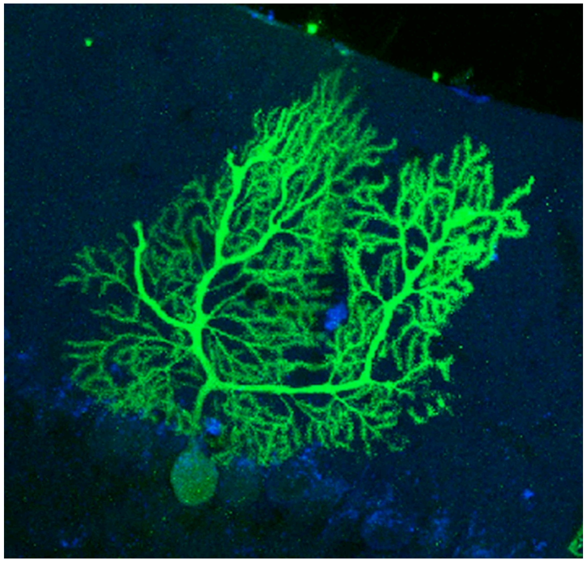
Ion channels, active dendrites, and computation

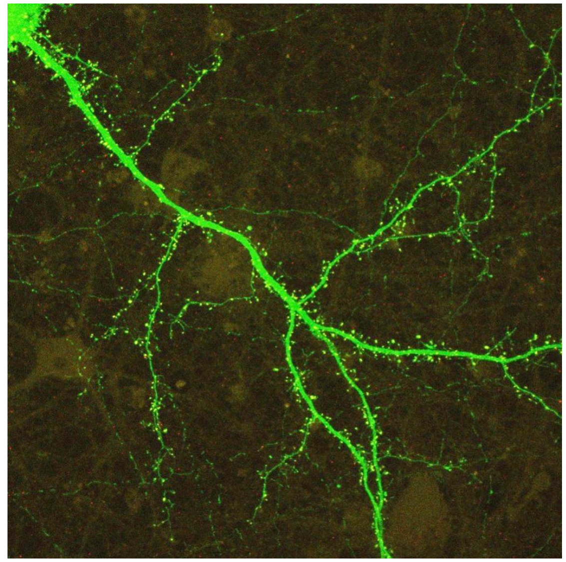
Weinan Sun

HHMI
Janelia Research Campus
Spruston Lab

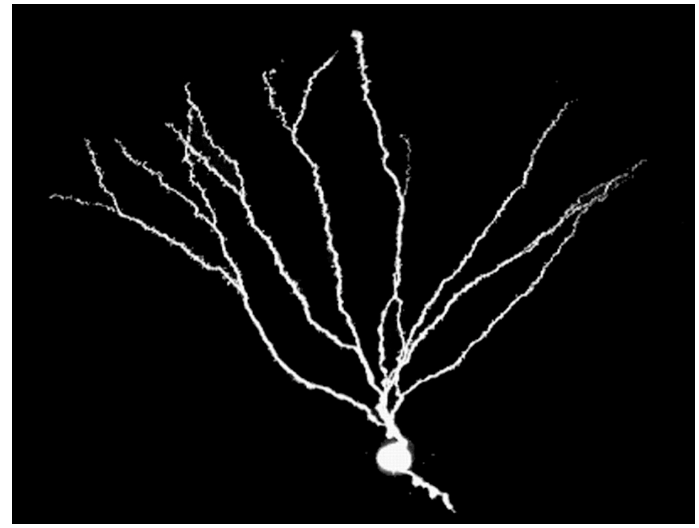
Neuronal diversity



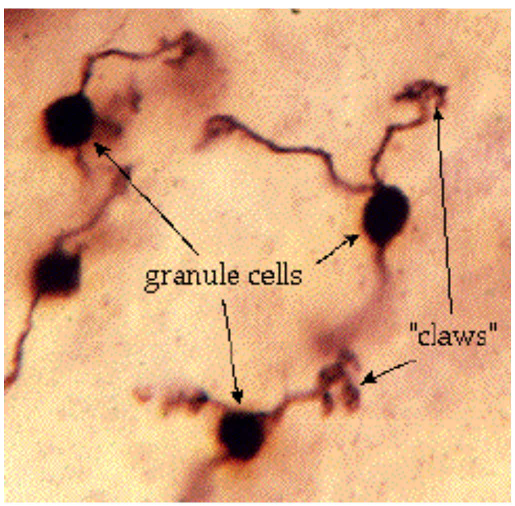
Cerebellar Purkinje cell



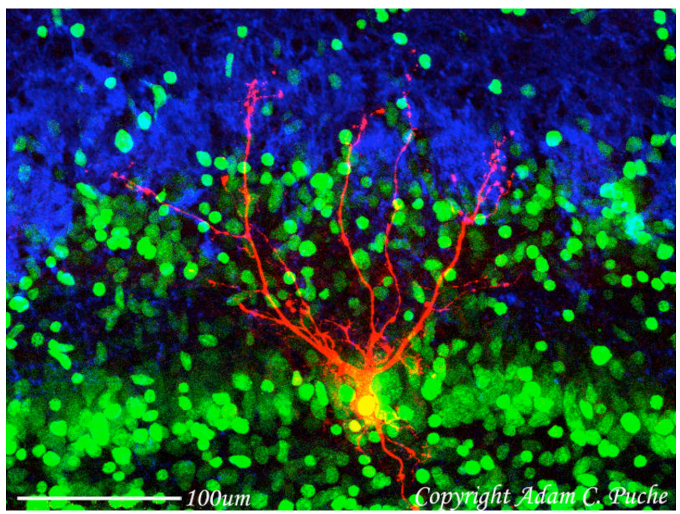
Striatal medium spiny neuron



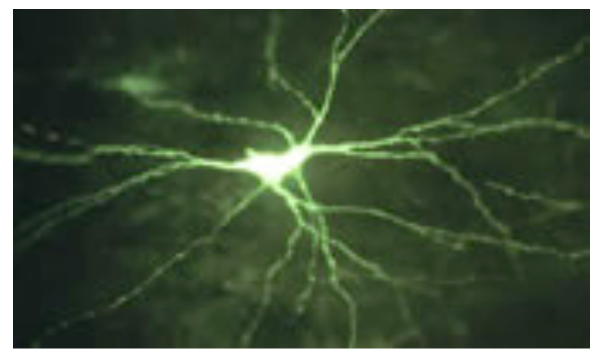
Dentate granule cell



Cerebellar granule cells

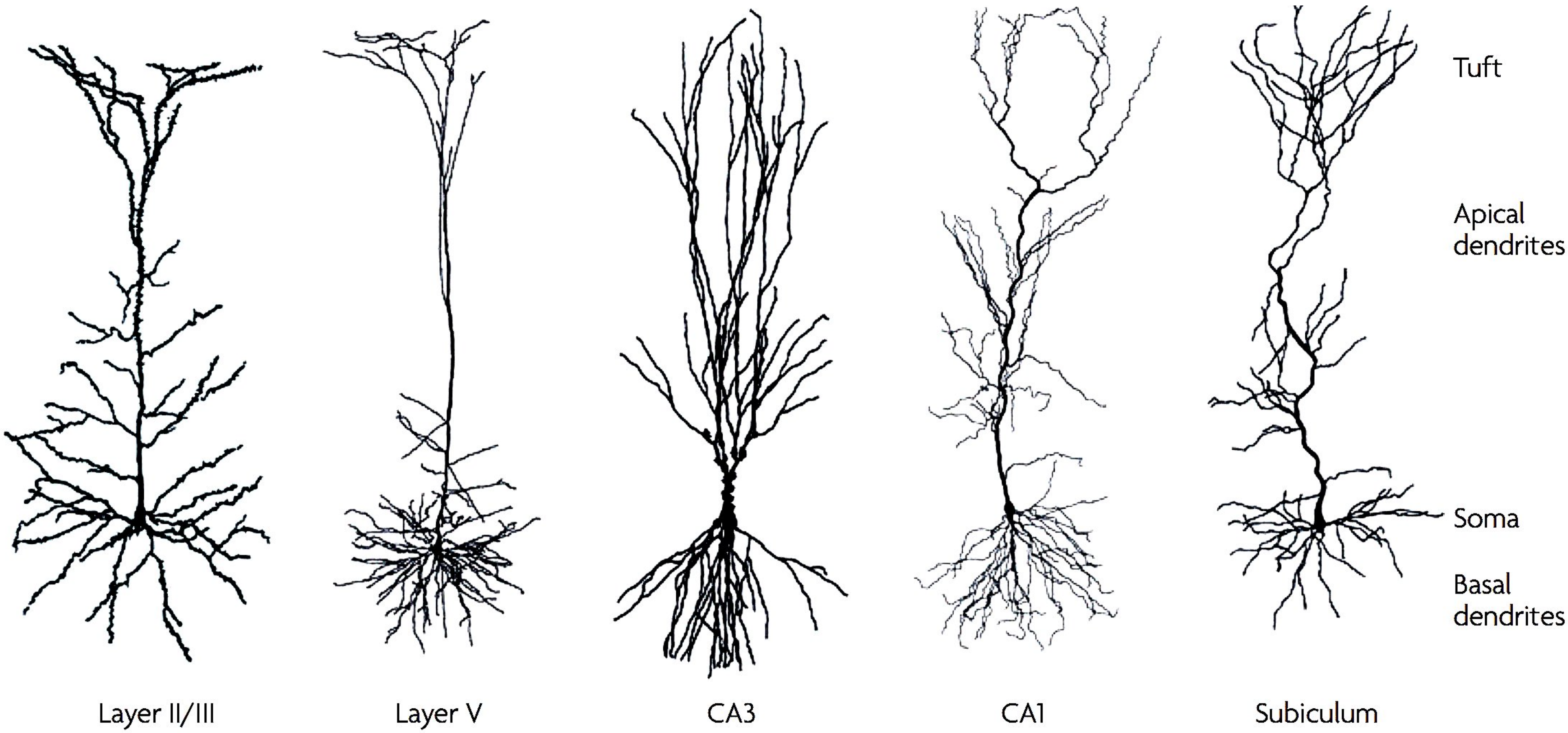


Olfactory mitral cell

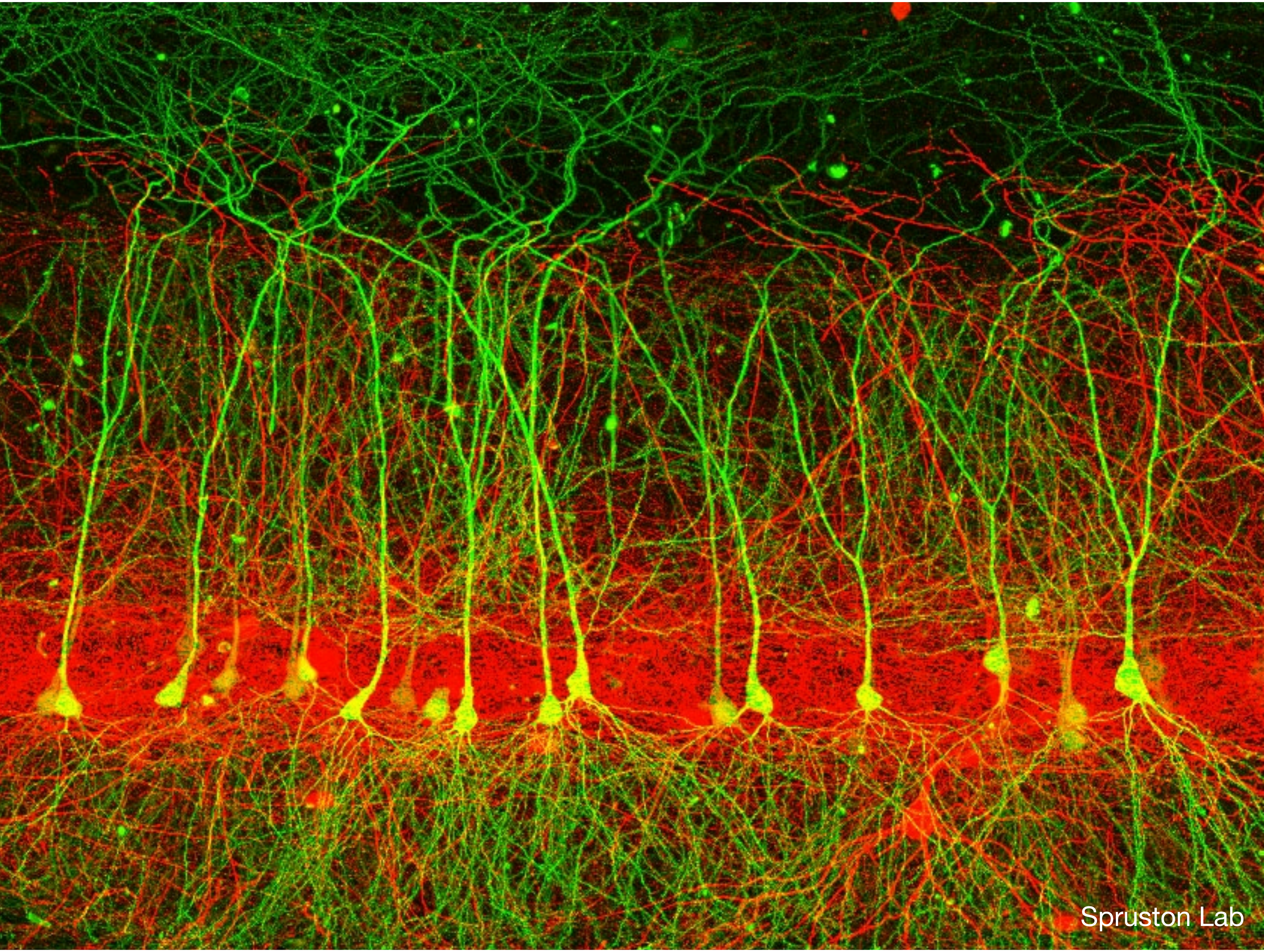


Spinal motor neuron

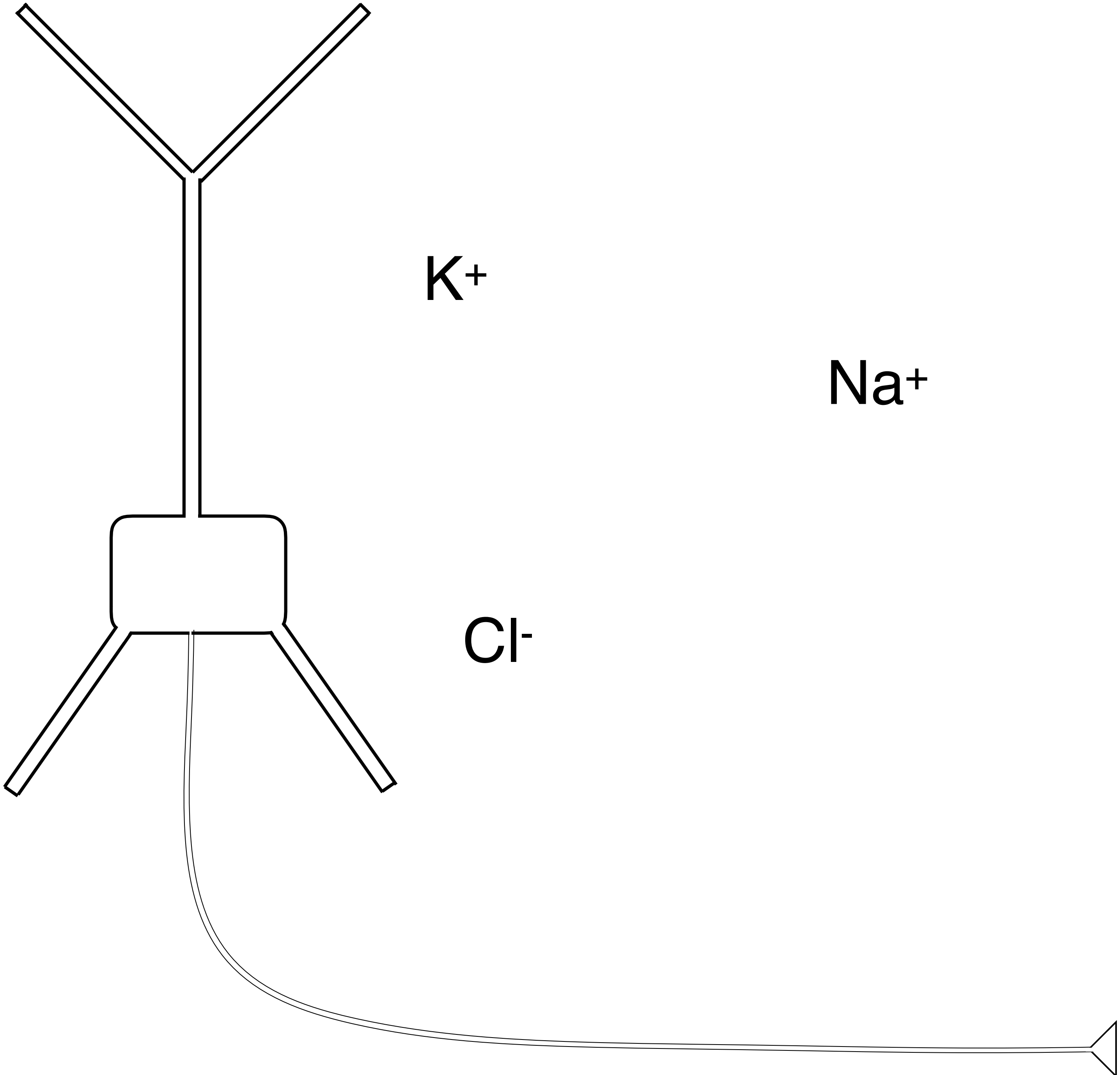
Pyramidal neurons



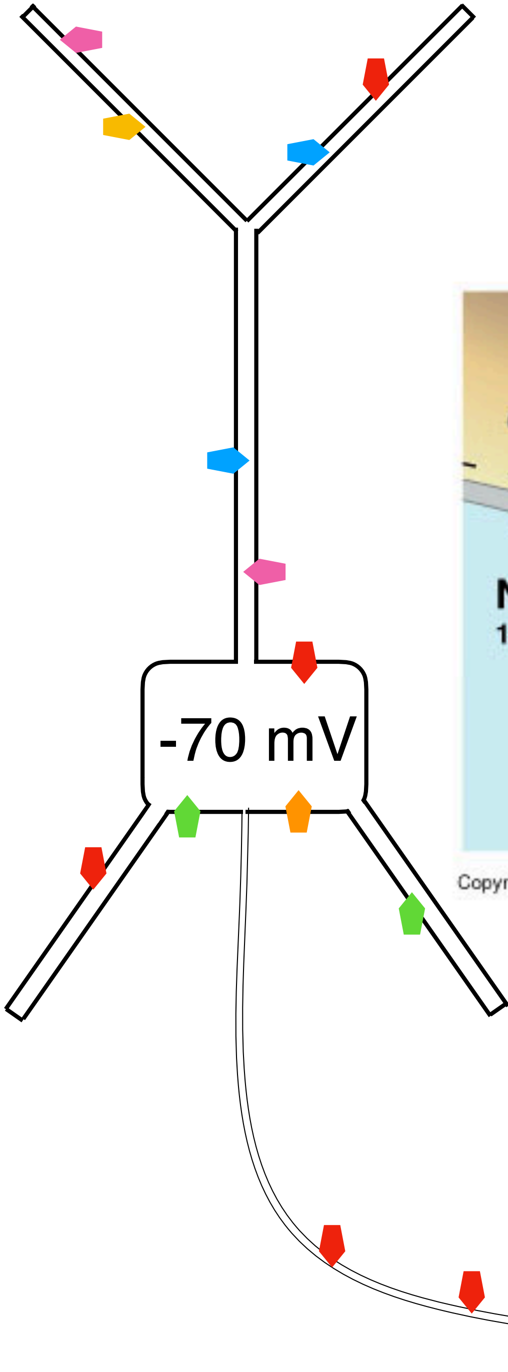
Spruston, 2008

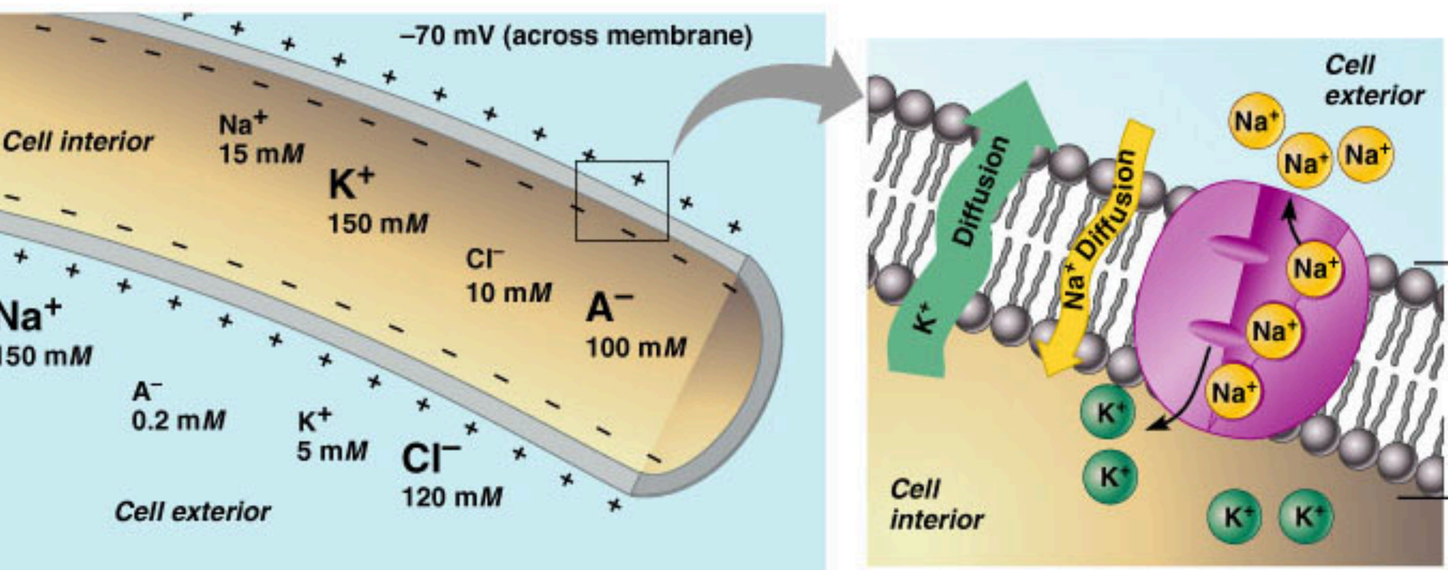

Spruston Lab

Lipids and ions

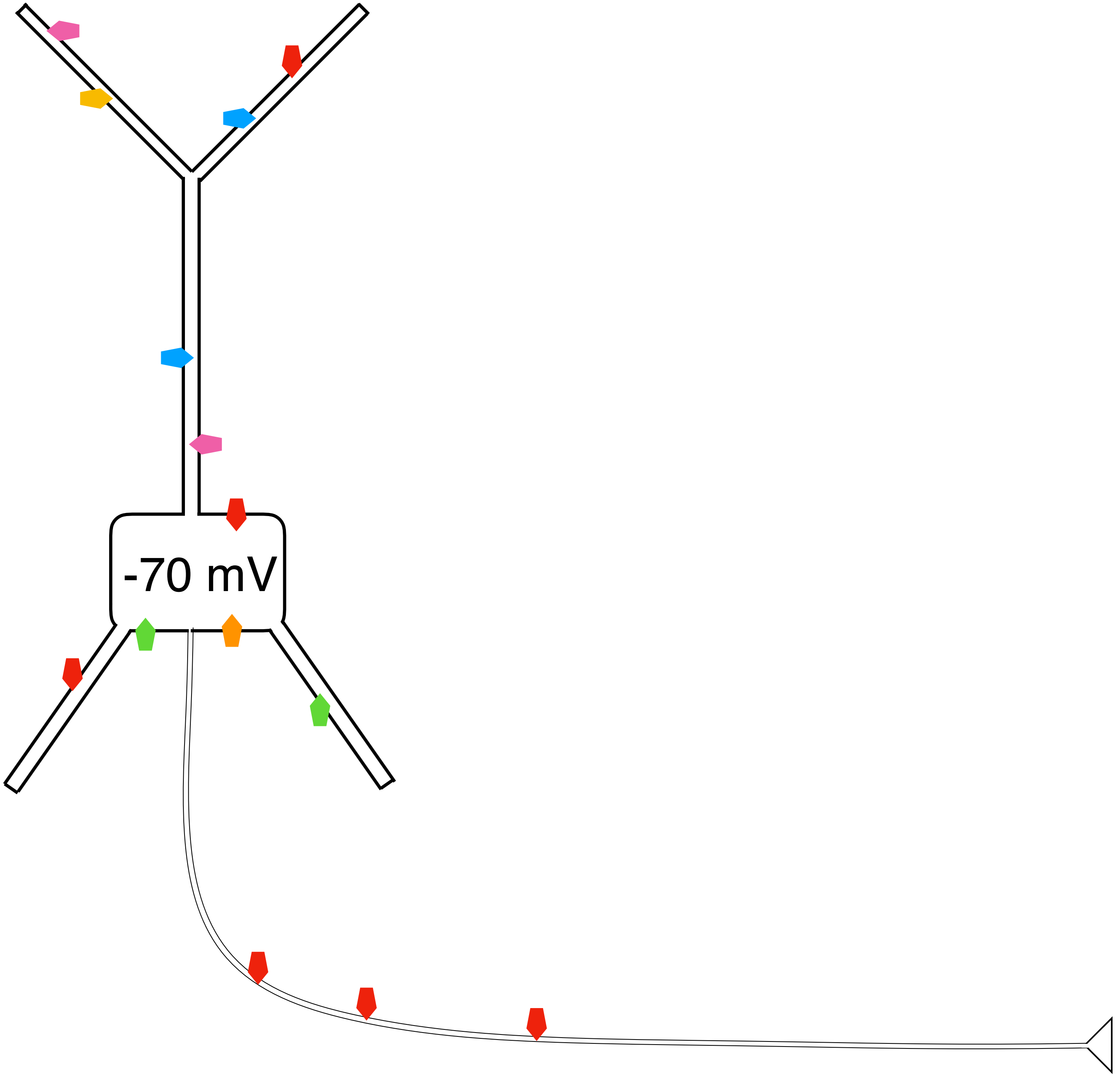


Membrane proteins are fundamental for electrical properties

