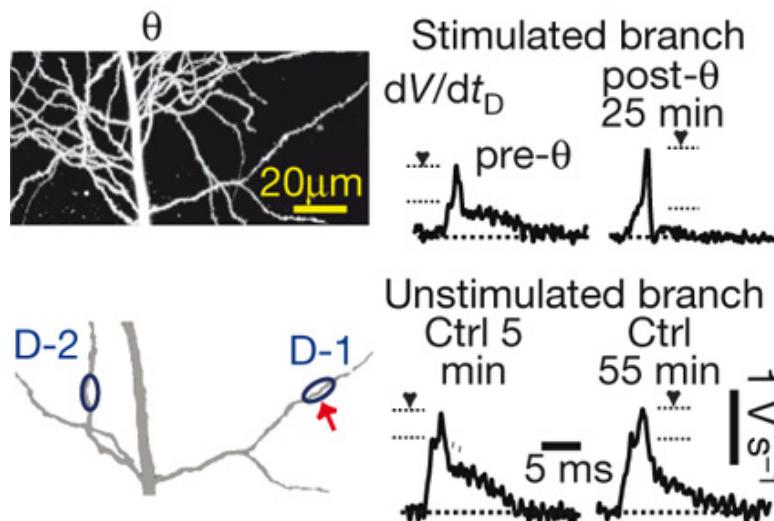
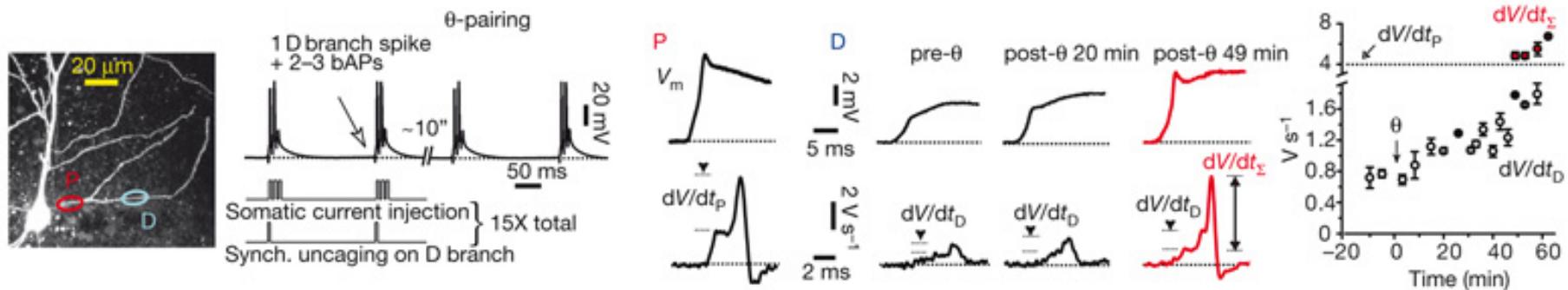
Localized plasticity in backpropagating action potentials



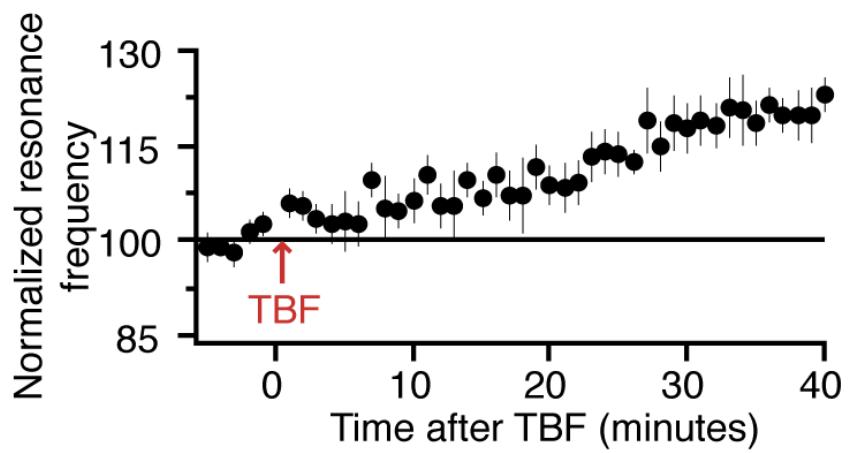
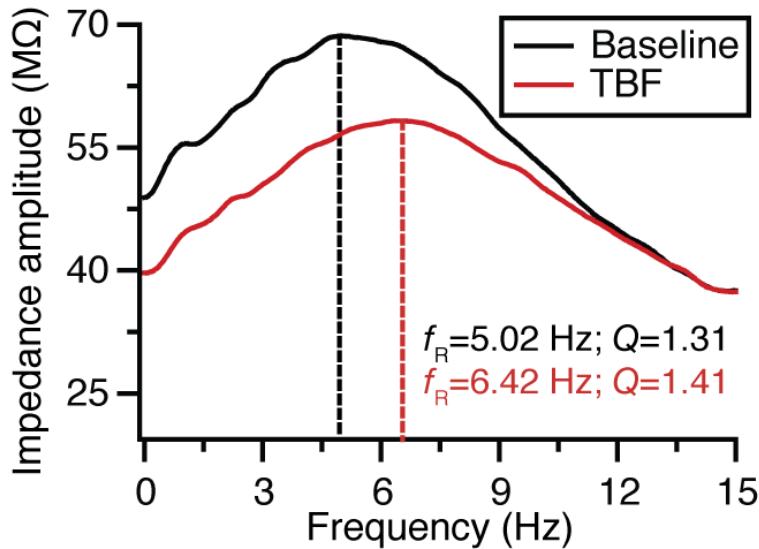
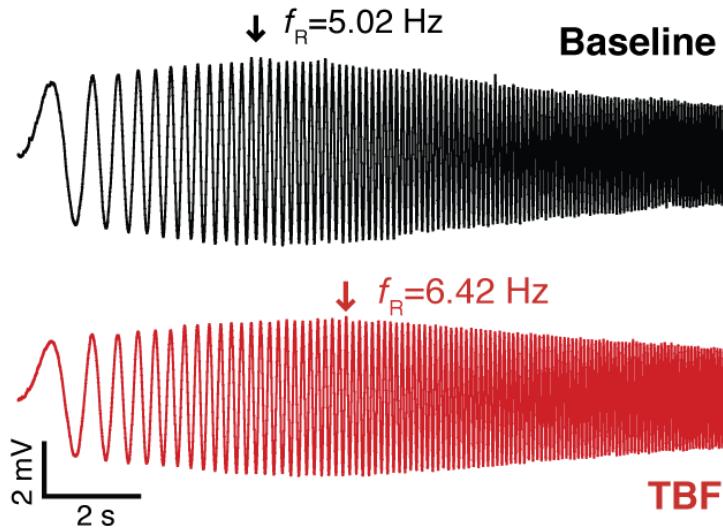
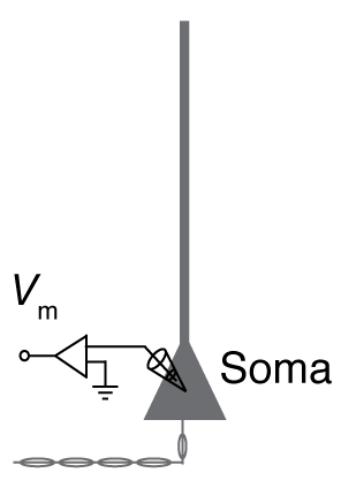
Frick et al., *Nature Neuroscience*, 2004

