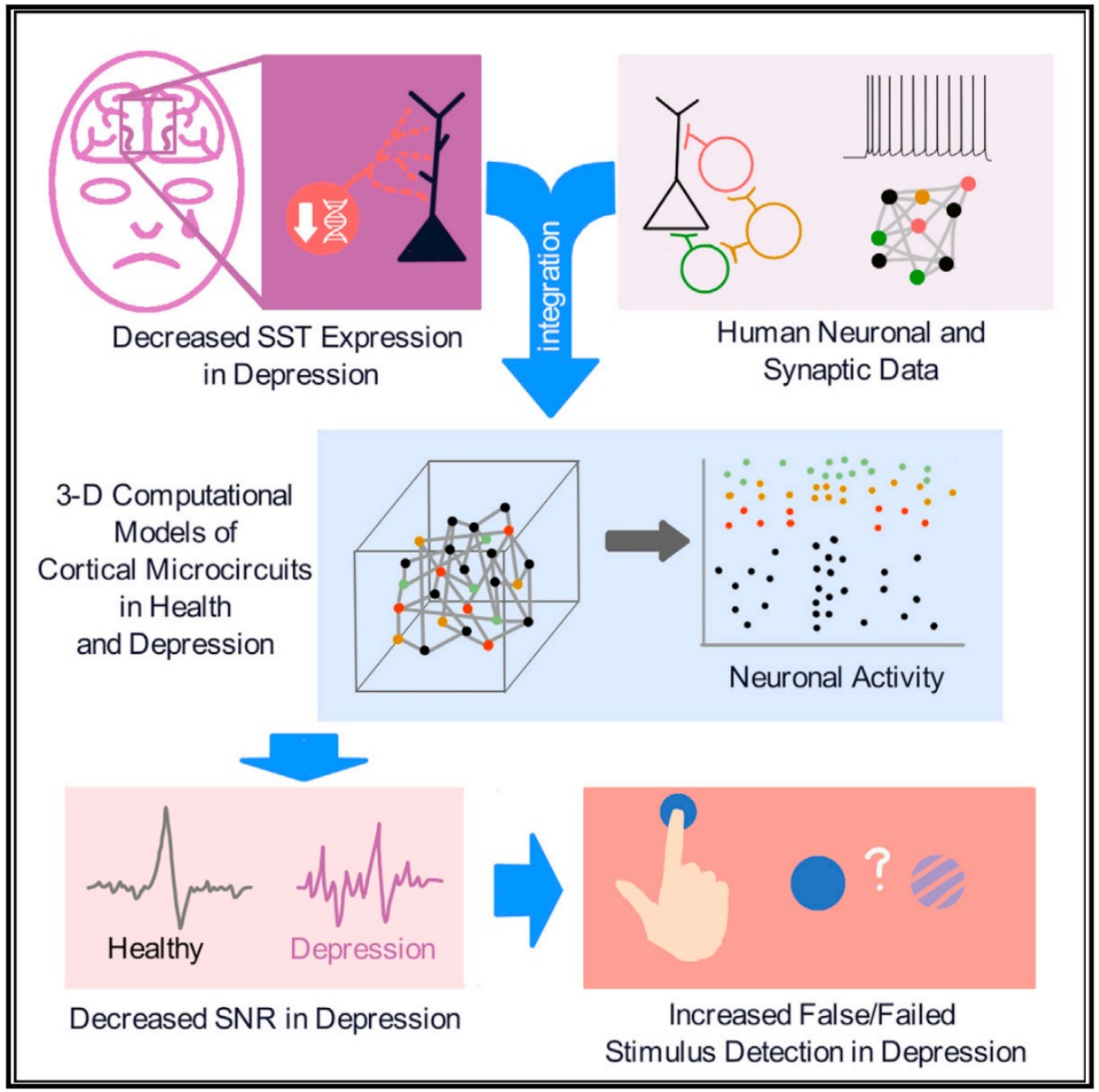
Effect of DCS on Morphologically Correct Neural Network

Nelson Wu, Anruo Shen



Reduced inhibition in depression impairs stimulus processing in human cortical microcircuits