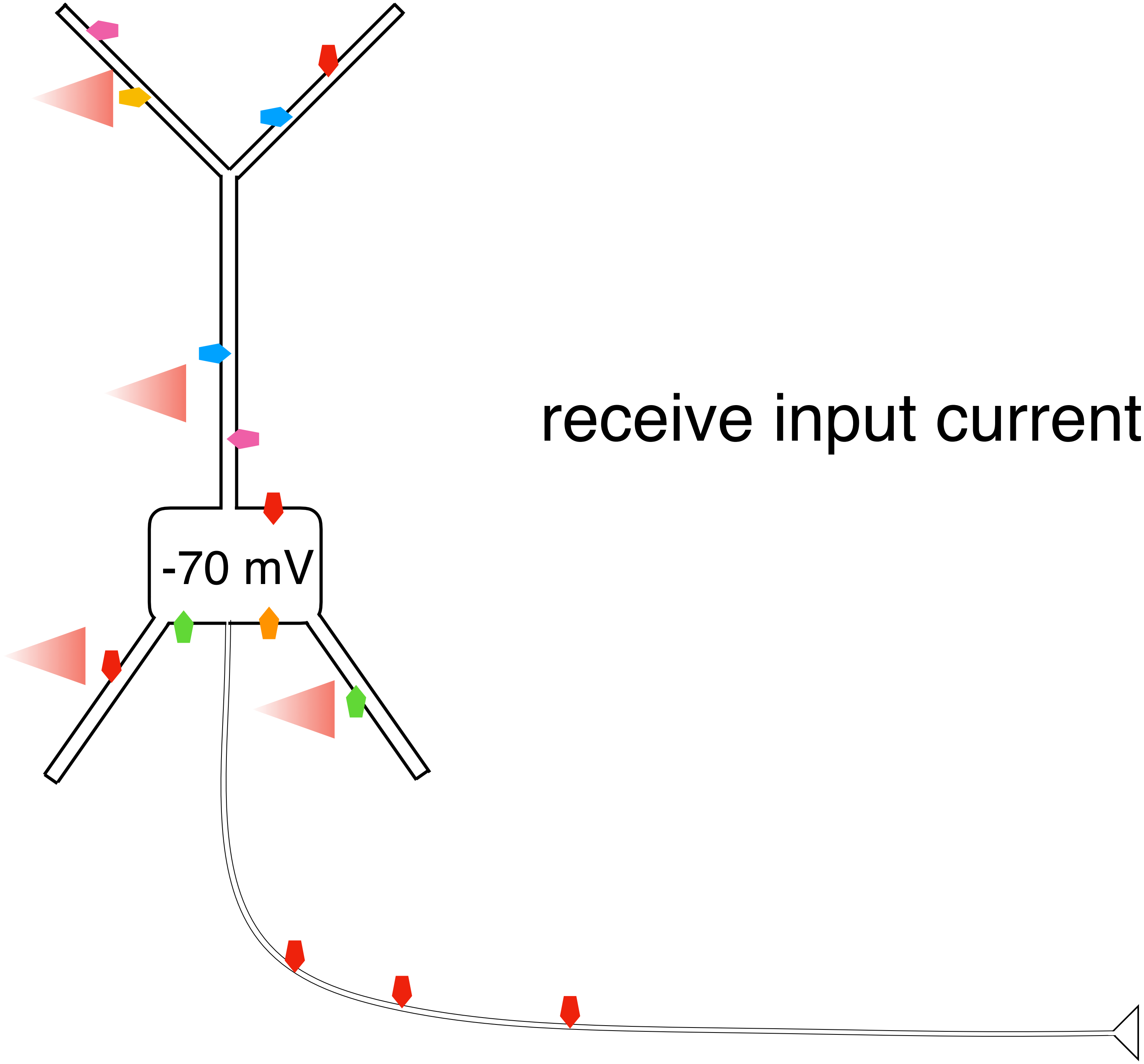




Input - output function of a neuron

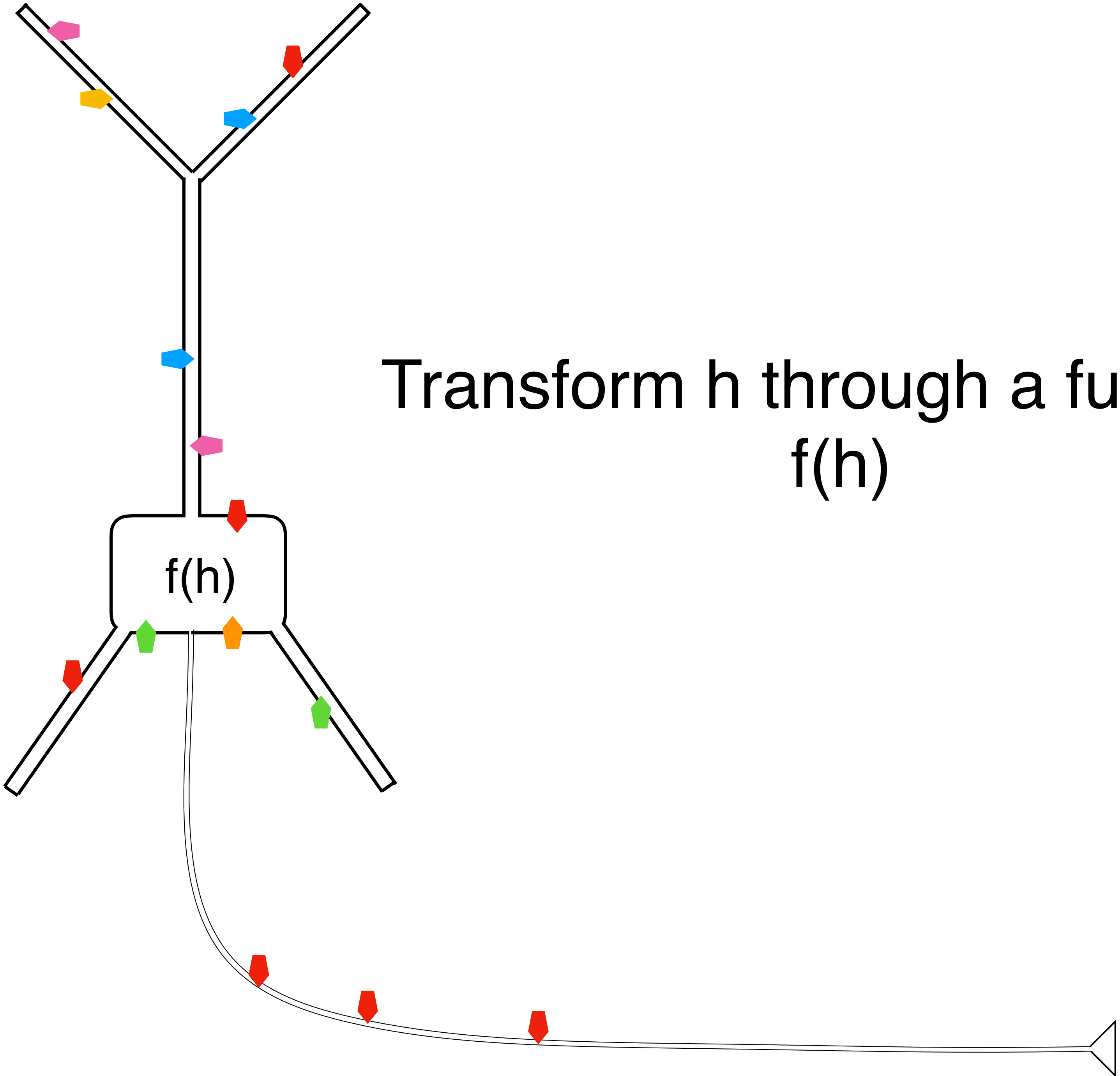


Input - output function of a neuron



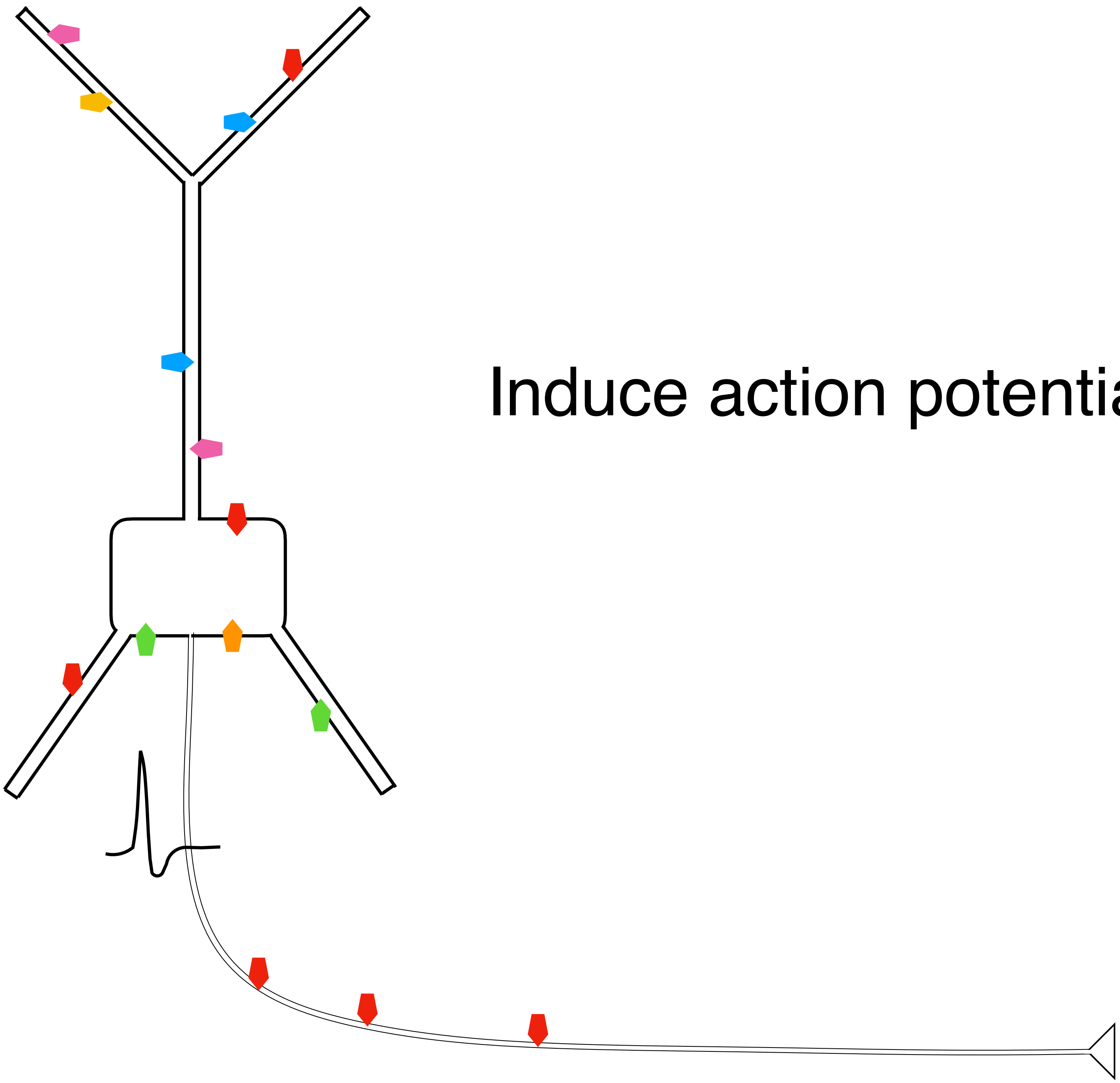
receive input current h

Input - output function of a neuron



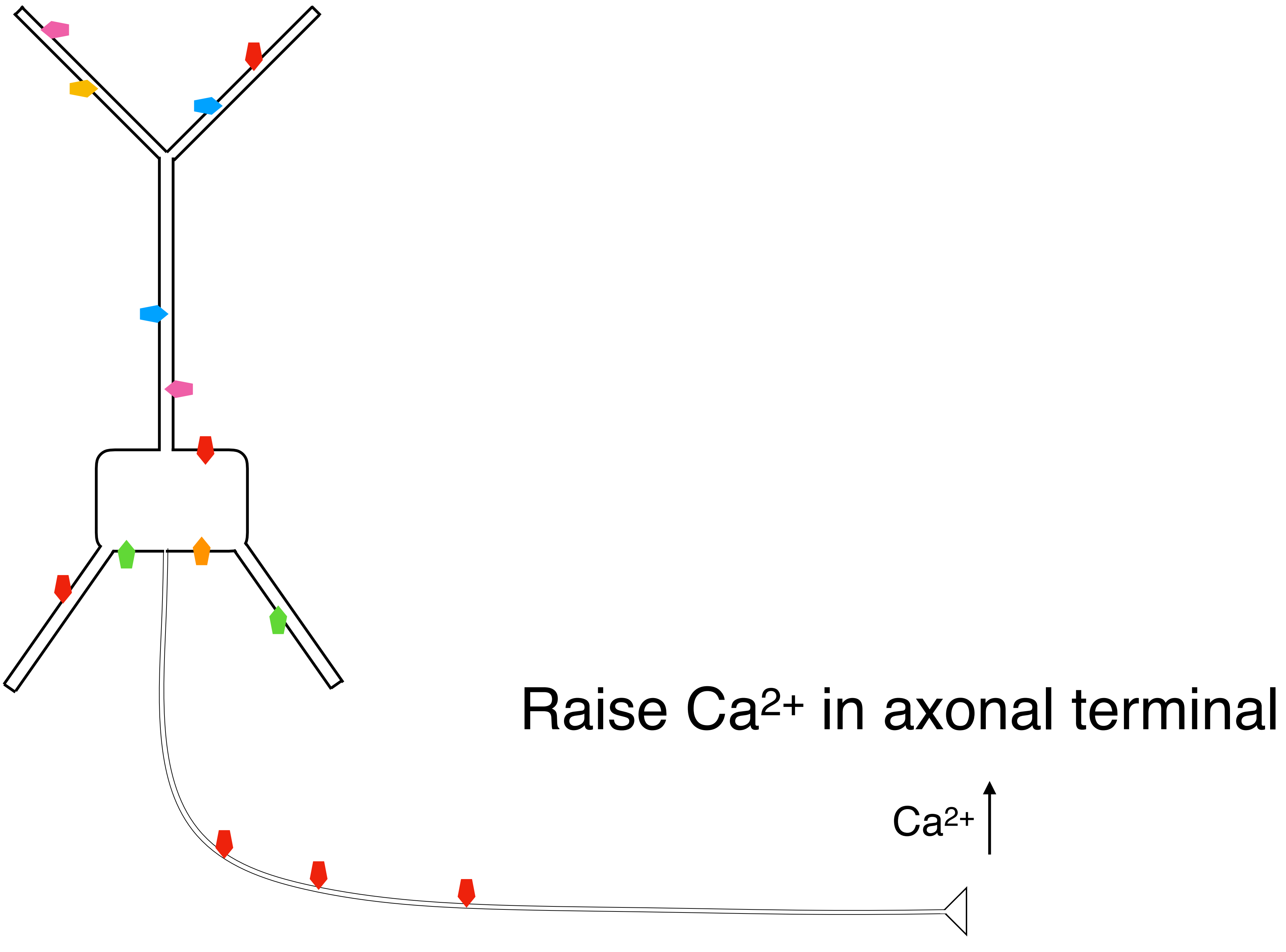
Transform h through a function f(h)

Input - output function of a neuron

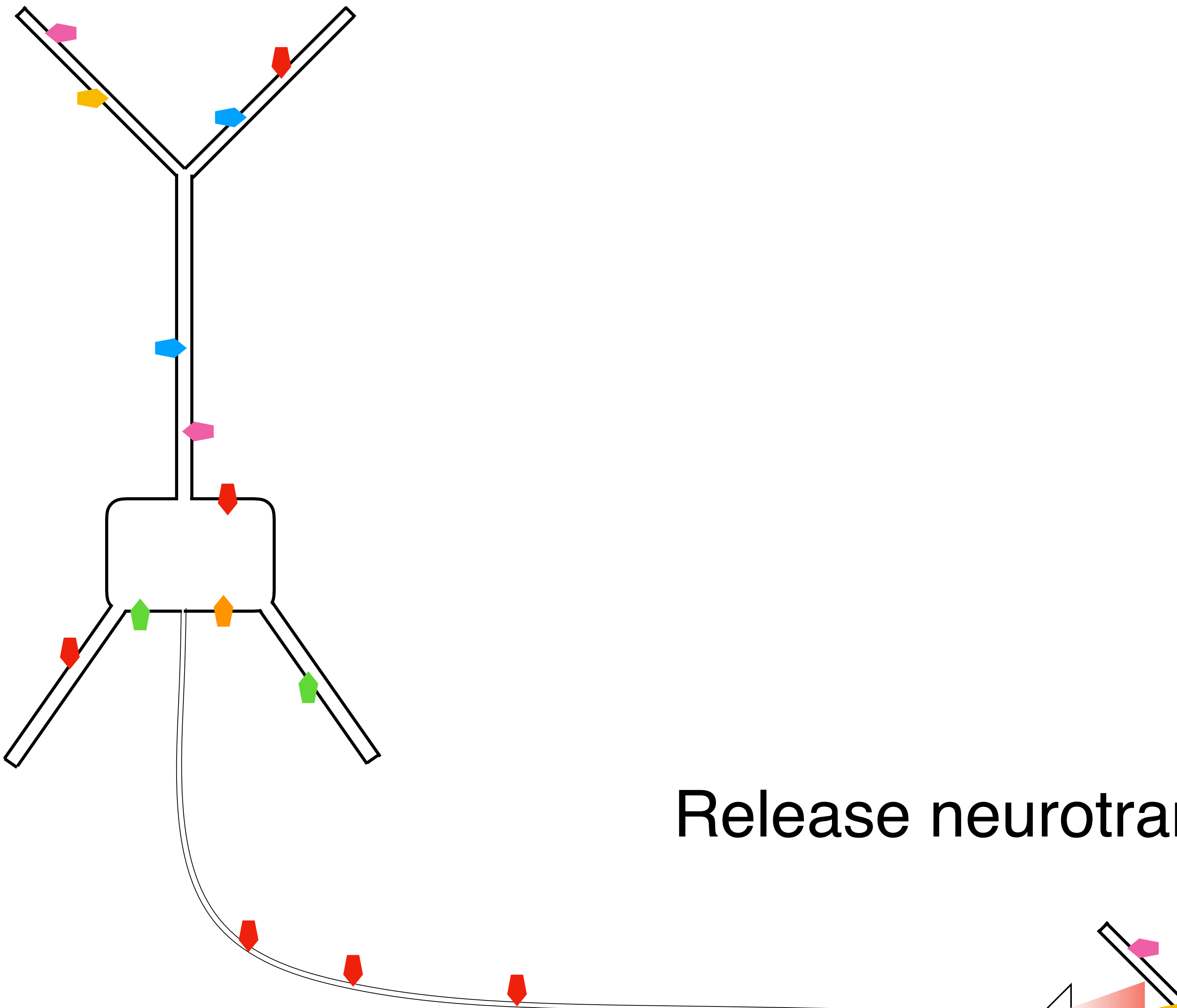


Induce action potential

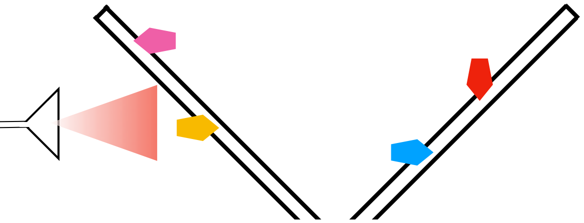
Input - output function of a neuron



Input - output function of a neuron

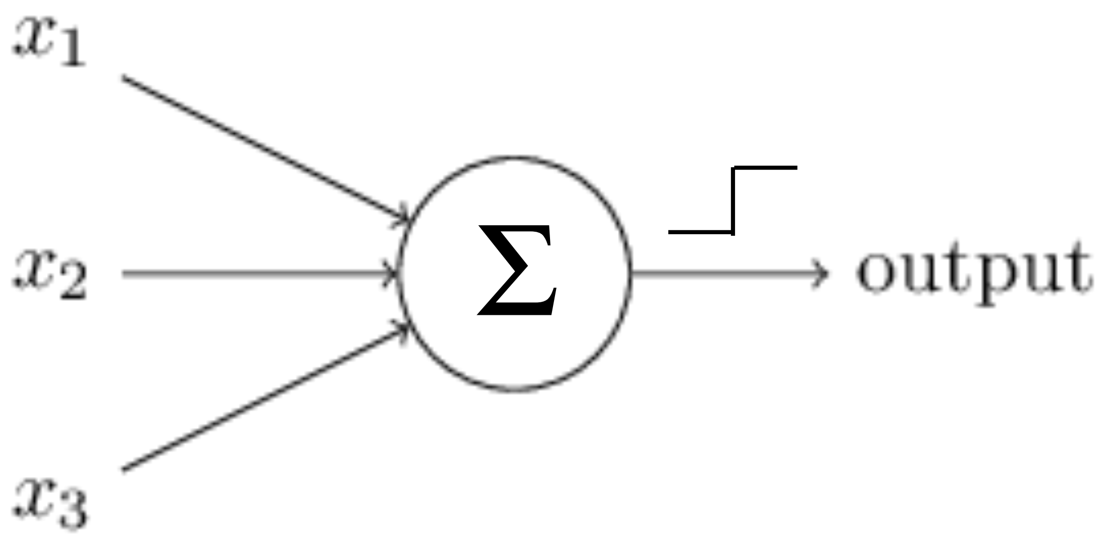


Release neurotransmitter



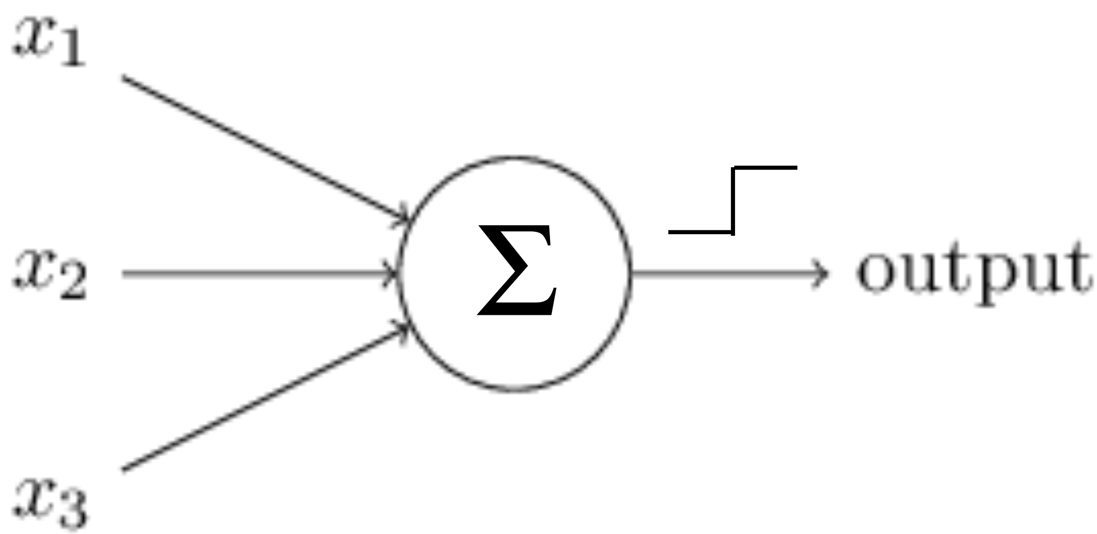
What's the input processing function?

McCulloch-Pitts Neuron



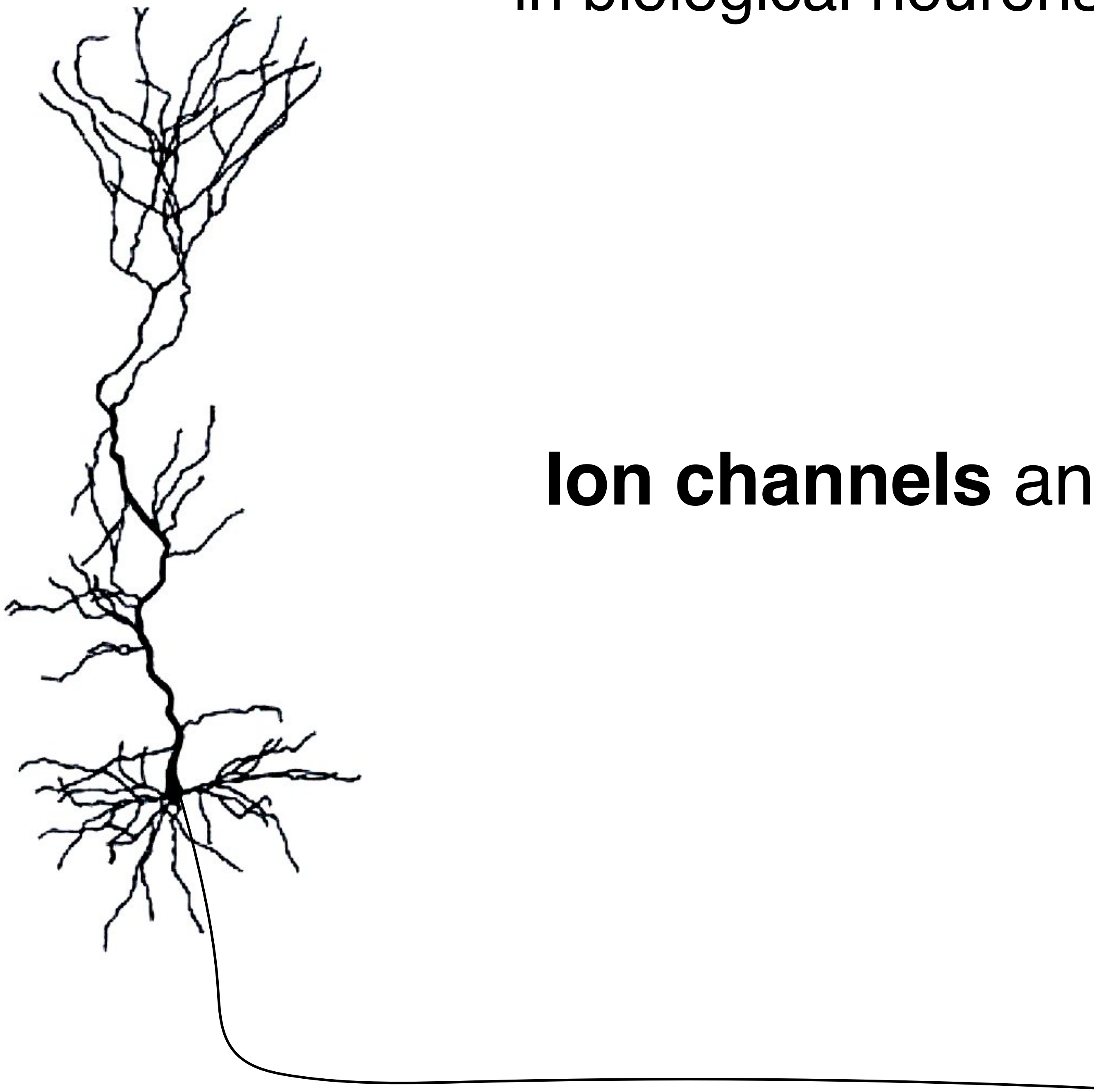
What's the input processing function?

McCulloch-Pitts Neuron



This simplified model does not capture some key features of real neurons.

