Subthreshold Mechanisms of Brain and Spinal Cord Stimulation

in four basic concepts.

Marom Bikson, The City College of New York

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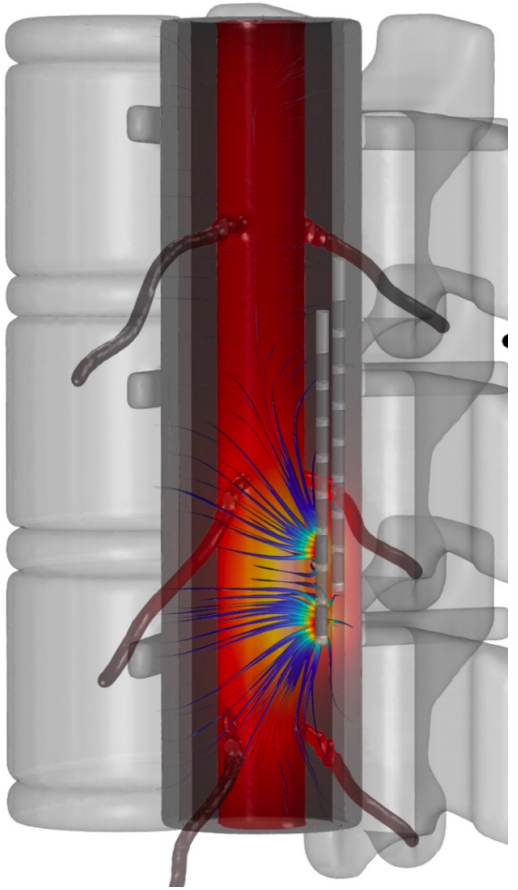

Disclosure

The City University of New York holds patents on brain stimulation with MB as inventor. MB has equity in Soterix Medical Inc. MB consults, received grants, assigned inventions, and/or served on the SAB of SafeToddles, Boston Scientific, GlaxoSmithKline, Biovisics, Mecta, Lumenis, Halo Neuroscience, Google-X, i-Lumen, Humm, Allergan (Abbvie), Apple, Ybrain, Ceragem, Remz.

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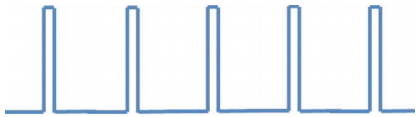
Slides:

@MaromBikson

What is **Supra-threshold Neuromodulation**

Stimulation waveforms built from pulses → Stimulation pulses driving some neurons to generate action potentials → Paced action potentials explain secondary (clinical) changes.



Innovation / research centers on pulse design

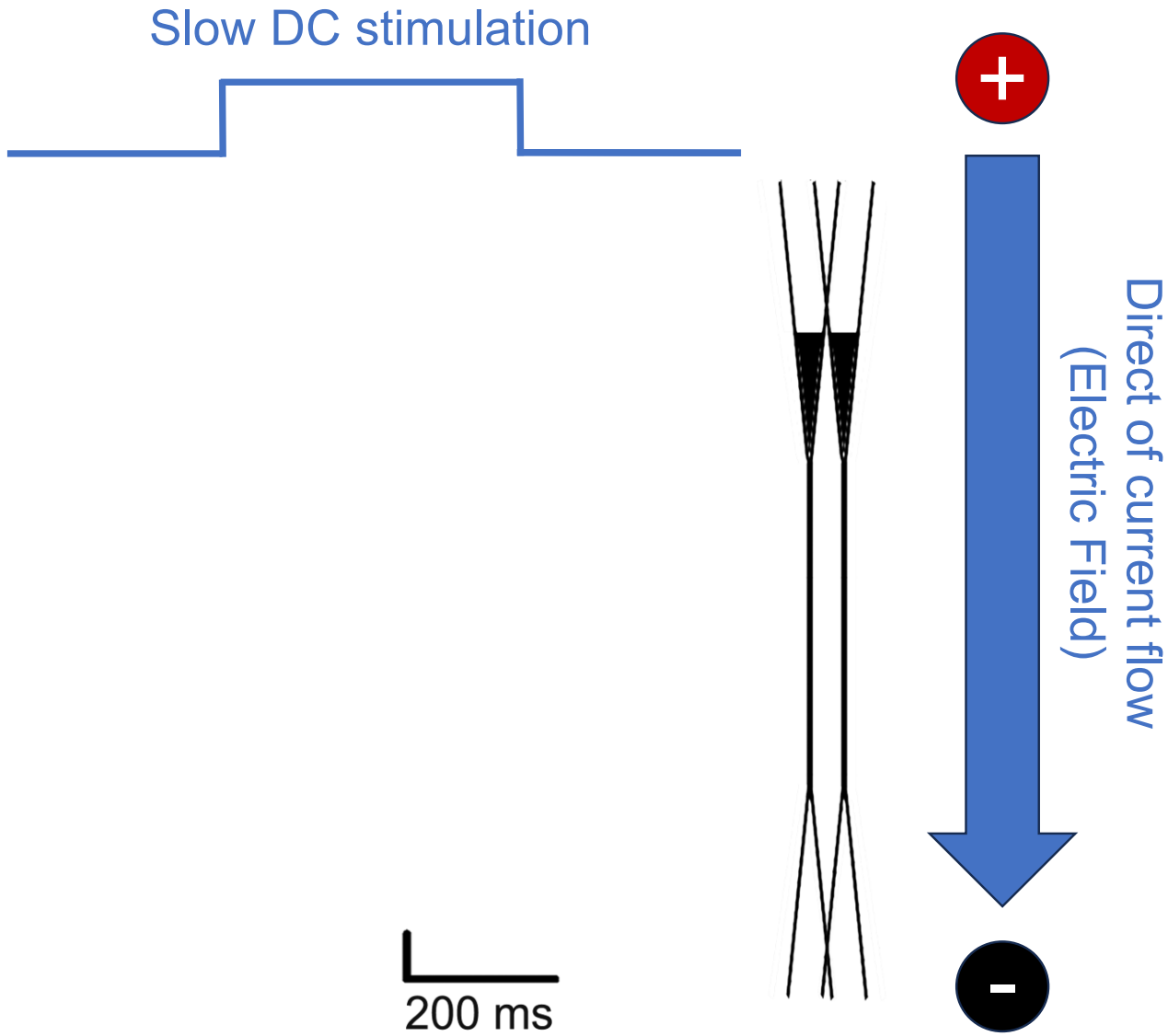
What is **Sub-threshold Neuromodulation**

Stimulation waveforms may or may not be pulsed based → Stimulation polarizes cells, changing how they function (process signals) → Secondary (clinical) changes

Innovation / research centers on pulse (waveform) design, based on sub-threshold mechanisms.

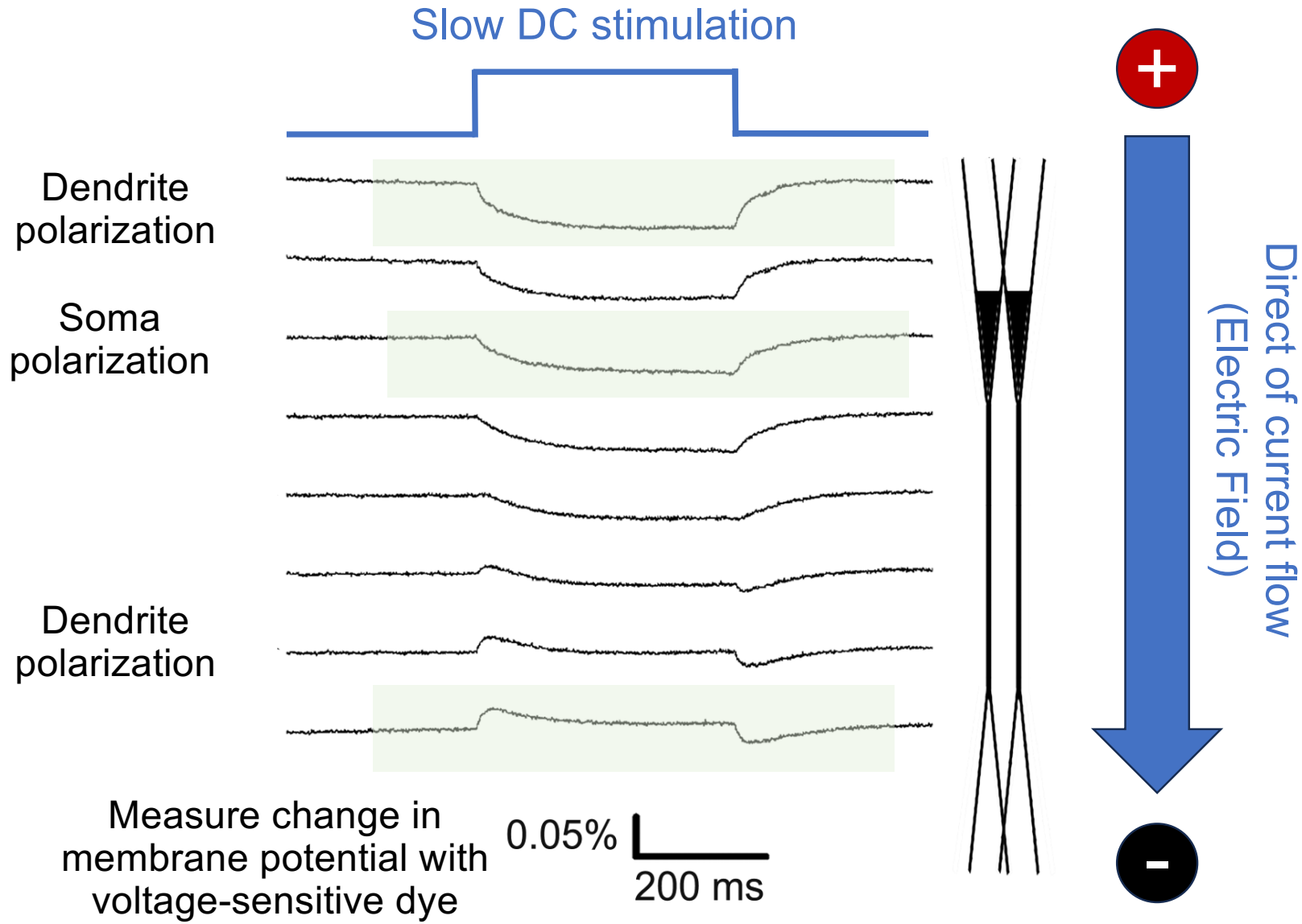
Leading to unique technology / therapies.

Thinking about long pulse (DC) low-intensity stimulation explains sub-threshold mechanism.



Bikson et al. Effects of uniform extracellular DC electric fields on excitability in rat hippocampal slice J Physiol 2004

- Compartments of the cell all polarize but with different amount.