Cell Reports Jan 2022

Working Plan

1. Single neuron

1.1 Polarization profile in radial/tangential electrical field (done!)

1.2 Neuron response to depolarizing/hyperpolarizing currents (done!)

2. Neural network

2.1 Bisynaptic inhibition loop (PRY-SST-PYR, 3 neurons)

2.1.1 Calibration to experimental data (done!)

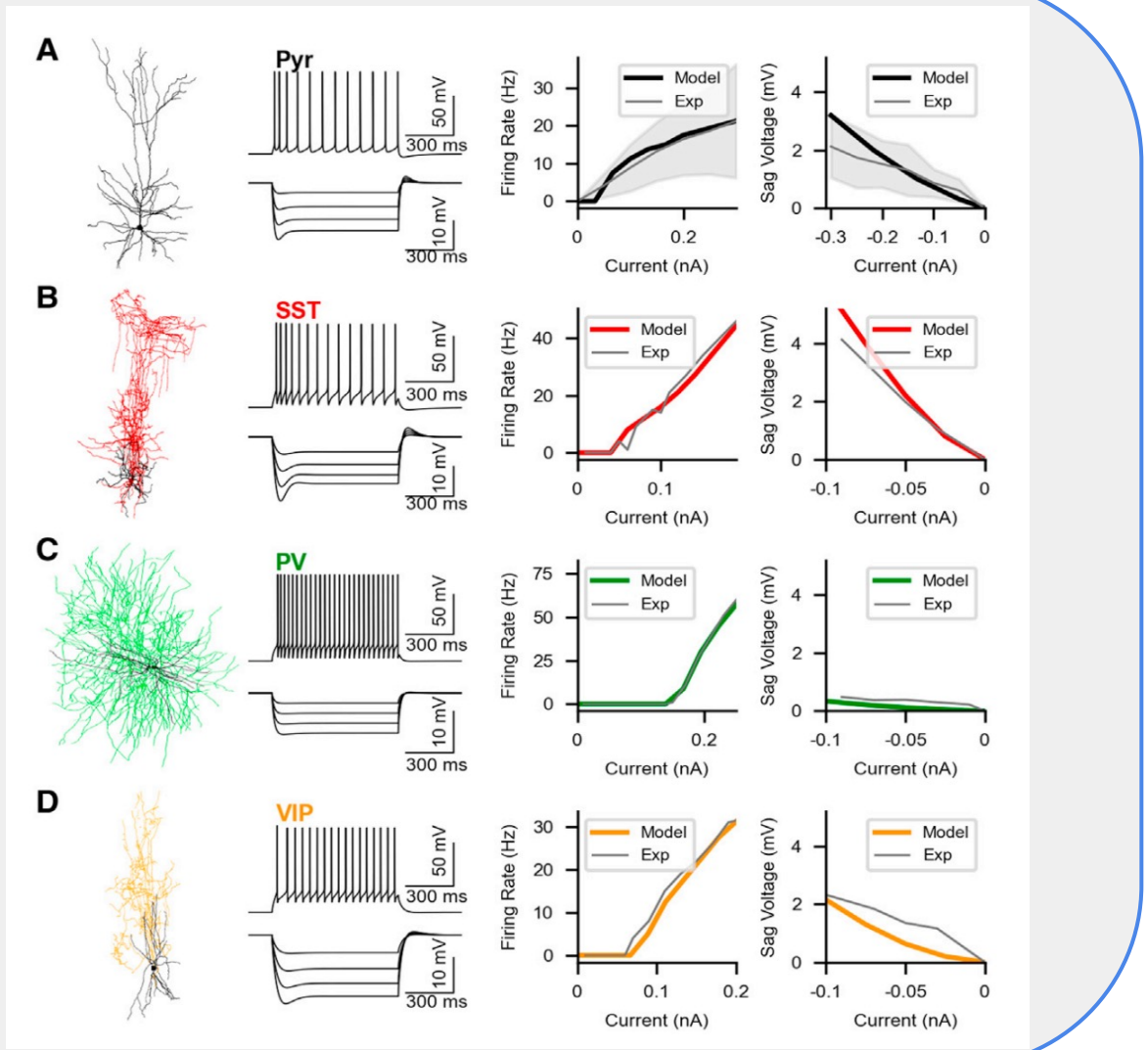
2.1.2 Firing rate response to DCS

2.2 Brain cortex (L2/3, 1000 neurons)

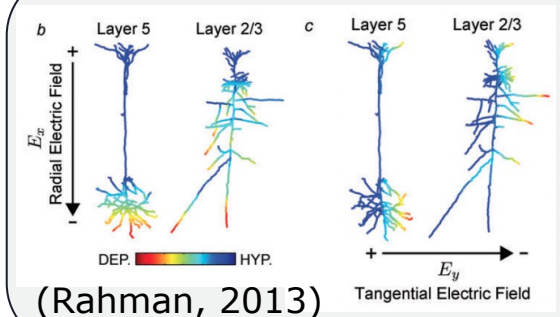
2.2.1 Calibration to experimental data

2.2.2 Firing rate response to DCS

1. Single Neuron



1.1 Polarization Profile in Radial/Tangential Electrical Field



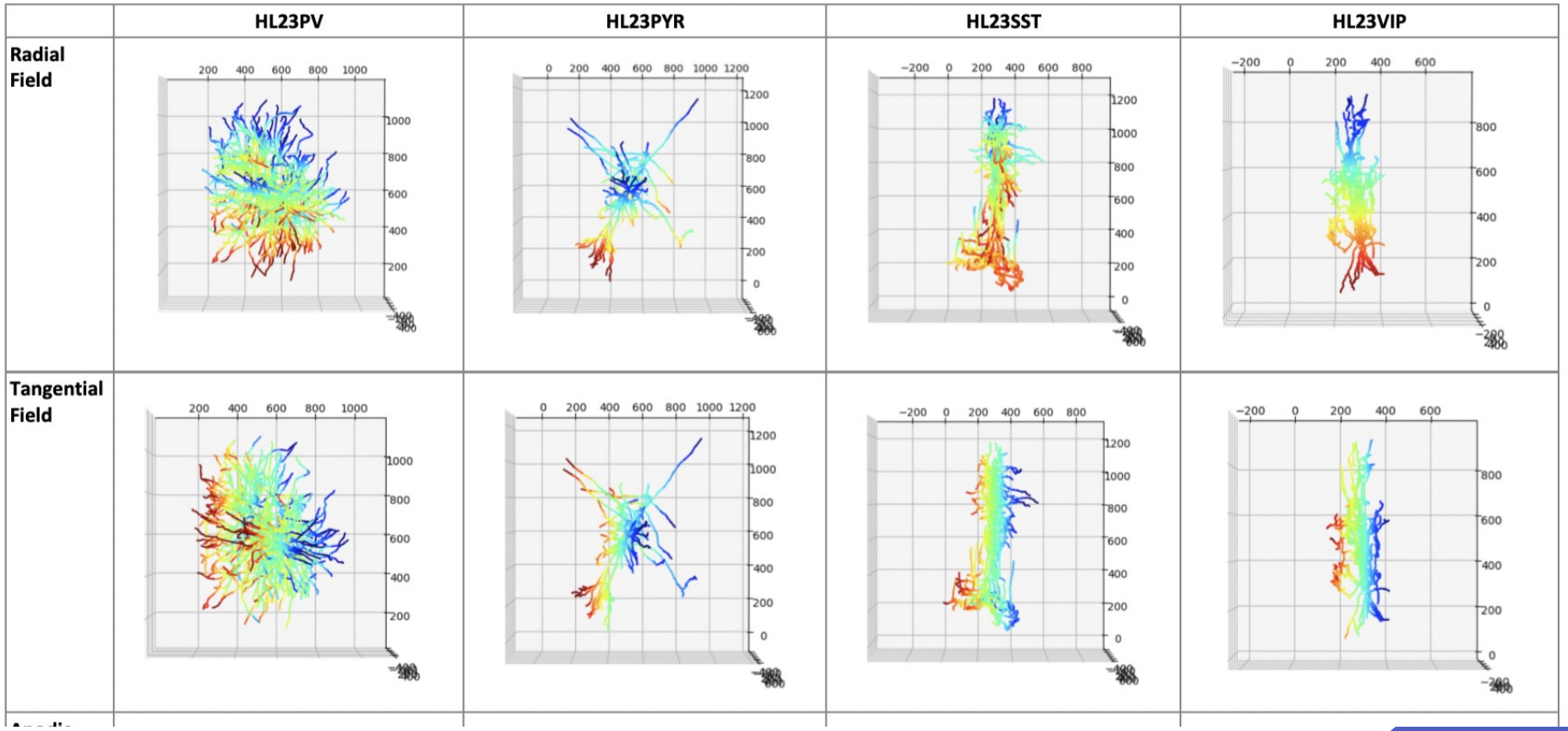
(Rahman, 2013)

PV: parvalbumin interneurons

PYR: pyramidal neuron

SST: somatostatin interneurons

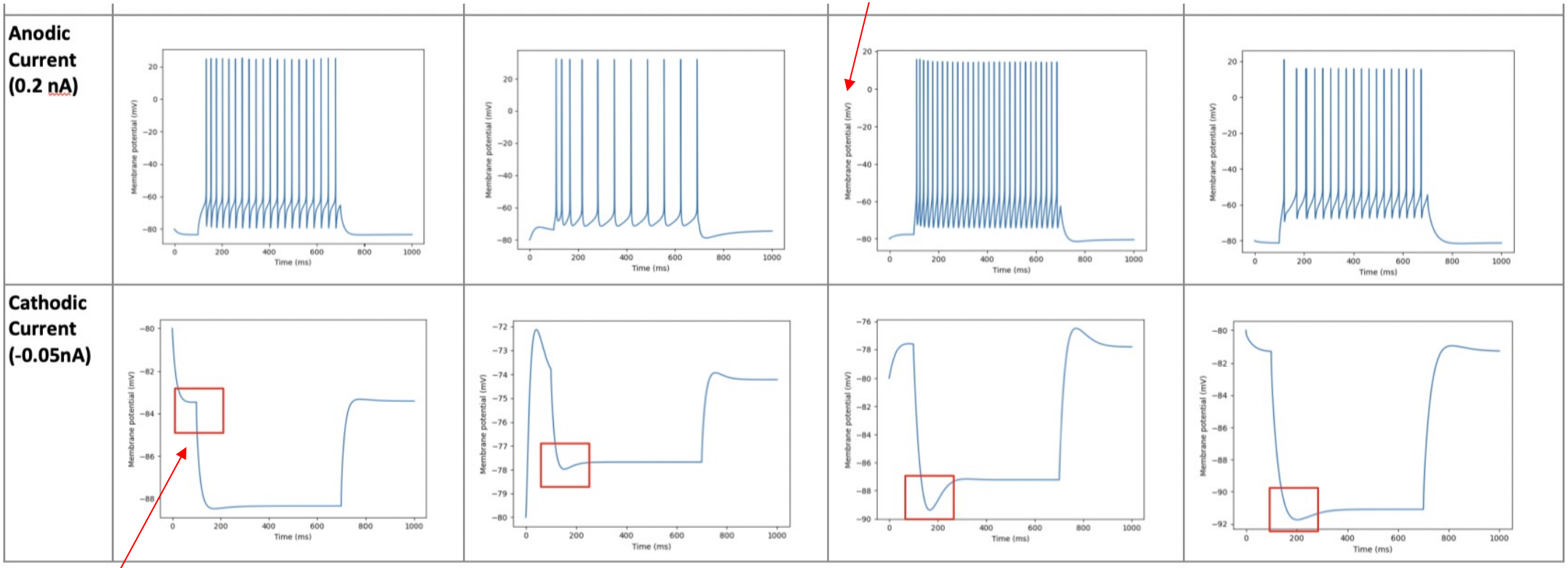
VIP: vasoactive intestinal peptide interneuron