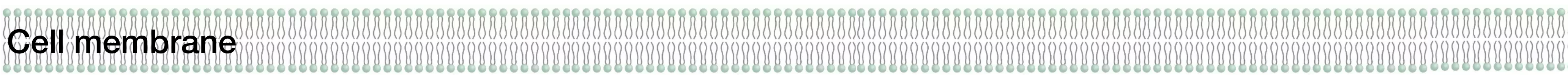
Two key components shaping input processing in biological neurons



Ion channels and **dendrites**

Membrane ion channels

Extracellular



Intracellular

Membrane ion channels

Extracellular

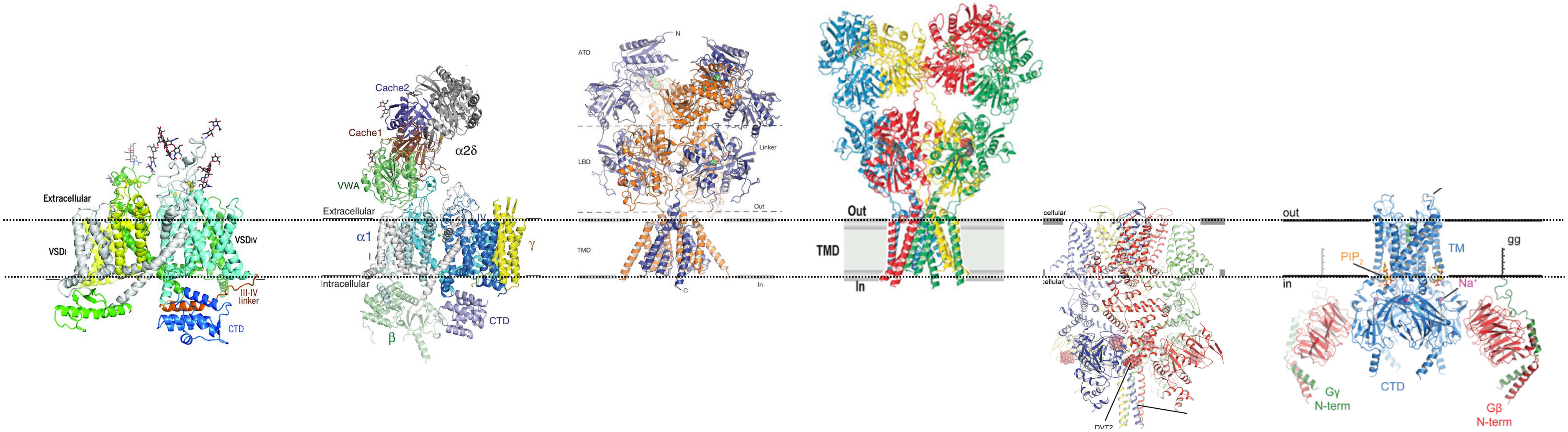
Cell membrane

4 nm

Intracellular

Membrane ion channels

Extracellular

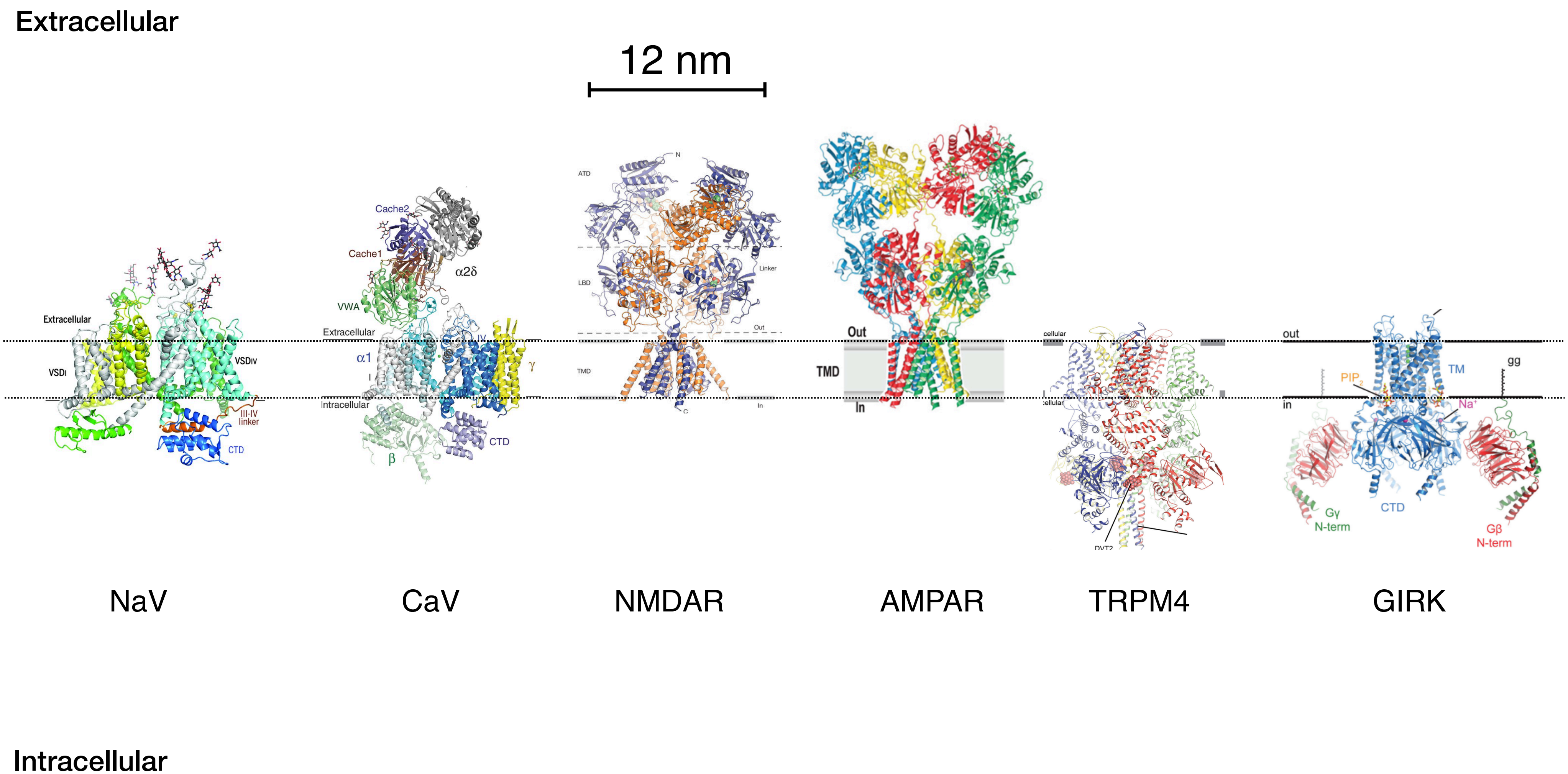


NaV CaV NMDAR AMPAR TRPM4 GIRK

Intracellular

Structures from Nieng Yan Lab/Eric Gouaux Lab/Wei Lu Lab/Matt Whorton Lab

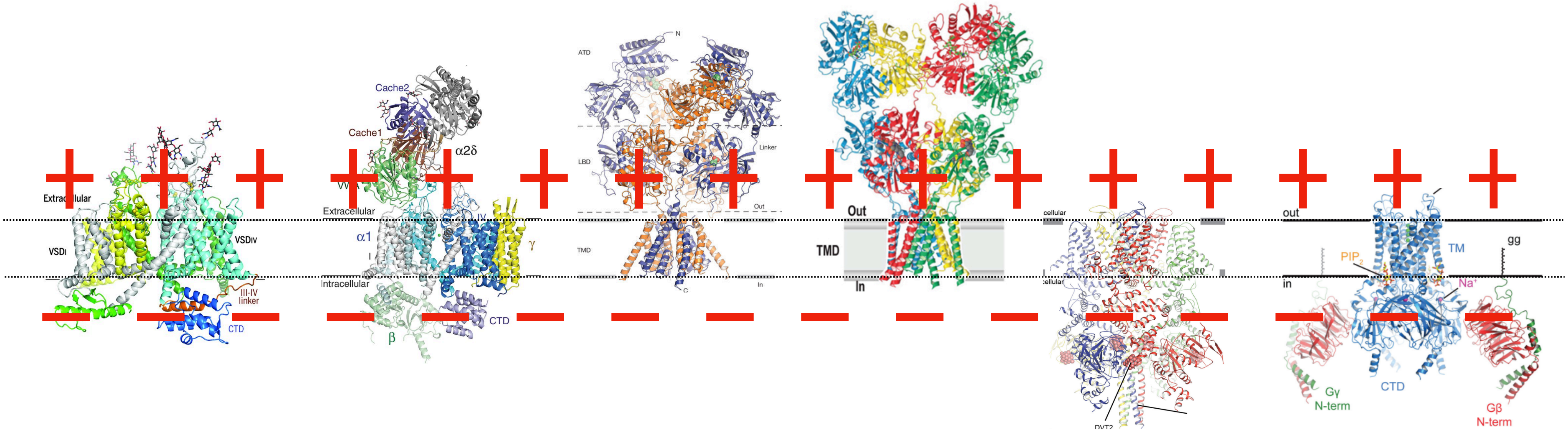
Membrane ion channels



Structures from Nieng Yan Lab/Eric Gouaux Lab/Wei Lu Lab/Matt Whorton Lab

Ion channels as basic computational elements

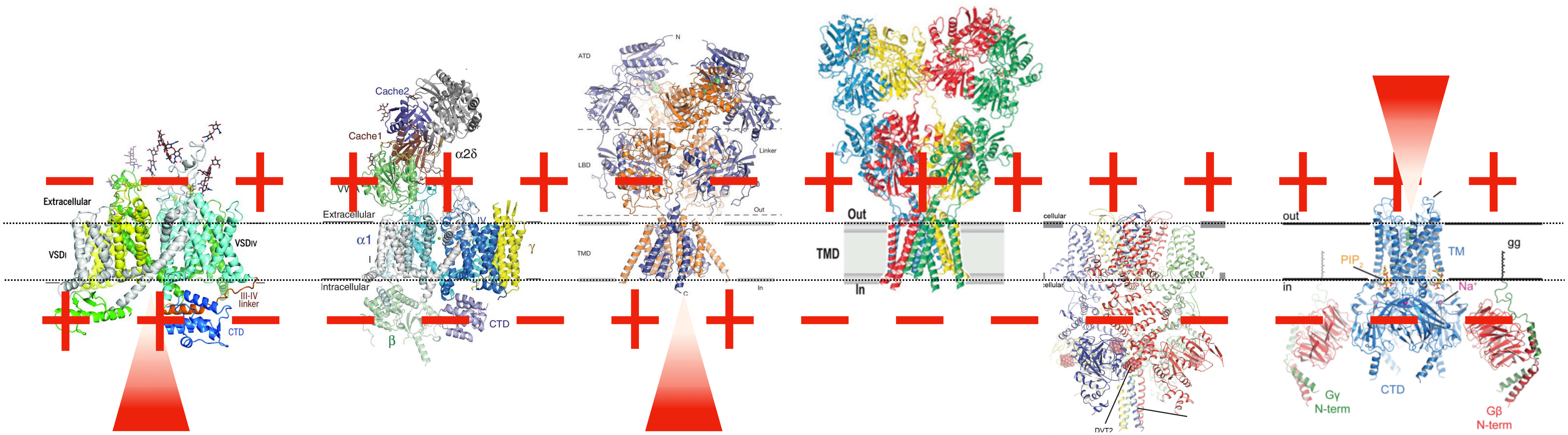
Extracellular



Intracellular

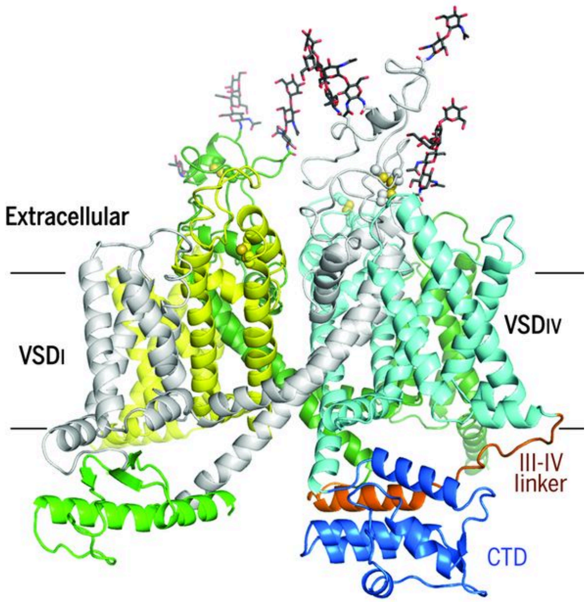
Ion channels as basic computational elements

Extracellular

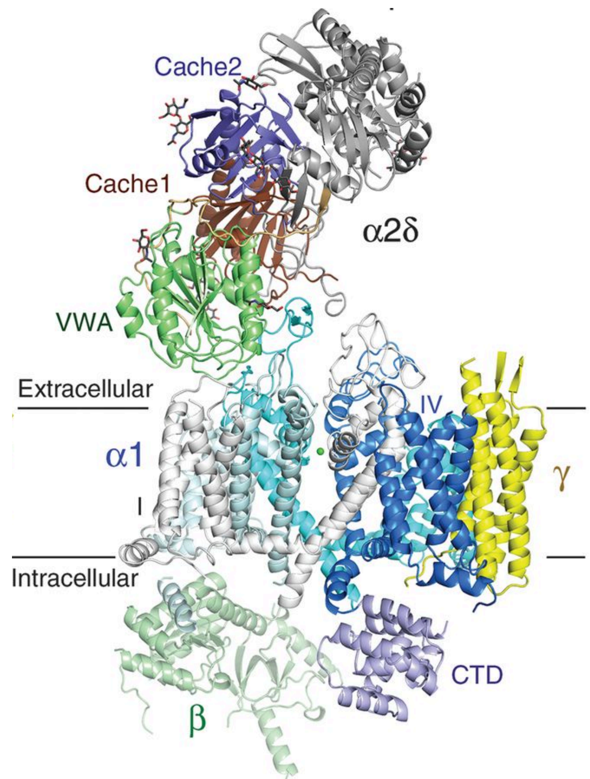


Intracellular

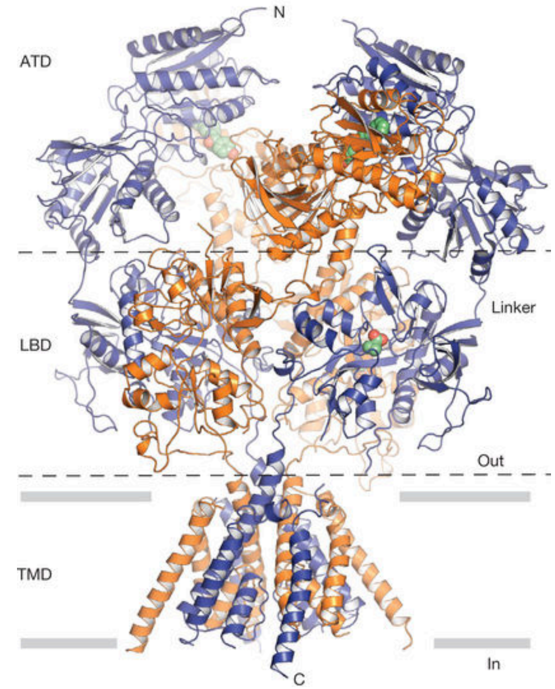
Three key players during input transformation



Voltage gated
Na^{+} channel



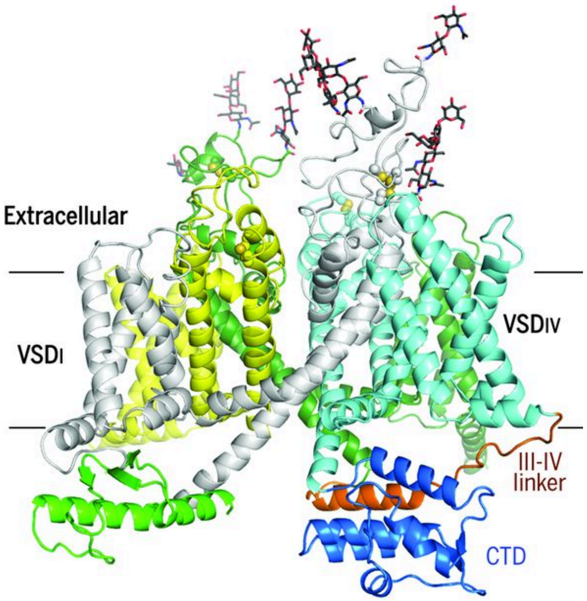
Voltage gated
Ca^{2+} channel

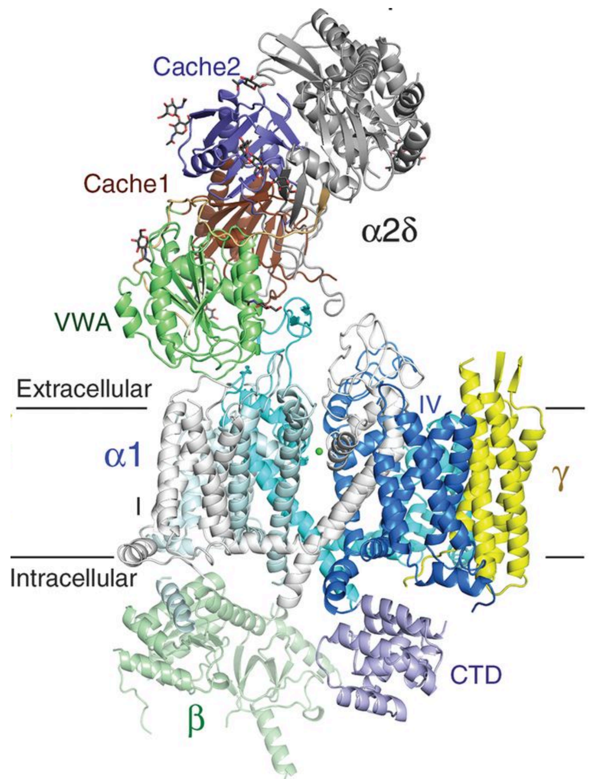


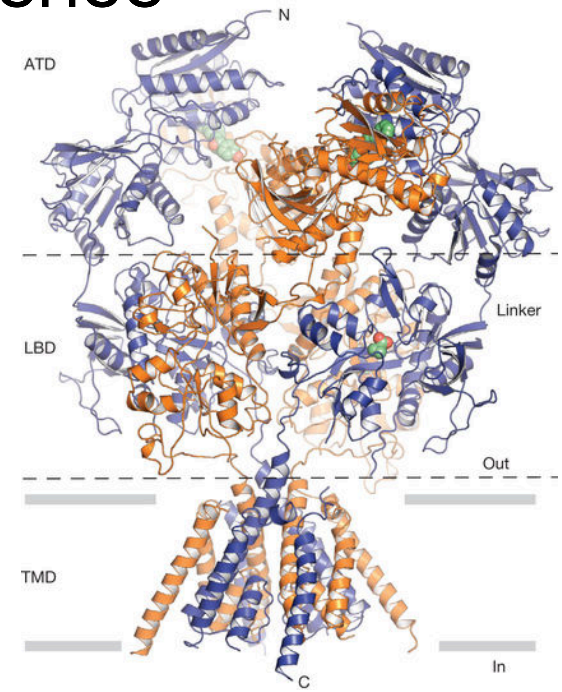
NMDA
receptor

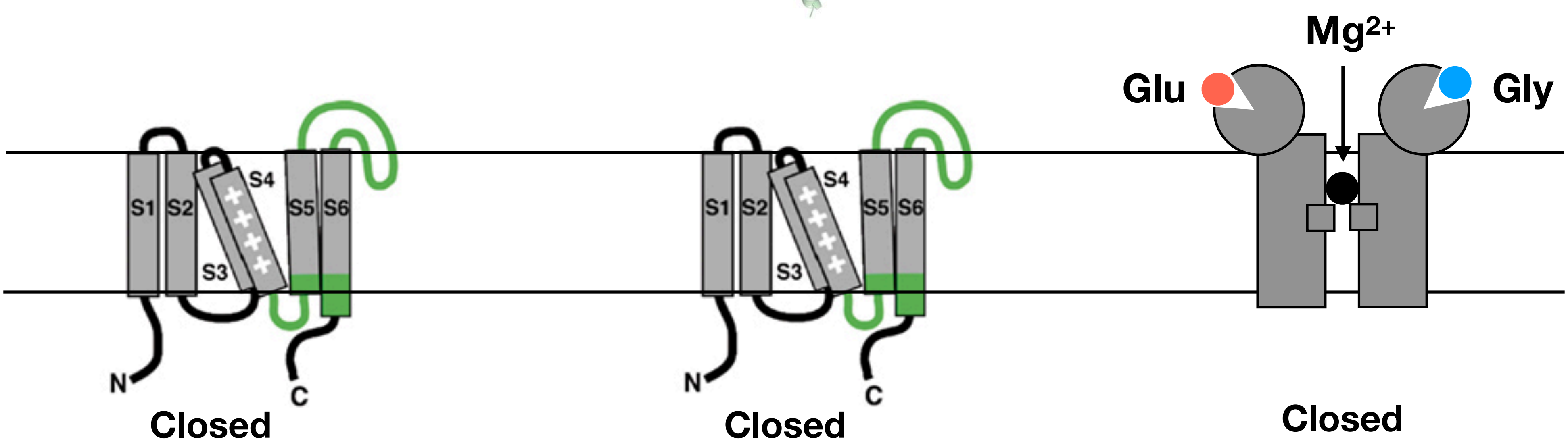
Structures from Nieng Yan Lab/Eric Gouaux Lab

Common feature: voltage dependence





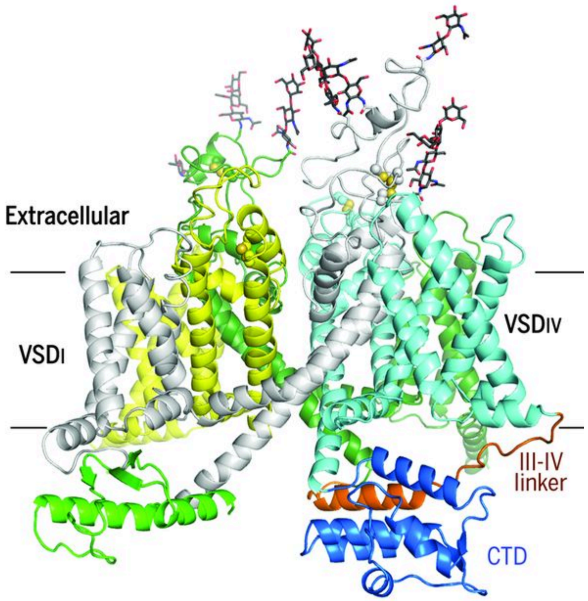


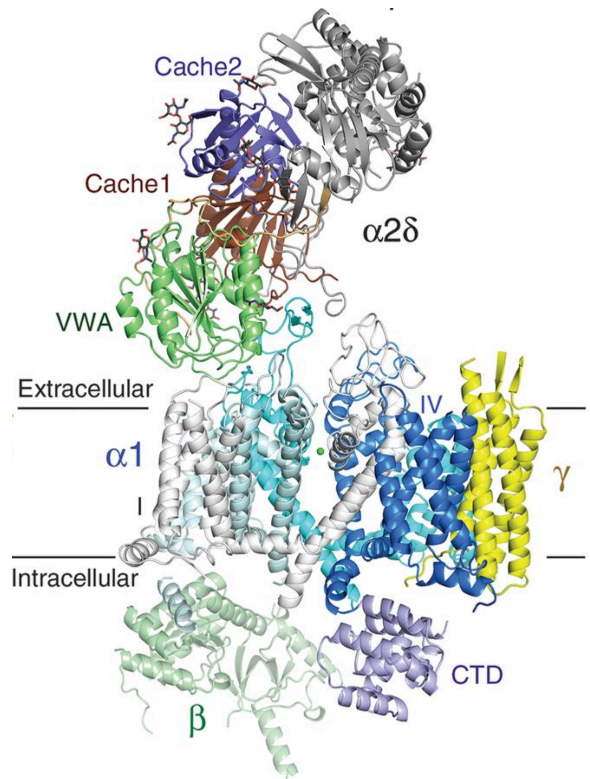


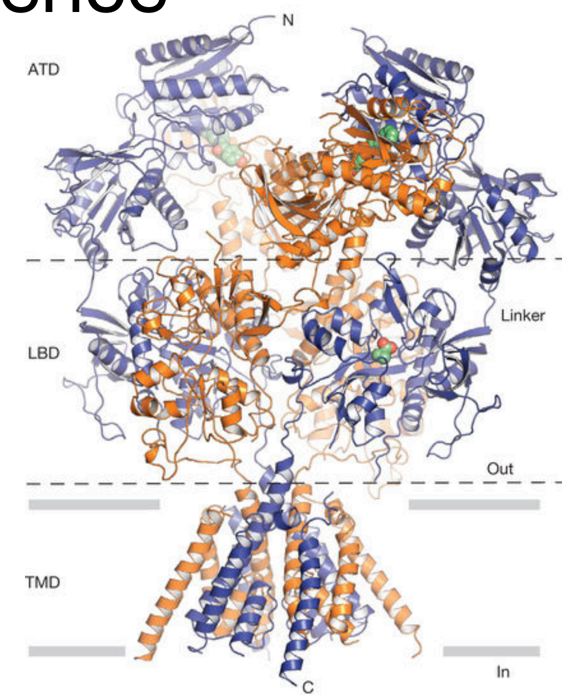
Rest (-70 mV)

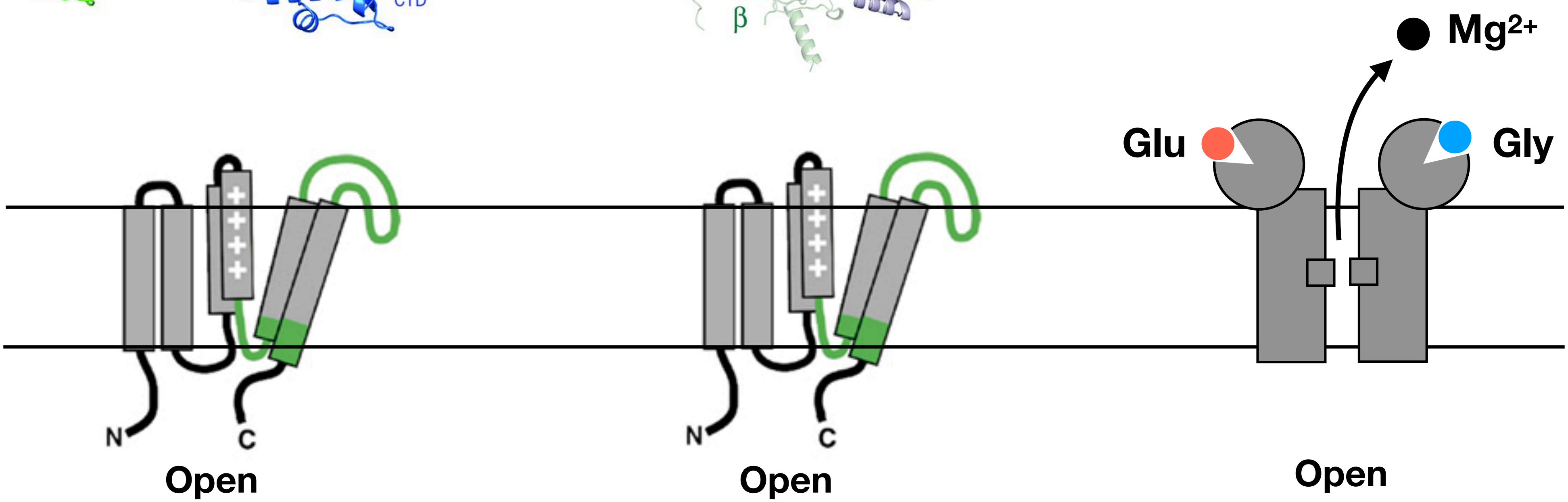
Structures from Nieng Yan Lab/Eric Gouaux Lab

Common feature: voltage dependence







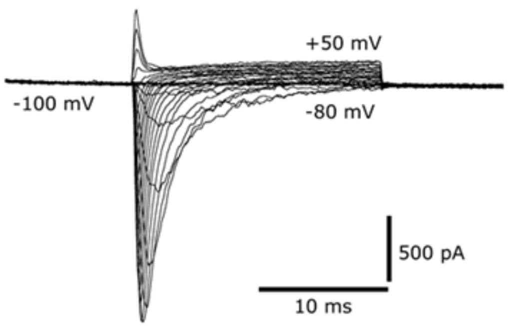


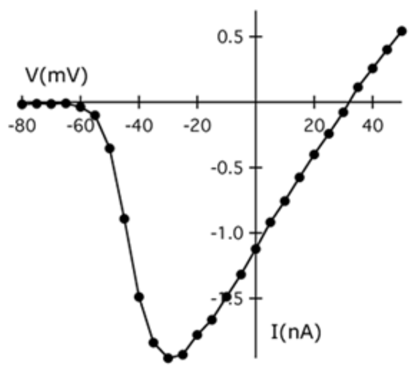
Depolarized (-40 mV)