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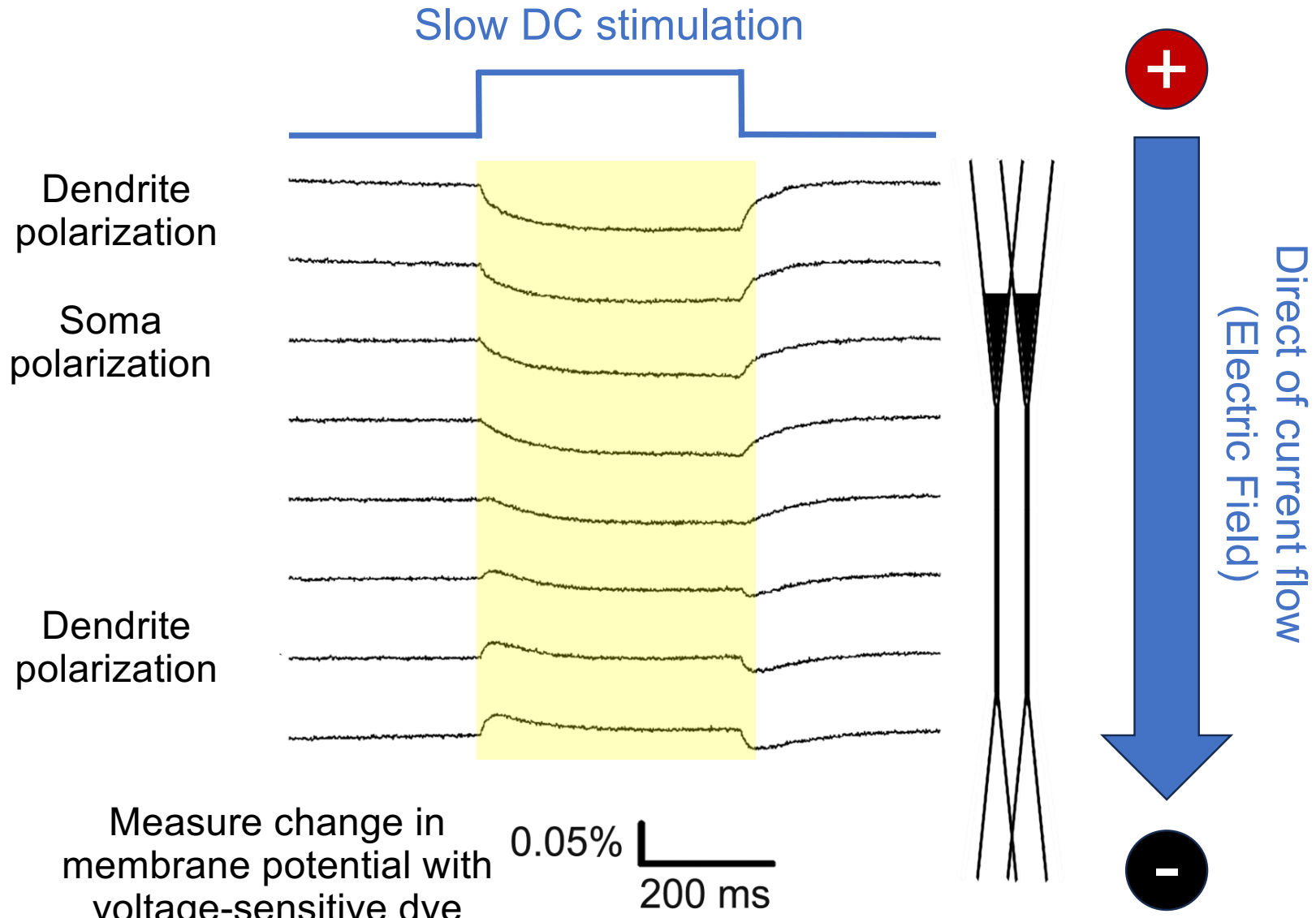
- Compartments of the cell all polarize but with different amount.
- The polarization “looks like” the stimulation. But with a charge up (time constant ~8 ms)
- Stimulation does not generate action potentials.



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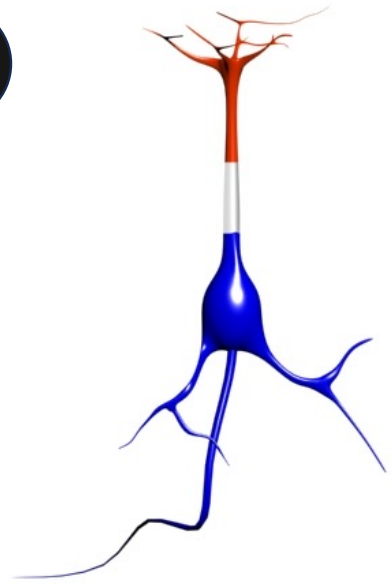
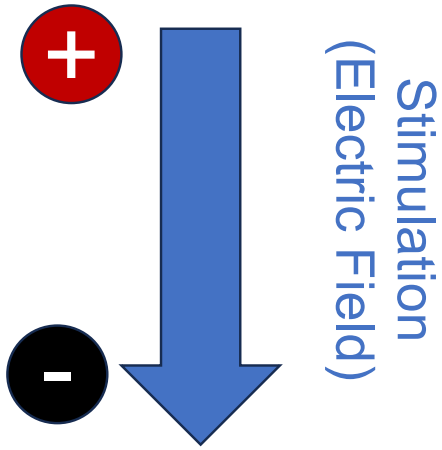
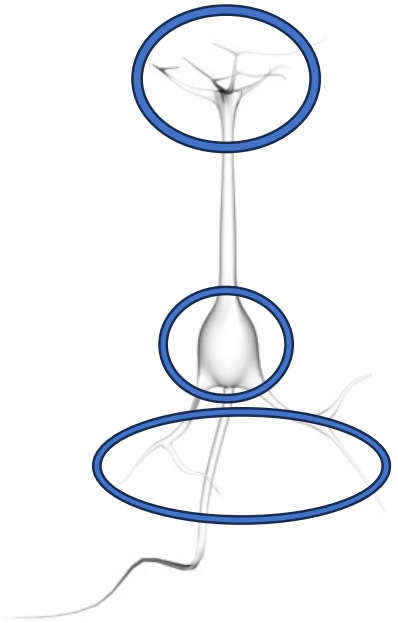






The polarization of a neuronal compartment (mV) = Intensity of stimulation Electric field (V/m) x Compartment coupling constant (mV per V/m)

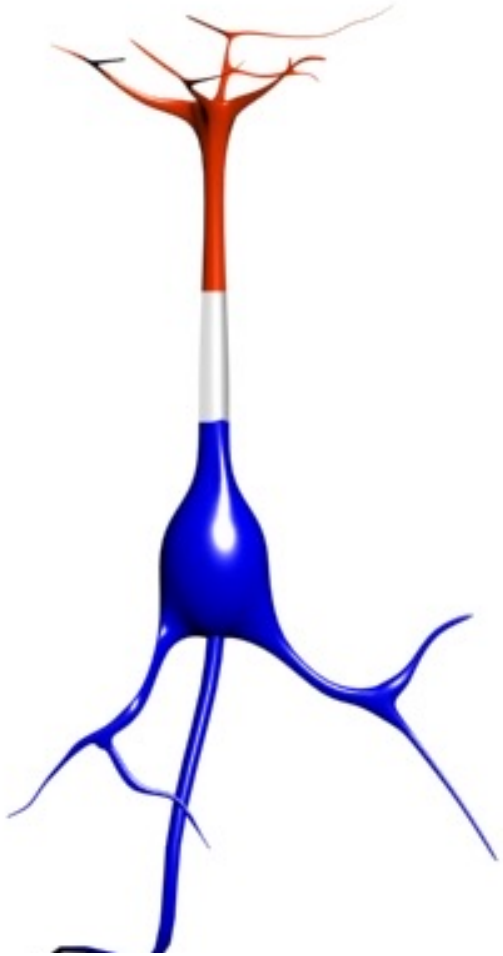
Polarization length (mm)

Neuronal compartment polarization of 5 mV = 10 V/m x 0.5 mV per V/m

Bikson et al. Effects of uniform extracellular DC electric fields on excitability in rat hippocampal slice J Physiol 2004

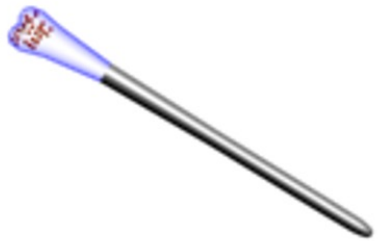
1

Coupling constants tell us which neuronal compartments are polarized (how much) by stimulation.

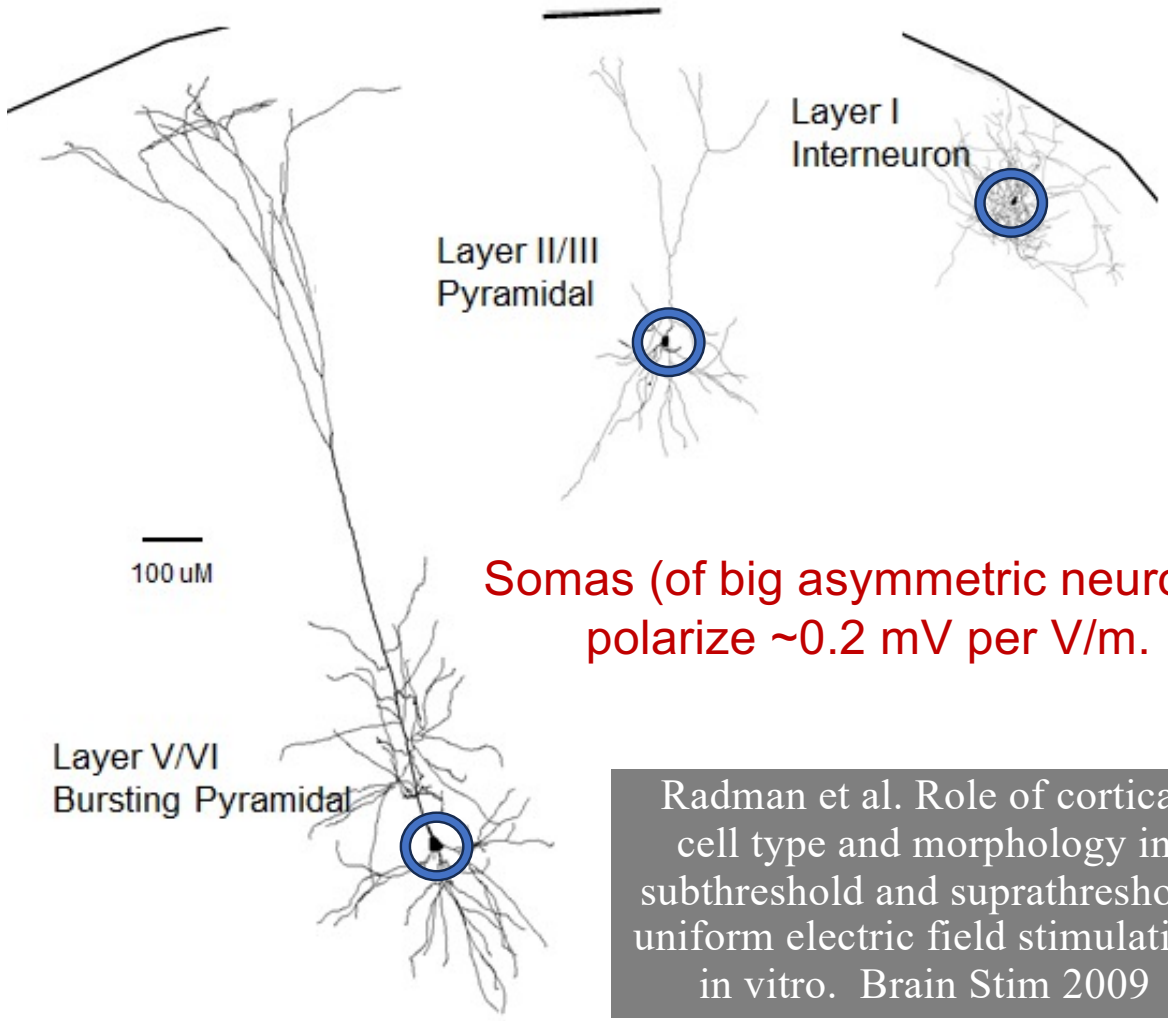


How big can a coupling constant get?

For a soma.
For a dendrite.
For an axon.



How big are coupling constants of soma, neuron, and axon neuron compartments?

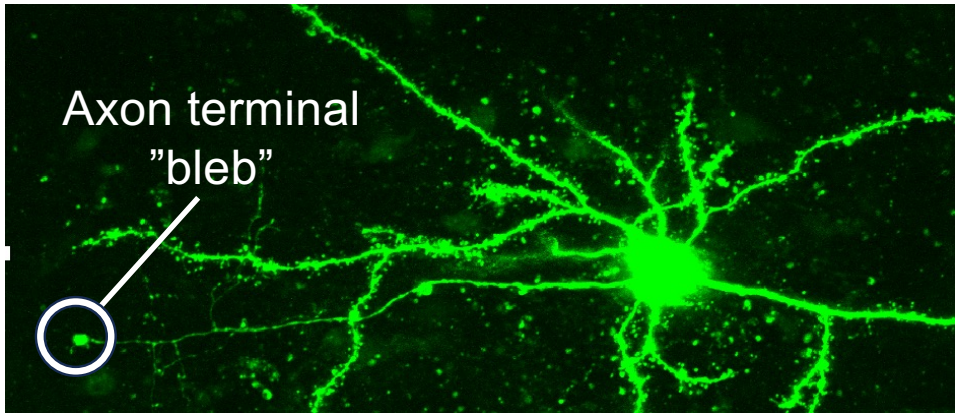


Somas (of big asymmetric neurons) polarize ~0.2 mV per V/m.

Radman et al. Role of cortical cell type and morphology in subthreshold and suprathreshold uniform electric field stimulation in vitro. Brain Stim 2009

10 years of research in 30 seconds

Chakraborty et al. Neuromodulation of Axon Terminals. Cereb Cortex 2018



Axon terminals polarize up to ~0.8 mV per V/m.

Dendrites polarize up to ~0.5 mV per V/m.