1.2 Neuron Response to Depolarizing/Hyperpolarizing Currents

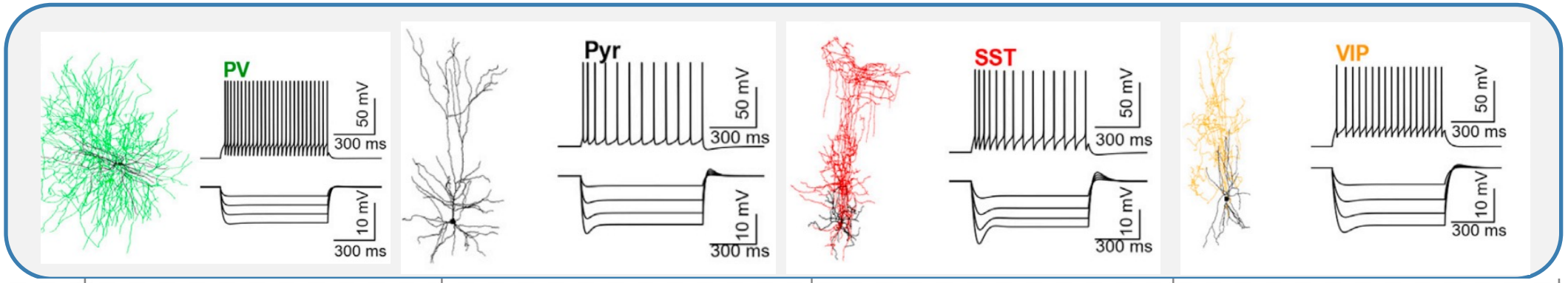
Step current applied

soma membrane potential

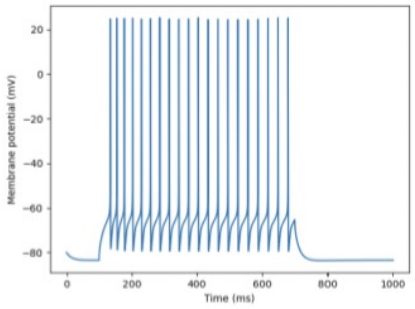
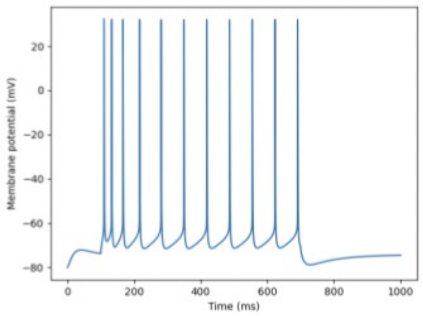
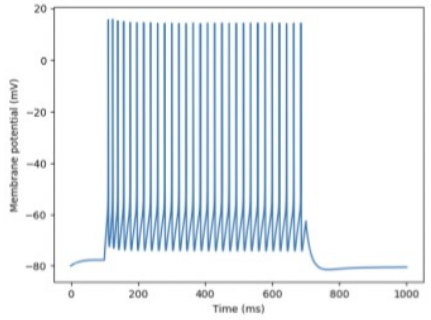
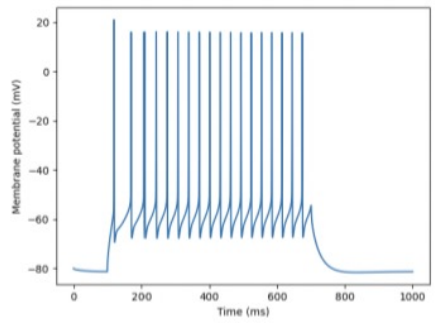
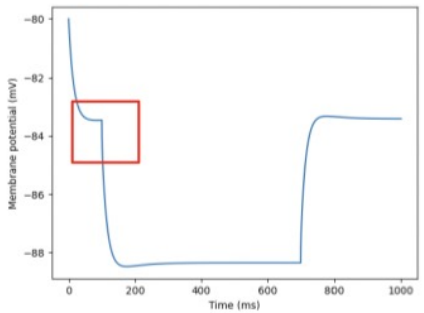
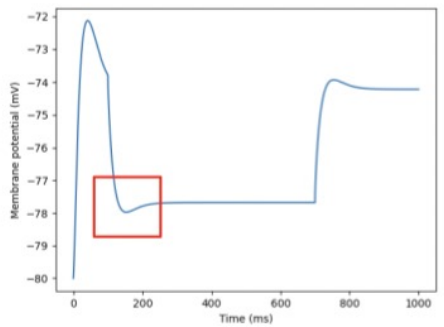
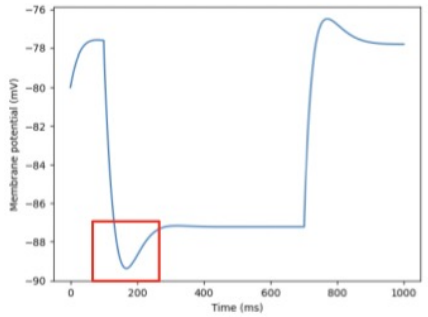
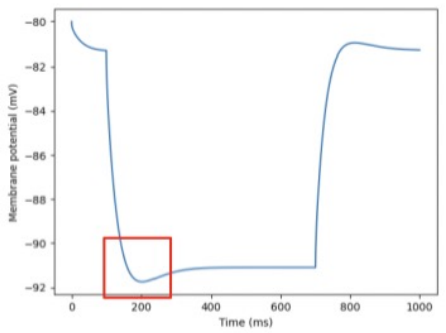


sag voltage recovered!

sag voltage (I-V sag): a phenomenon observed in some types of neurons during **hyperpolarizing current injection**. This is often associated with **the activation of the hyperpolarization-activated cation current, commonly known as Ih or HCN**.



Identical!