Structures from Nieng Yan Lab/Eric Gouaux Lab

Nonlinear voltage current relationship

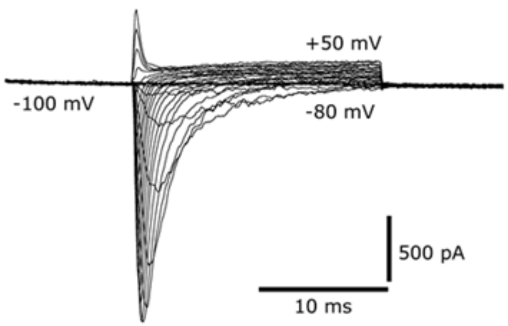
Voltage gated Na+ channel

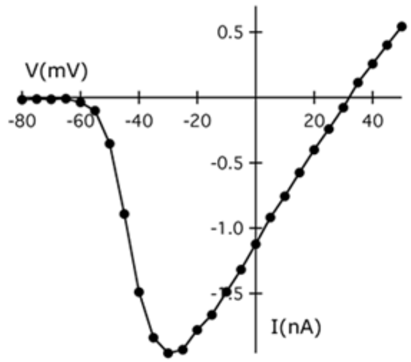




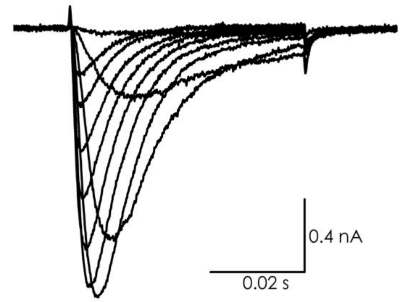
Nonlinear voltage current relationship

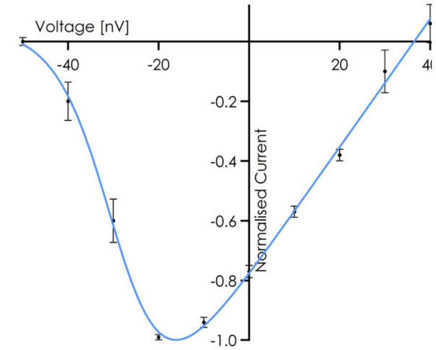
Voltage gated Na+ channel



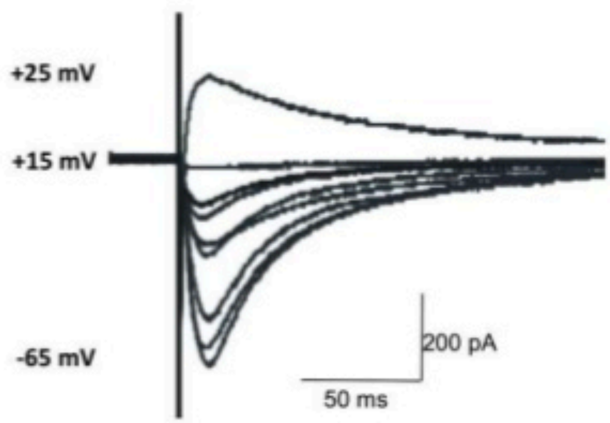


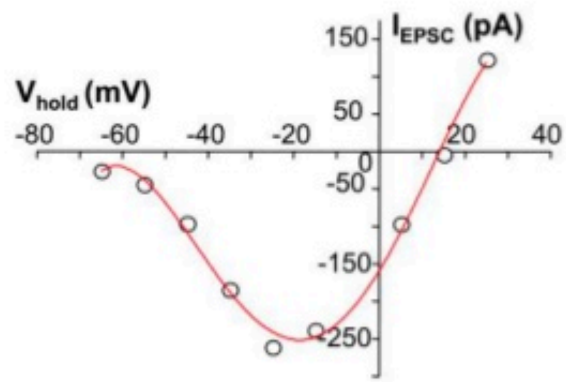
Voltage gated Ca^{2+} channel





NMDA receptor





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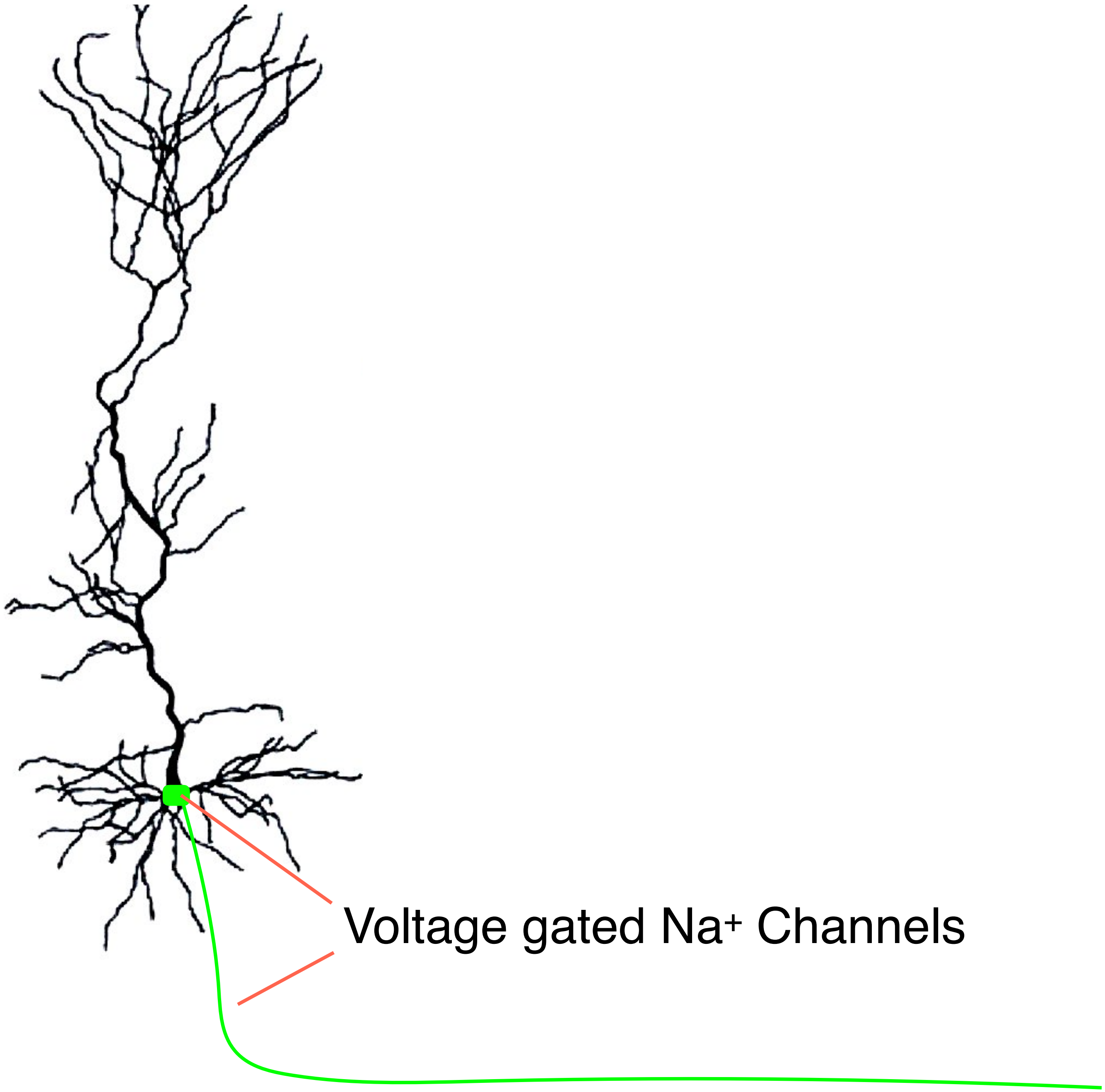
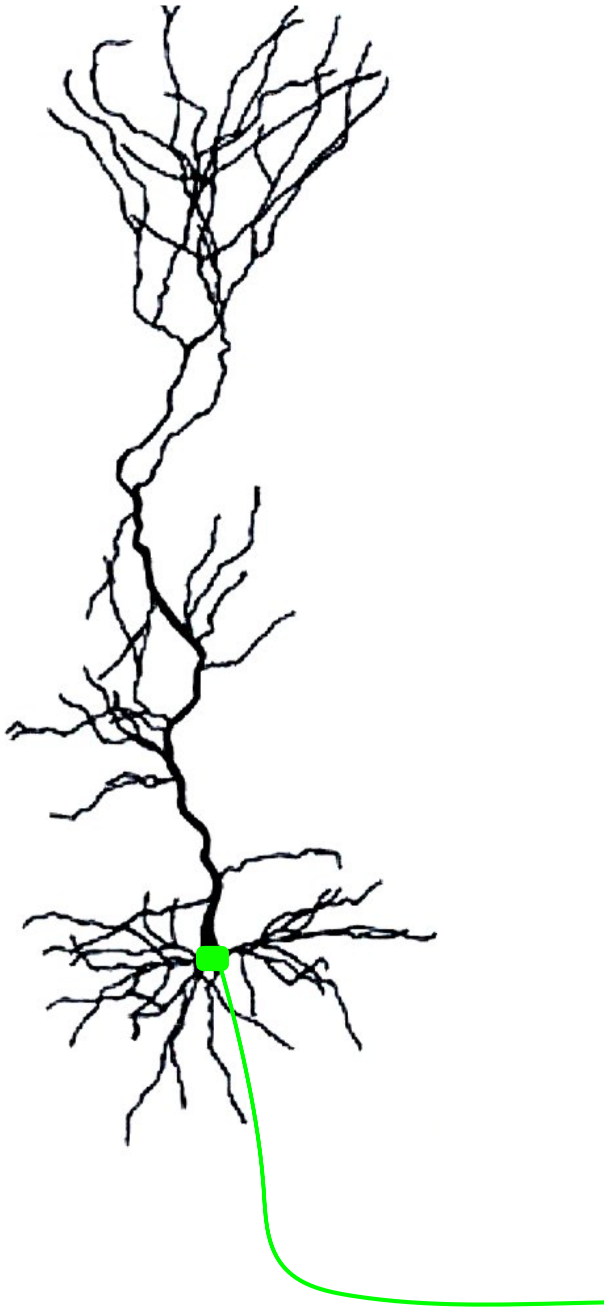
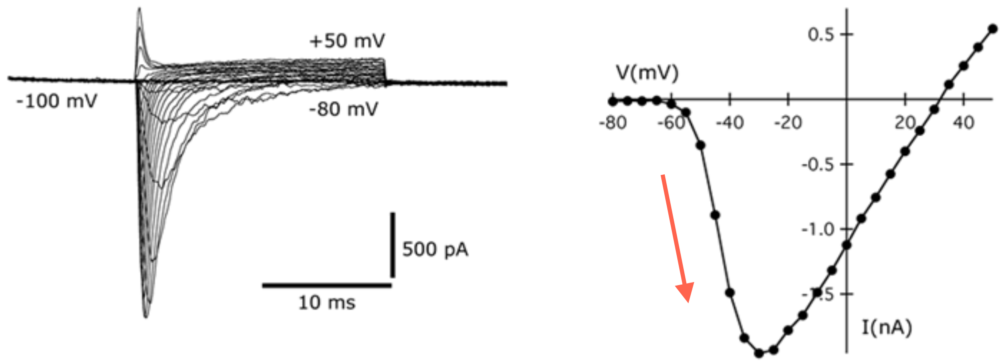
Regular Na^{+} spike: the action potential



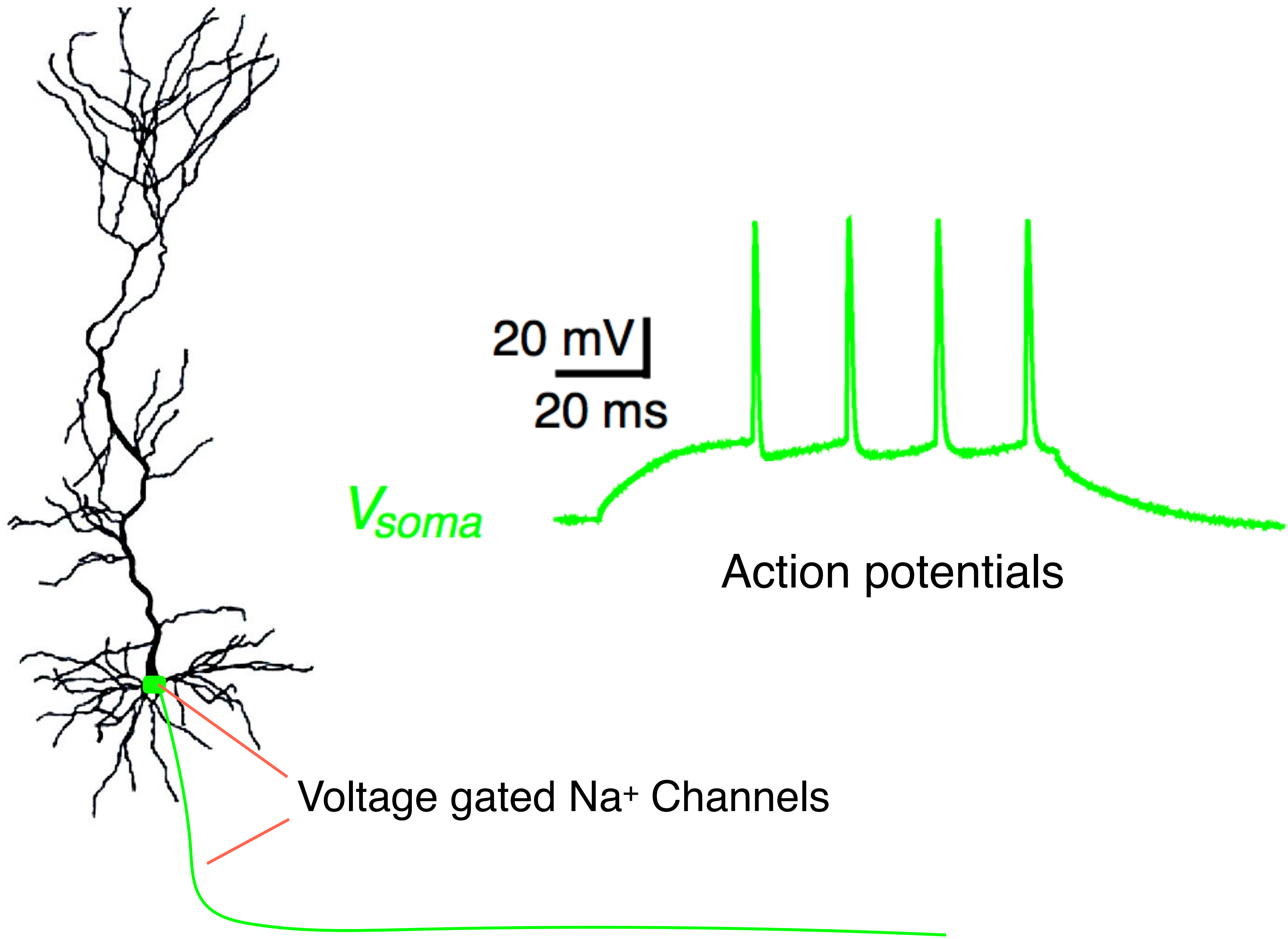
Regular Na^+ spike: the action potential



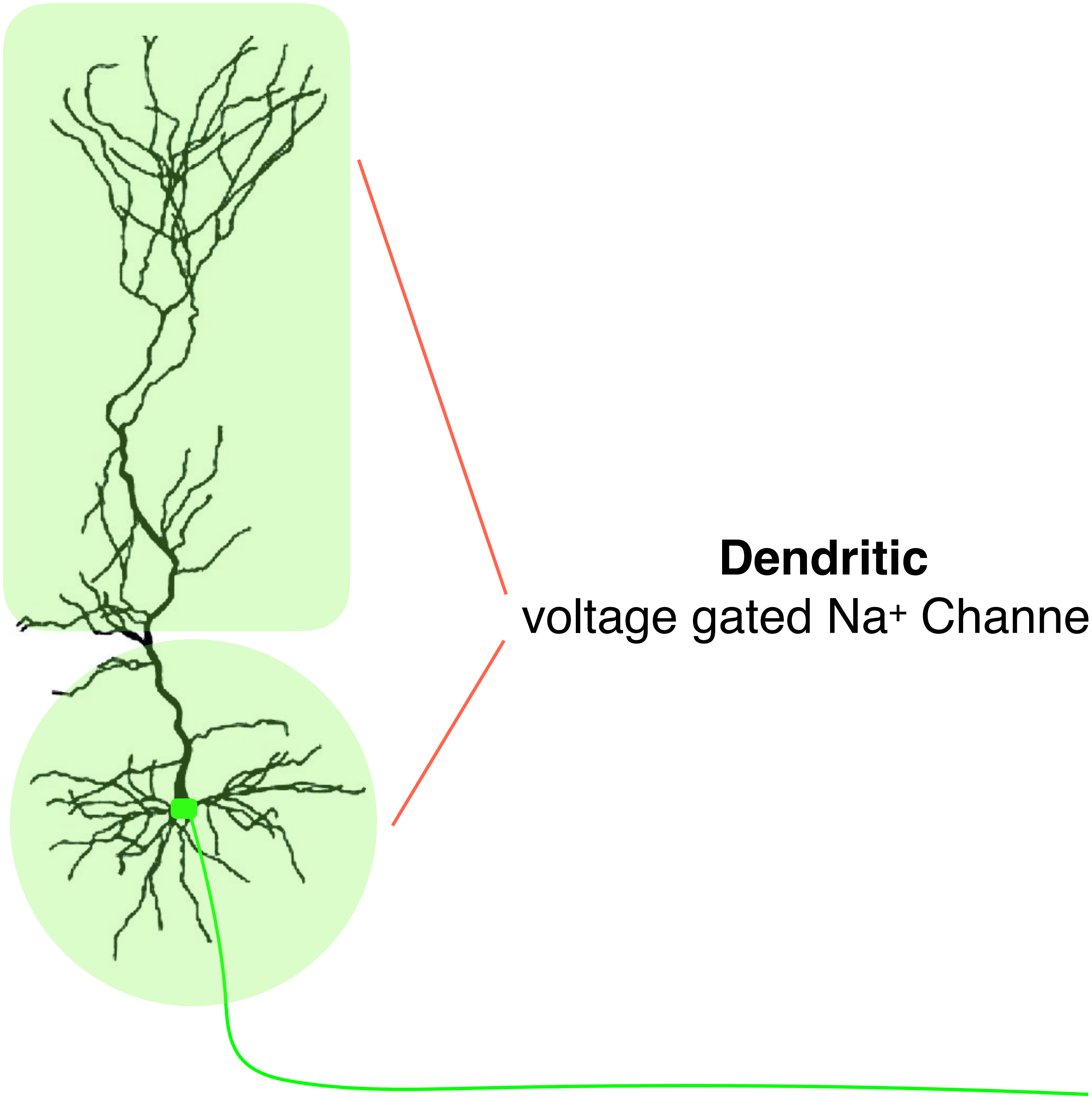
Voltage gated Na+ channel



Regular Na^+ spike: the action potential



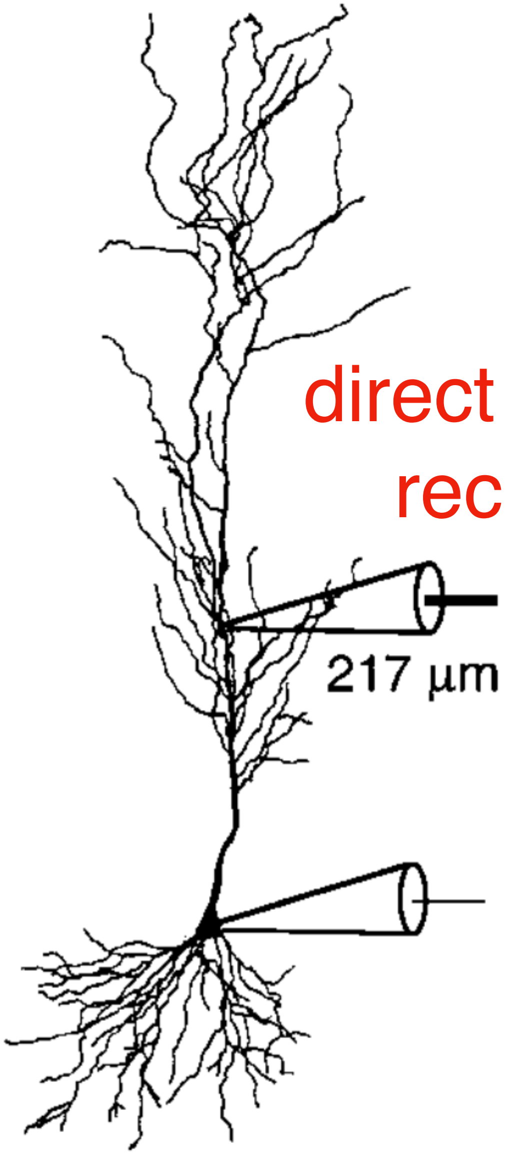
Dendritic Na^+ spike?