Joucla & Yvert. The "mirror" estimate: an intuitive predictor of membrane polarization during extracellular stimulation. Biophys J. 2009

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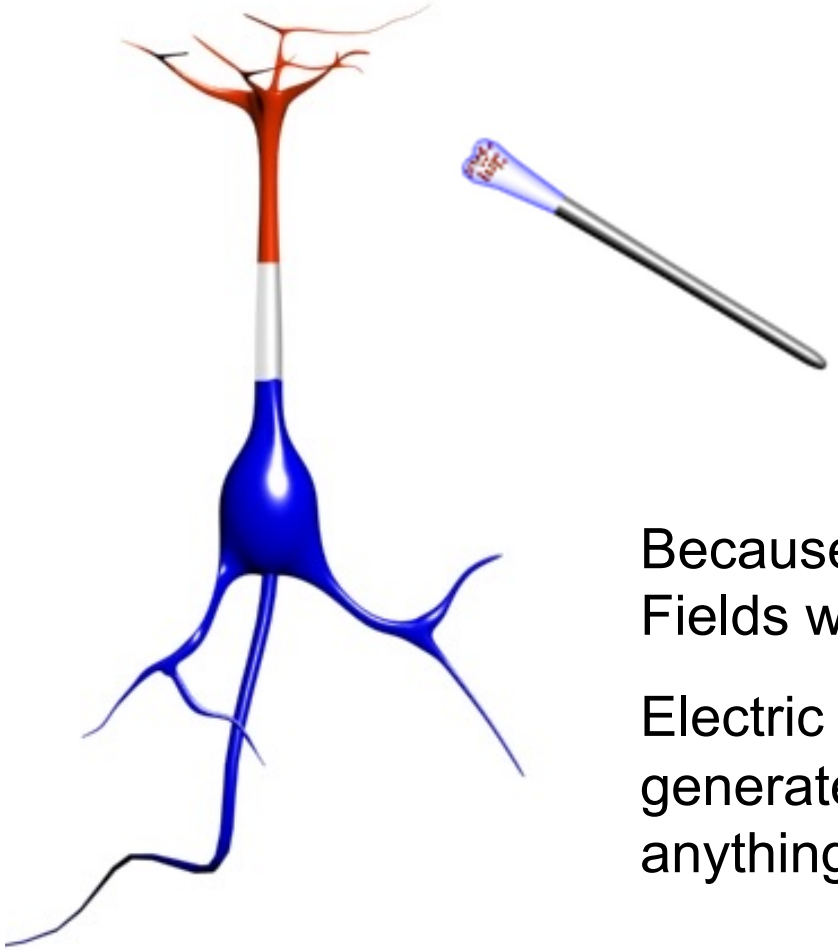


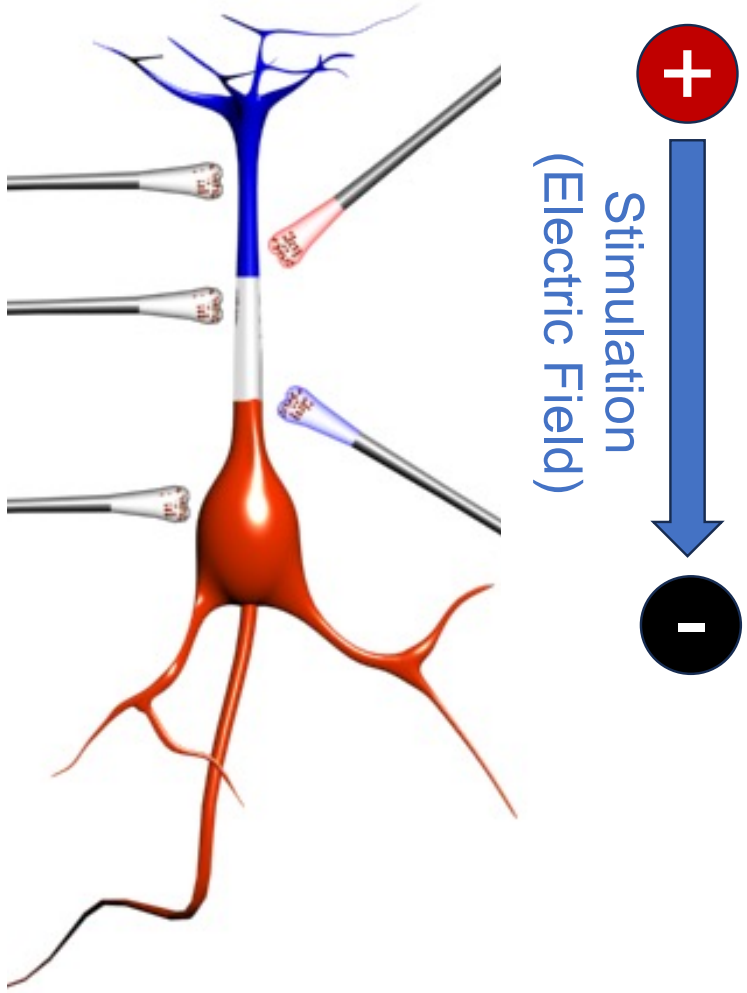
How big can a coupling constant get?
For a soma ~0.2 mV per V/m For a dendrite ~0.5 mV per V/m For an axon terminal ~0.8 mV per V/m

Because coupling constants are not so big, only very large Electric Fields will polarize neurons enough to generate action potentials.

Electric Fields generated during stimulation may not be enough to generate action potentials. But this does not mean they don't do anything : Sub-threshold Neuromodulation

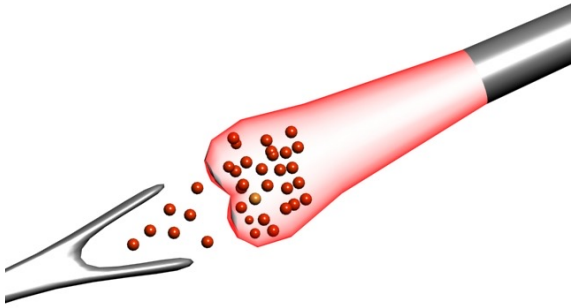
Jackson et al. Animal models of transcranial dc stimulation: Methods & mechanisms. Clinical Neurophysiol. 2016

How do Electric Fields that are not large enough to trigger action potentials, but still produce neuronal polarization (of soma, dendrite, axon terminal) modulate brain function?



Not by generating action potentials but by changing the processing of ongoing activity including synaptic efficacy.

If a synapse is already active, how does the addition of polarization by an electric field change how the synapse works.



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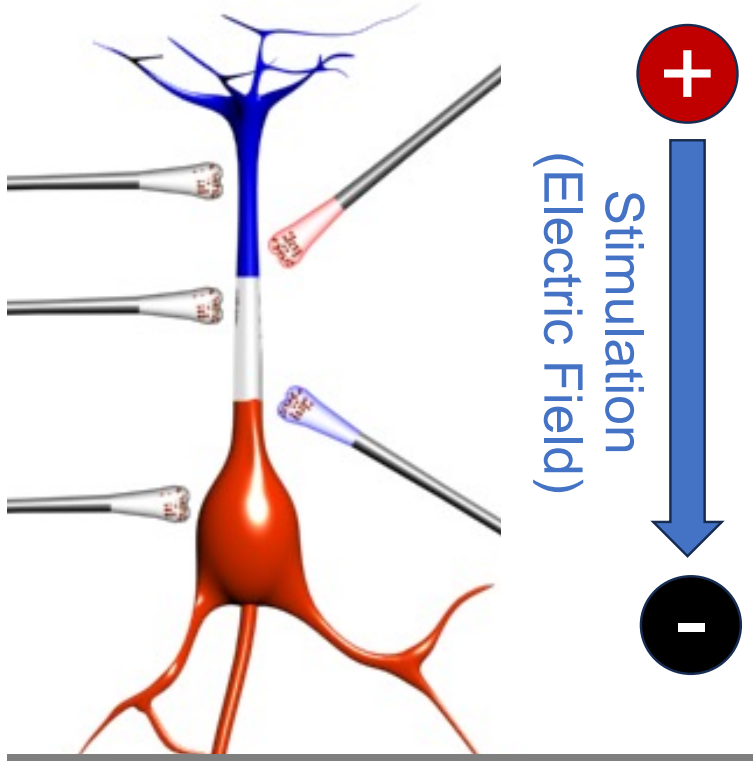
How neuron (compartment) polarization changes synaptic processing?

2

15 years of research in 60 seconds



Stimulation with long dc pulse

||||

Measure ongoing of specific synaptic pathway (field) excitatory post-synaptic potentials

||||

Measure modulation of ongoing activity

Lafon, Rahman et al. Direct Current Stimulation Alters Neuronal Input/Output Function. Brain Stim. 2017

Rahman et al. Cellular effects of acute direct current stimulation: somatic & synaptic terminal effects. J Physiol 2013

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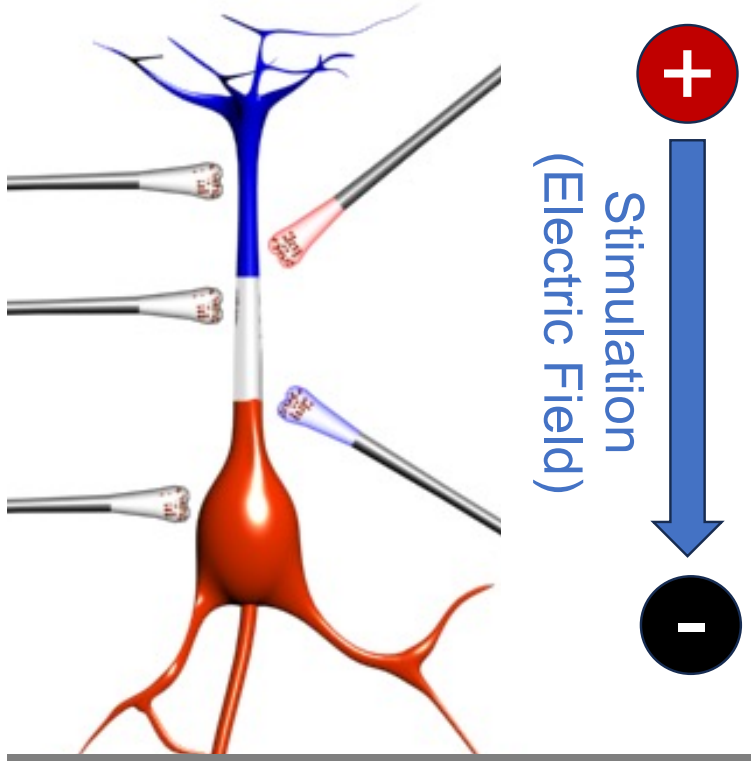

The polarization of neuronal compartments involved in processing synaptic activity will of course change synaptic efficacy.

- Axon terminal (synapse) hyperpolarization favors increased synaptic efficacy.
- Dendrite hyperpolarization favors increased synaptic current.
- Soma depolarization favors lowering action potential threshold.

~1% change in synaptic efficacy per V/m electric field

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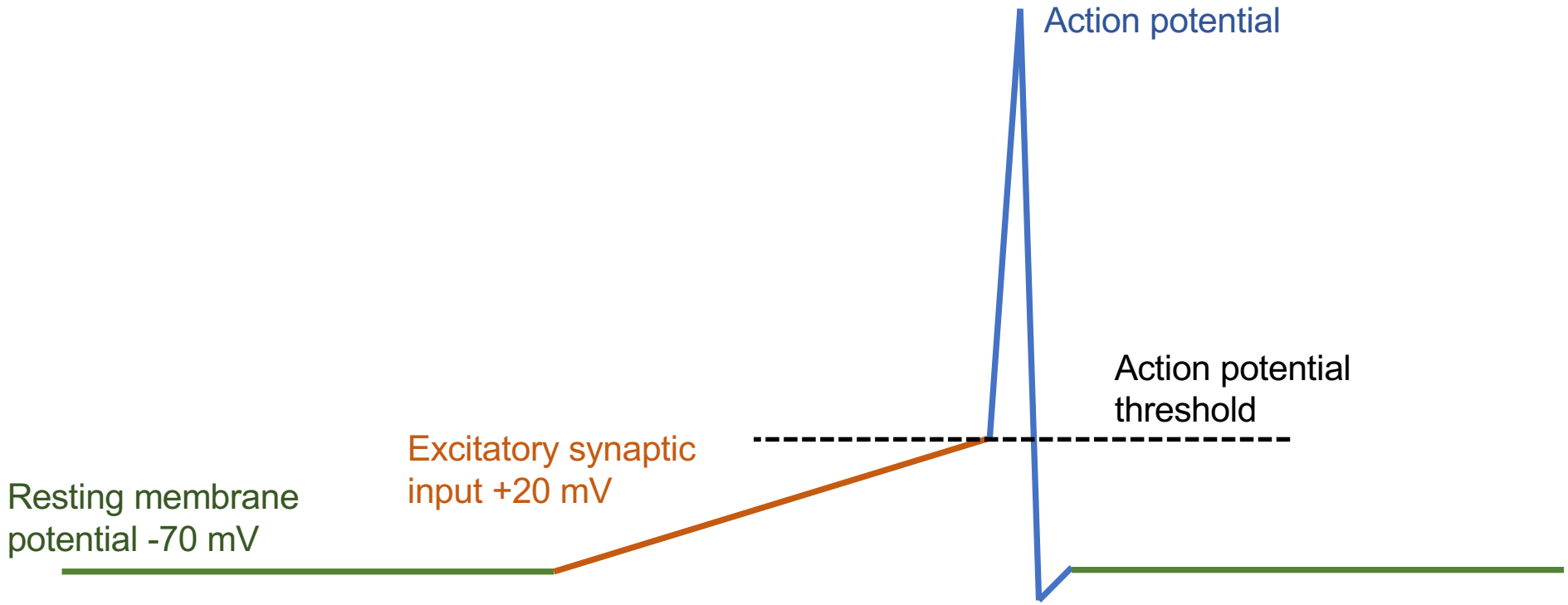
Brain function depends on action potentials. Sub-threshold stimulation must ultimately modulate action potentials to change brain function.
This is not by pulse-based pacing but rather changing how ongoing activity might lead to action potentials.