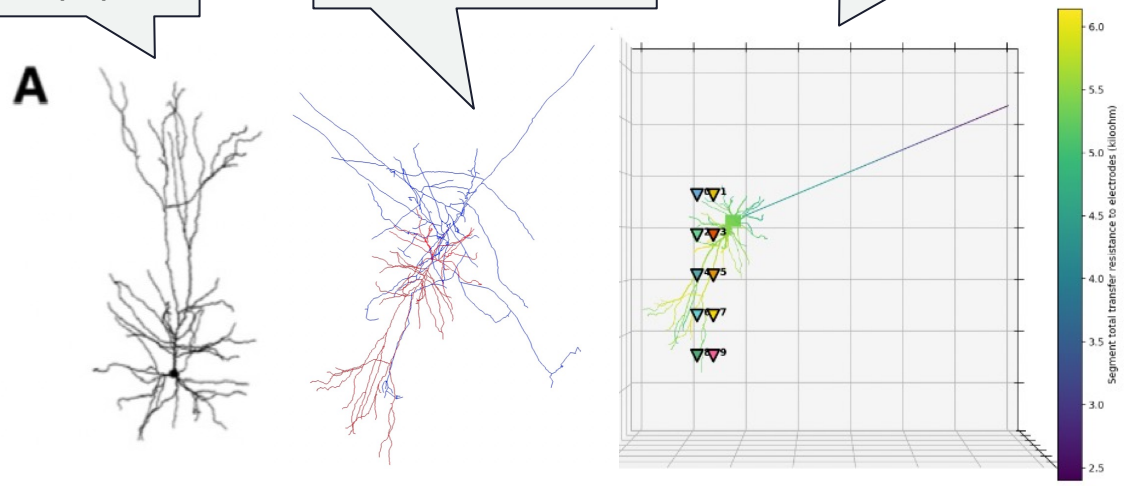
Anodic Current (0.2 nA)				
Cathodic Current (-0.05nA)				

*LFP Recording Visualization (not needed any more)