Dendritic
voltage gated Na^+ Channels

Magee and Johnston, 1995

Dendritic Na^+ spike

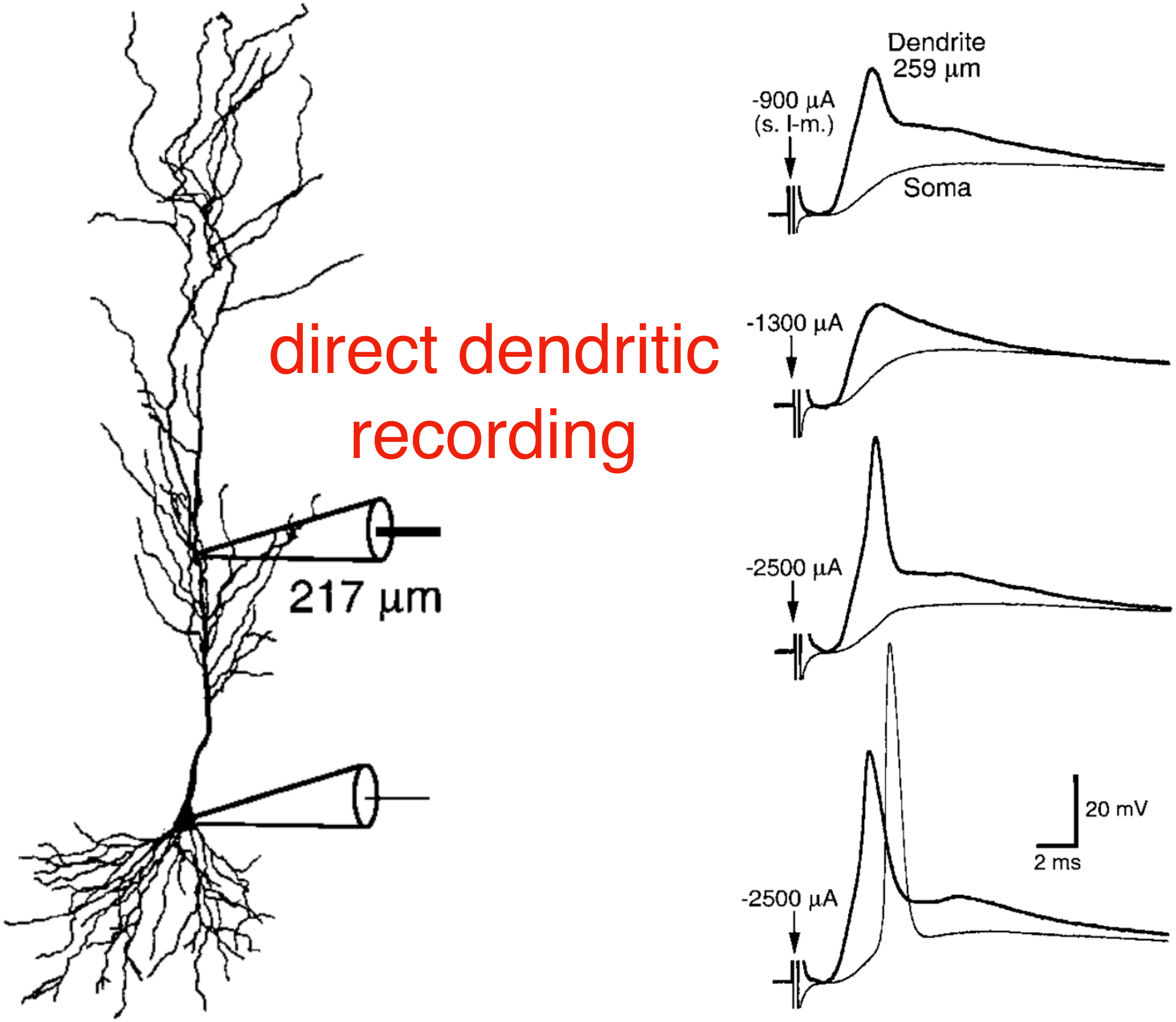


direct dendritic recording

CA1 pyramidal neuron

Golding and Spruston, 1998

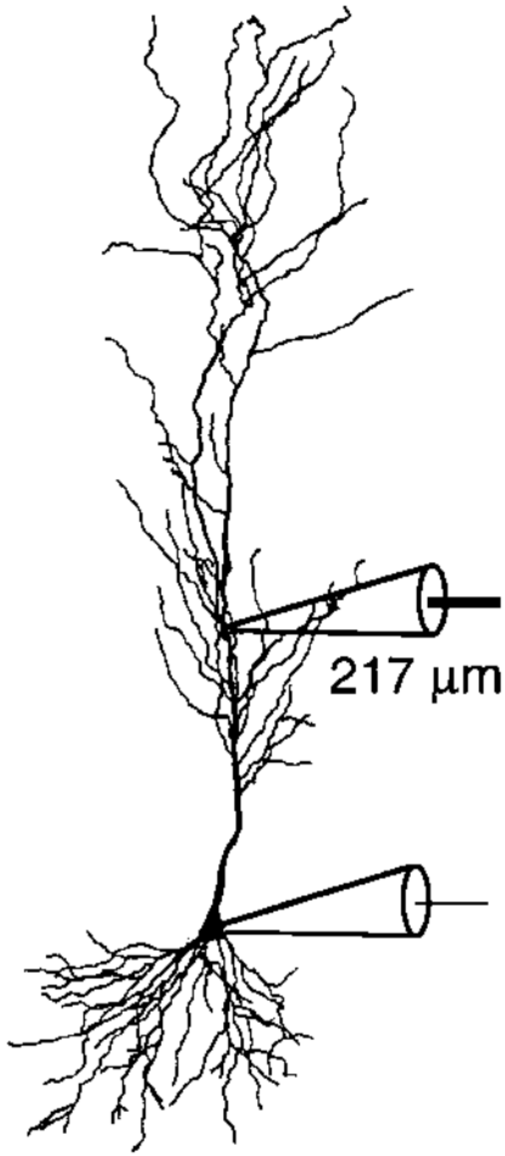
Dendritic Na^+ spike



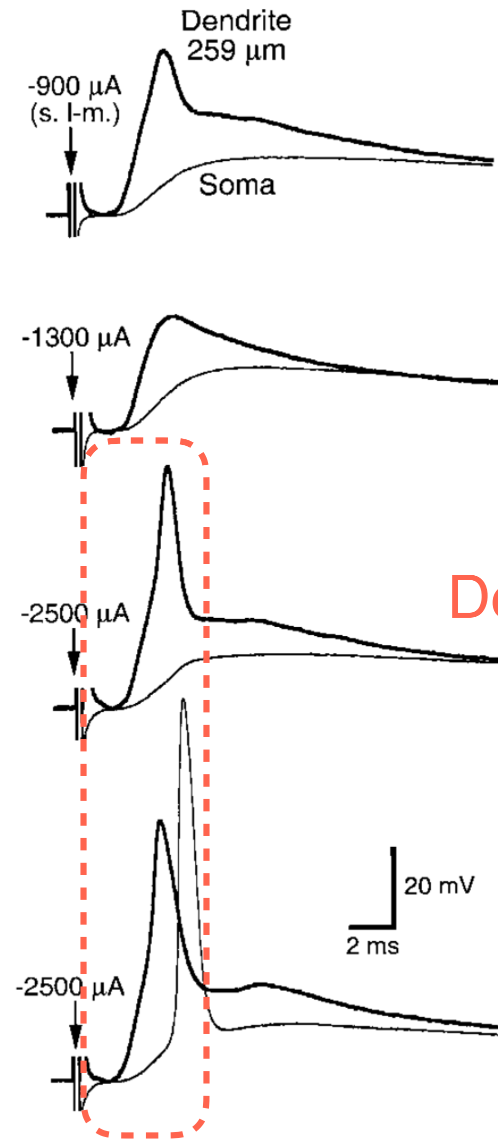
CA1 pyramidal neuron

Golding and Spruston, 1998

Dendritic Na^+ spike



CA1 pyramidal neuron

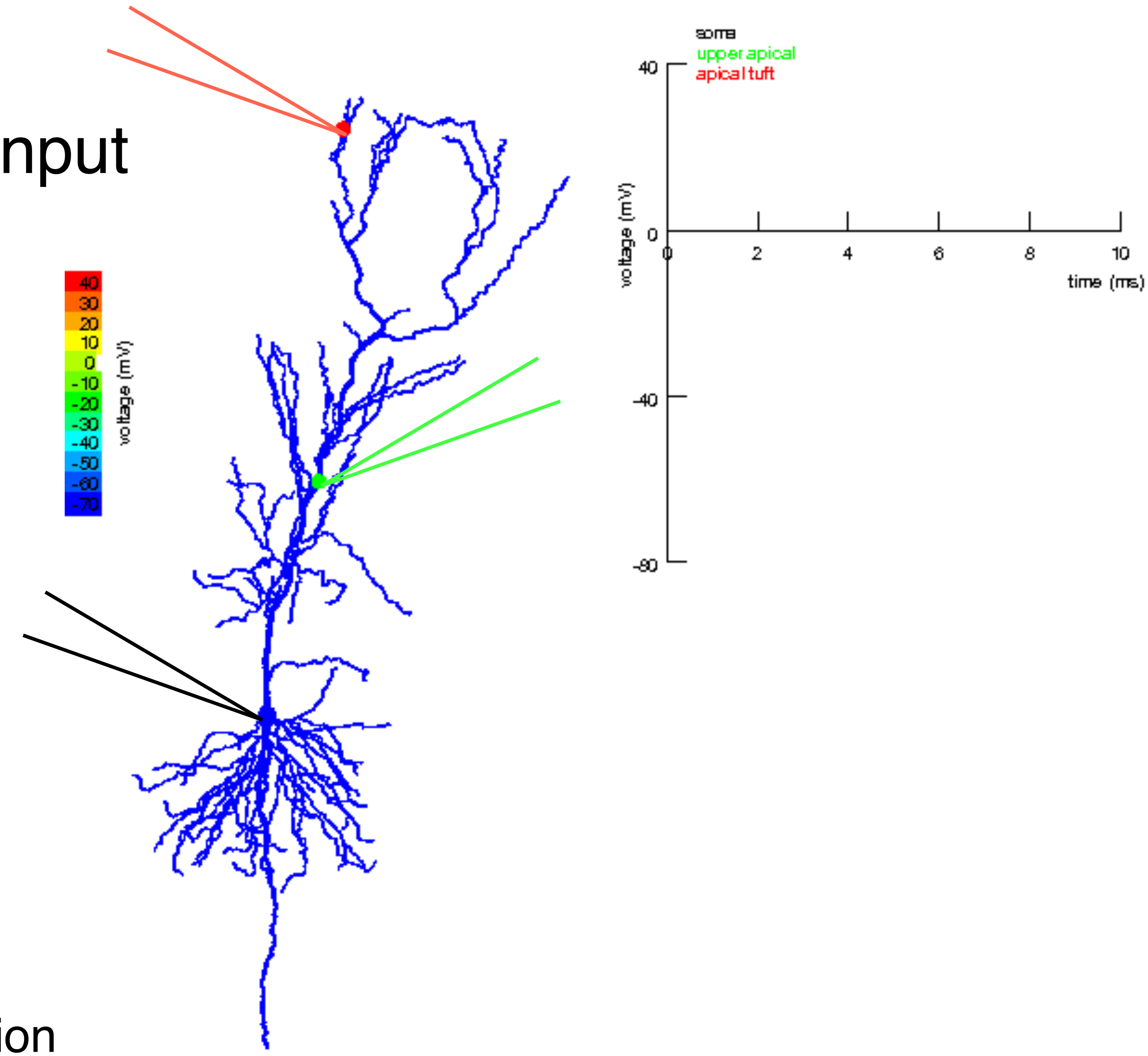


Dendrites are active and nonlinear

Golding and Spruston, 1998

Gating of distal input by proximal input

Distal input

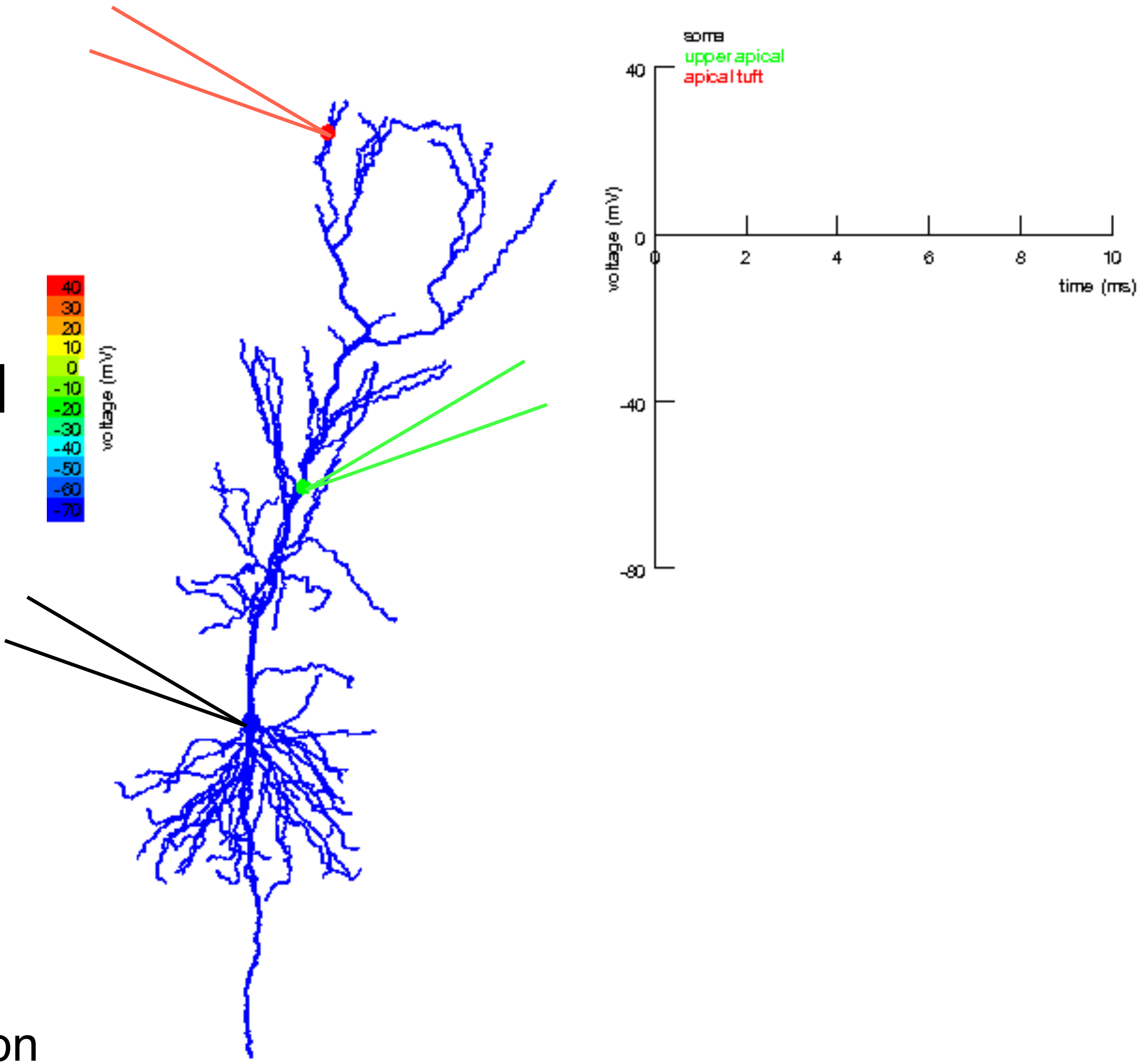


Simulation

Spruston Lab

Gating of distal input by proximal input

Proximal input



Simulation

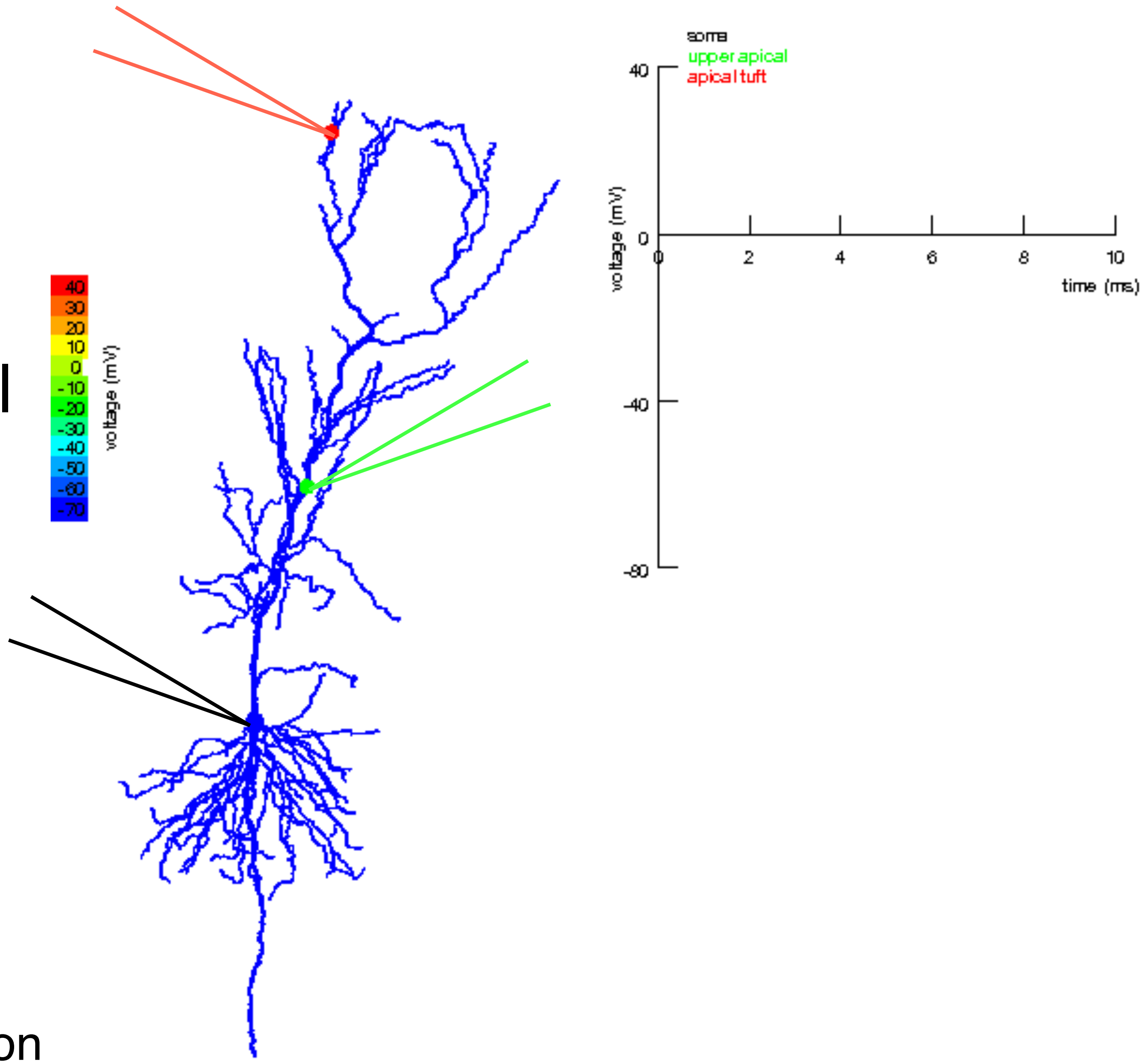
Spruston Lab

Gating of distal input by proximal input

Distal input

+

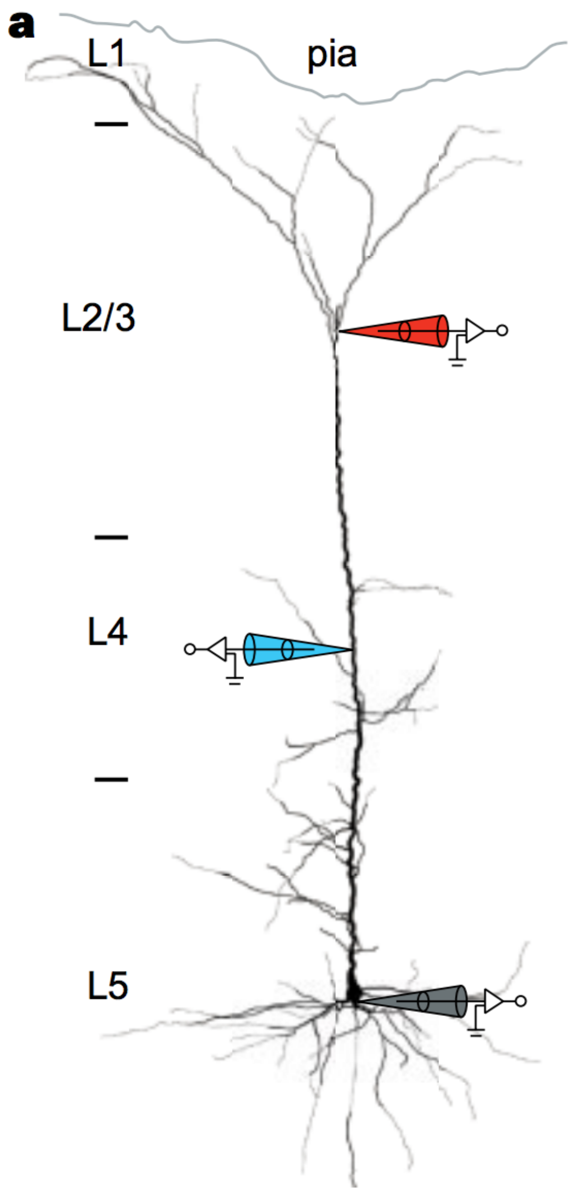
Proximal input



Simulation

Spruston Lab

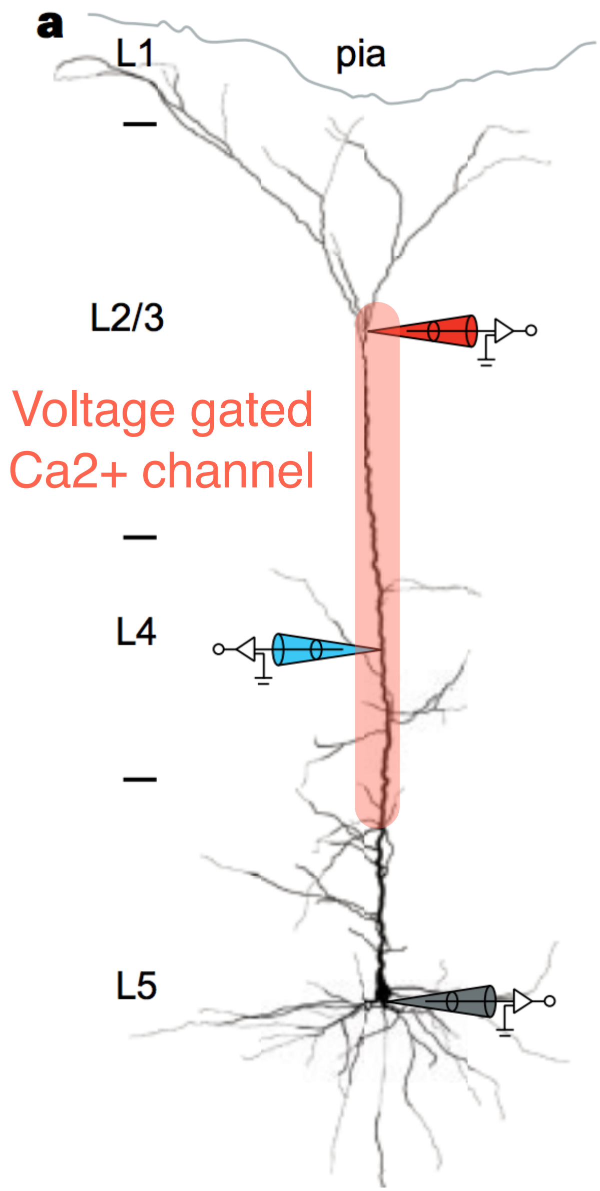
Dendritic Ca^{2+} spike



Layer 5 pyramidal neuron

Larkum et al., 1999

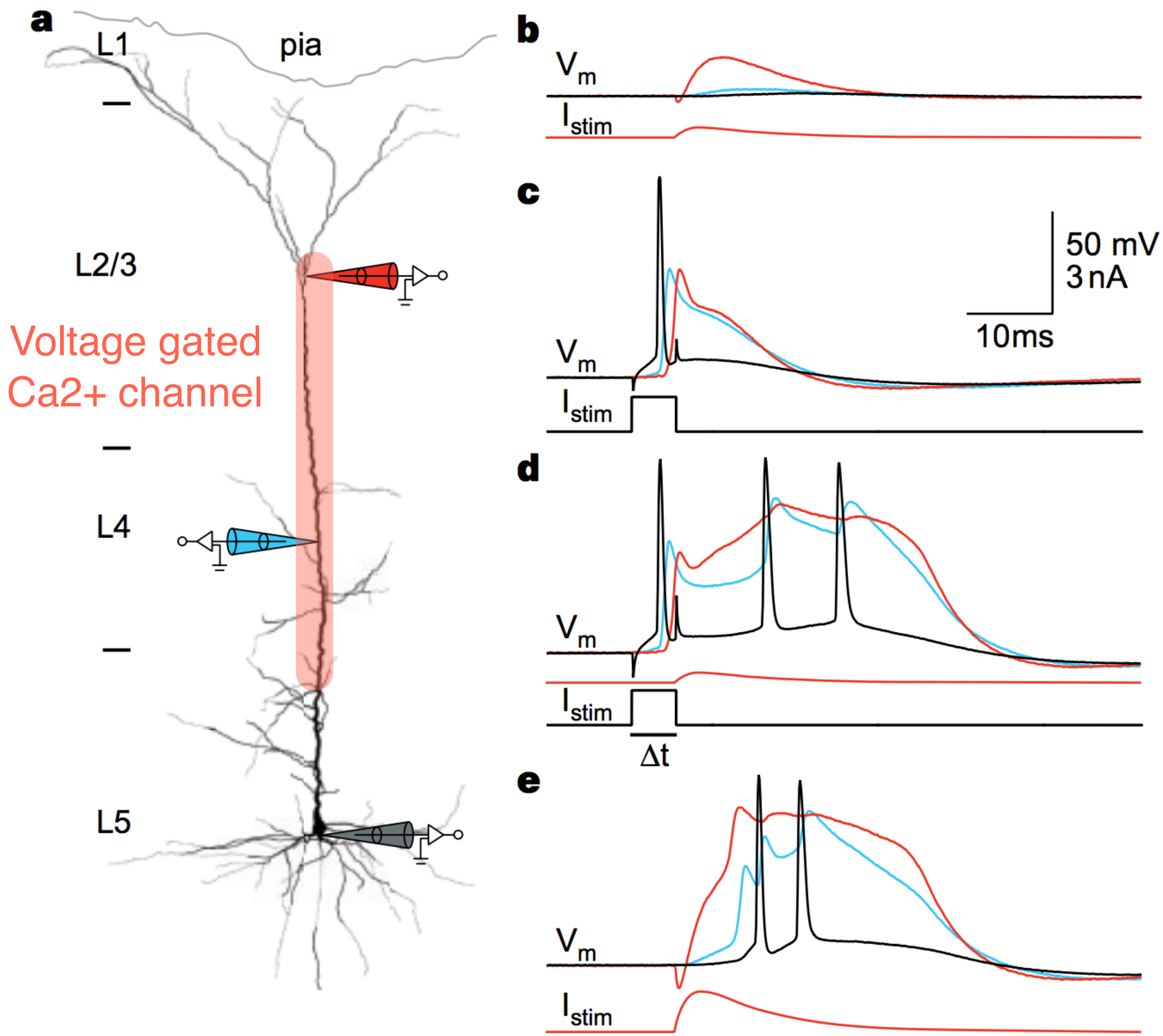
Dendritic Ca^{2+} spike



Layer 5 pyramidal neuron

Larkum et al., 1999

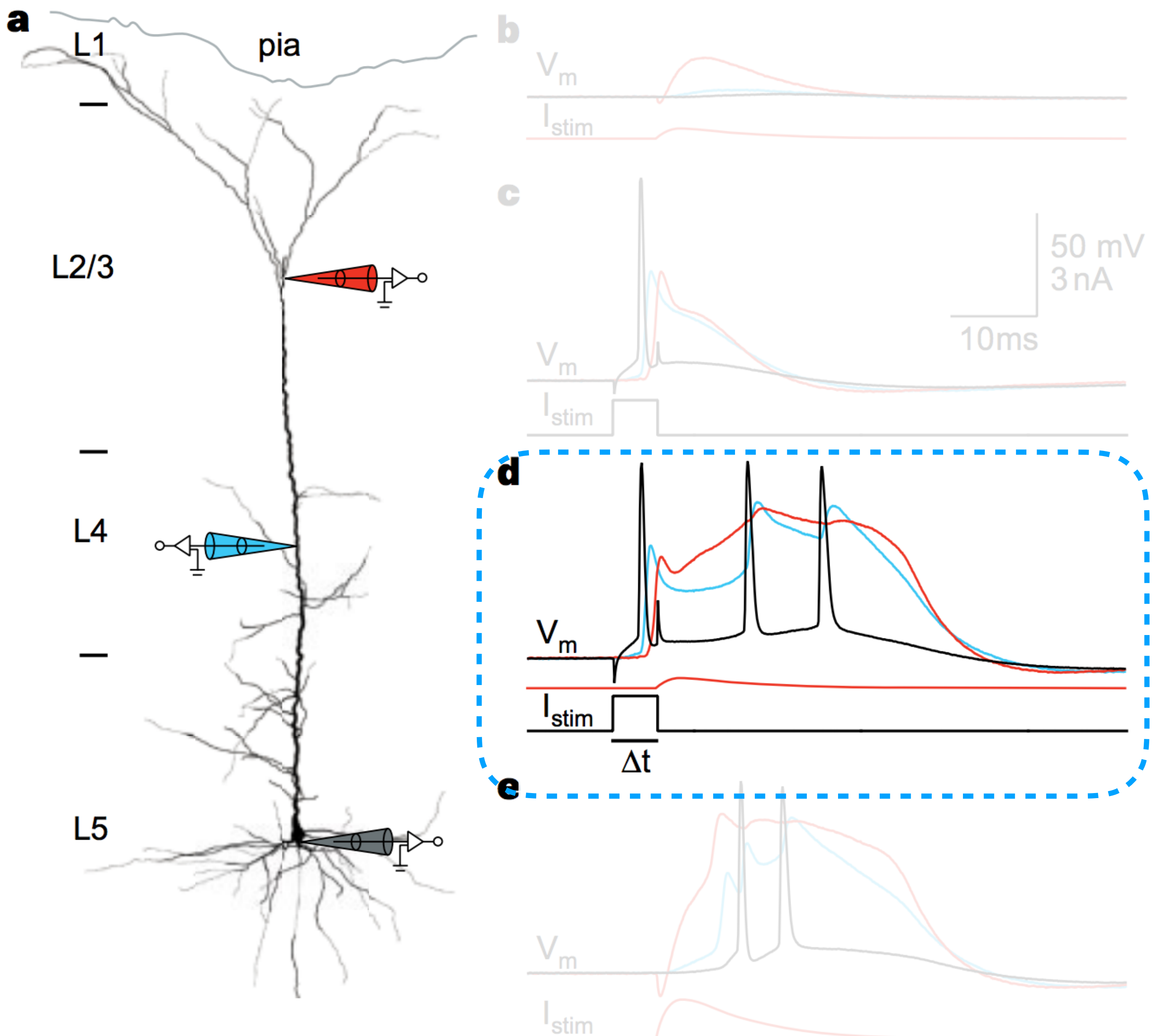