Radman et al. Spike timing amplifies the effect of electric fields on neurons. J Neurosci 2007

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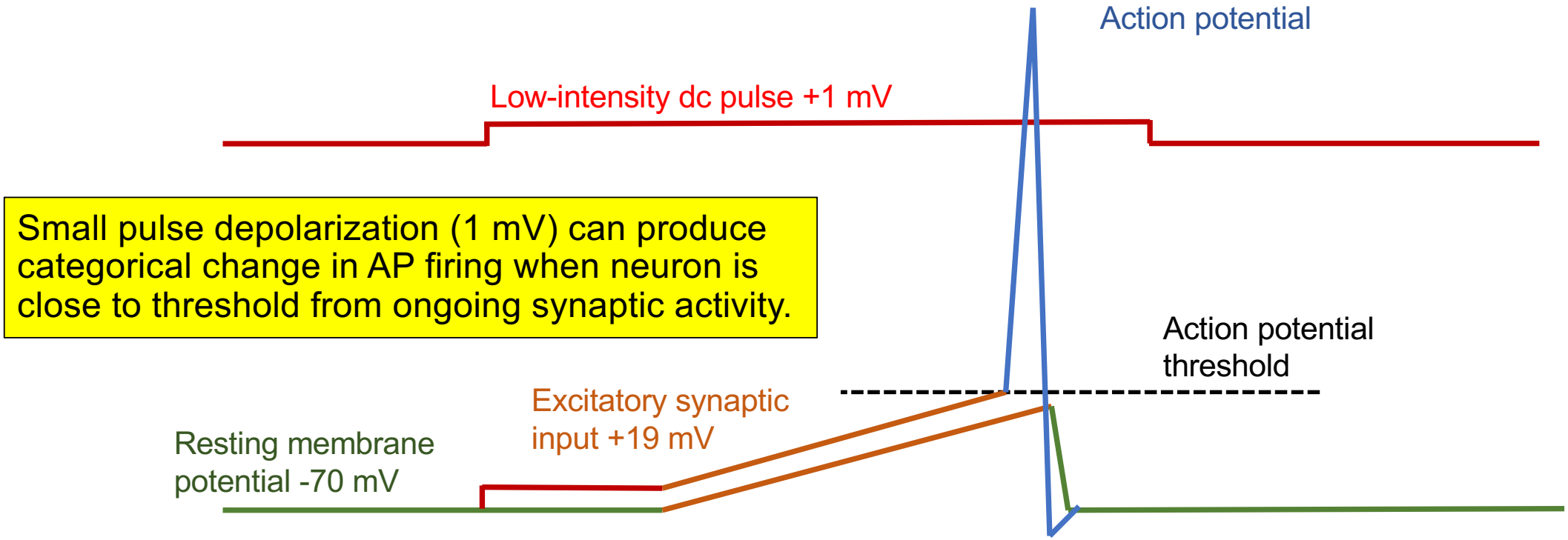

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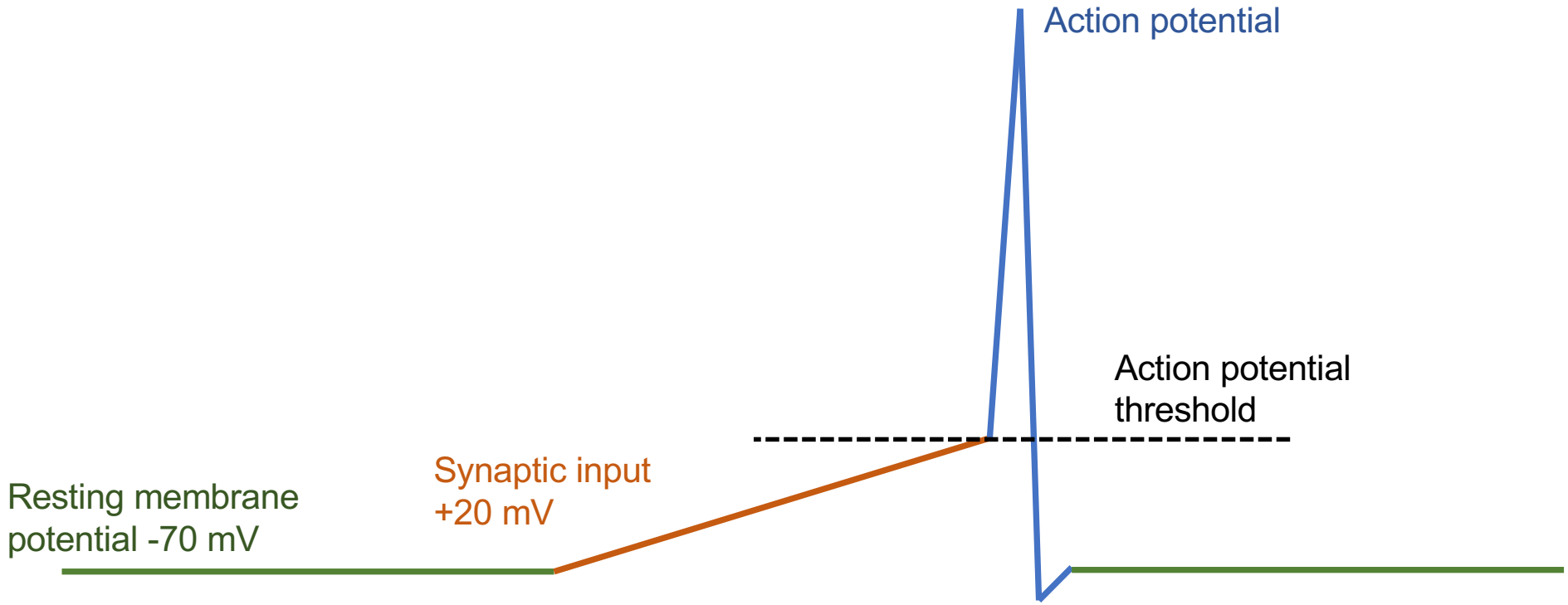

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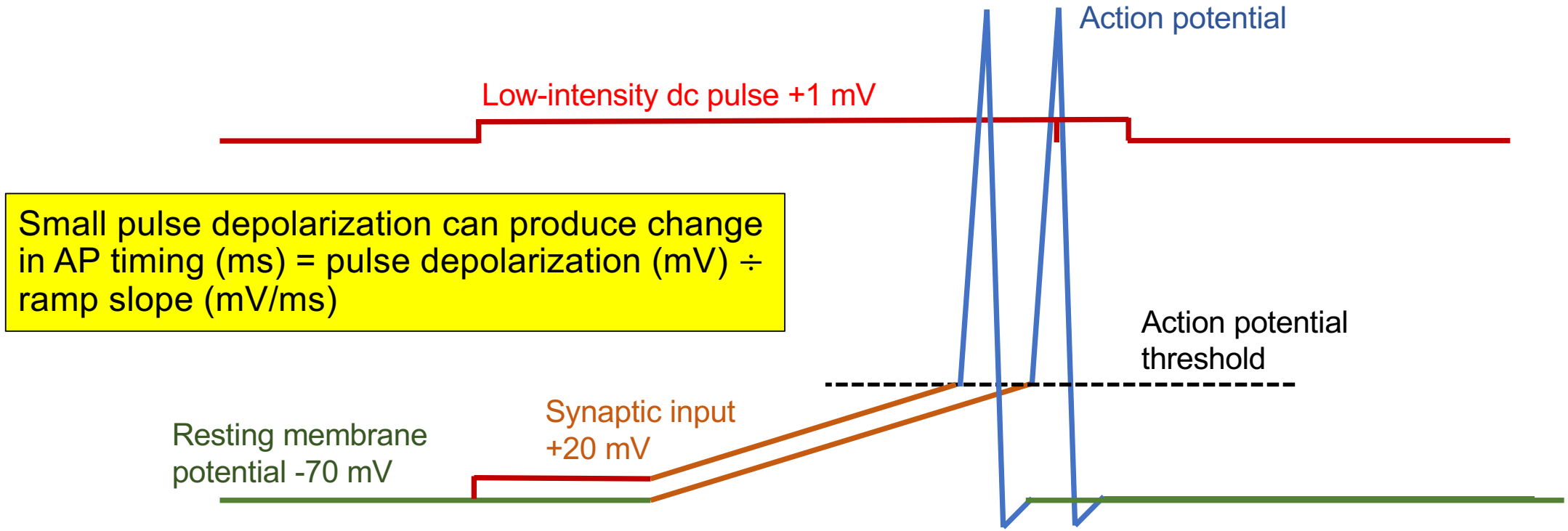

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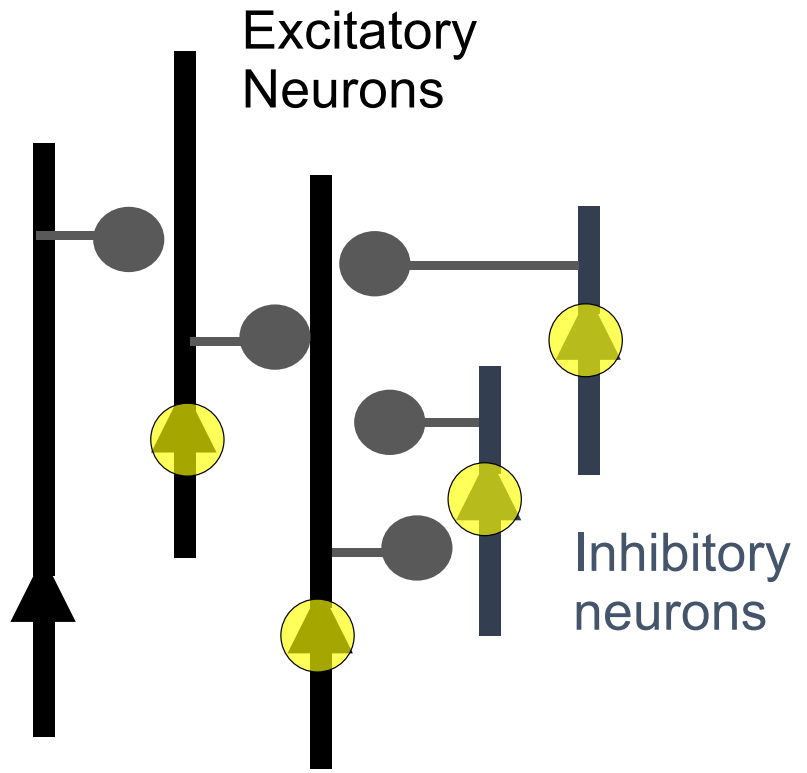
Oscillations are network brain states with many neurons closed/crossing action potential threshold, making individual neurons in the network sensitive to sub-threshold stimulation. The cohesion of the network itself provides further sensitization.