# Local intrinsic plasticity accompanying synaptic plasticity

## Localized plasticity in branch strength

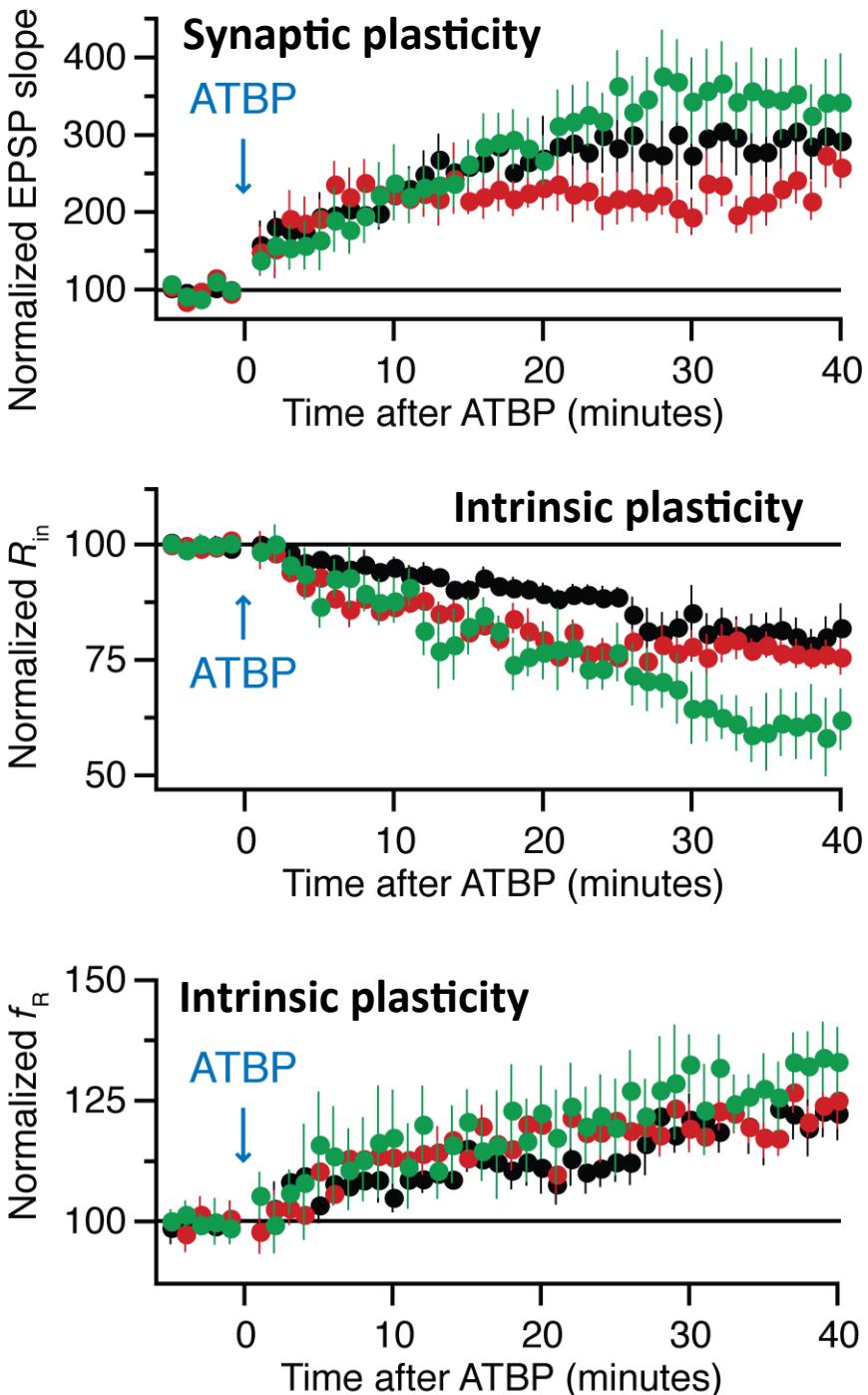
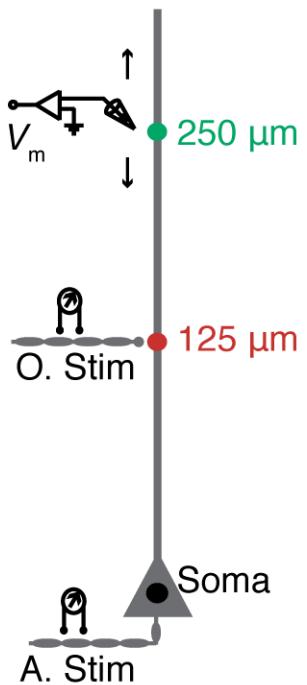
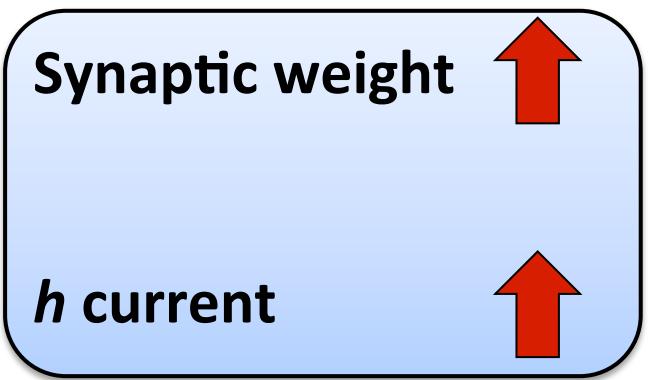


# Example: Plasticity in optimal response frequency of a neuron accompanies synaptic plasticity



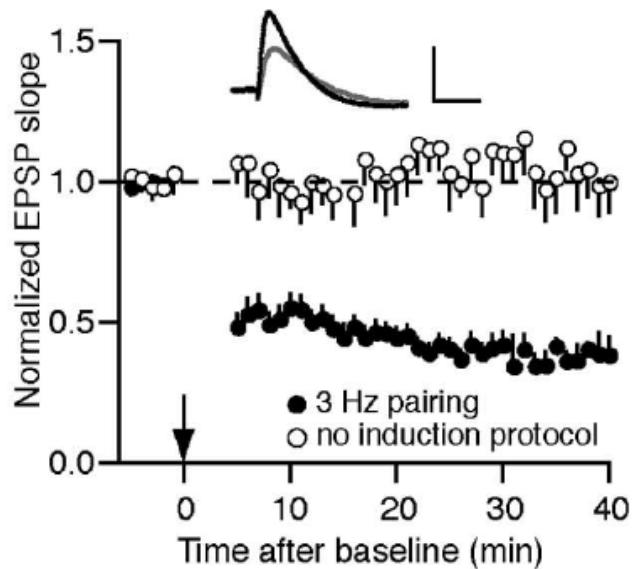
# Global plasticity in resonance frequency map accompanies synaptic plasticity

This is consequent to increases in a specific ion channel conductance: The  $h$  conductance