Dendritic Ca^{2+} spike



Layer 5 pyramidal neuron

Larkum et al., 1999

Dendritic Ca^{2+} spike

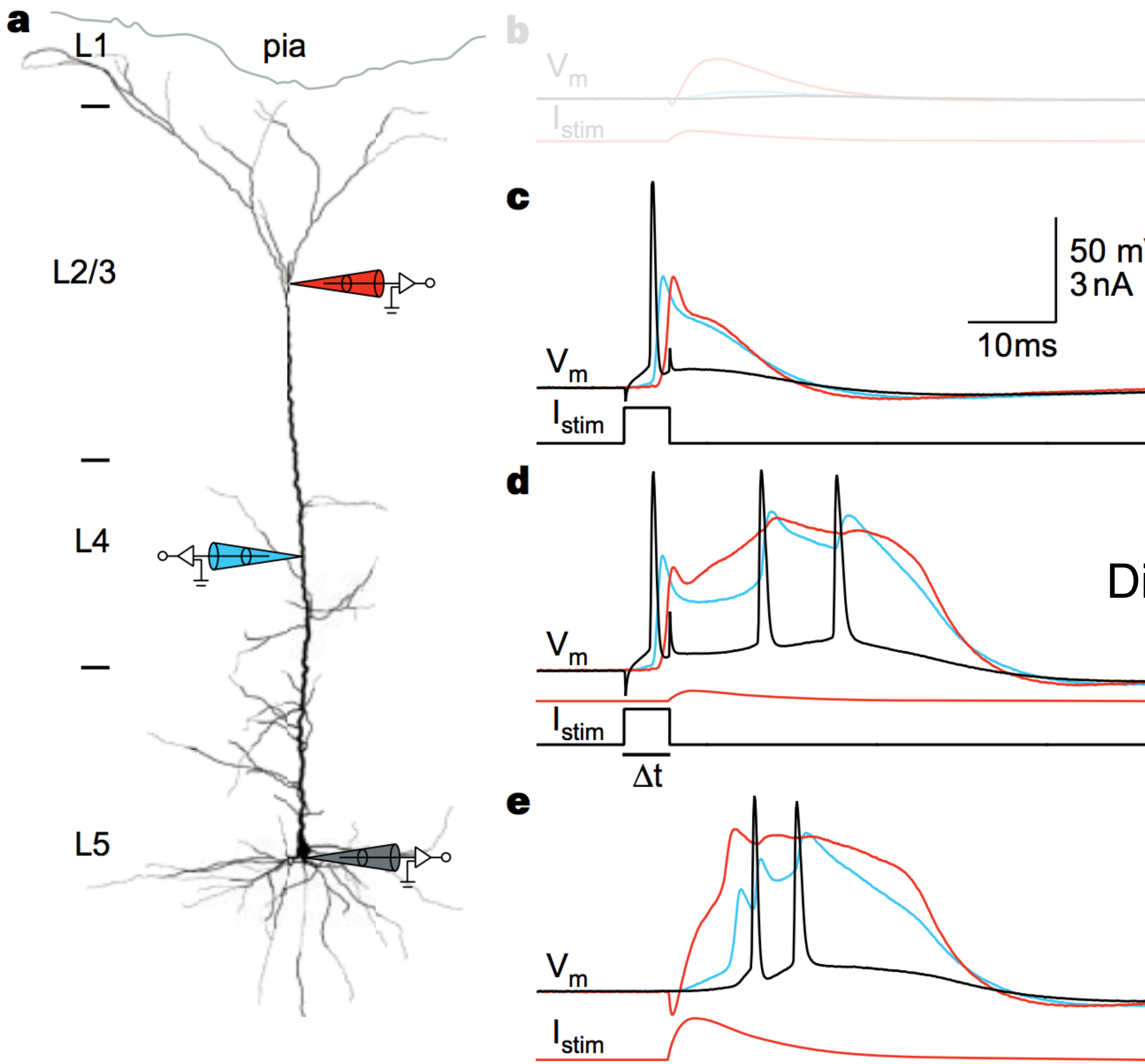


Coincidence detection

Layer 5 pyramidal neuron

Larkum 1999

Dendritic Ca^{2+} spike



Proximal input
Single spike

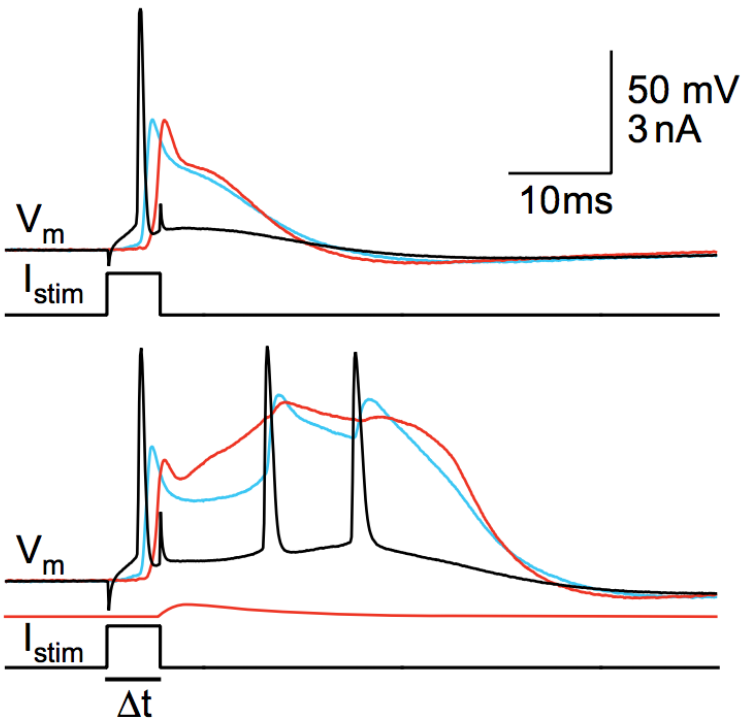
Distal + Proximal
Bursting

Strong distal
Bursting

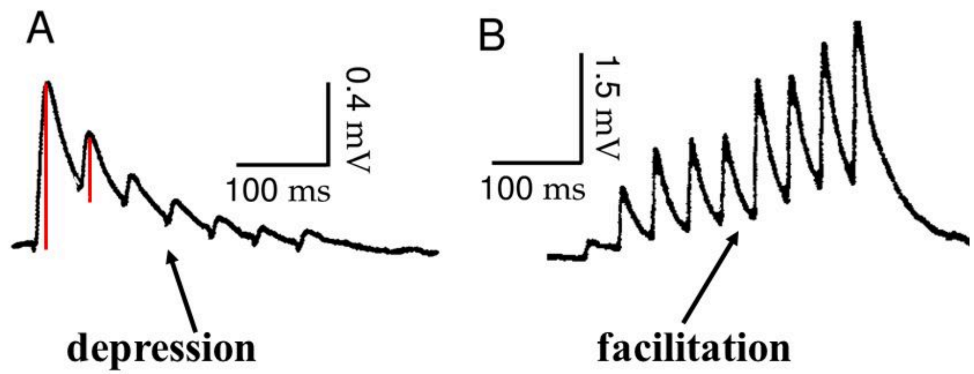
Layer 5 pyramidal neuron

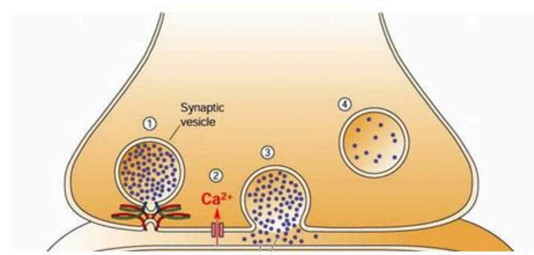
Larkum 1999

Single spike and bursting can convey multiplex code



Recruit different set of synapses

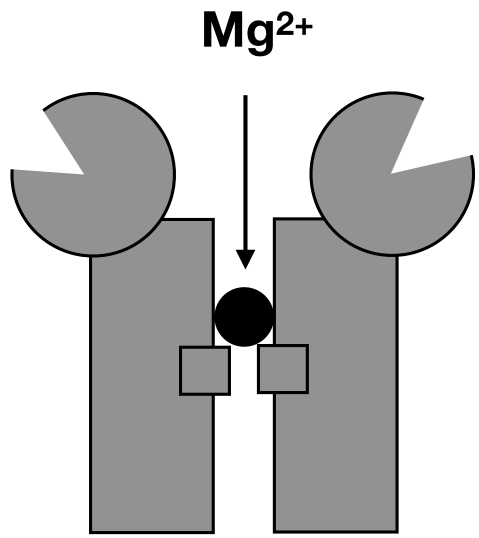




Wesley Paul

NMDA receptor

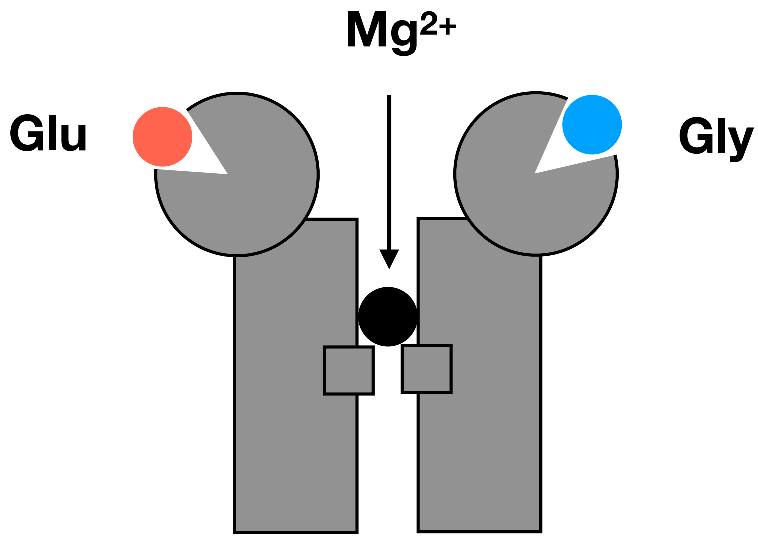
NMDA receptor



both ligand gated and voltage gated

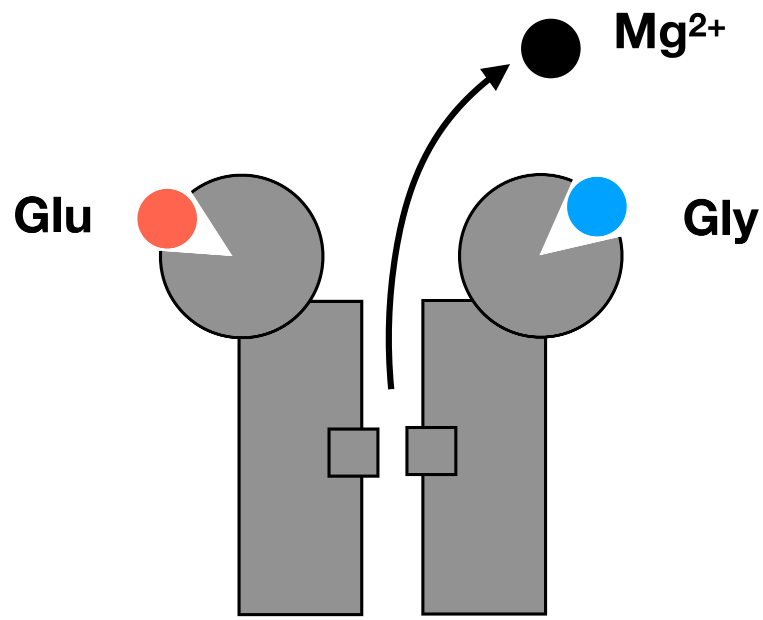
NMDA receptor

transmitter binding



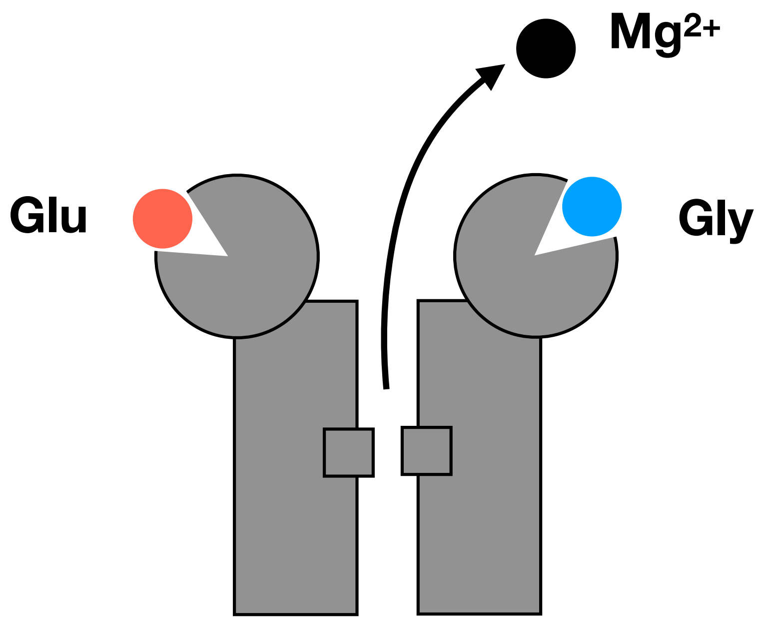
liganded but silent due to Mg^{2+} block

NMDA receptor



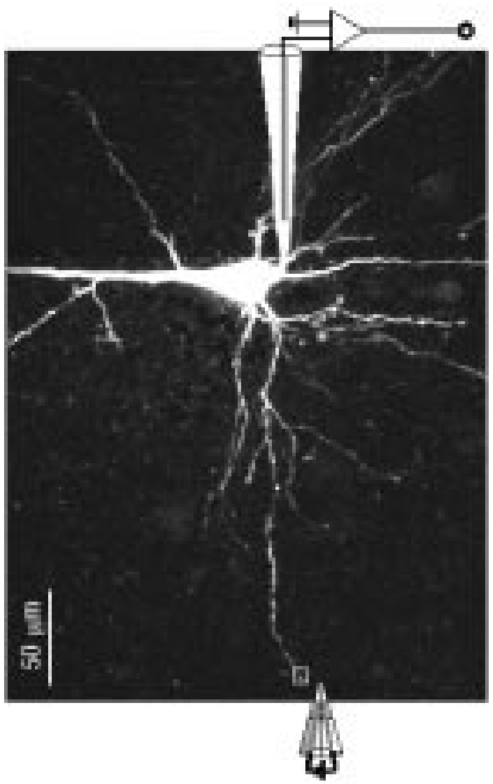
Neurotransmitter binding + depolarization

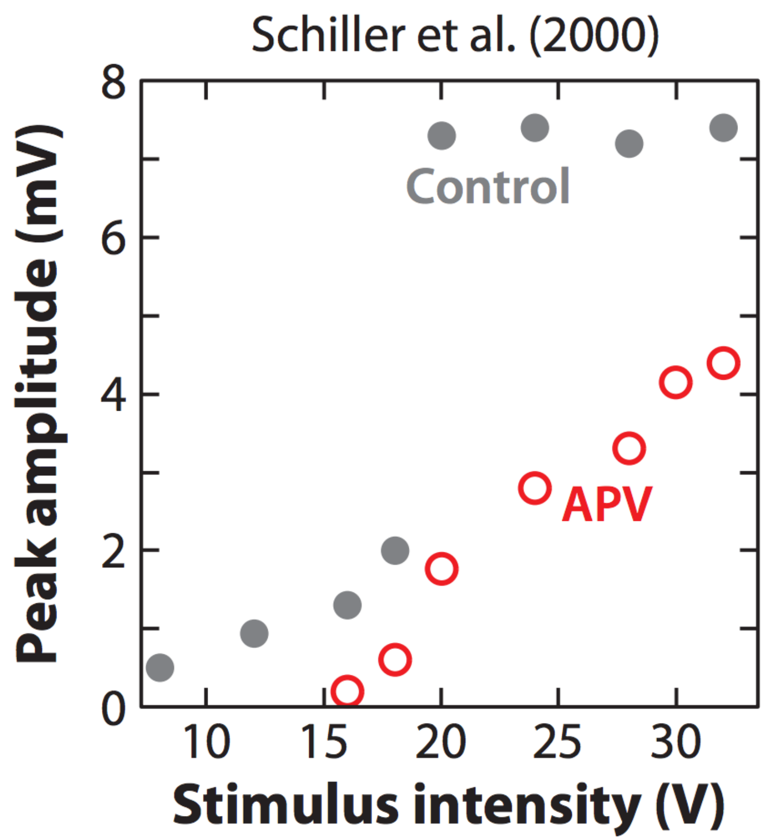
NMDA receptor

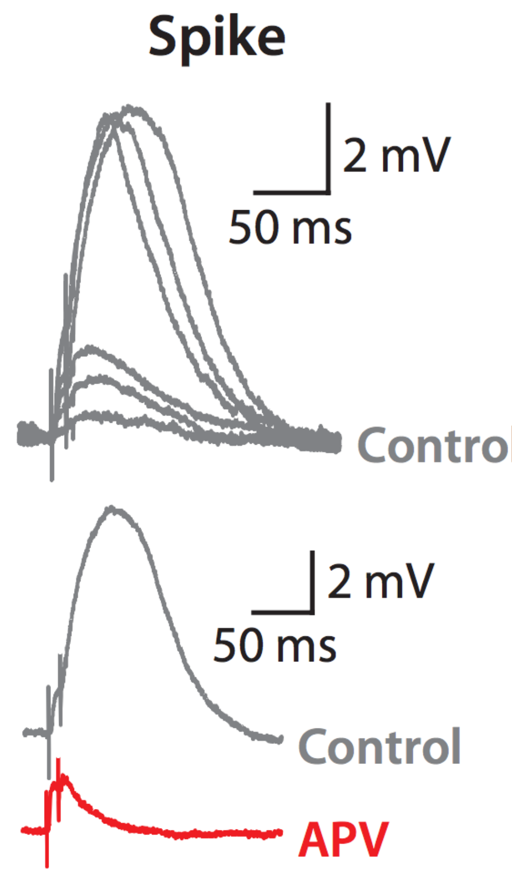


Neurotransmitter binding + depolarization
(itself a coincidence detector)