Reato, Rahman, Bikson & Parra. Low-intensity electrical stimulation affects network dynamics by modulating population rate and spike timing. J Neurosci 2010

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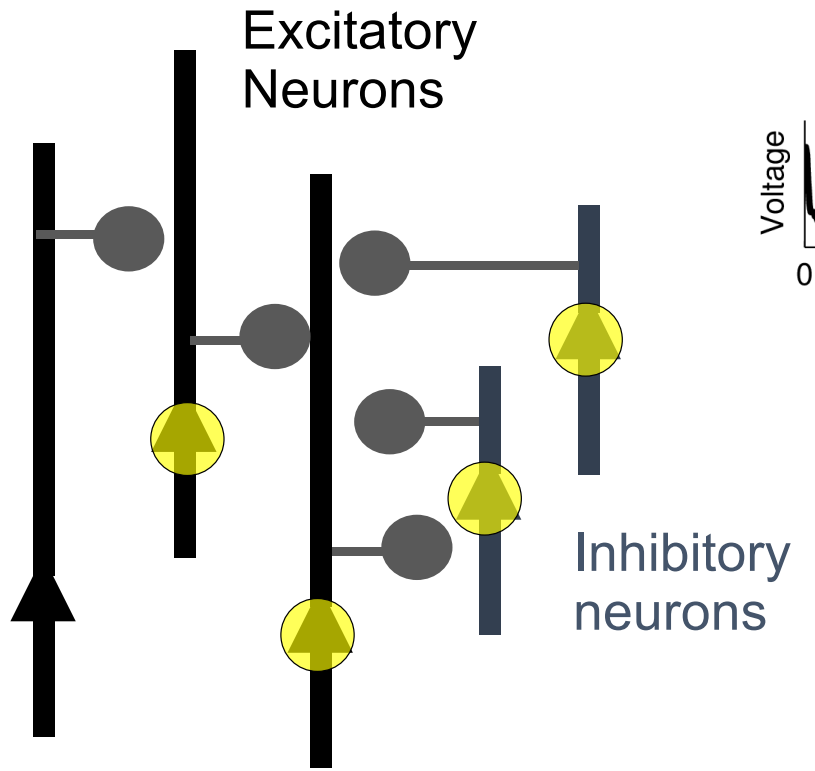

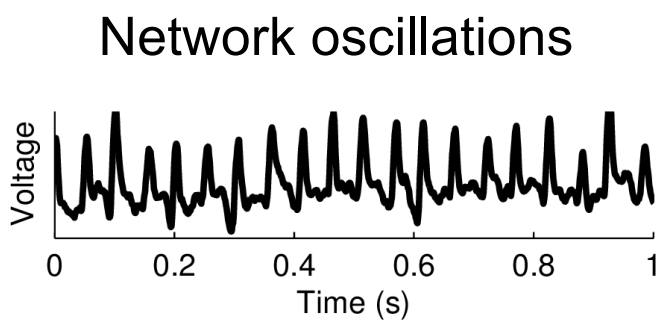

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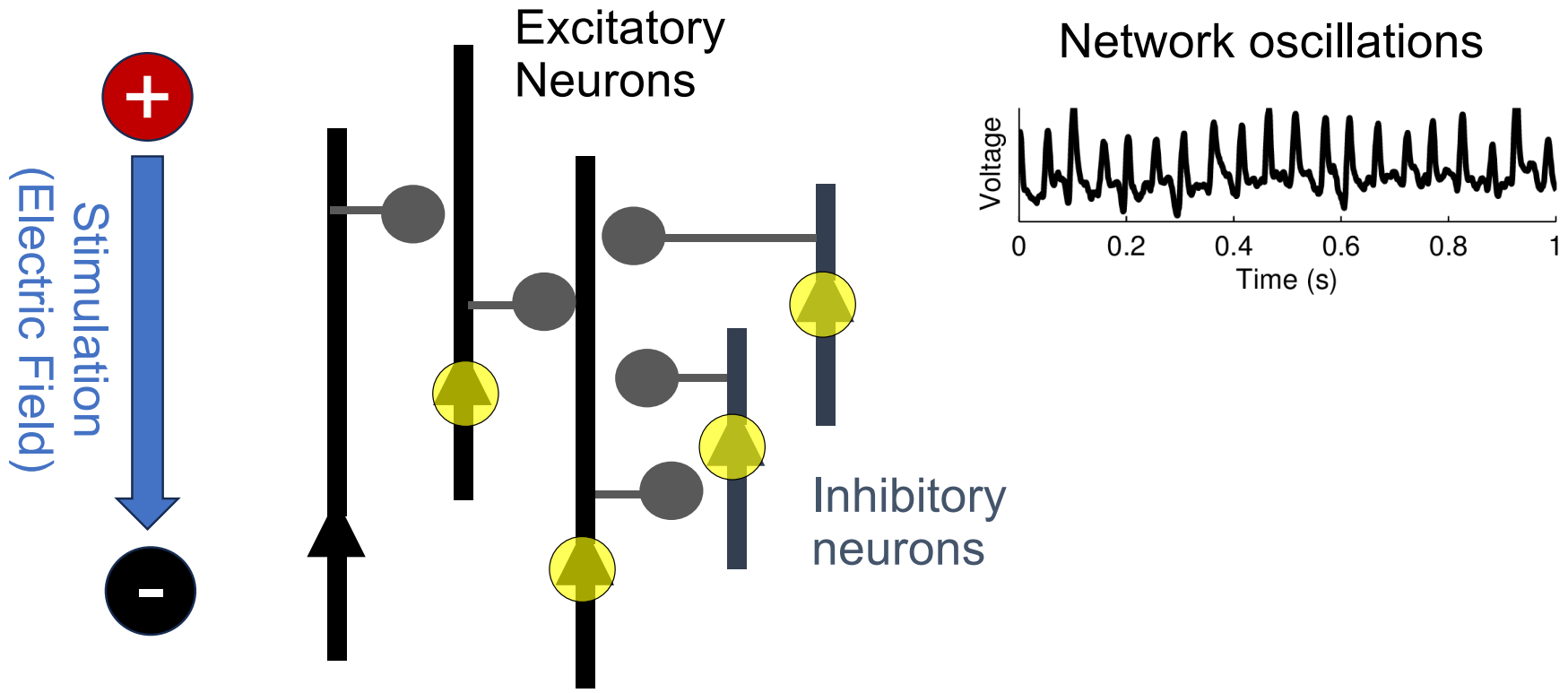

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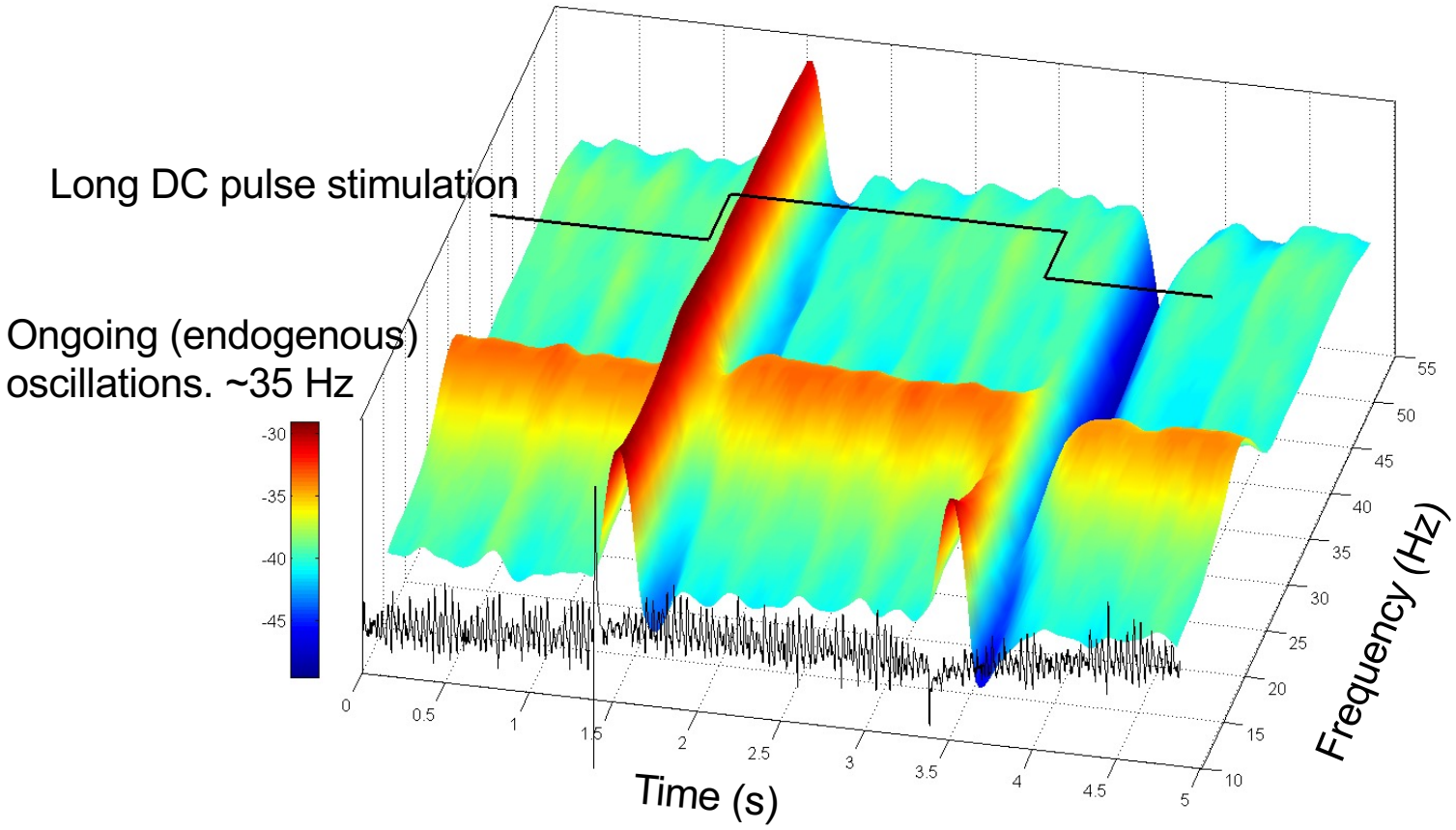
- Oscillating neuronal networks demonstrate high sensitivity to electric fields.
- Network response depend on nature of oscillation and field – are explained with computational models.



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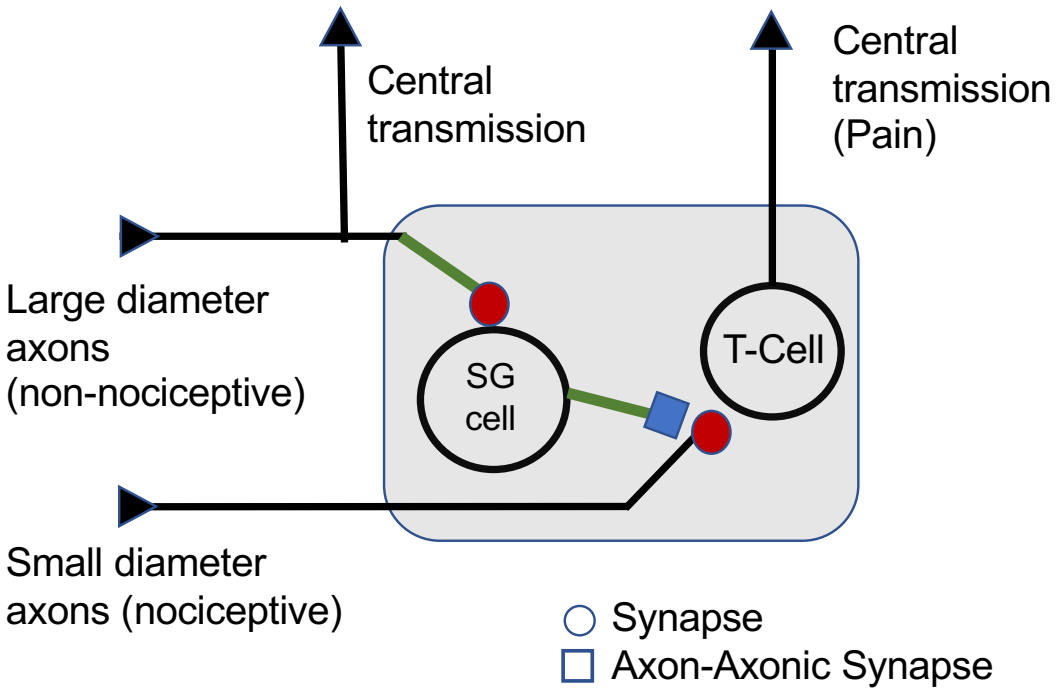
Gate control theory of pain (Melzack and Wall 1965)

Activation of inputs to spinal dorsal horn (through excitatory synapses), closes the pain gate (activates synaptic inhibition)



Excitatory synapse Inhibitory synapse Pathways for negative synaptic feedback of noncoercive input