# Bidirectionality: Decrease in $h$ current accompanies decrease in synaptic strength

## Synaptic plasticity



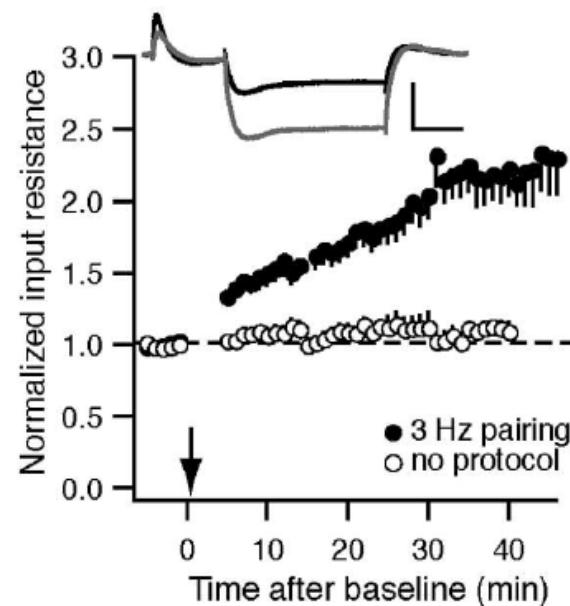
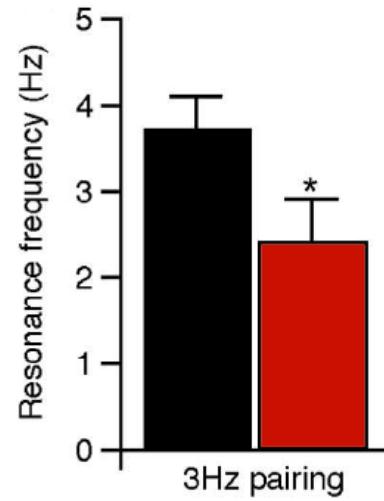
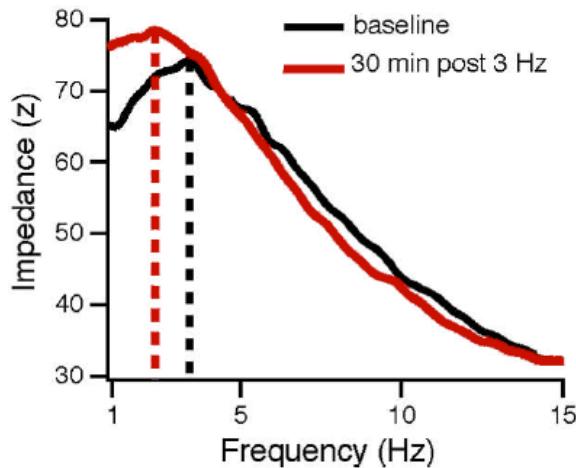
Synaptic weight