from paper

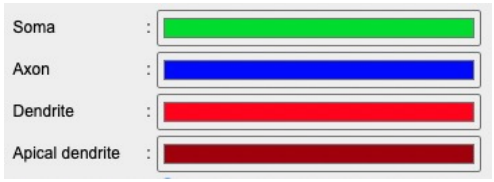
viewed by HBP Neuron Morphology Viewer

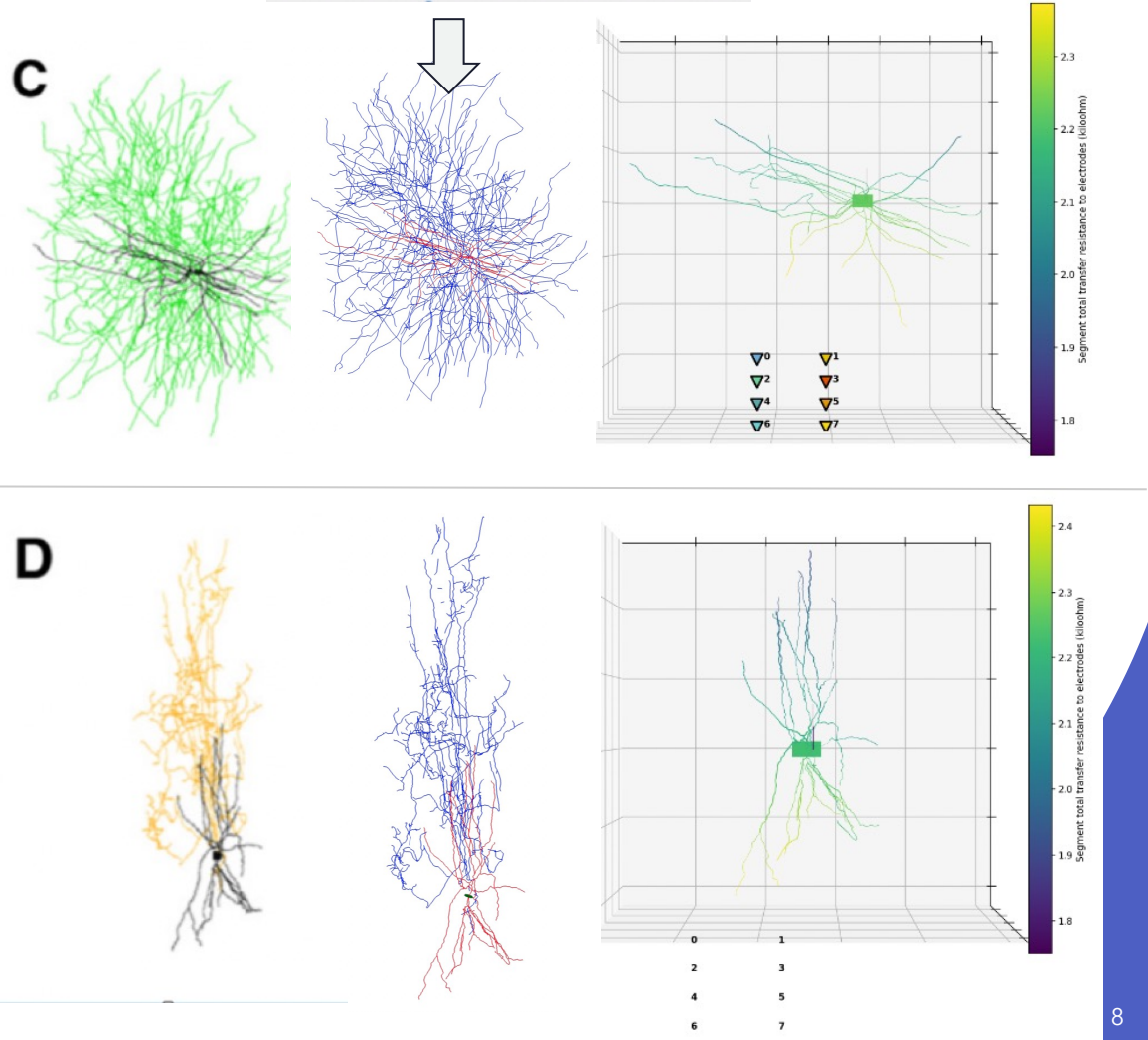
by **NetPyNE**



morphology only

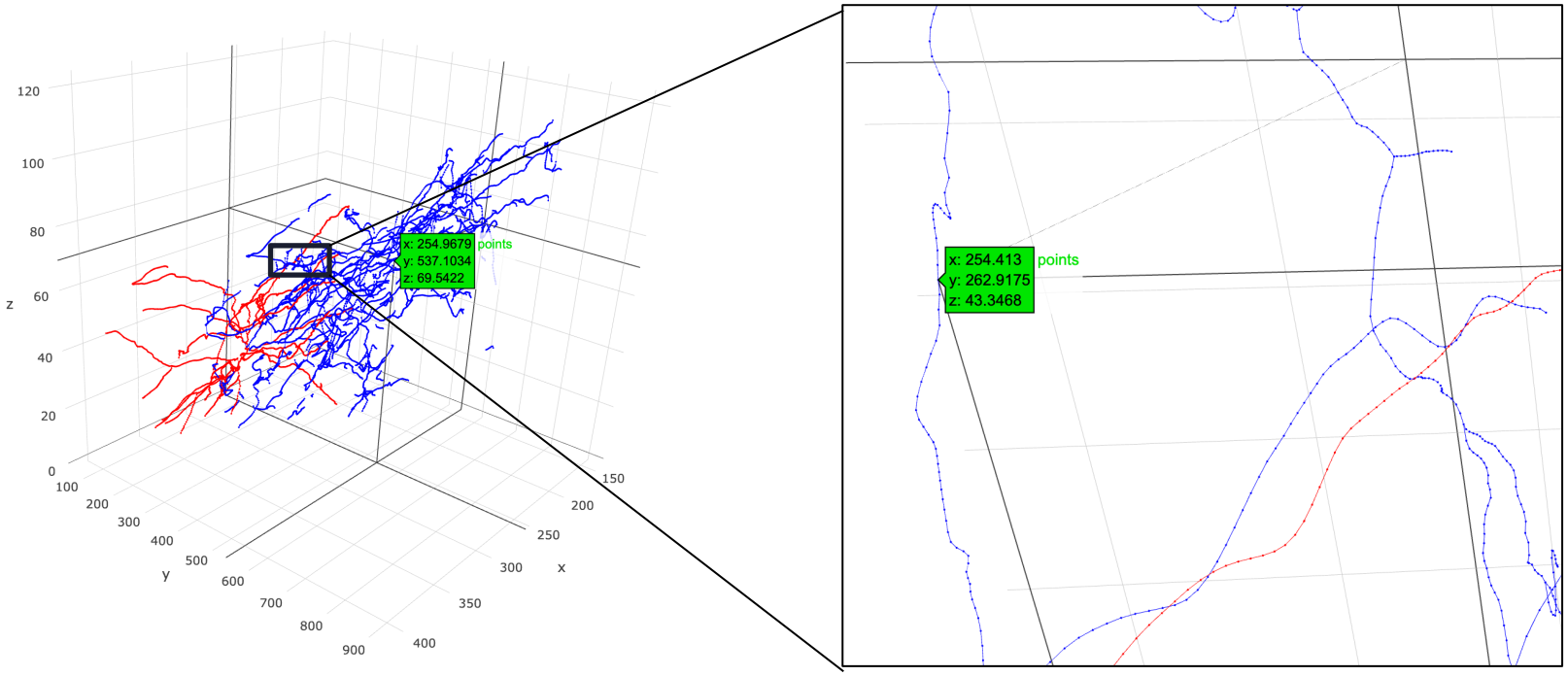
electrodes arrangement + LFP recording



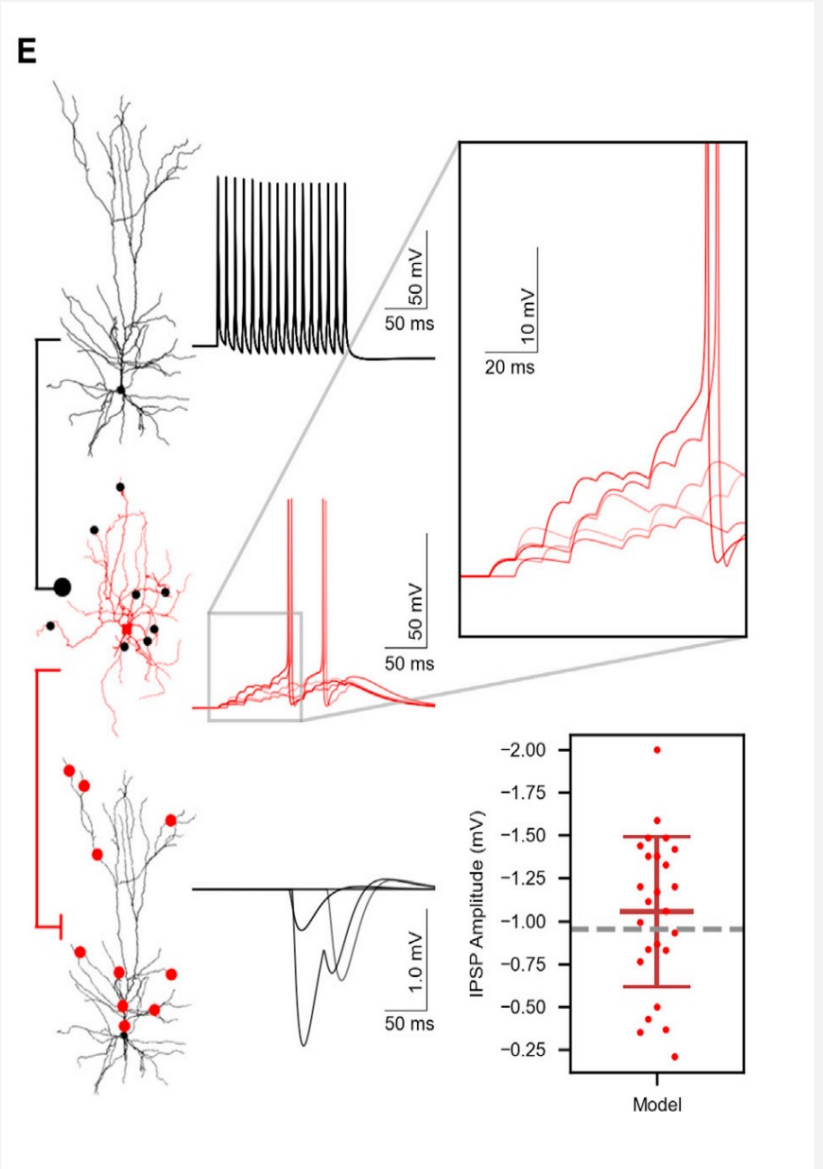


* Electrode Coordination (not needed any more)

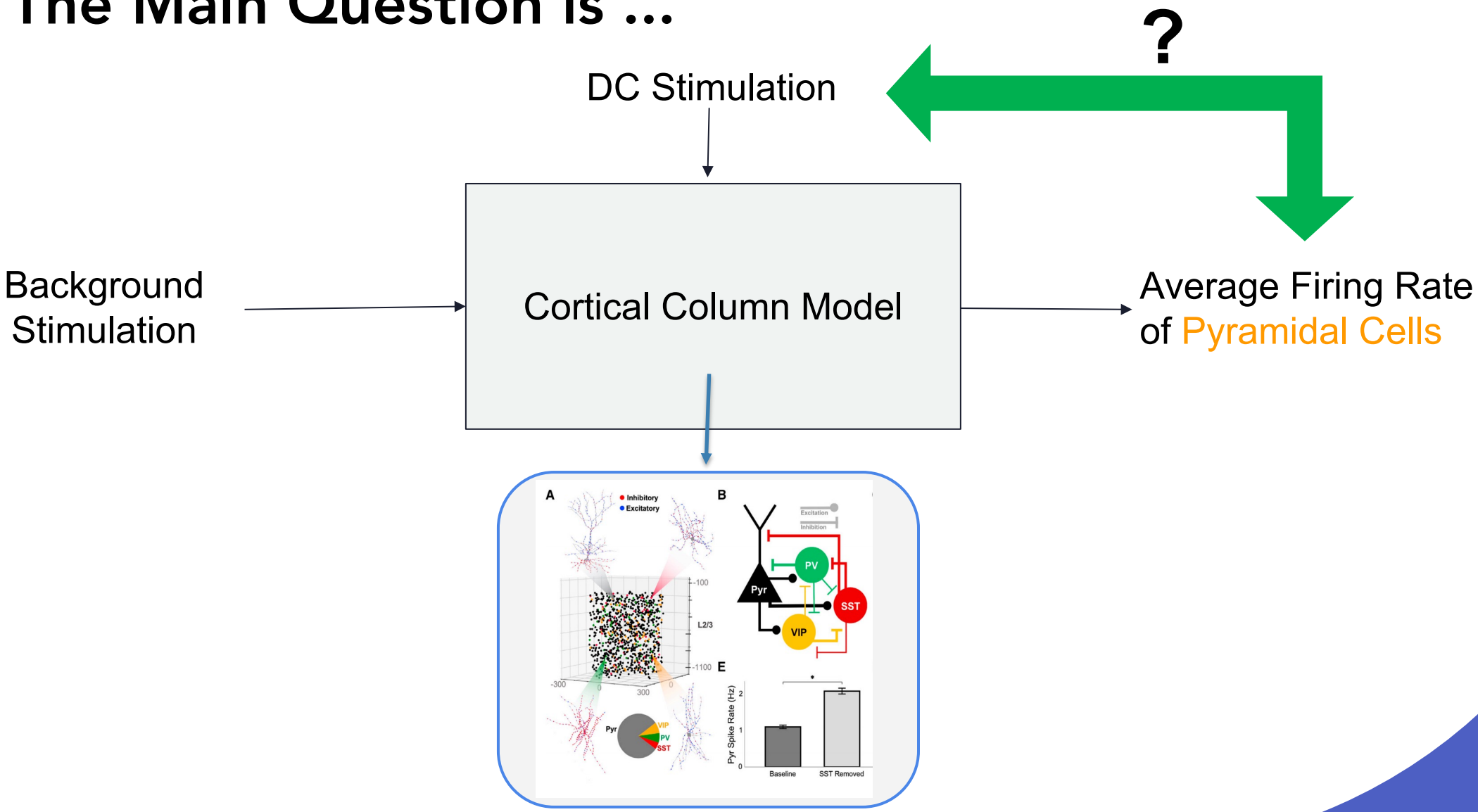
Based on plotly (3D interactive visualization)