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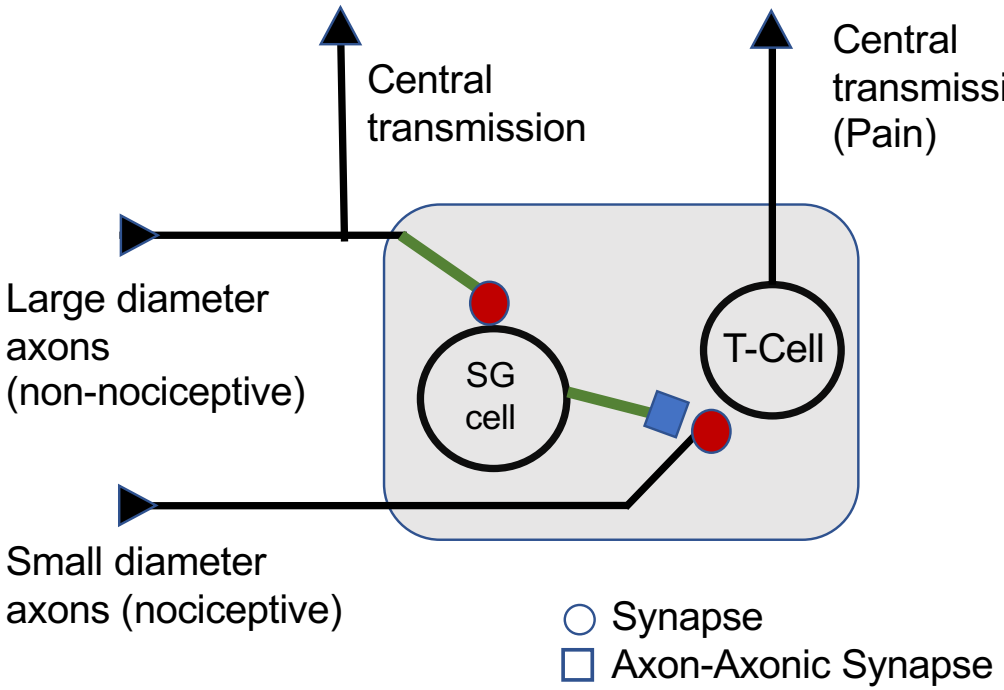

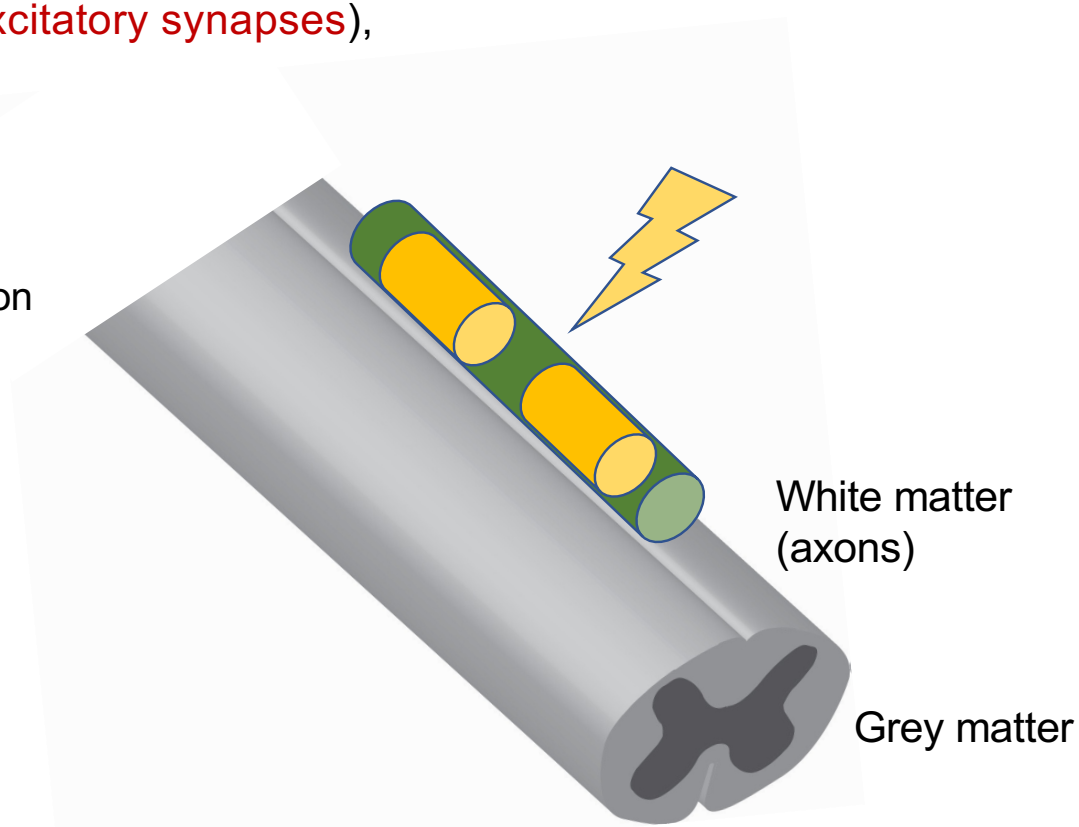

Pain relief derive from synaptic networks in grey matter (gate control)

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Sharma & Bikson. A brief history of slow spinal potentials, gate theory of pain, & spinal cord stimulation. Neuromodulation, *in press*

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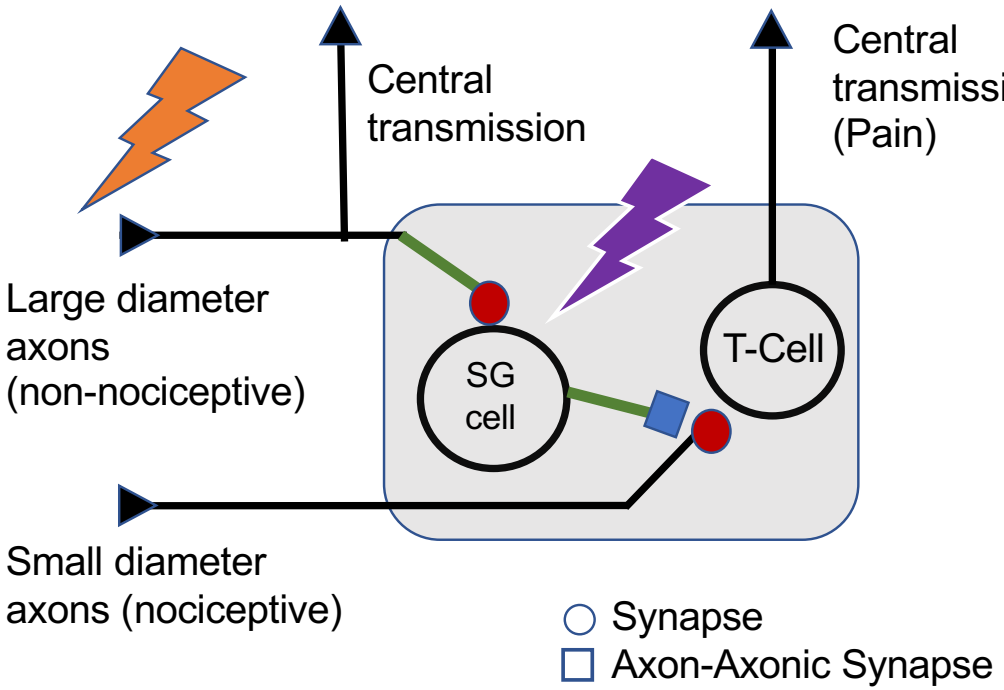

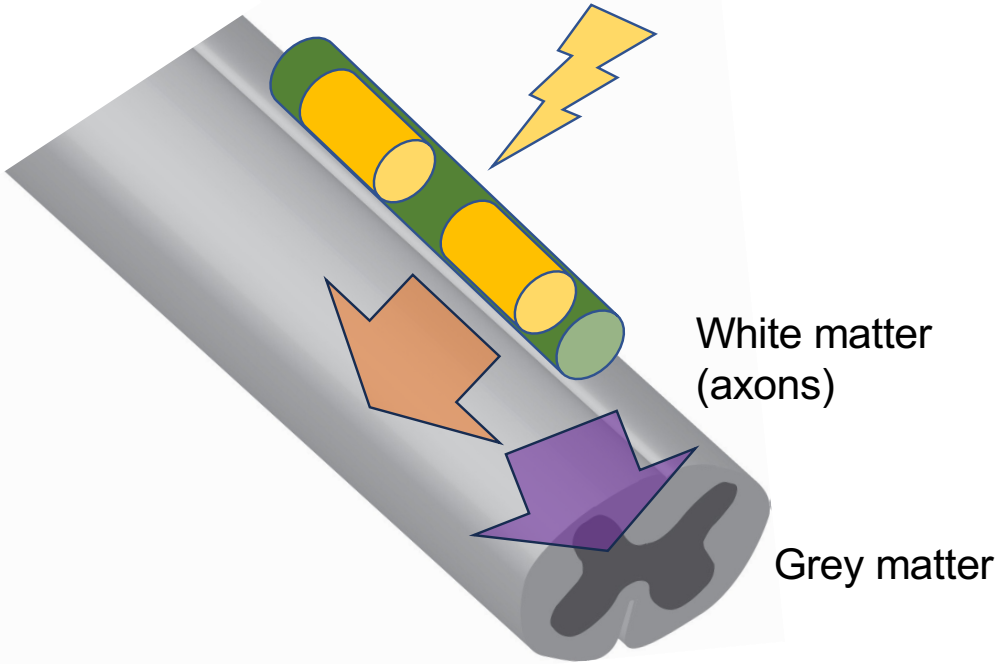

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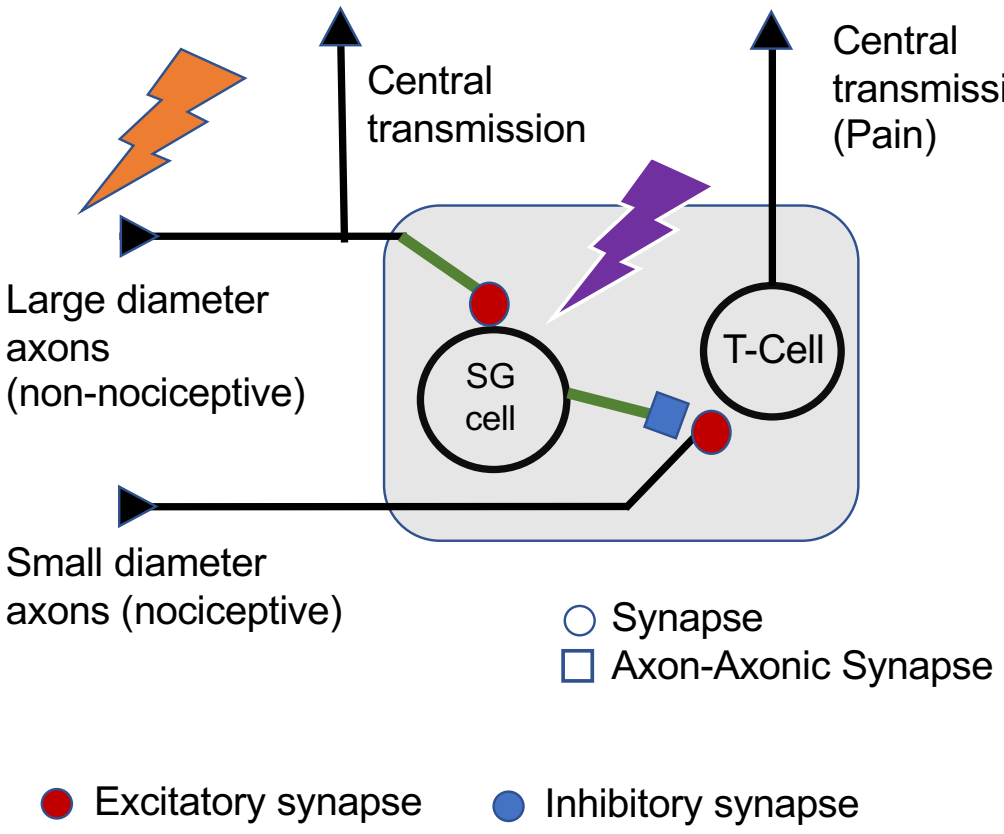
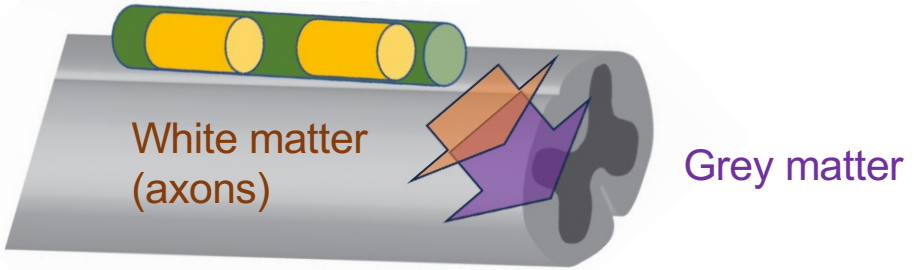


Why focus on white matter for 50 years?