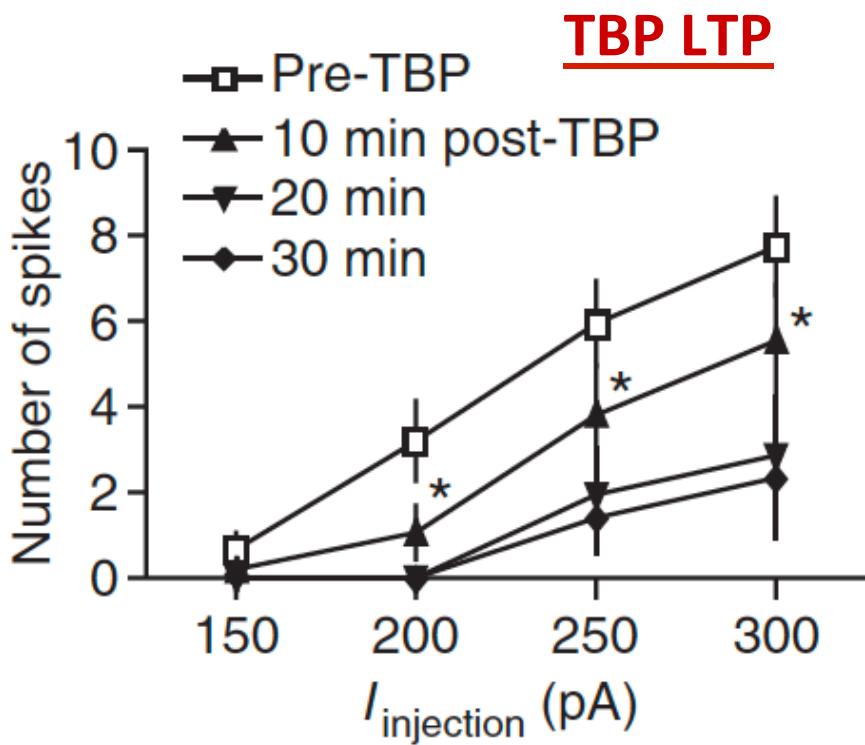
$h$  current



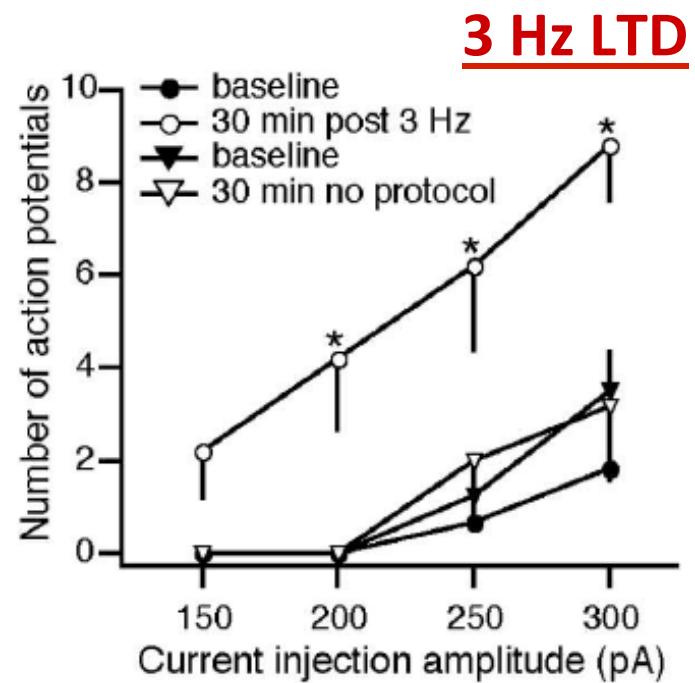
## Intrinsic Plasticity



# Changes in $h$ current imply changes in action potential firing frequency as well



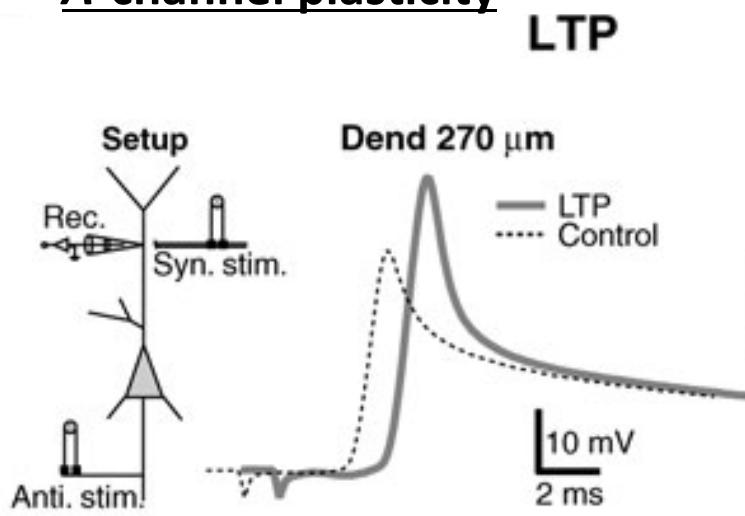
Fan et al., Nat. Neurosci., 2005



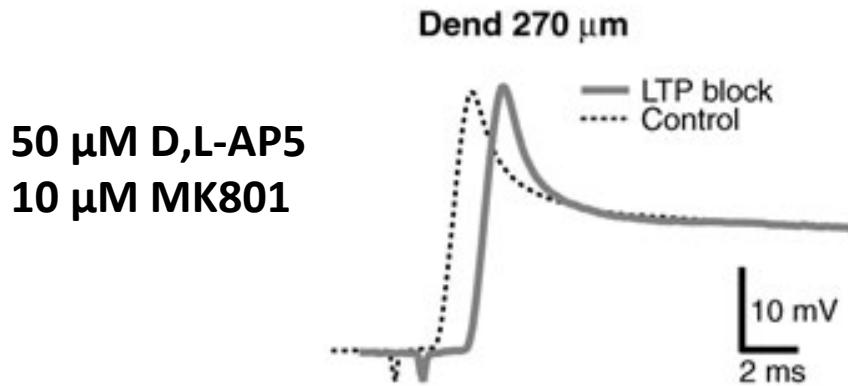
Brager and Johnston, JNS, 2007

# Blocking LTP also blocks intrinsic changes

## A-channel plasticity

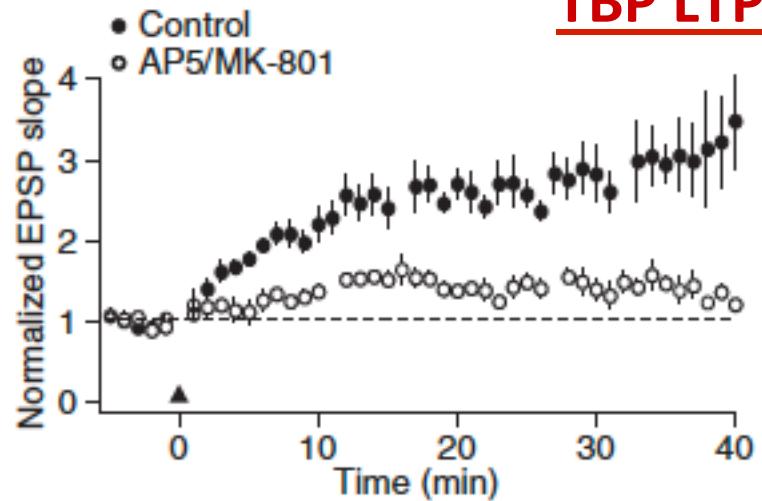


## **LTP block**

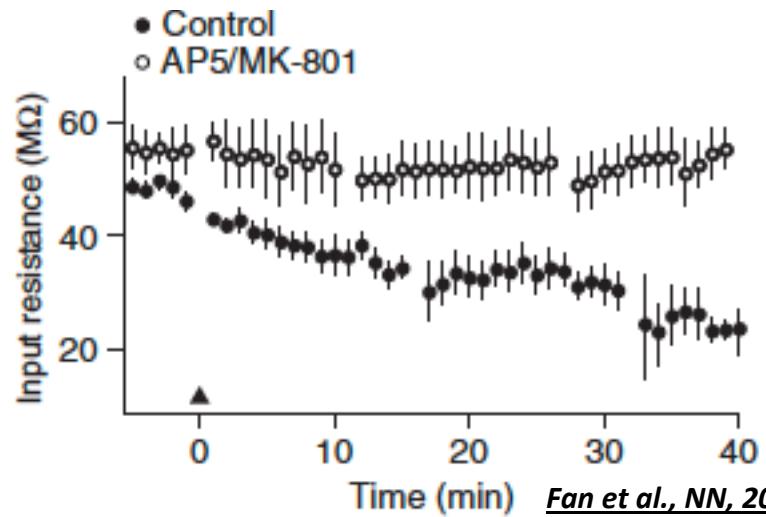


Frick et al., *NN*, 2004

## TBP LTP

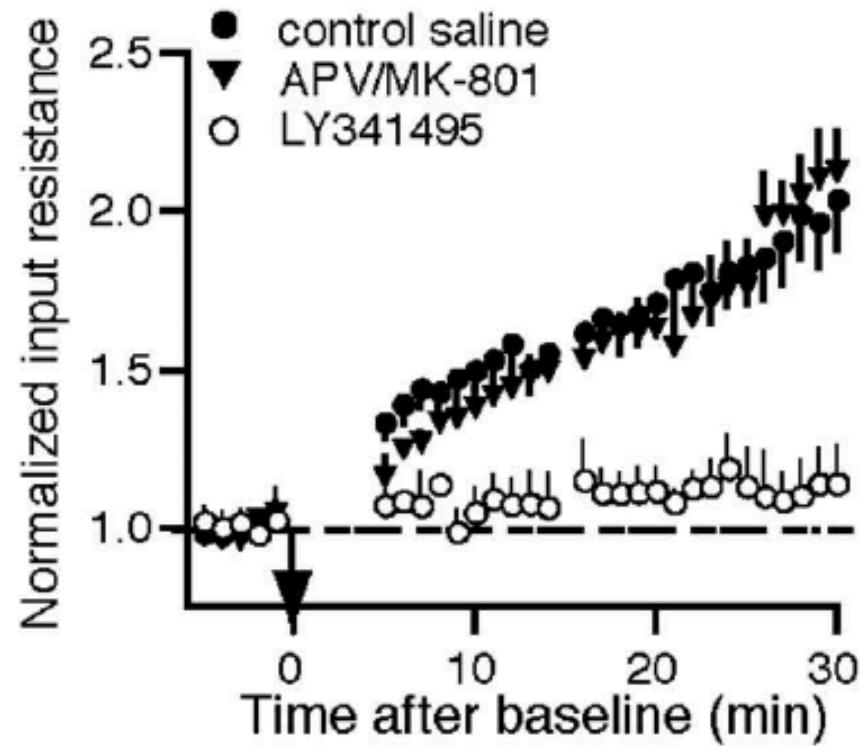
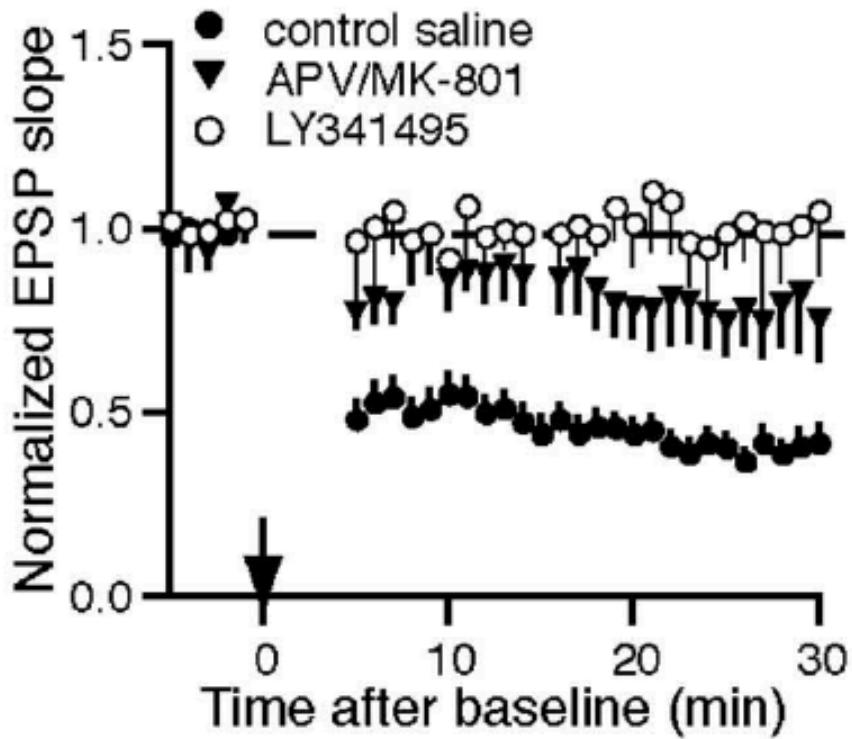