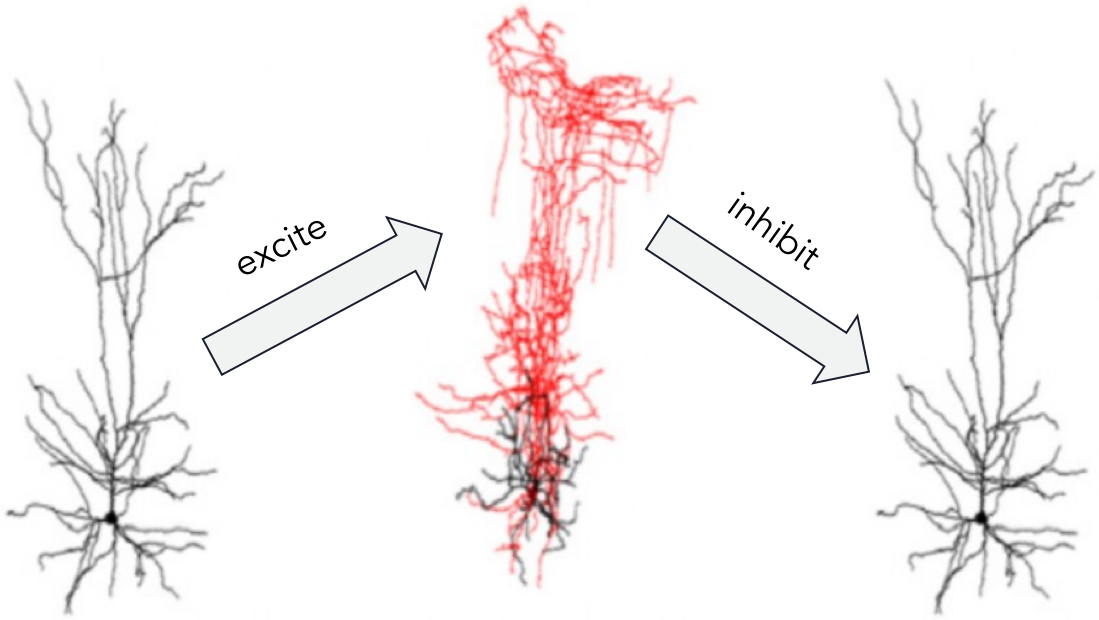
2. Neural Network



The Main Question is ...



2.1 Simple Neural Net: Bi-synaptic Inhibition loop



1 * excitatory connection
1 * inhibitory connection
3 neurons in total

to reveal the most fundamental pattern from the simplest network first

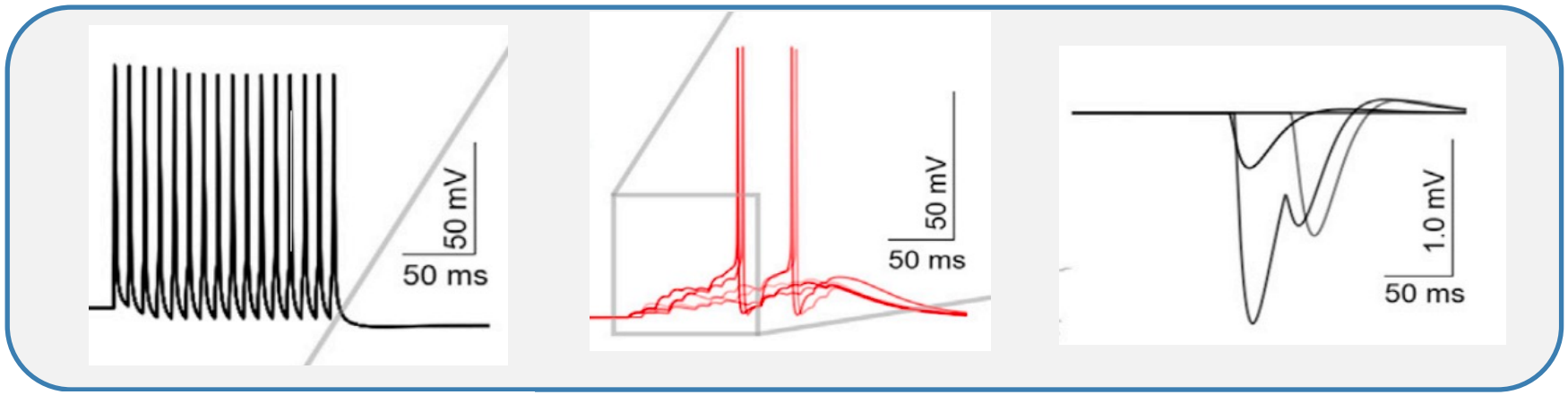
"A **Pyr (left)** neuron fired 15 spikes at 100 Hz, and the resulting EPSP summation in an **SST (middle)** interneuron triggered two spikes, which elicited IPSPs in another **Pyr (right)** neuron."

Synaptic connections are determined by quantity and Gaussian distribution

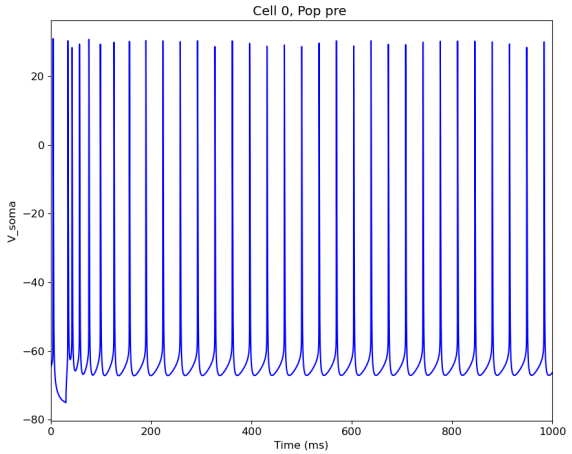
2.1.1 Calibration to Experimental Data

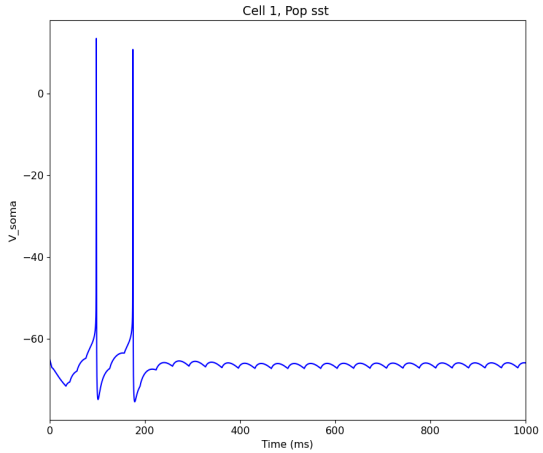
Simulated Voltage Traces for the three neurons