- Dependence on paresthesia suggests dorsal column axon pacing required.
- Early (and ongoing) computational models show Electric Fields in grey matter below threshold. Sub-threshold.

SCS generates sub-threshold Electric Fields in the dorsal horn, modulating ongoing synaptic (pain) processing.



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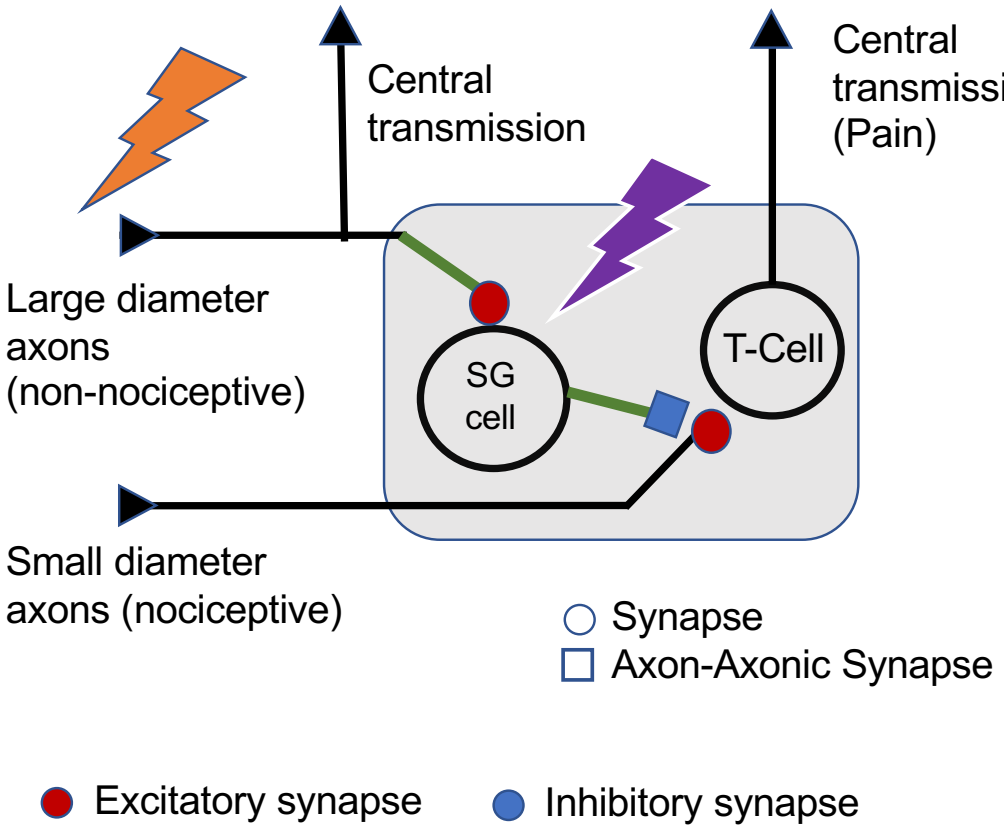
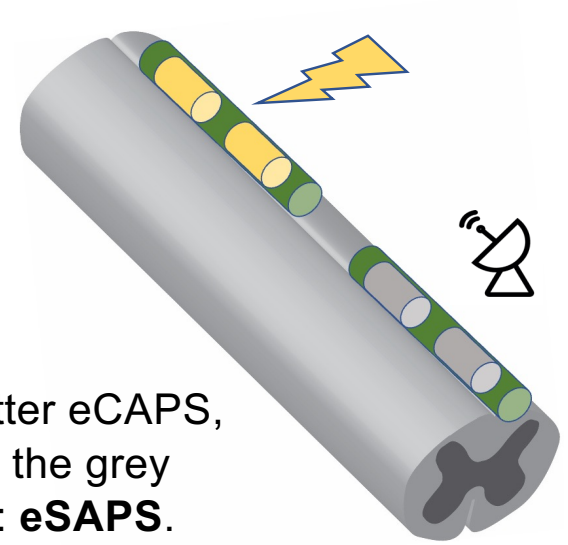
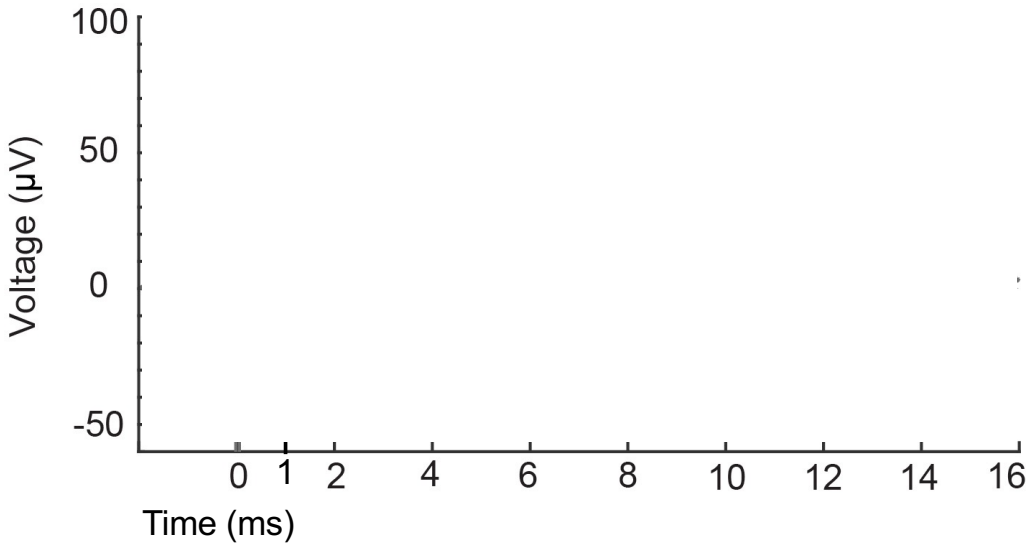




In addition to white matter eCAPS, a synaptic signals from the grey mater can be recorded: **eSAPS**.



Sharma et al. Novel Evoked Synaptic Activity Potentials (ESAPs) Elicited by Spinal Cord Stimulation. eNeuro 2023

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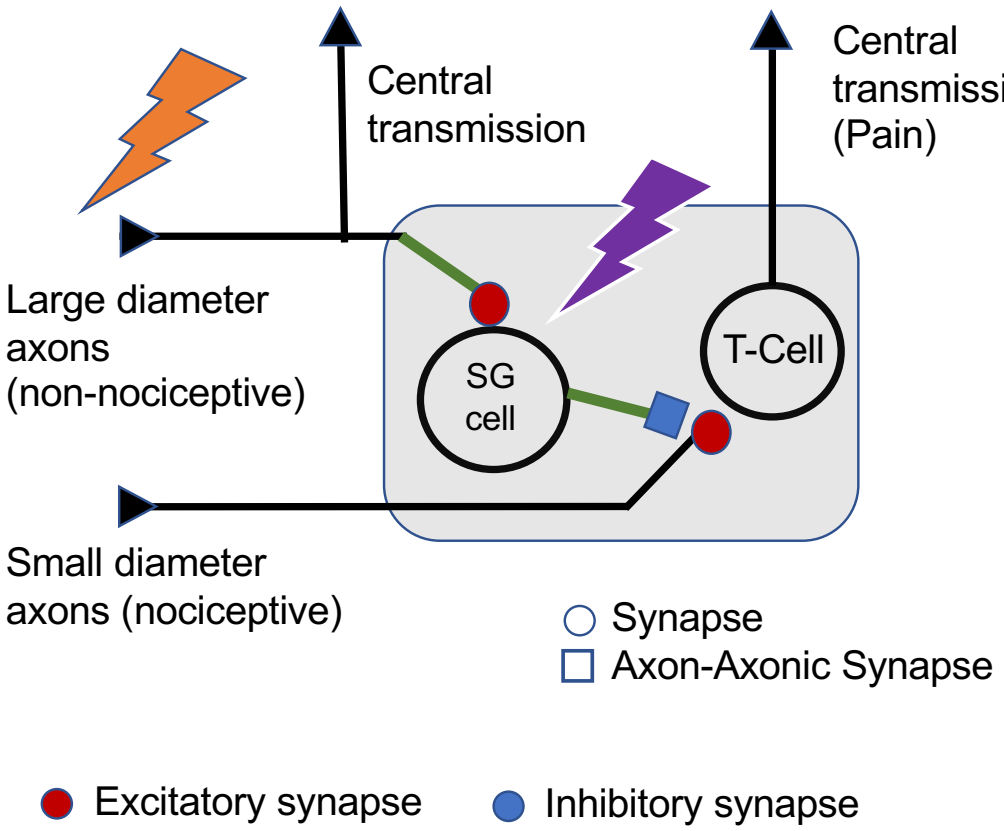

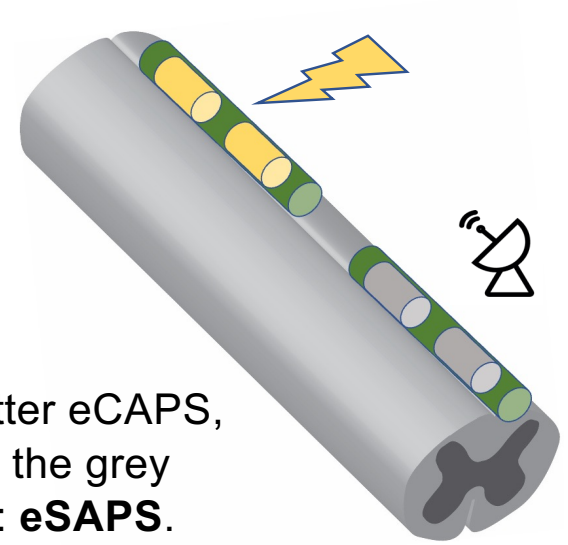

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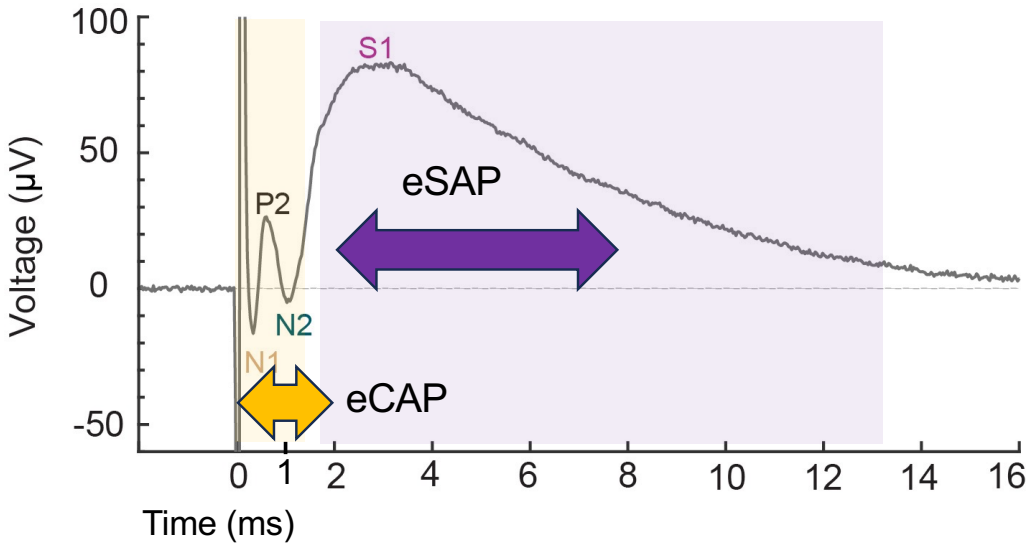