## h-channel plasticity



Fan et al., *NN*, 2005

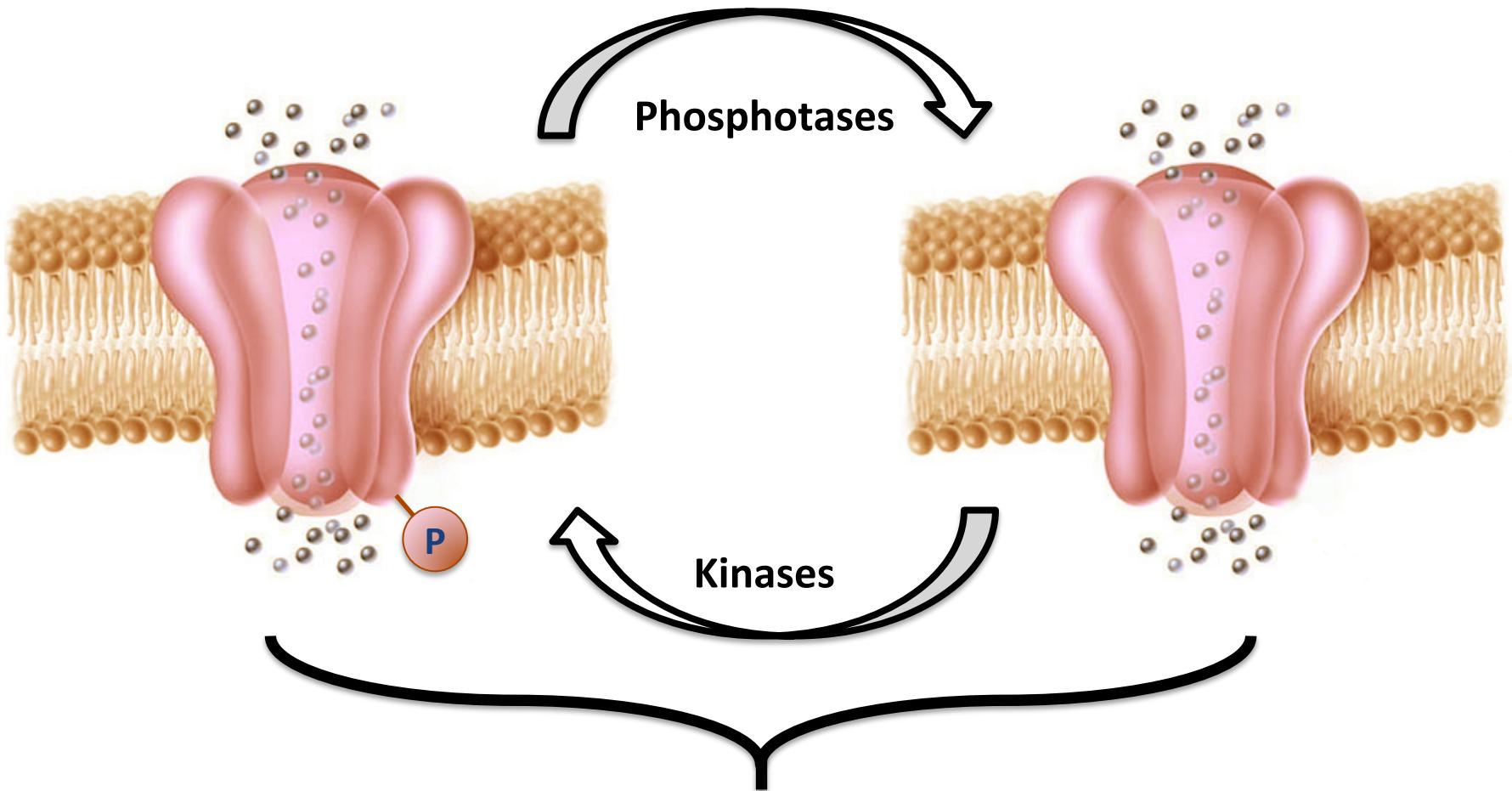
## Blocking LTD also blocks intrinsic changes



LTD is mostly blocked by NMDAR antagonists, but not change in input resistance

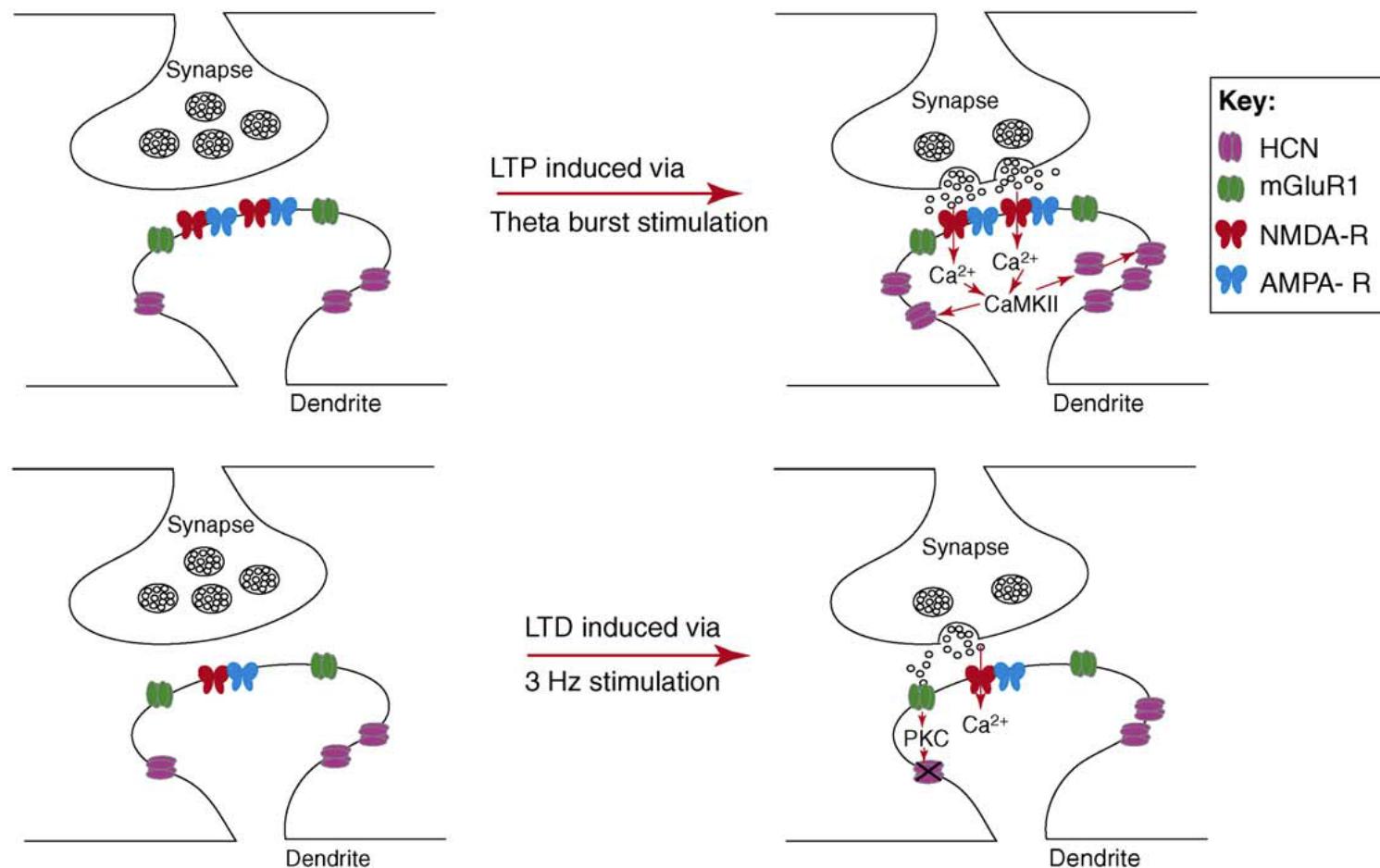
LY341495: mGluR antagonist.