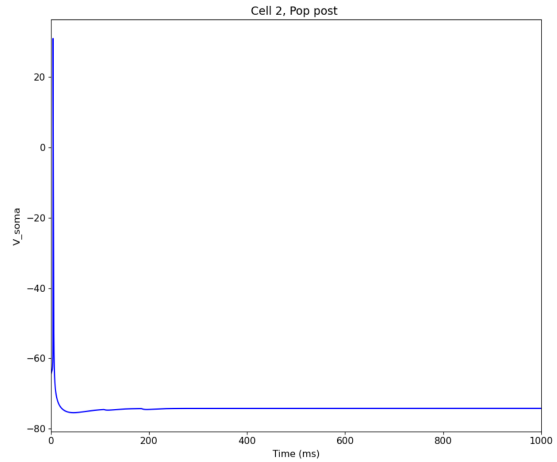
The 1st PYR | Interneuron SST | The 2nd PYR



serve as calibration







2.1.2 Firing rate response to DCS

- **Background stimulation:** net stimulation
- **Monopolar stimulation:**
  1. Write a function to calculate extracellular voltage about distances
  2. Assign different distributions of cell population at different layers
  3. Determining the size relationship between electrodes and neural networks with superimposed electric field effects
- **Average firing rate of PYR**

2.2 Brian Cortex

- Steps are similar to 2.1 but with more complex neural network

Some backup slides…

- Originally prepared for group meeting presentation in May ☺

Direct Current (DC)

- **Applying DC through a metal electrode in contact with body fluids can excite, inhibit and modulate sensitivity of neurons. (Fridman, 2013)**

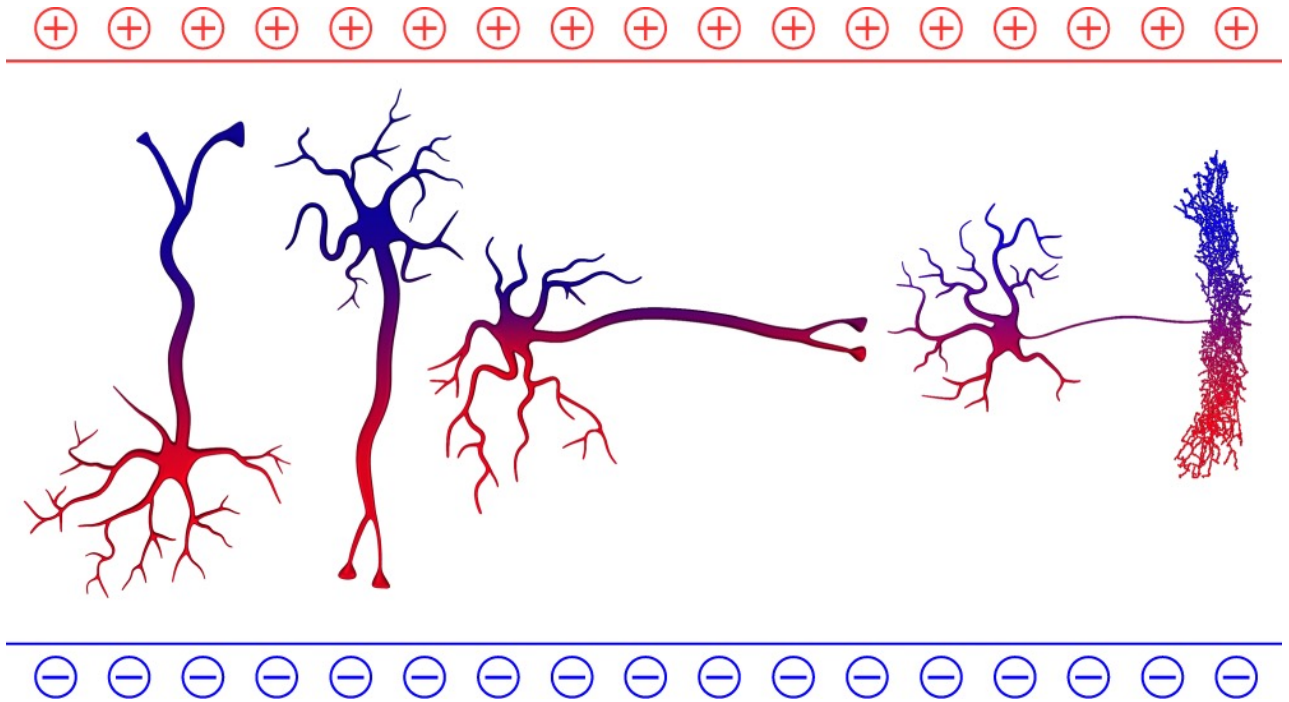
- **DCS can induce changes in neural excitability, and it has both acute and long-lasting effects on synaptic efficacy and plasticity (Rahman, 2013)**
  - **tDCS modulates cortical excitability in the primary motor cortex**

- **Which compartment is responsible for the facilitation/inhibition of spontaneous activity and synaptic efficacy?**

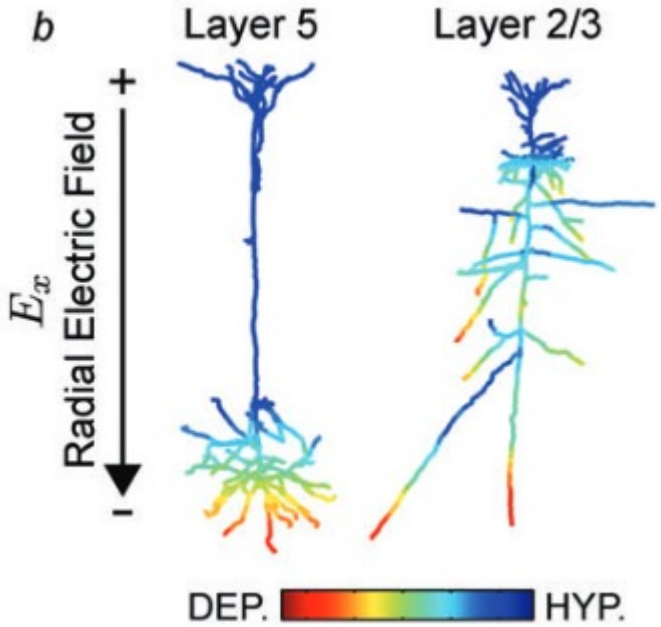
  - **Soma**
  - **Axons/terminals**
  - **Dendrites**

Single Neuron

- **General Finding: Opposite polarization profile along the direction of uniform EF (positive ⇔ hyperpolarization & negative ⇔ depolarization)**



(Liu, 2018)



(Rahman, 2013)