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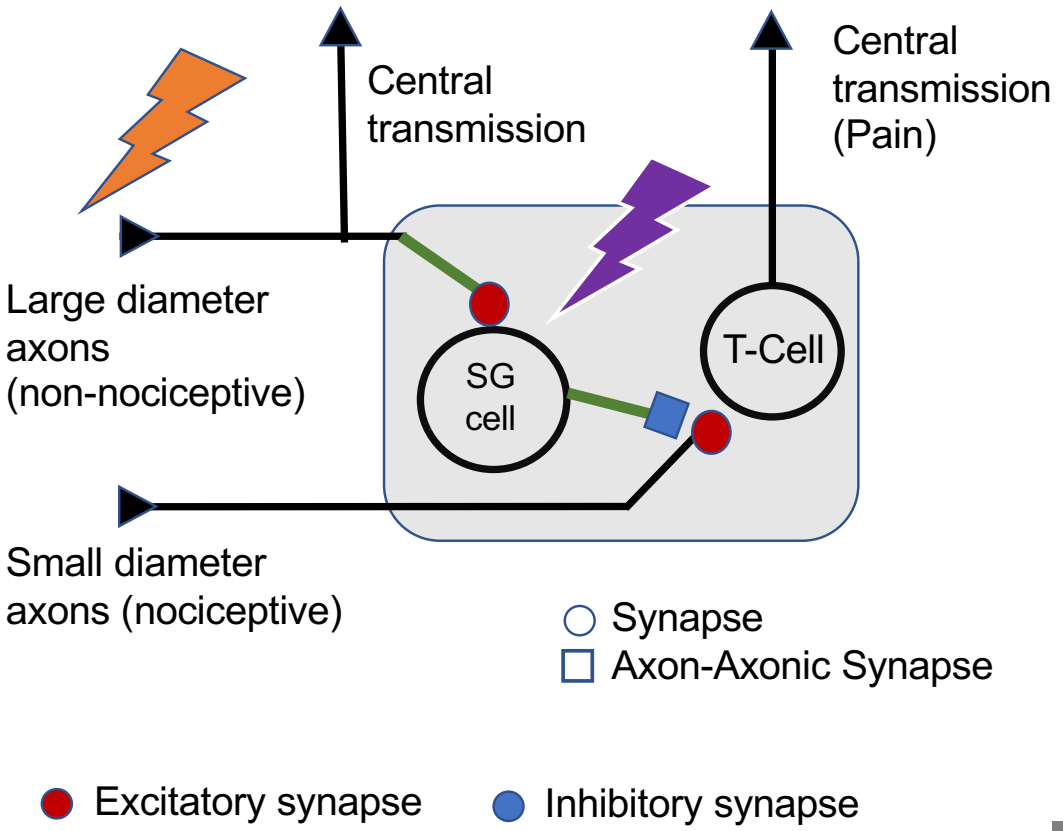
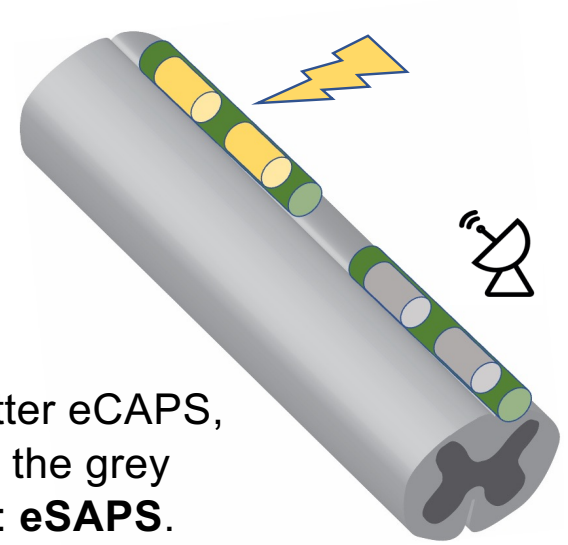




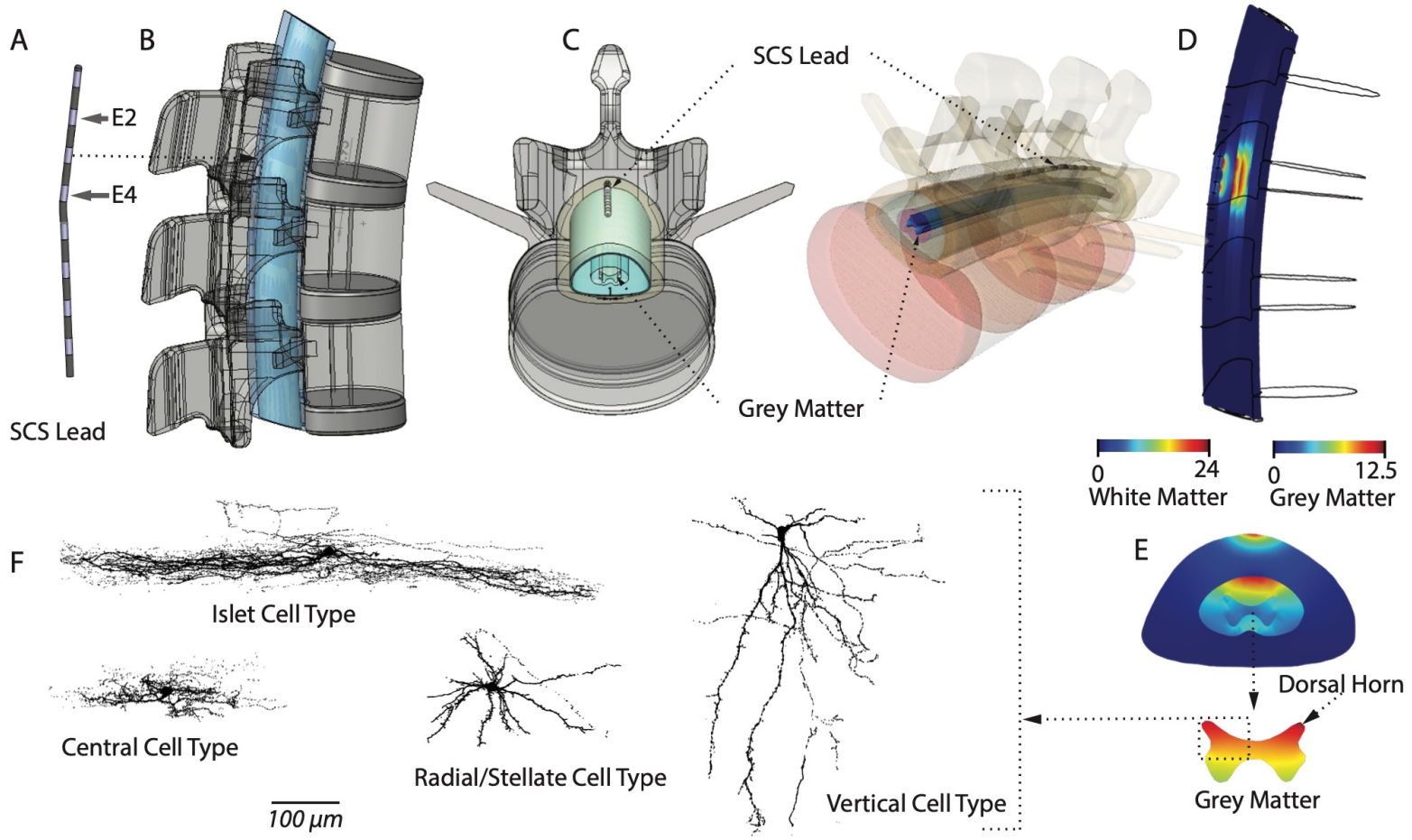
In addition to white matter eCAPS, a synaptic signals from the grey mater can be recorded: **eSAPS**.

If you can record dorsal horn synaptic activity with epidural electrodes,
Can you stimulate synaptic processes with epidural electors .

Reciprocity: “Read / write the pain gate”

Sharma et al. Novel Evoked Synaptic Activity Potentials (ESAPs) Elicited by Spinal Cord Stimulation. eNeuro 2023

Spinal cord stimulation polarizes the dendrites of dorsal horn interneuron by few mV : sufficient for sub-threshold modulation of synaptic process (e.g. pain gate)



Zannou, Koochesfahani, Russo, Bikson. Dorsal horn dendrite polarization during Spinal Cord Stimulation (SCS) predicted using the quasi-uniform-mirror assumption. bioRxiv. 2024

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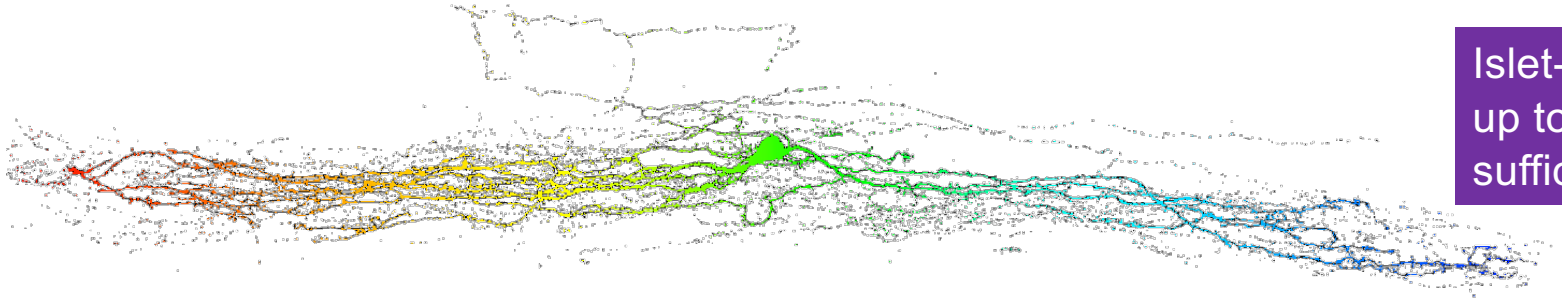
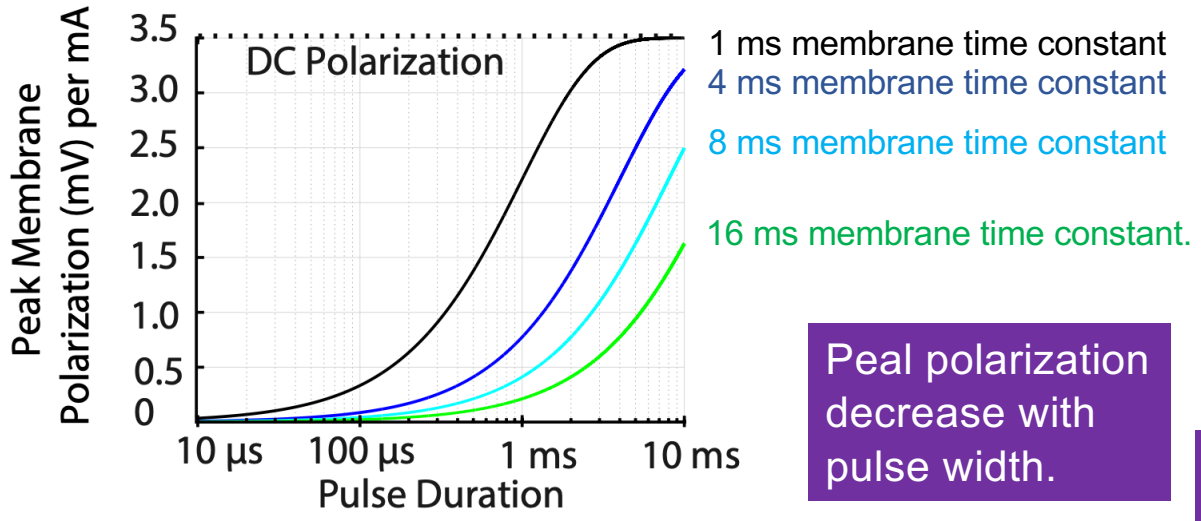
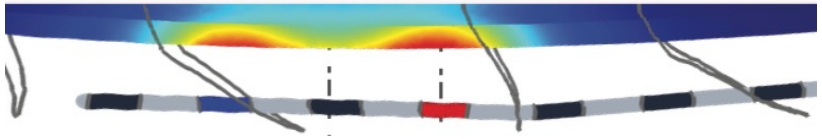


Islet-type cells dendrite polarize up to 3.5 mV per mA applied for sufficient long pulses.



Islet-type most polarized between stimulation electrodes. Other cell types (Vertical) most polarized under electrodes



Peal polarization decrease with pulse width.

Pulse density determines duty cycle (time) of polarization)

Zannou, Koochesfahani, Russo, Bikson. Dorsal horn dendrite polarization during Spinal Cord Stimulation (SCS) predicted using the quasi-uniform-mirror assumption. bioRxiv. 2024

Subthreshold Mechanisms of Brain and Spinal Cord Stimulation

in four basic concepts.

Marom Bikson, The City College of New York

Adantchede Louis Zannou, Mojtaba Belali Koochesfahani, Mahima Sharma. Lucas Parra, Marc Russo, Greg Kronberg, Abhishek Datta, Niranjan Khadka, Zeinab Esmaeilpour, Belen Lafon, Mohamad FallahRad, Mark Jackson, Tianhe Zhang, Rosana Esteller, Asif Rahman, Darpan Chakraborty Dennis Truong, Hanoch Kaphzan, Vividha Bhaskar, Thomas Radman