# Calcium activates kinases or phosphatases



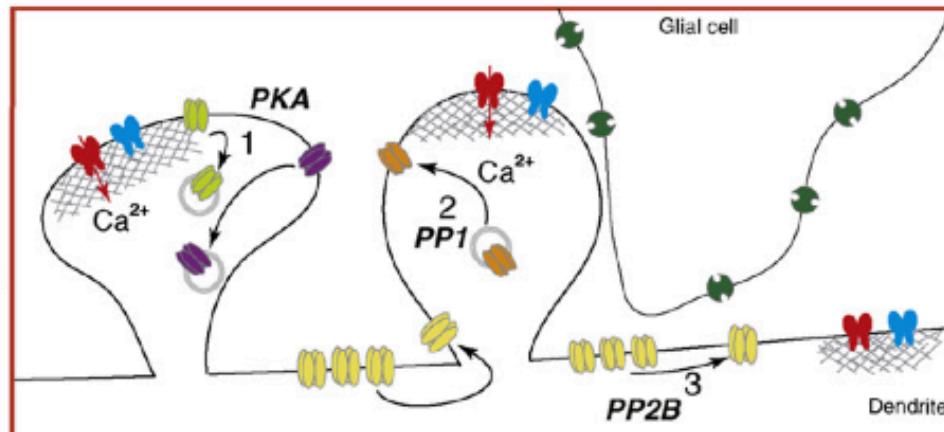
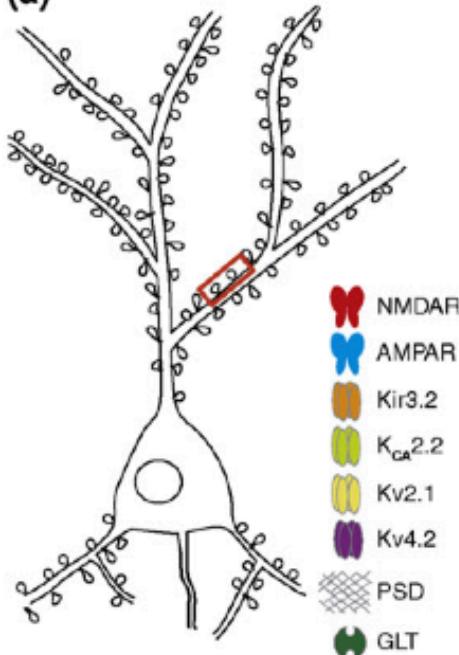
**Surface expression/internalization of channels  
and/or change in their properties!**

# Synaptic and intrinsic plasticity are mediated by the same downstream signaling pathways



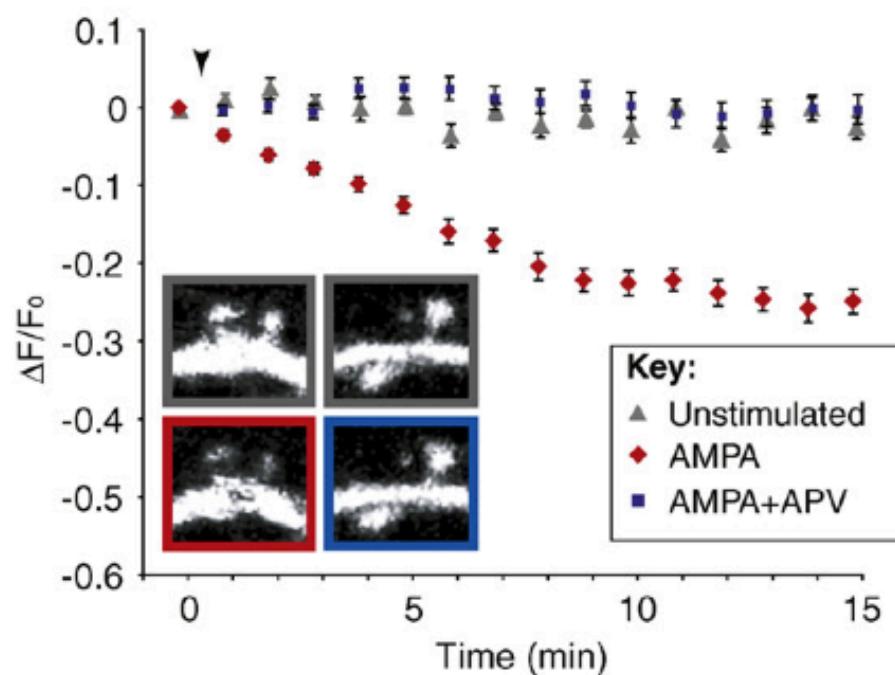
TRENDS in Neurosciences

Shah et al., TINS, 2010; also see references therein

**(a)**

KC<sub>a</sub>2.2 encodes SK

1. Internalization during LTP
2. Insertion necessary for depotentiation
3. Lateral translocation affecting intrinsic excitability

**(b)**

## Plasticity in potassium channels

**Internalization of EGFP-tagged K<sub>v</sub>4.2 channels**

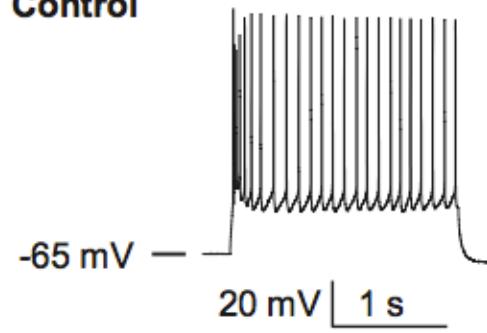
# Each channel in each neuron has specific signaling pathways associated with it — DO NOT GENERALIZE!

Channel Subtype	Dendritic localization	Role in dendritic excitability	Type of plasticity	Second messenger required	Trafficking mechanism
K <sub>v</sub> 4.2	Apical, oblique and basal dendrites of several types of central neurons	Determining bAP amplitude and width; limiting propagation of dendritic spikes; curtailing Ca <sup>2+</sup> influx due to bAP and synaptic potentials.	LTP; chemical neuronal activation (AMPA, KCl, glycine)	PKA activation	Clathrin-mediated endocytosis
K <sub>Ca</sub> 2.2	Apical dendrites and spines of hippocampal and amygdala lateral neurons	Maintenance of membrane potential; limiting NMDA-R activation in spines	LTP; chemical neuronal activation	PKA activation	Clathrin-mediated endocytosis
K <sub>i</sub> r	Hippocampal and neocortical apical dendrites and spines	Maintenance of membrane potential	Depotentiation (KCl, glutamate, NMDA, glycine)	PP1 activation	Membrane insertion via recycling of endosomes
K <sub>v</sub> 2.1	Somatodendritic compartments as well as AIS	Regulation of membrane repolarization following APs	Enhanced neuronal activity	PP2B (calcineurin) activation	Lateral dispersion of subunits
K <sub>v</sub> 1.1	Hippocampal dendrites	?	Reduced neuronal activity	mTOR inhibition	Enhanced local protein synthesis
HCN	Hippocampal CA1 apical dendrites and Spines	Regulation of resting membrane potential, EPSP shapes and integration	LTP induced by theta-burst stimulation	CaMKII activation	?
HCN	Prefrontal cortex spines	Regulation of resting membrane potential, EPSP shapes and integration	α2-adrenoreceptor-mediated	cAMP inhibition	?
HCN	Hippocampal CA1 apical dendrites and spines	Regulation of resting membrane potential, EPSP shapes and integration	LTD	PKC activation	?
Ca <sub>v</sub> 2.3	Hippocampal spines	?	LTP	CaMKII activation	?
Na <sub>v</sub>	Apical dendrites	Boosting bAPs and generation of dendritic spikes	Intrinsic plasticity	CaMKII activation	?