NMDA spike/plateau potential

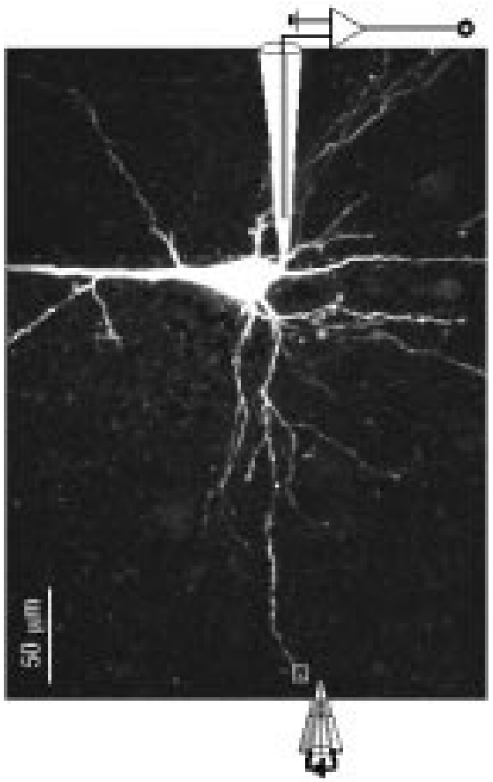


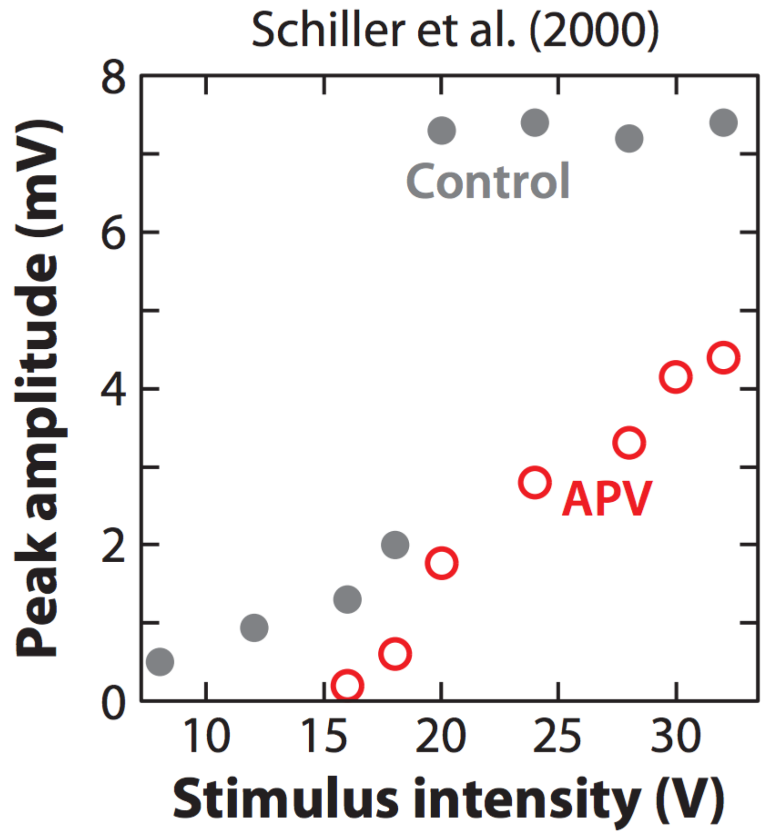


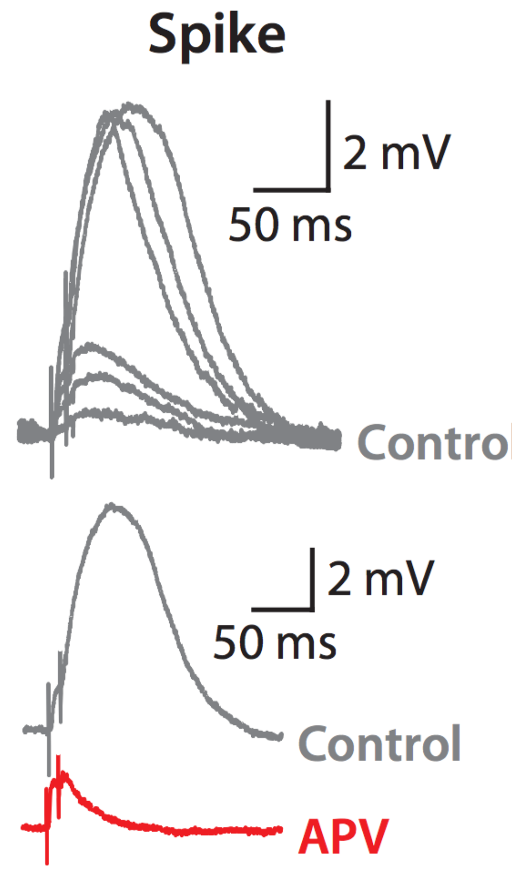


Schiller, 2000

NMDA spike/plateau potential



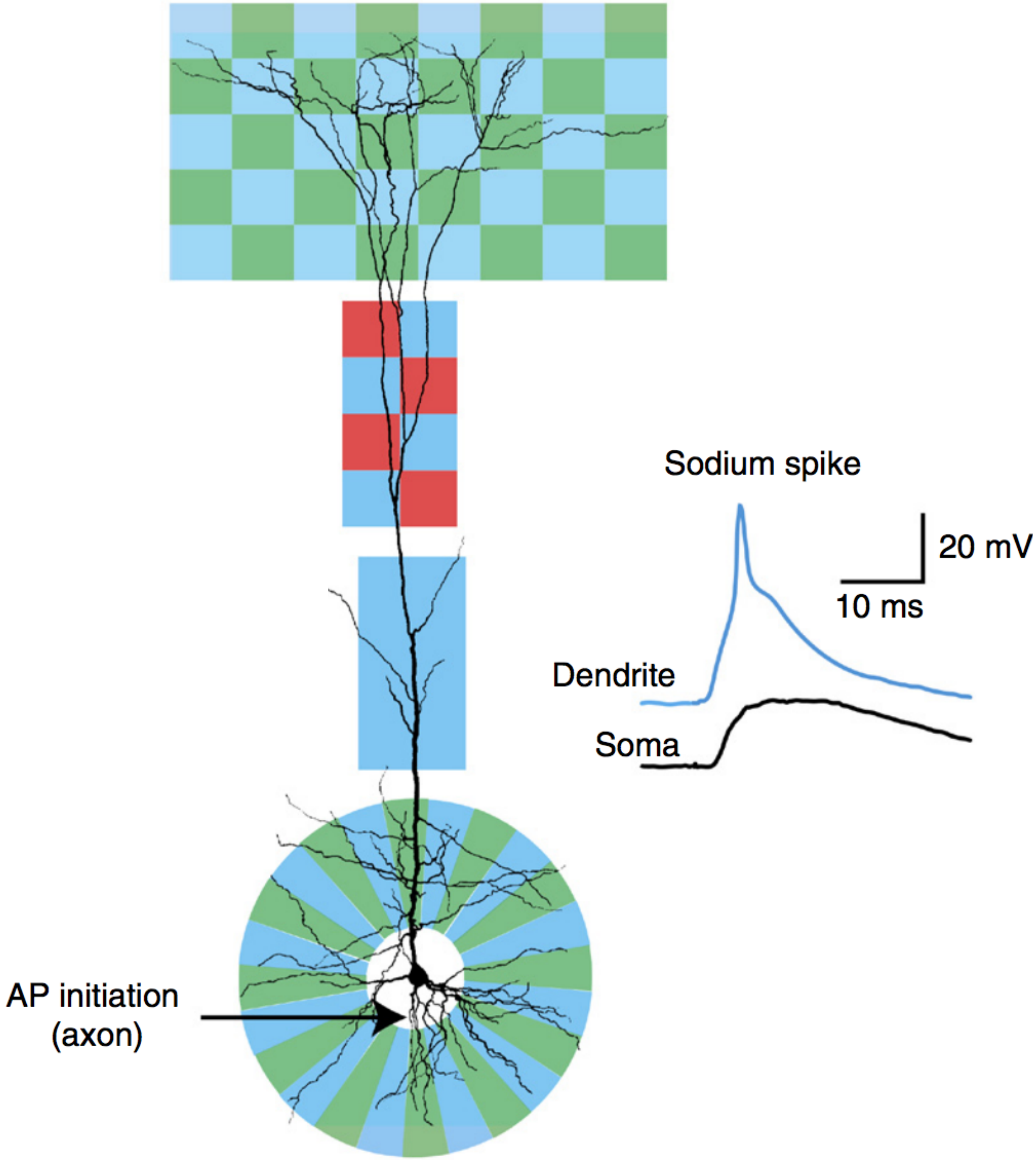


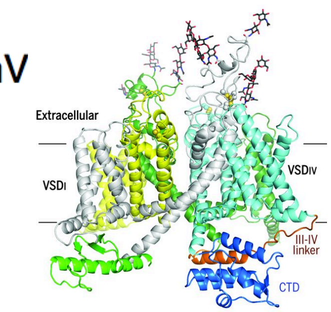


NMDA receptors detect clustered inputs within the same branch

Schiller, 2000

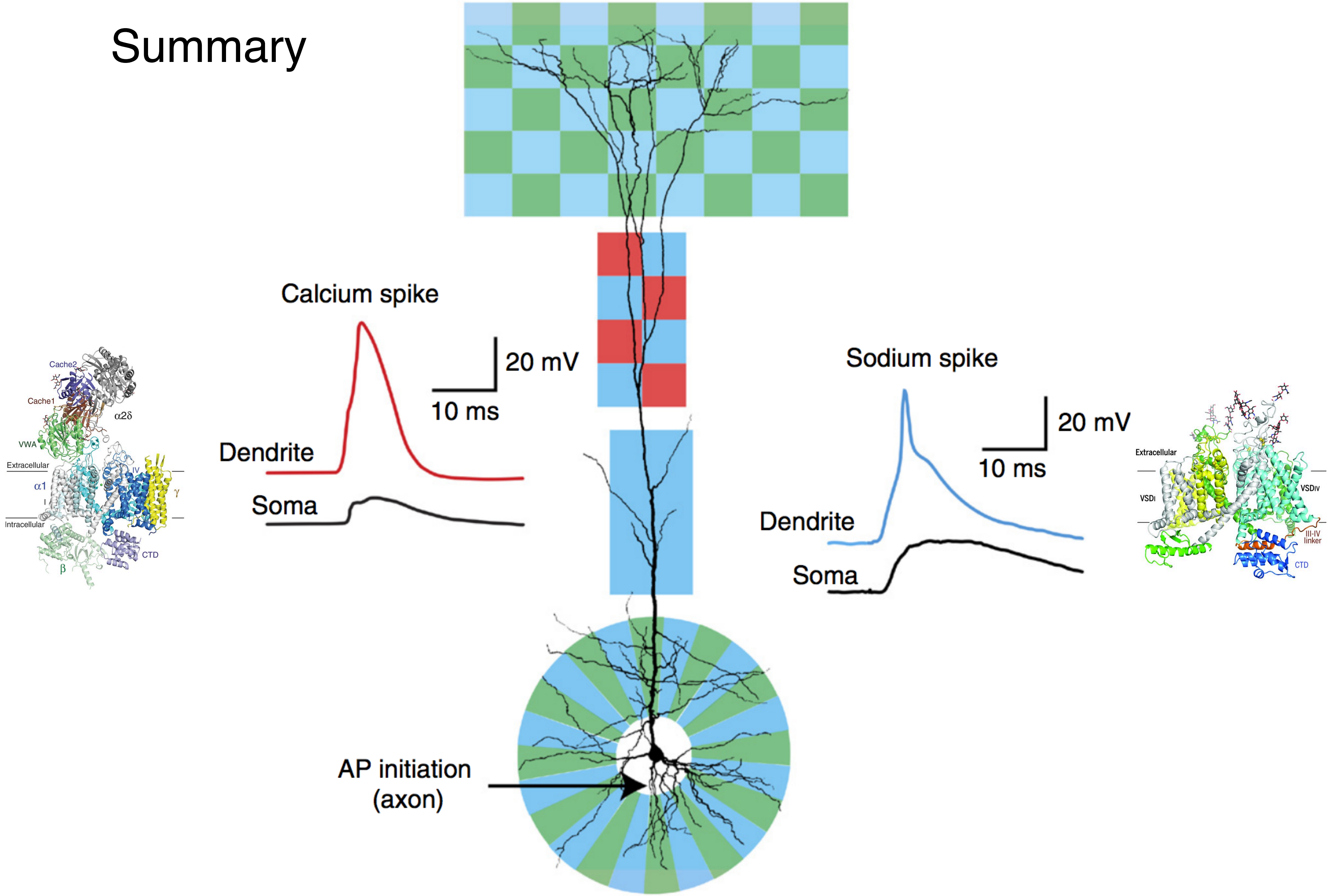
Summary





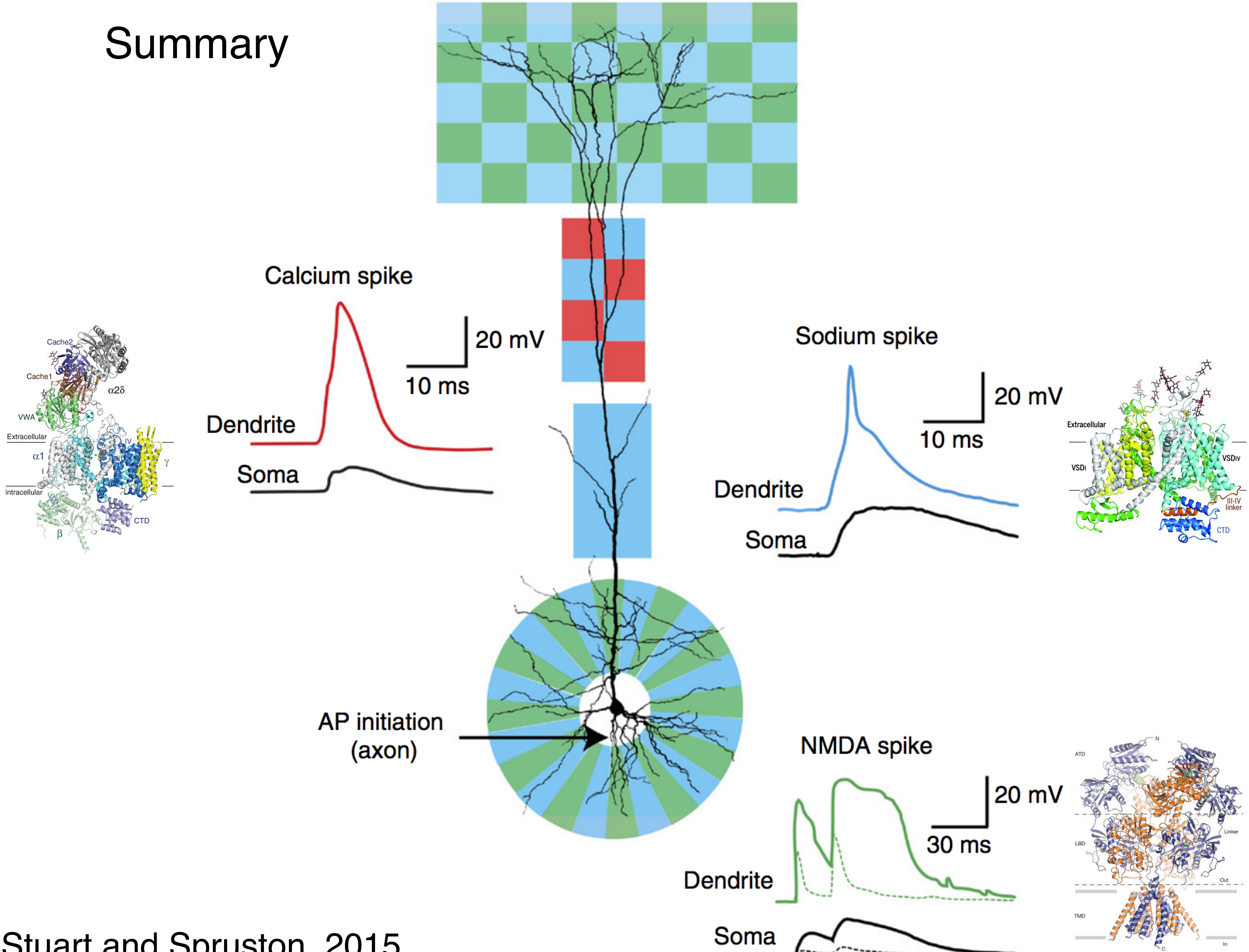
Stuart and Spruston, 2015

Summary



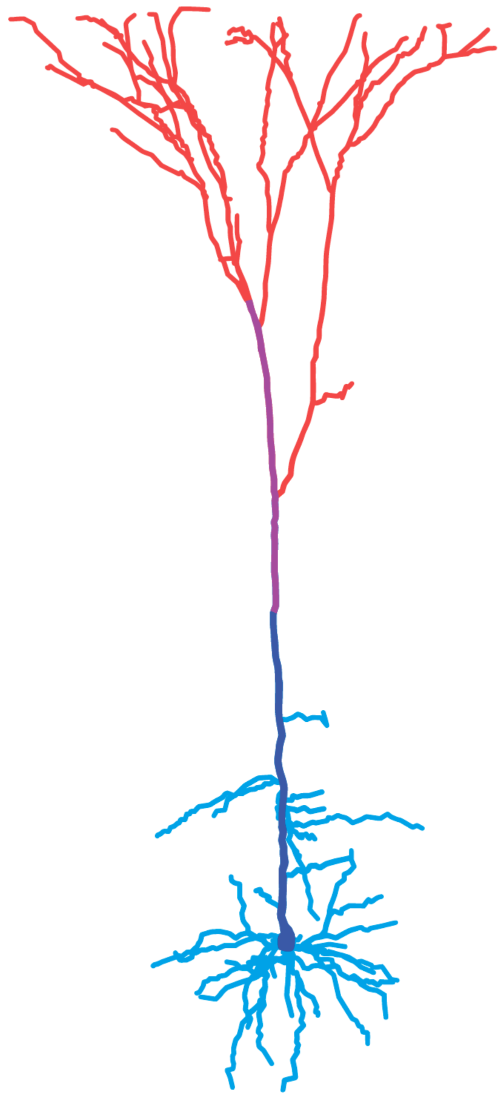
Stuart and Spruston, 2015

Summary



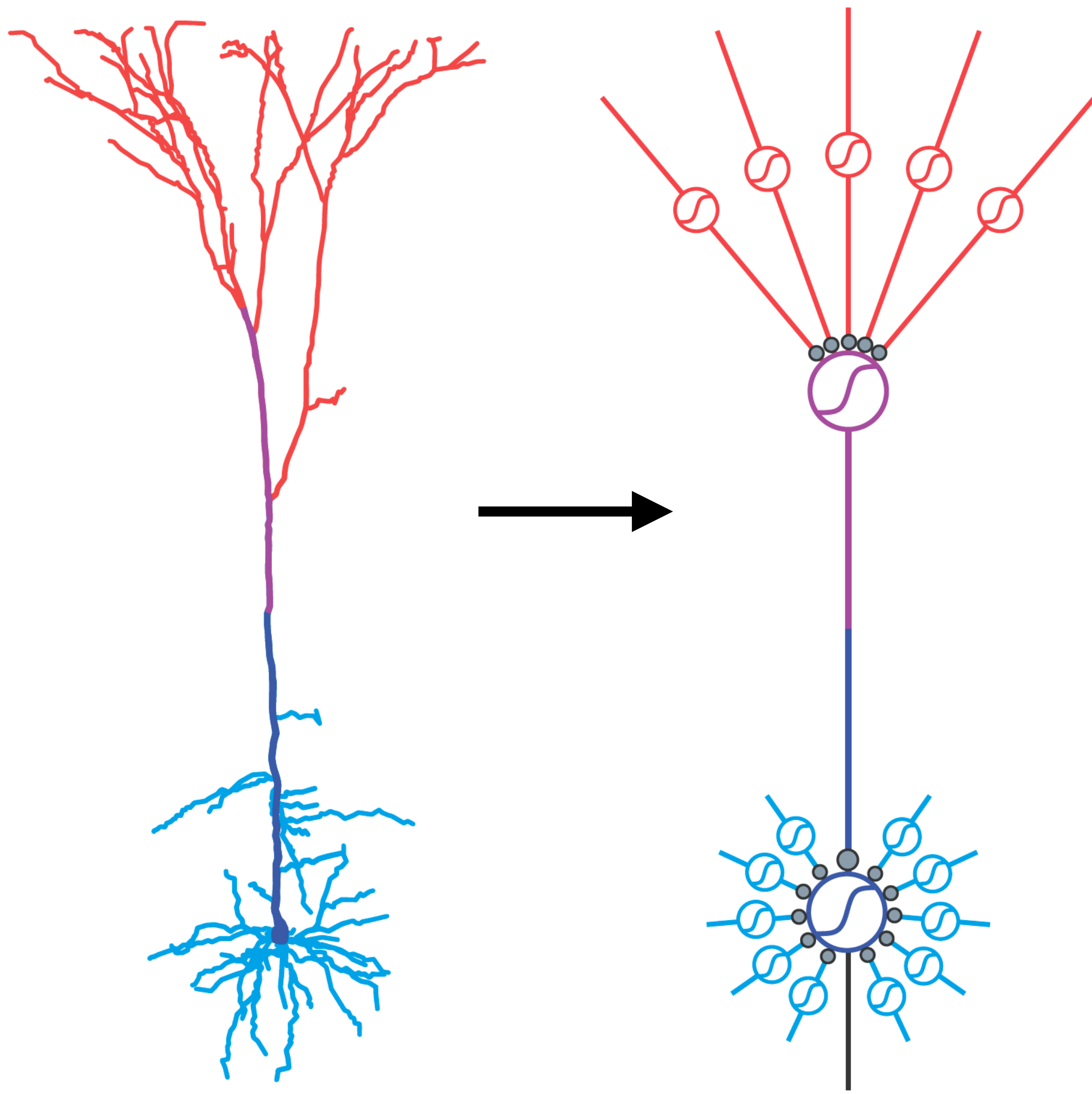
Stuart and Spruston, 2015

Emerging picture



Häusser & Mel 2003

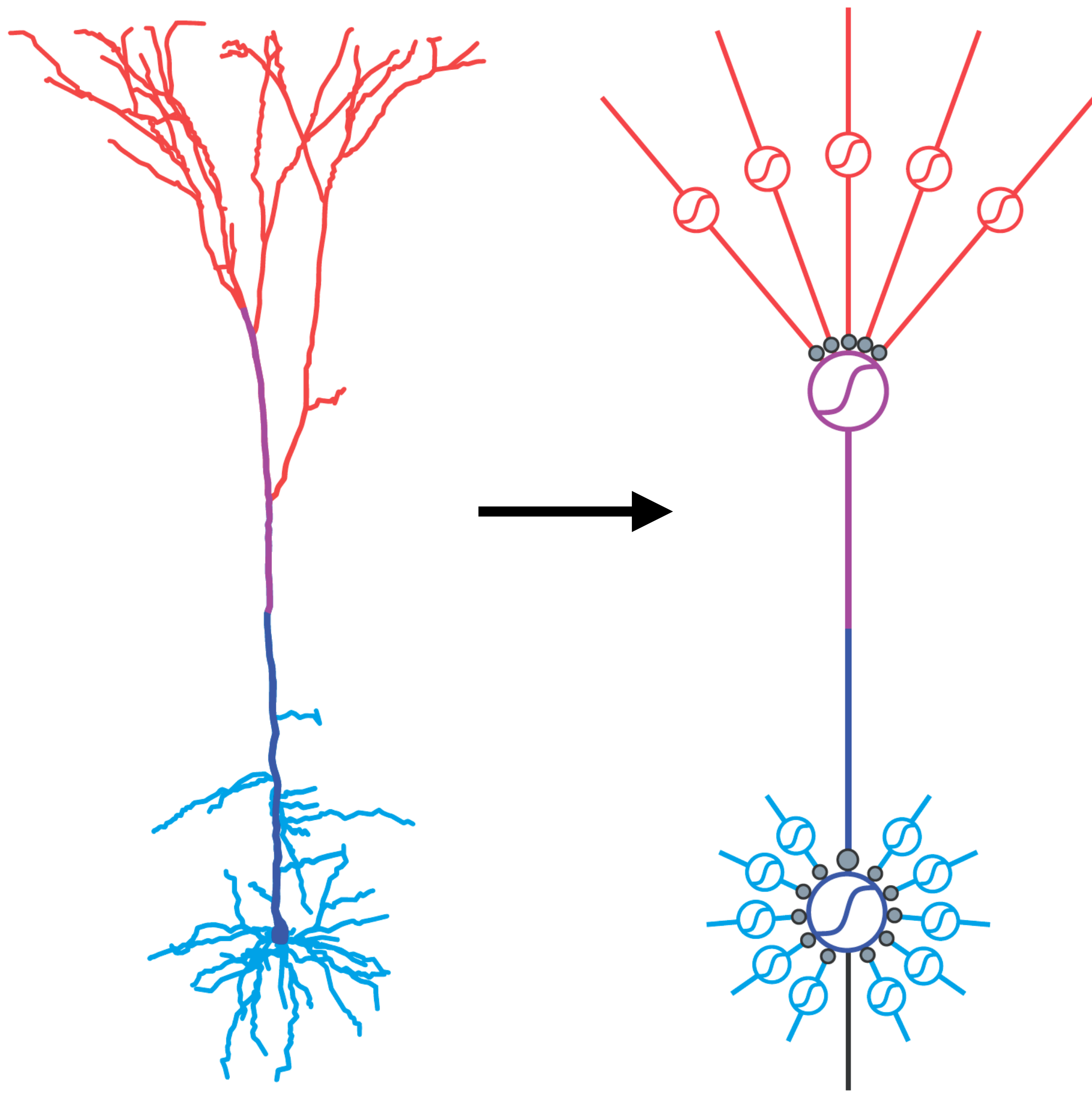
Emerging picture



dendrites as active computational units

Häusser & Mel 2003

Emerging picture

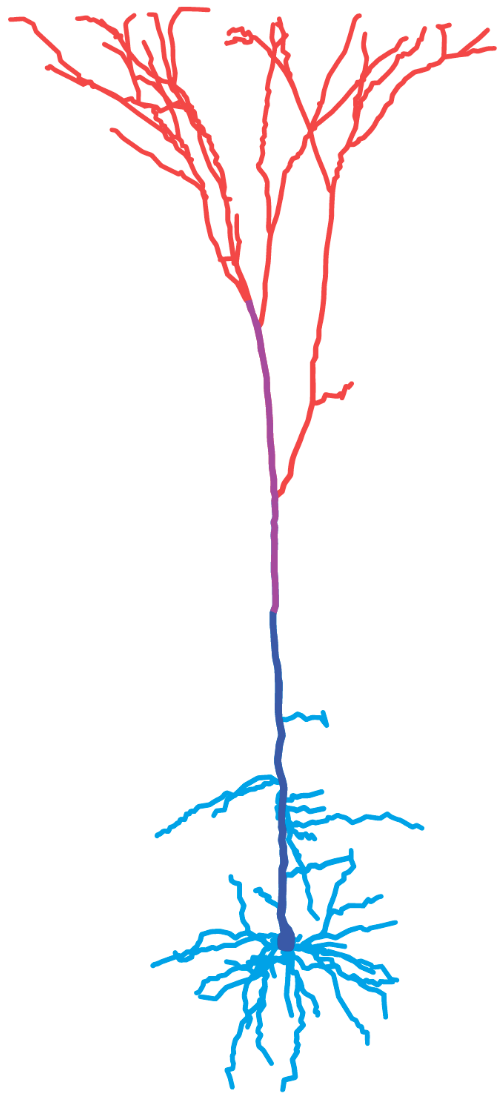


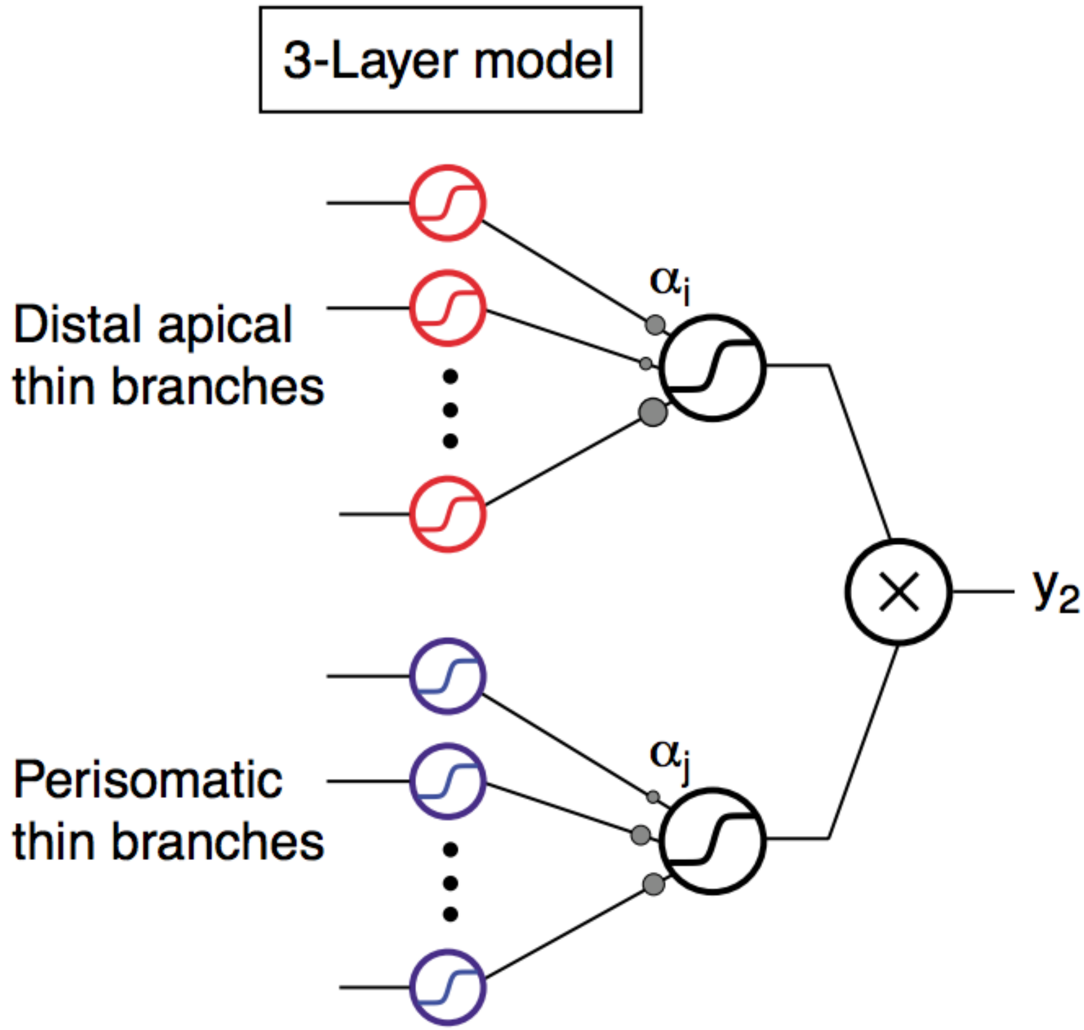
dendrites as active computational units

multiple integration zones

Häusser & Mel 2003

Emerging picture





Häusser & Mel 2003

Summary

- Ion channels are complex computational elements.

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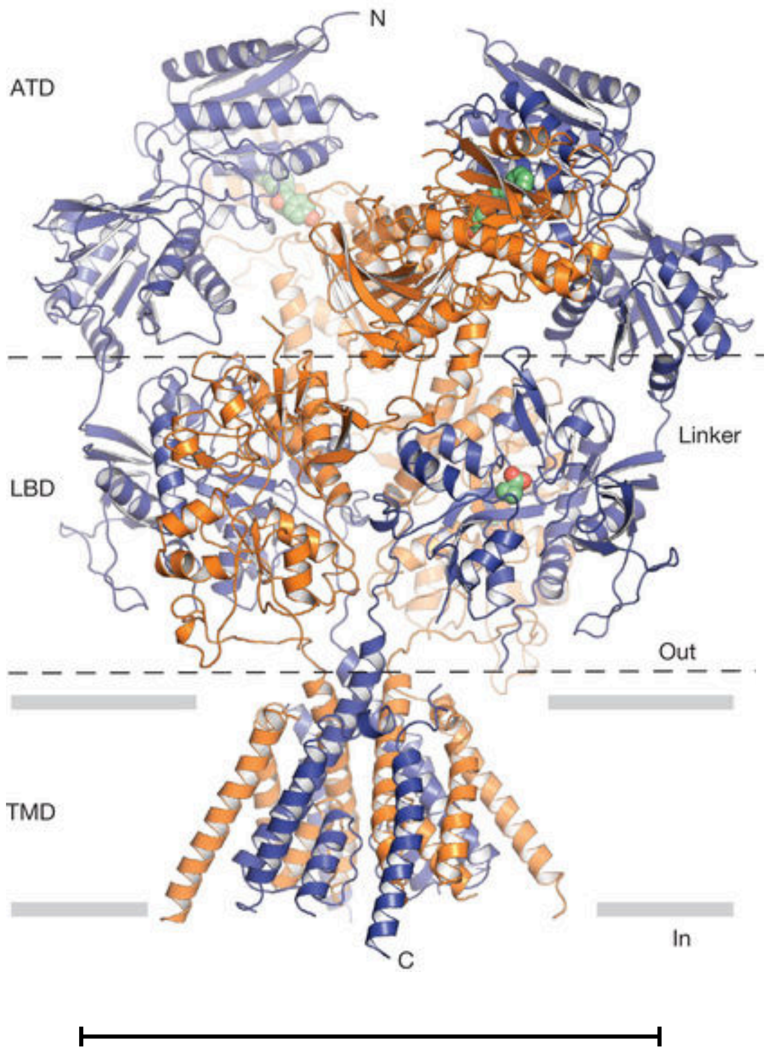
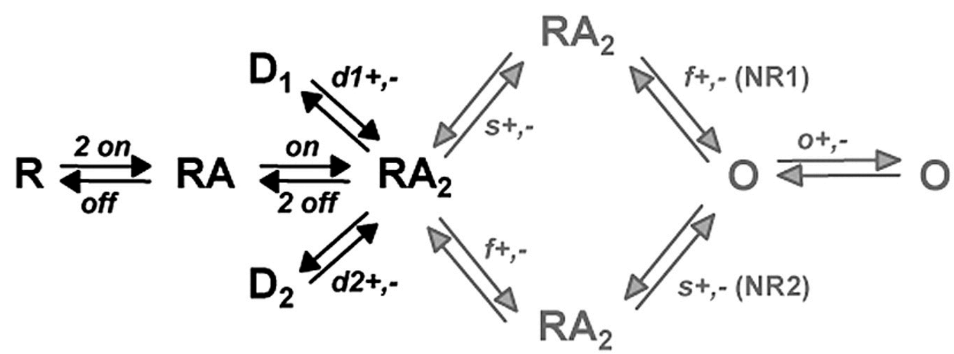


12 nm

Multiple gating mechanism with complex dynamics.

Markov model

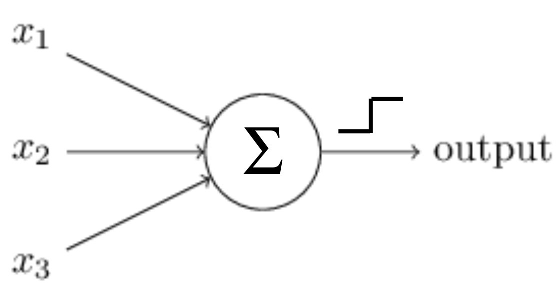


Erreger, 2005

Summary

- Point neuron model does not fully capture neuronal function.

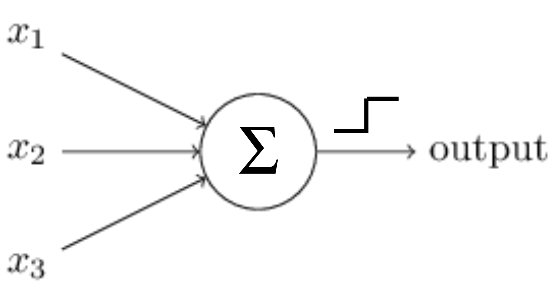
Point neuron

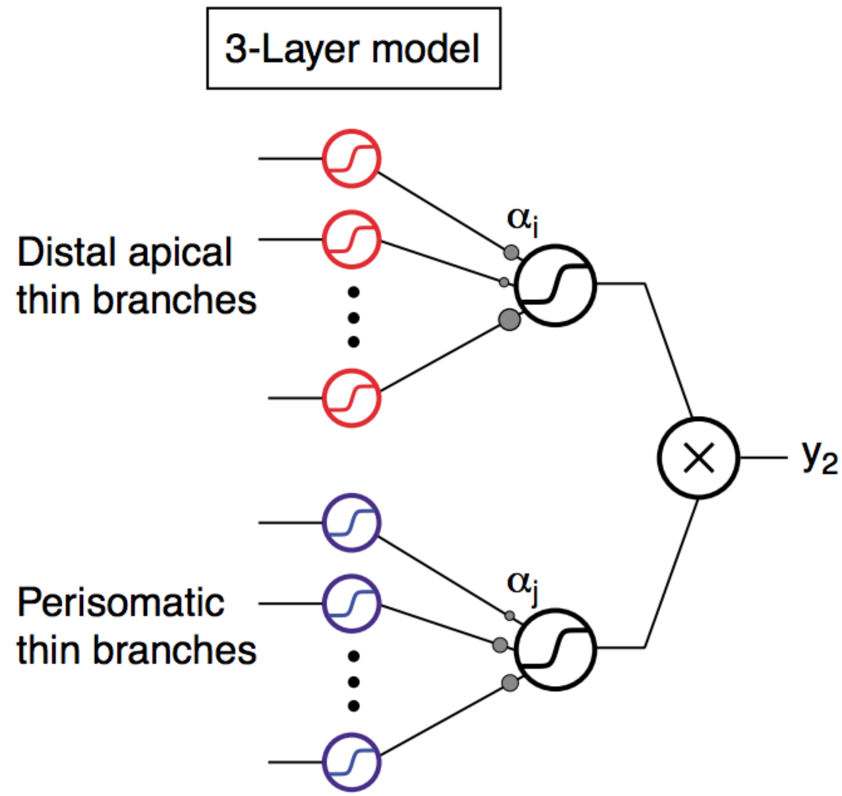


Summary

- Point neuron model does not fully capture neuronal function.
- Dendritic spikes increase the computational power of a single neuron .

Point neuron





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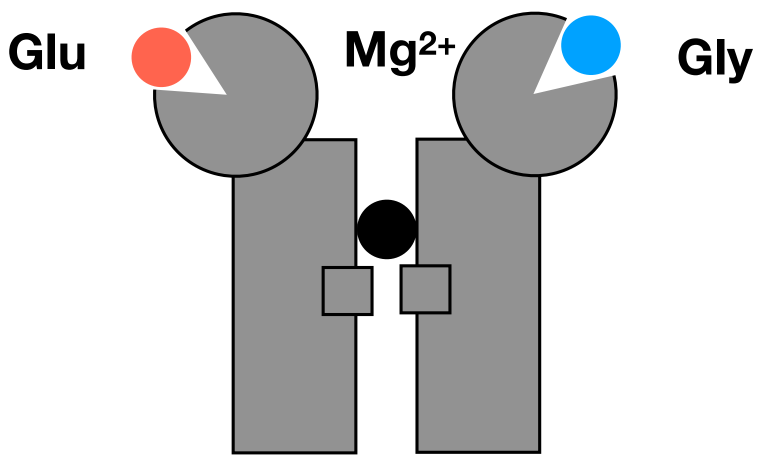
- NMDA spike is unique due to the double-gated mechanism of NMDA receptors.