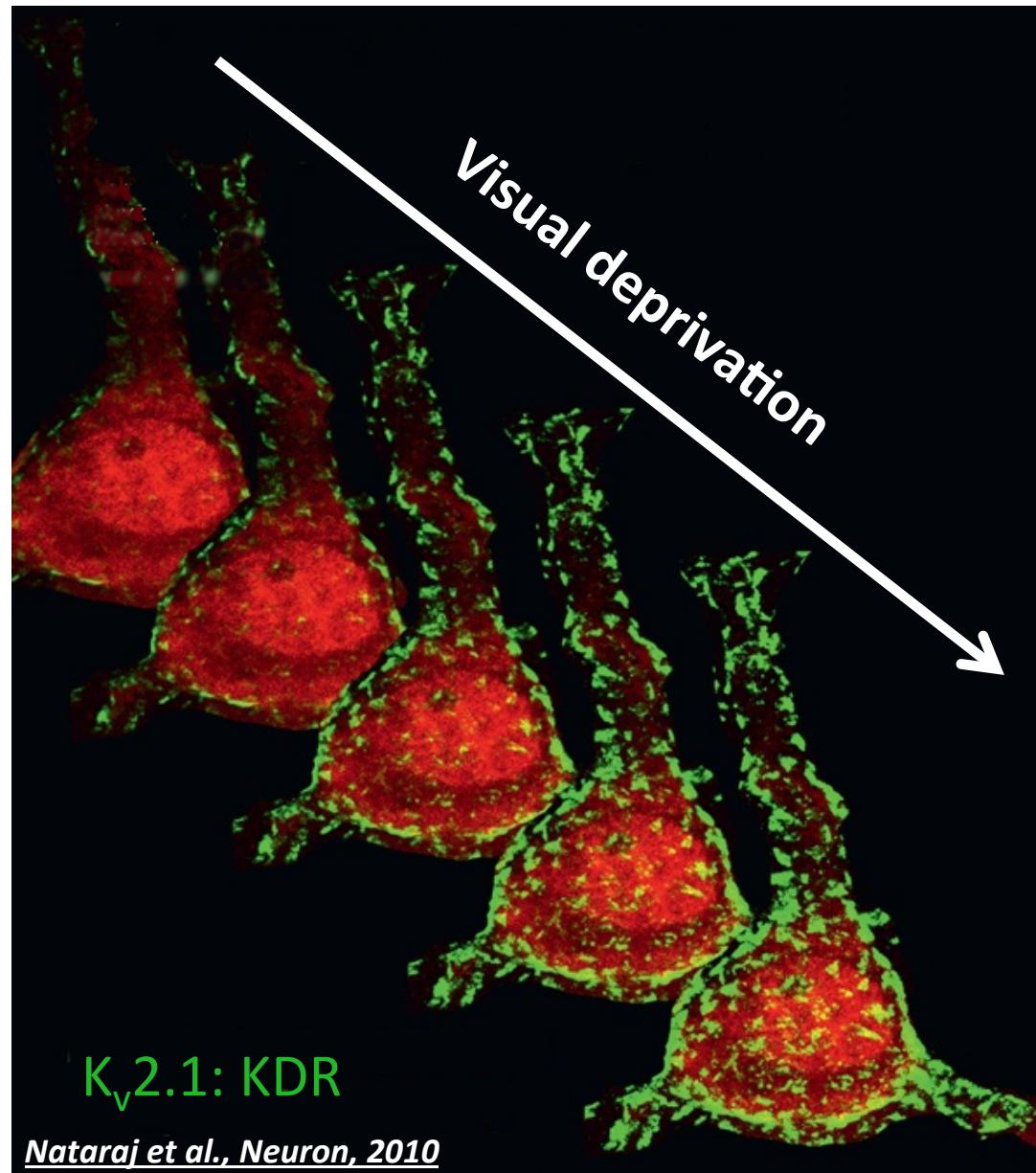
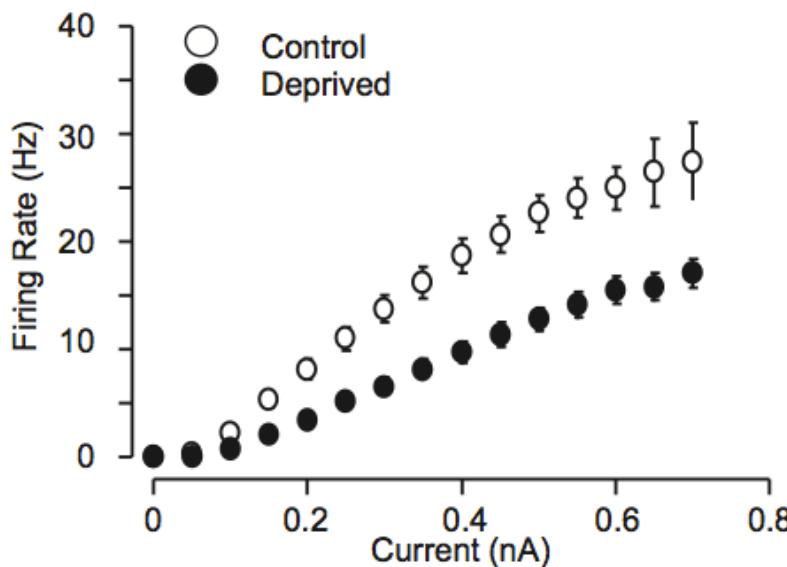
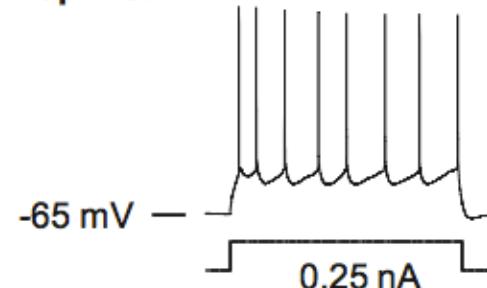
# **Experience-dependent intrinsic plasticity**

# Experience-dependent intrinsic plasticity through K<sup>+</sup> channels

Control

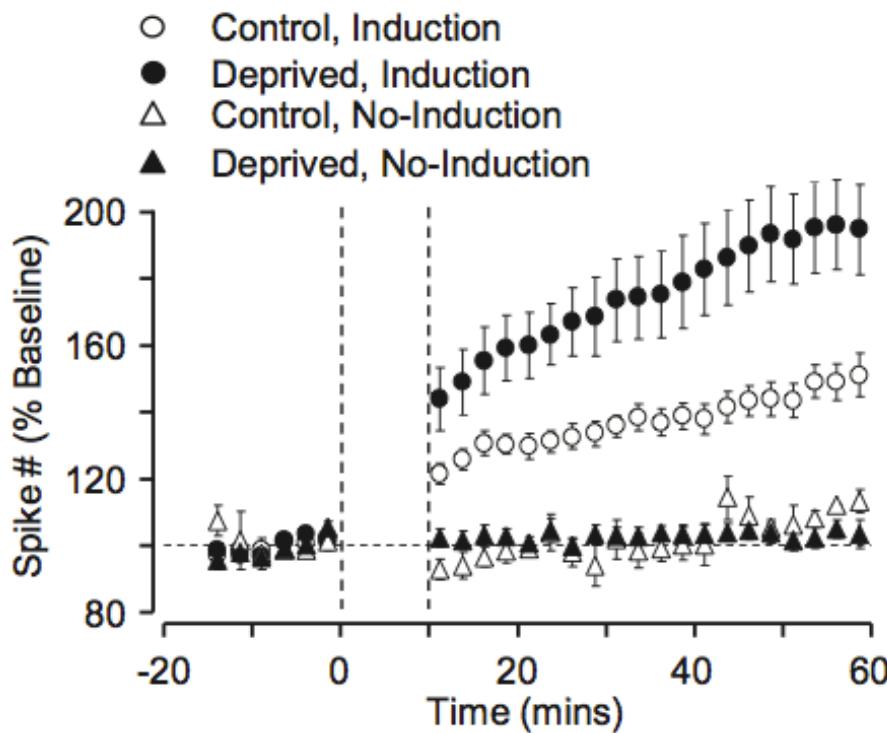
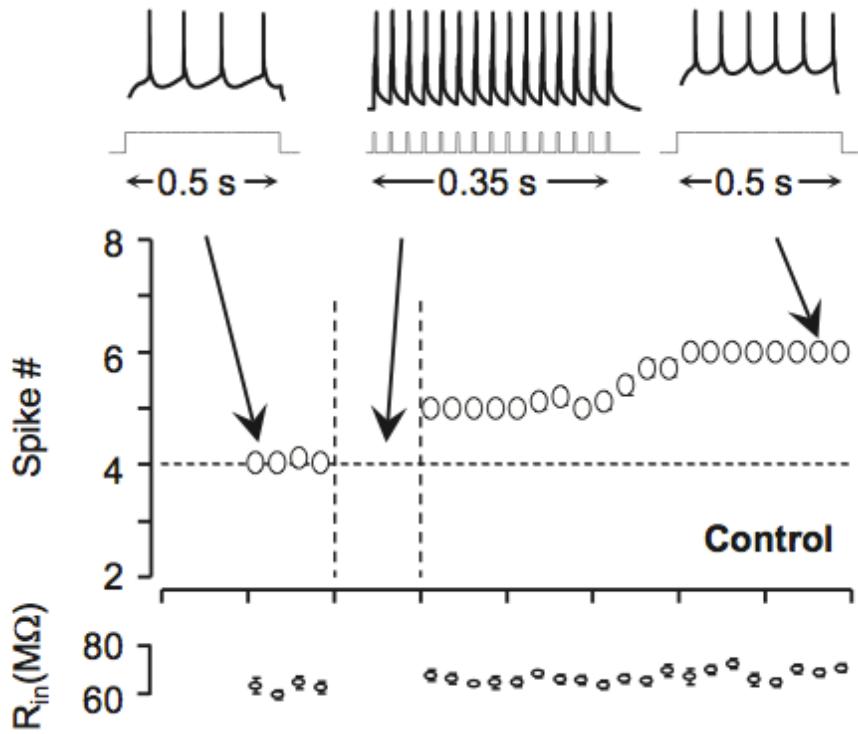


Deprived

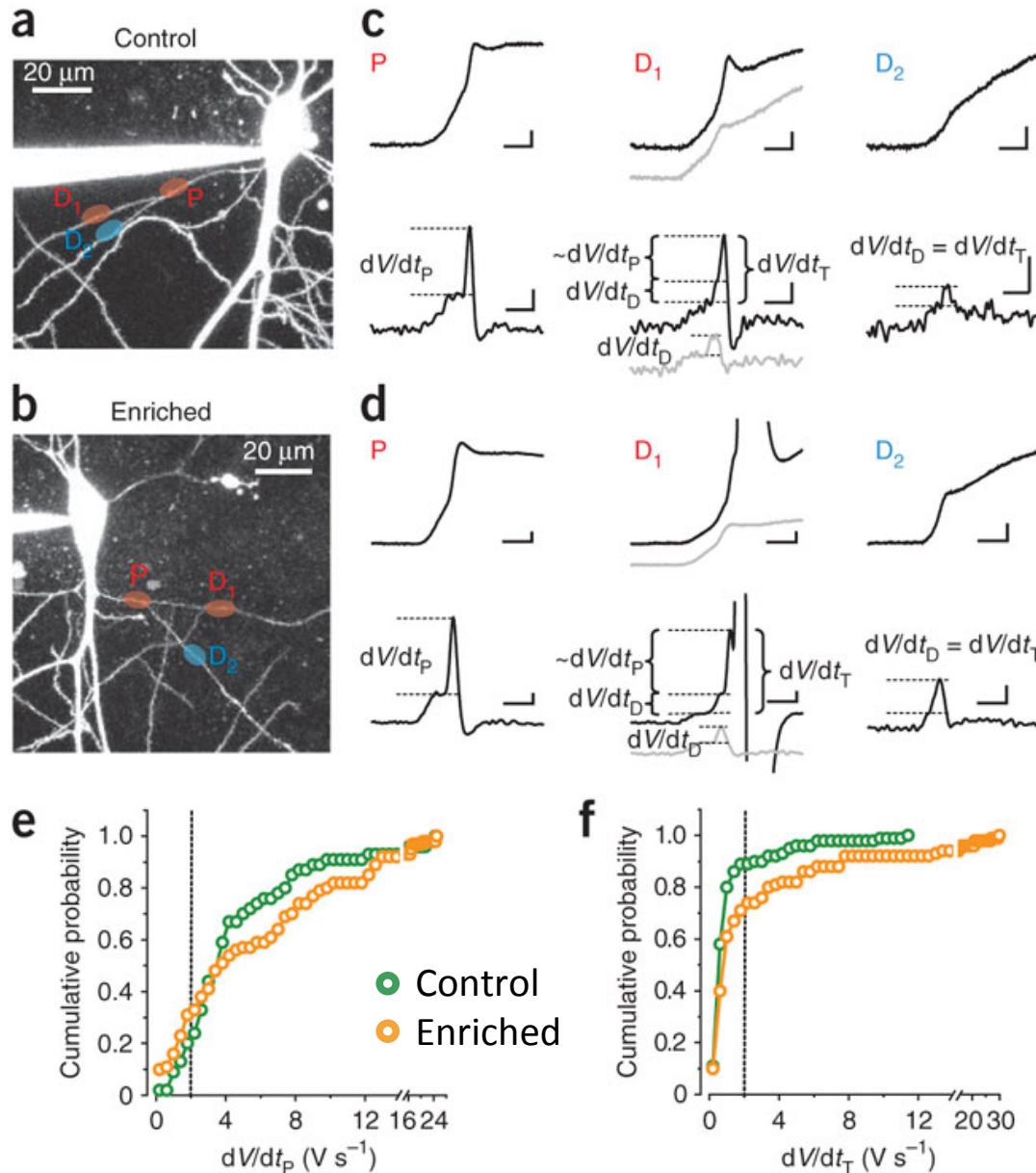


# Monocular deprivation also alters plasticity of intrinsic excitability

15 spikes at 40 Hz, every 4 s for 5 mins



# Experience-dependent intrinsic plasticity



Exposure of rats to enriched environment reduces A-type current in dendritic branches, thus increasing their ability to generate dendritic spikes

See (Mozzachiodi and Bryne, TINS, 2010) and (Zhang and Linden, NRN, 2003) for more studies showing learning-dependent intrinsic plasticity

# Summary of Oversimplification #2

Synaptic plasticity protocols result in concurrent plasticity in several ion channels mediated by the same downstream mechanisms as that of synaptic plasticity.

Ion channel plasticity has been shown with several learning paradigms as well

## Dendritic ion channel trafficking and plasticity

*Trends in Neurosciences* Vol.33 No.7

Mala M. Shah<sup>1</sup>, Rebecca S. Hammond<sup>2,3</sup> and Dax A. Hoffman<sup>3</sup>

Also see Zhang and Linden, Nat. Rev. Neurosci. 2002; Kim and Linden, Neuron, 2008; Narayanan and Johnston, J. Neurophysiol., 2012.

## More than synaptic plasticity: role of nonsynaptic plasticity in learning and memory

*Trends in Neurosciences* Vol.33 No.1

Riccardo Mozzachiodi<sup>1</sup> and John H. Byrne<sup>2</sup>

If you are interested in adding evidence for learning/memory (in a behavioral task) being solely mediated by any form of plasticity (synaptic, intrinsic or structural) in one set of synapses/neurons, be sure to ask yourself:

“Are you sure nothing else is changing in neurons (cells) of the same brain region or the others, which could be mediating/contributing to the observed behavioral changes?”

And also remember:

- (i) Correlation does not imply causation!
- (ii) Not measuring other forms of plasticity or plasticity in other brain regions does not mean they don't exist!!

## **Summary and Conclusions**

**The old view:** Cajal's law of dynamic polarization, passive dendrites performing algebraic sum of inputs with a single nonlinearity at the soma. Changes in synapses form the locus for learning and memory

**The new view:** The presence and plasticity of voltage-gated ion channels (VGIC) in the dendrites of a single neuron make it a really powerful information processing machine. Intrinsic plasticity also is a putative substrate for learning and memory

**Plasticity rules for different VGICs:** Incorporation of the VGICs and their plasticity into neural network models through appropriate rules will help us unravel the roles of intrinsic plasticity in learning and memory

**Synergy between synaptic and intrinsic plasticity:** Synergistic interactions between synaptic plasticity and intrinsic plasticity across the dendritic arbor could be postulated to accomplish the twin goals of efficient encoding of incoming stimuli and concurrent homeostasis to accommodate encoding-induced plasticity.