Agonist-bound
but blocked state

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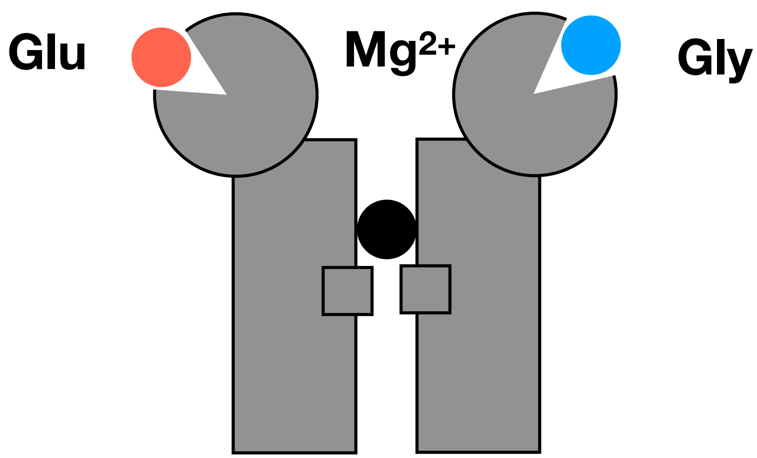

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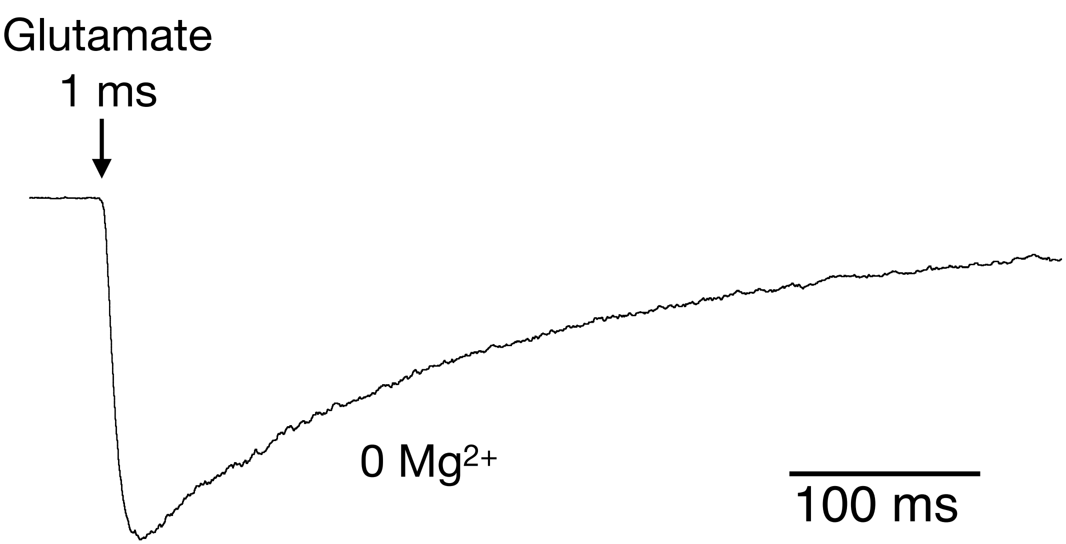
but blocked state



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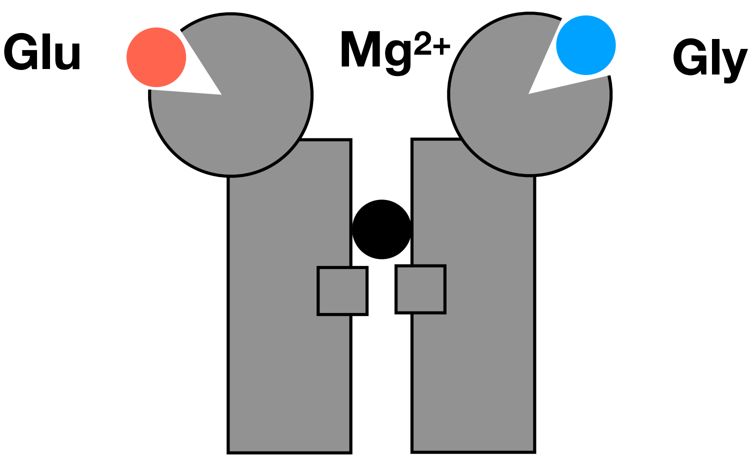

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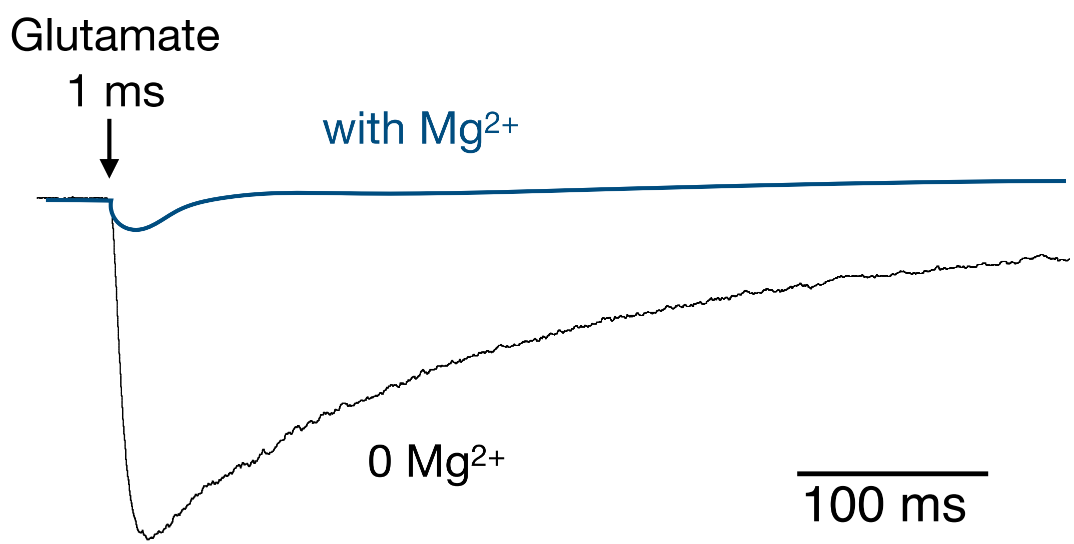

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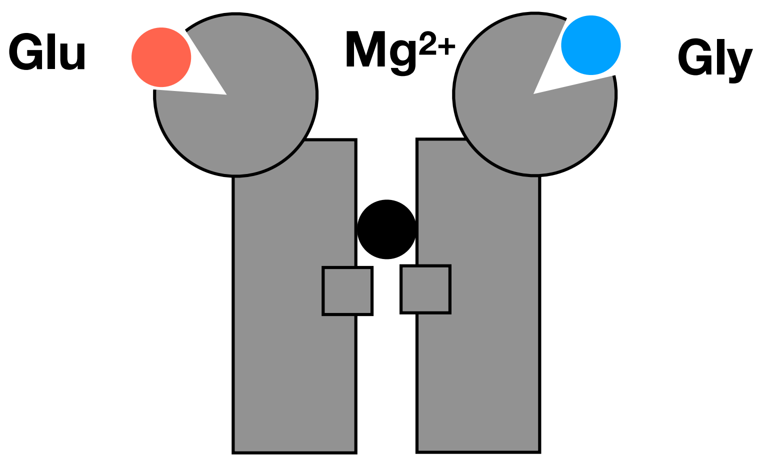

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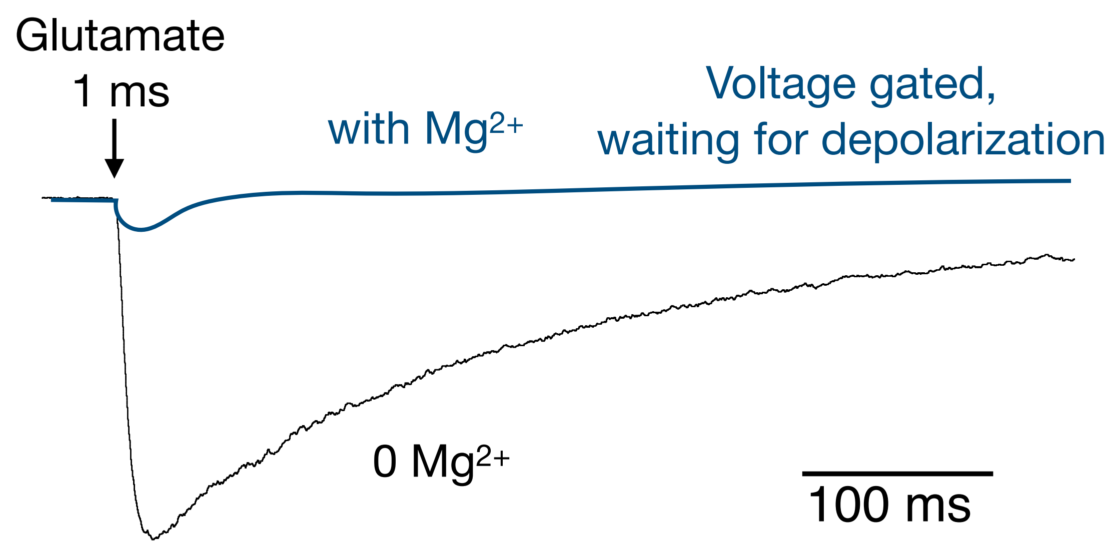

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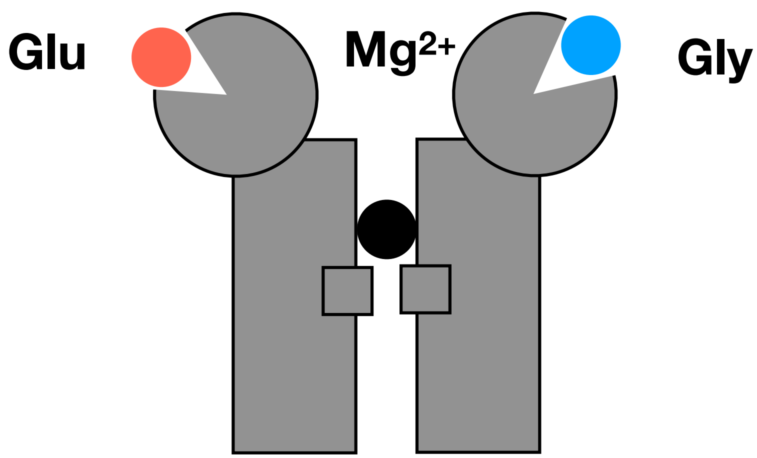
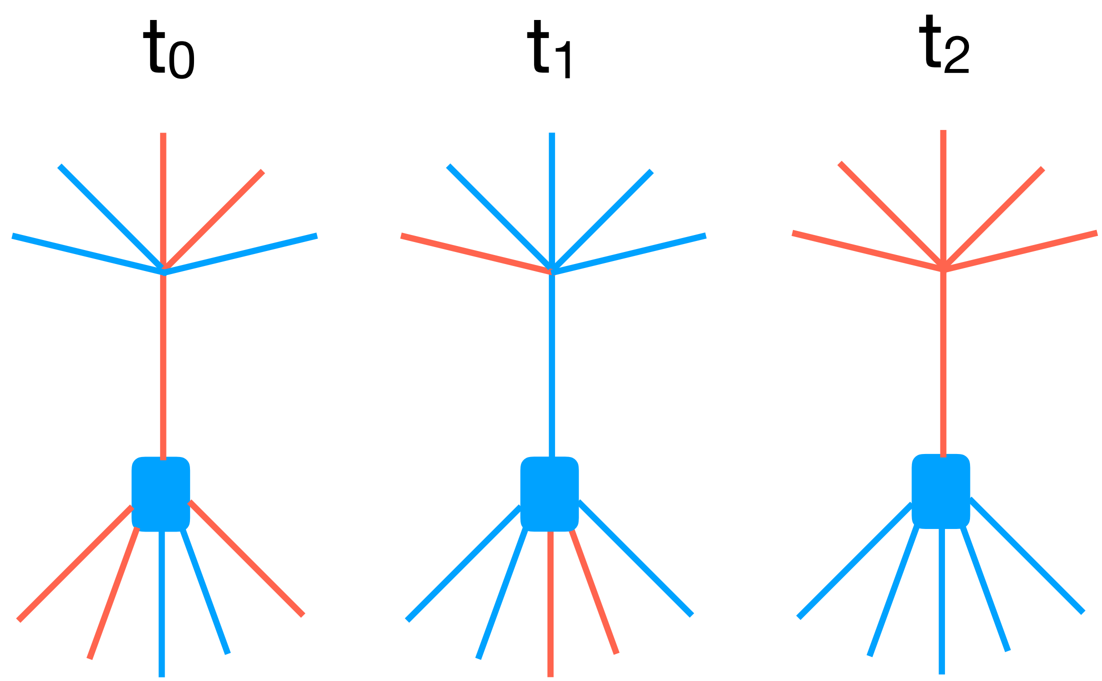


Agonist-bound but blocked state

Glutamate release at different branches



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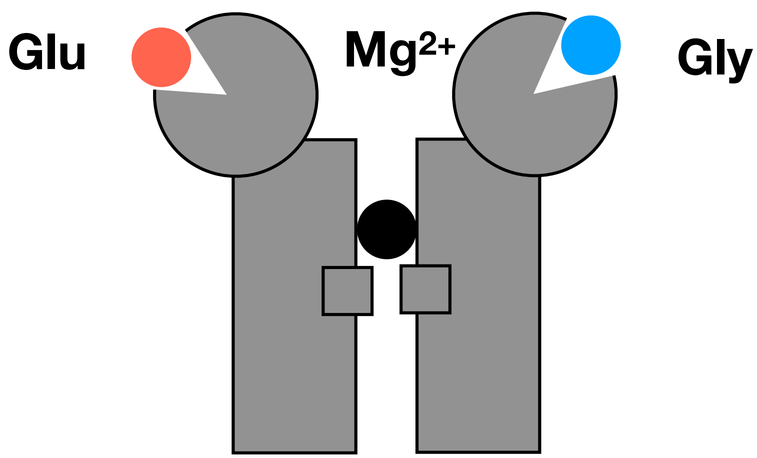
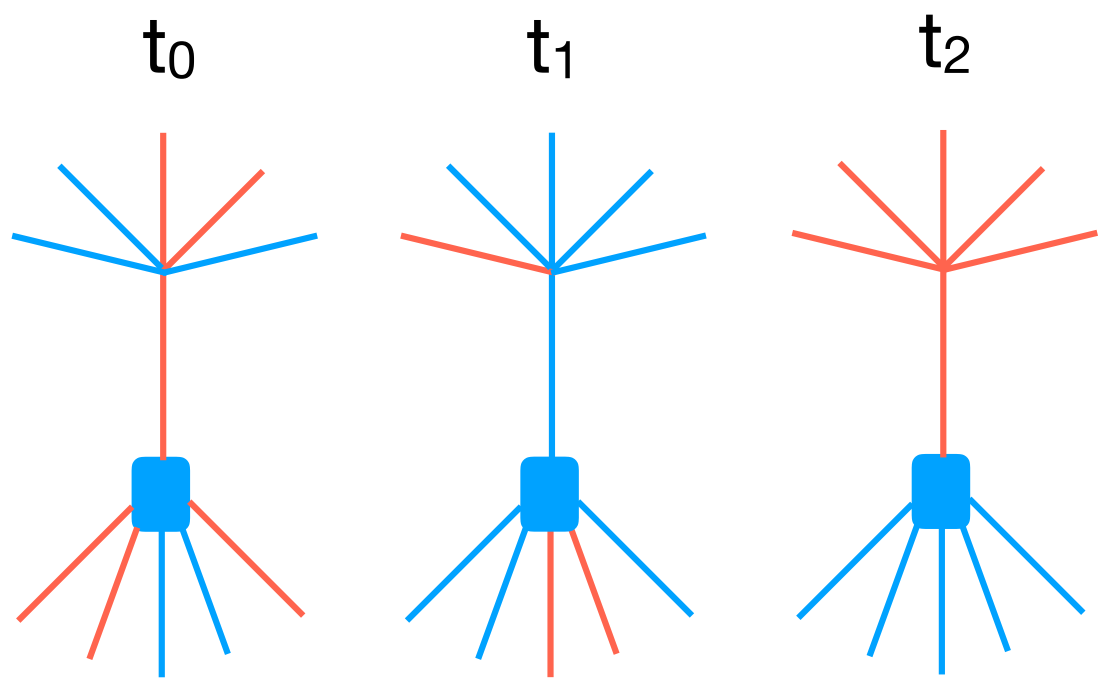


Agonist-bound but blocked state

Enable active dendrites for 100s of milliseconds



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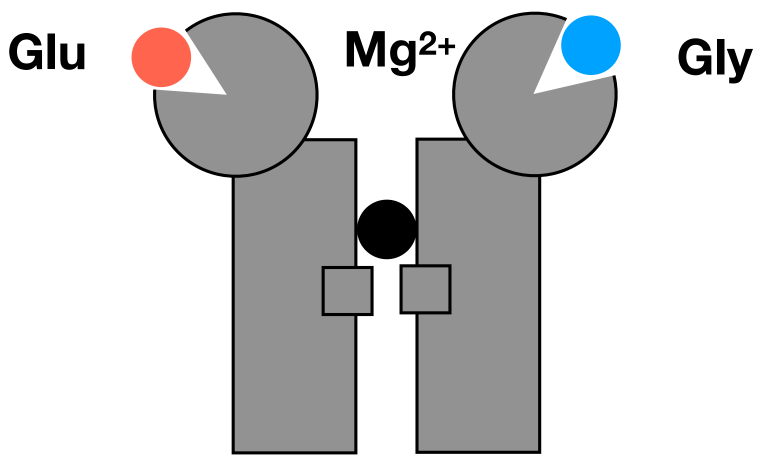

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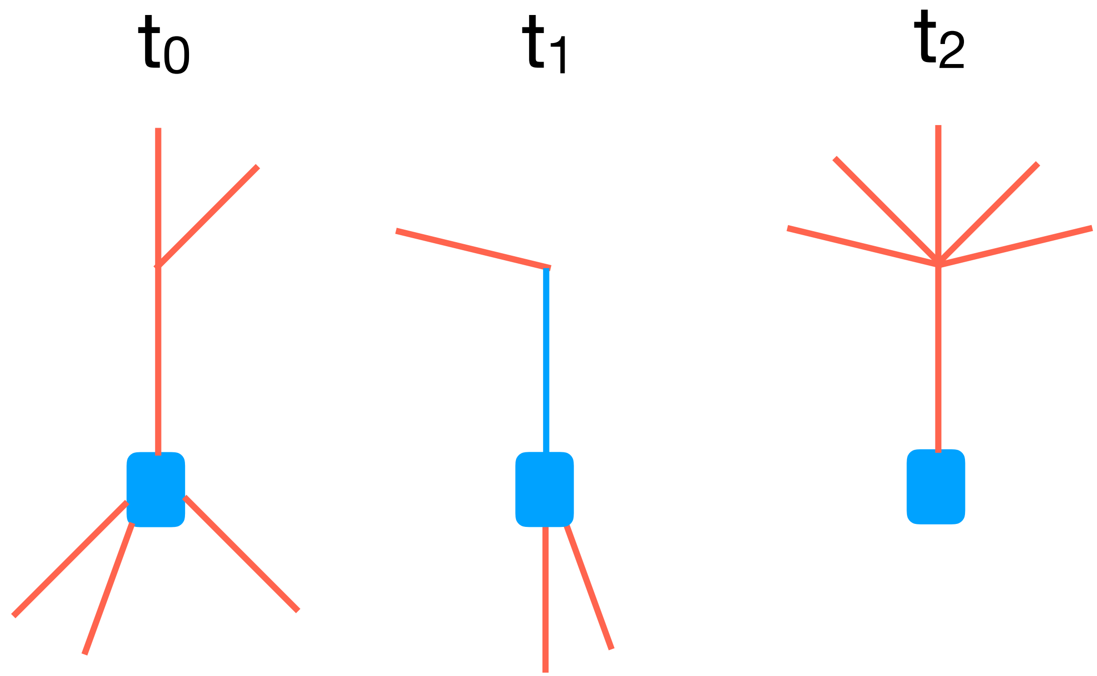

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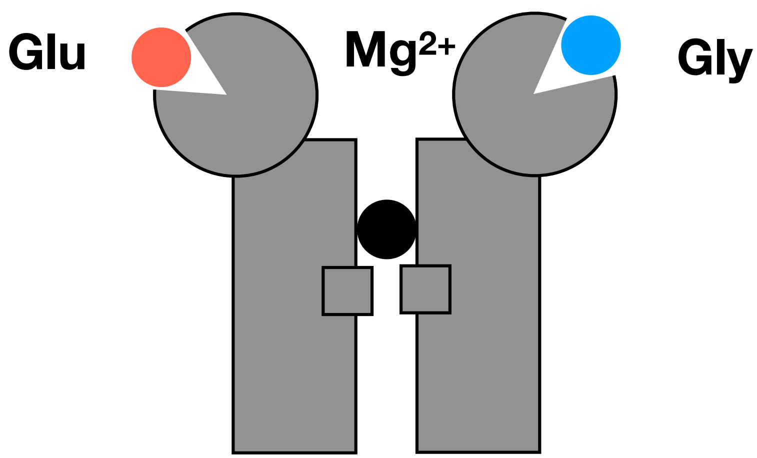

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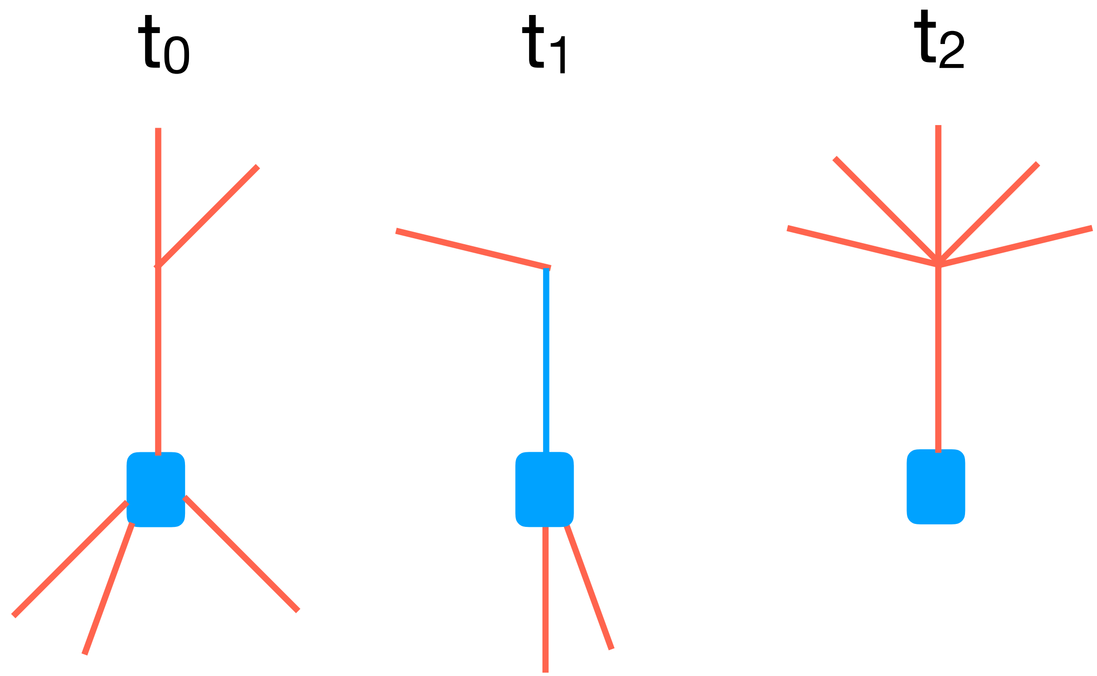


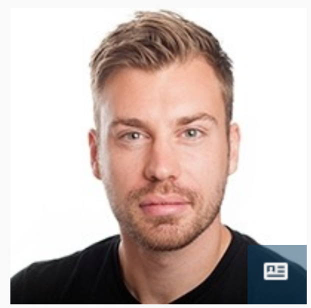
Online re-configuration of circuits, with minimal energy cost (ligand binding with no current flow).

Acknowledgments

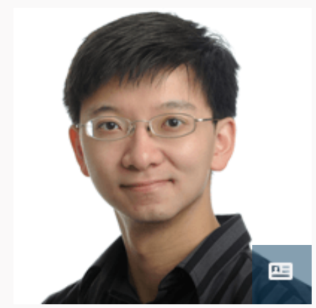
Nelson Spruston

POSTDOCTORAL ASSOCIATE
Xinyu Zhao

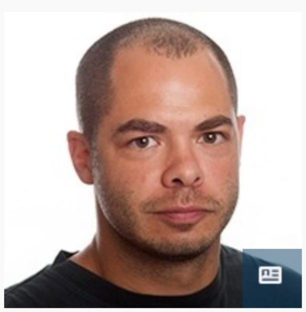
RESEARCH SCIENTIST
Erik Bloss



RESEARCH SCIENTIST
Mark Cembrowski



RESEARCH SCIENTIST
Ching-Lung Hsu



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POSTDOCTORAL ASSOCIATE
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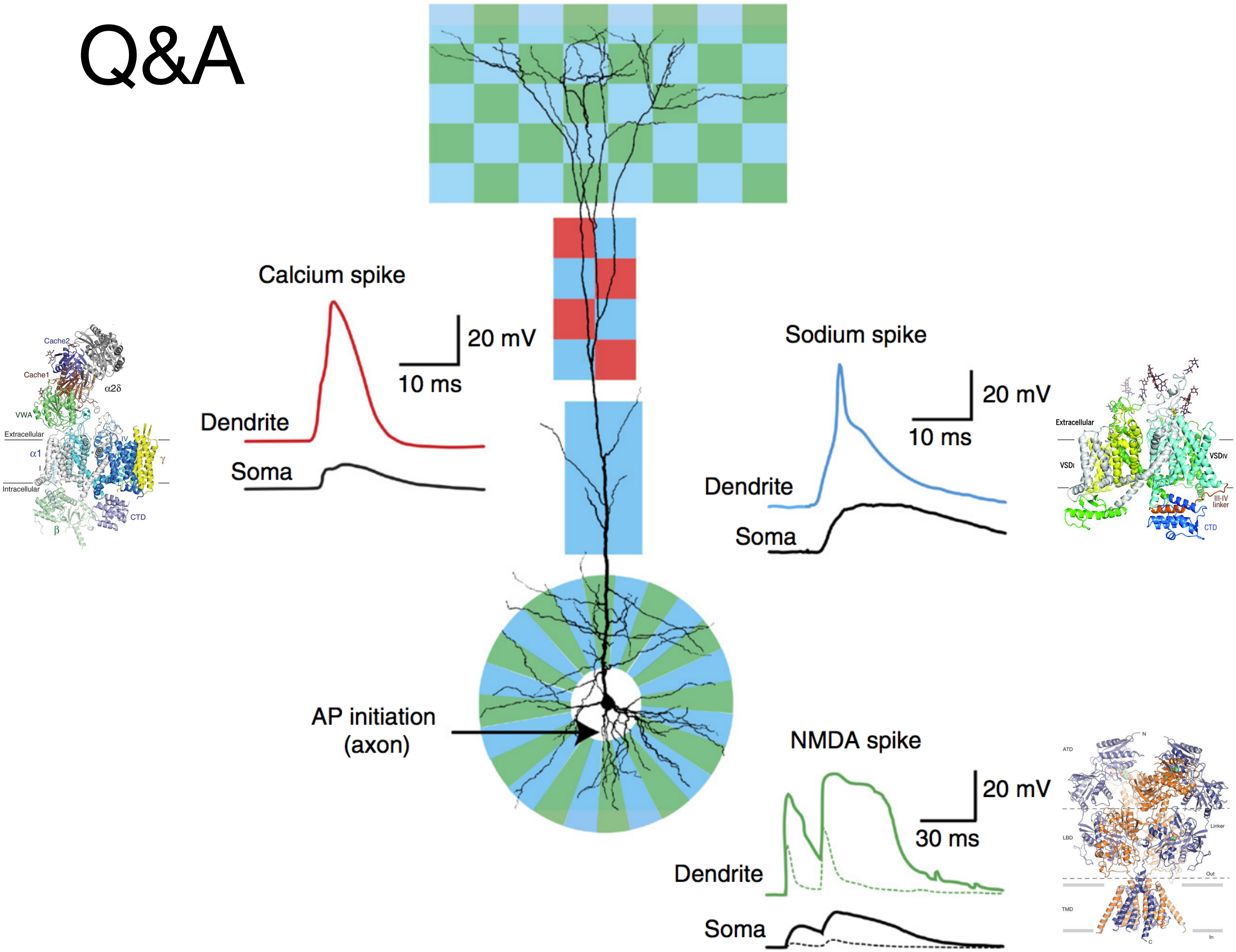
TEAM LEAD, LAB ADMINISTRATION
Christine Morkunas

POSTDOCTORAL ASSOCIATE
Johan Winnubst

Thank you!

Q&A



Stuart and Spruston, 2015