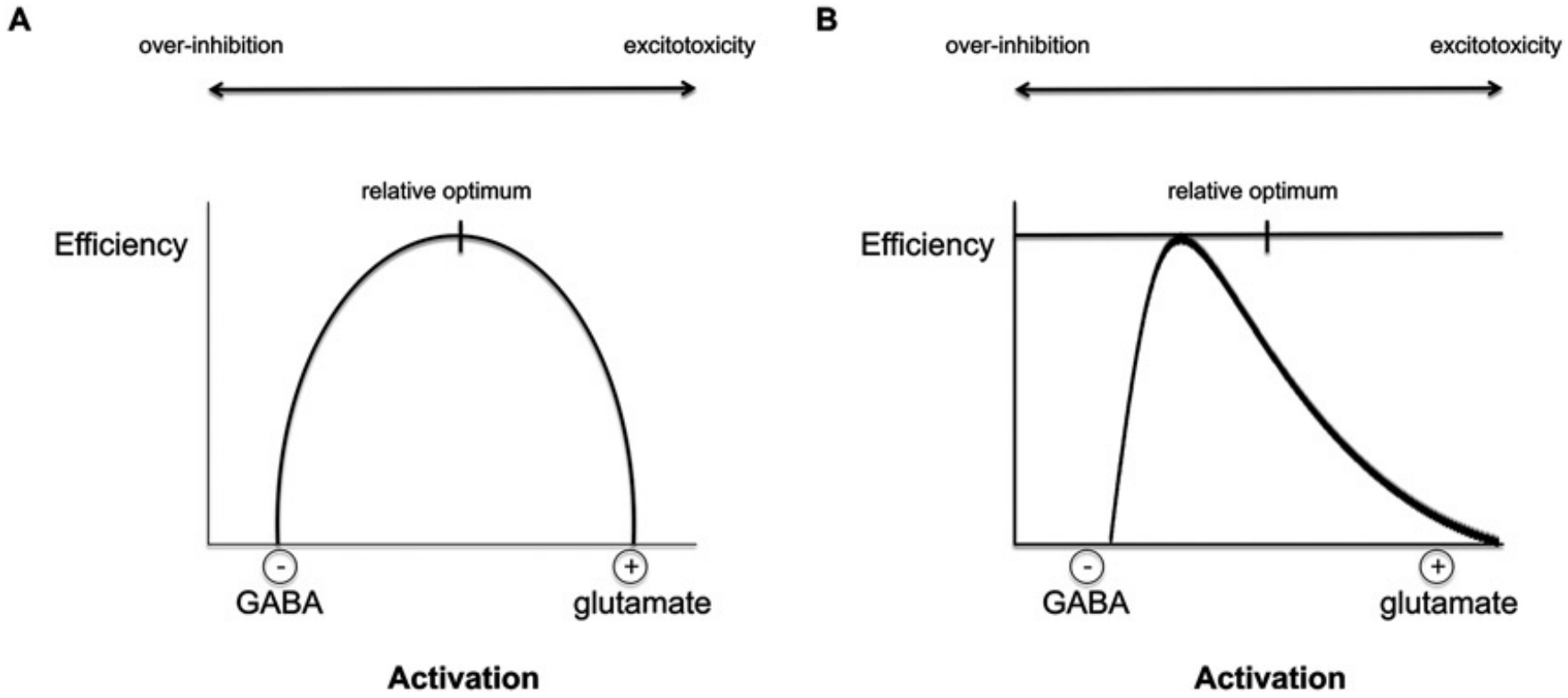
	Single Neuron	Network
Anodal Stimulation	Depolarization, Increased Excitability	Increased Excitability & Activity, Synchronization
		*Reduces local concentrations of the inhibitory neurotransmitter GABA
Cathodal Stimulation	Hyperpolarization, Decreased Excitability	Decreased Excitability & Activity, Desynchronization
		*Reduces excitatory glutamate levels

Influencing factors:

- electrode size, positioning, current intensity, duration of the stimulation, etc.
- neuron morphology, network connection, regulation of neurotransmitters, membrane ion channels, etc.

** Krause B, Márquez-Ruiz J, Cohen Kadosh R. The effect of transcranial direct current stimulation: a role for cortical excitation/inhibition balance? Front Hum Neurosci. 2013 Sep 24;7:602. doi: 10.3389/fnhum.2013.00602. PMID: 24068995; PMCID: PMC3781319.*

E/I Balance

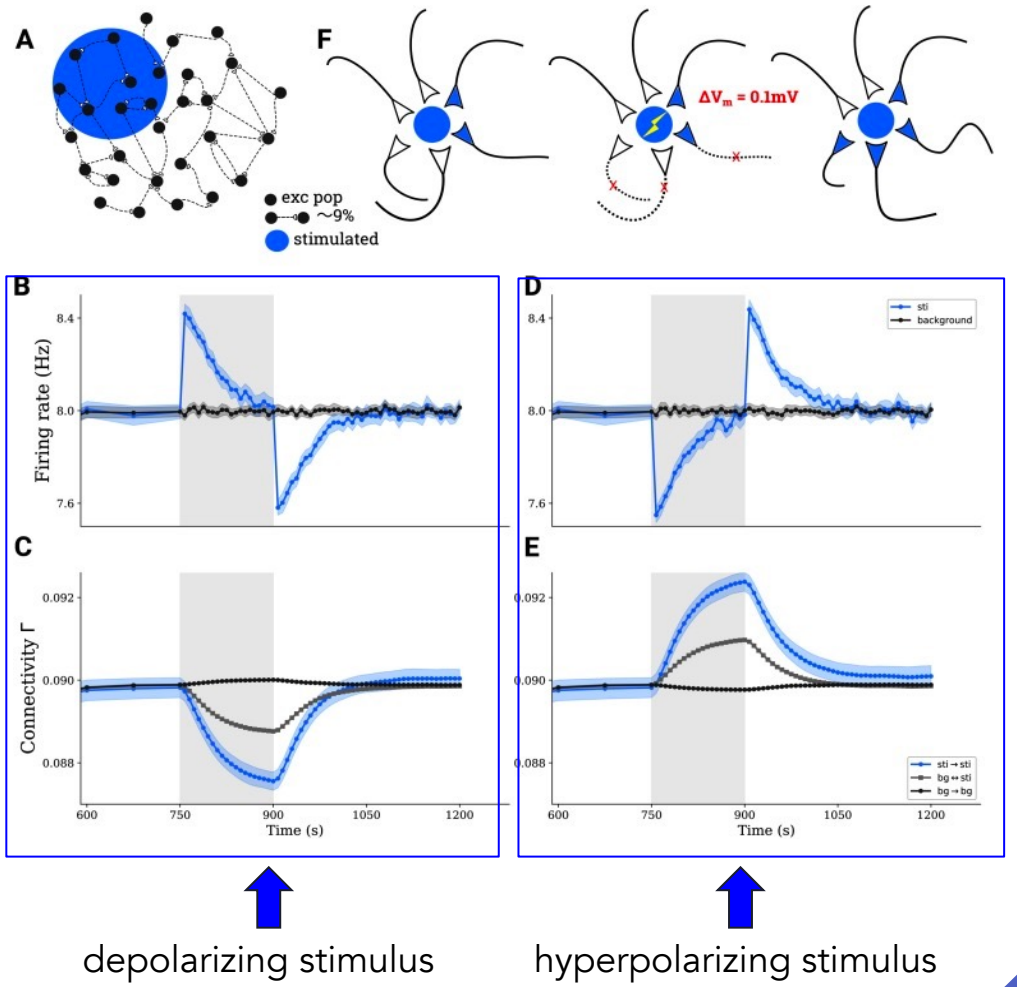


- Formation and migration of neurons
- Formation and maturation of synapses
- Refinement of synapses

Sousa B, Martins J, Castelo-Branco M, Gonçalves J. Transcranial Direct Current Stimulation as an Approach to Mitigate Neurodevelopmental Disorders Affecting Excitation/Inhibition Balance: Focus on Autism Spectrum Disorder, Schizophrenia, and Attention Deficit/Hyperactivity Disorder. J Clin Med. 2022 May 18;11(10):2839. doi: 10.3390/jcm11102839. PMID: 35628965; PMCID: PMC9143428.

DC Effect on Network

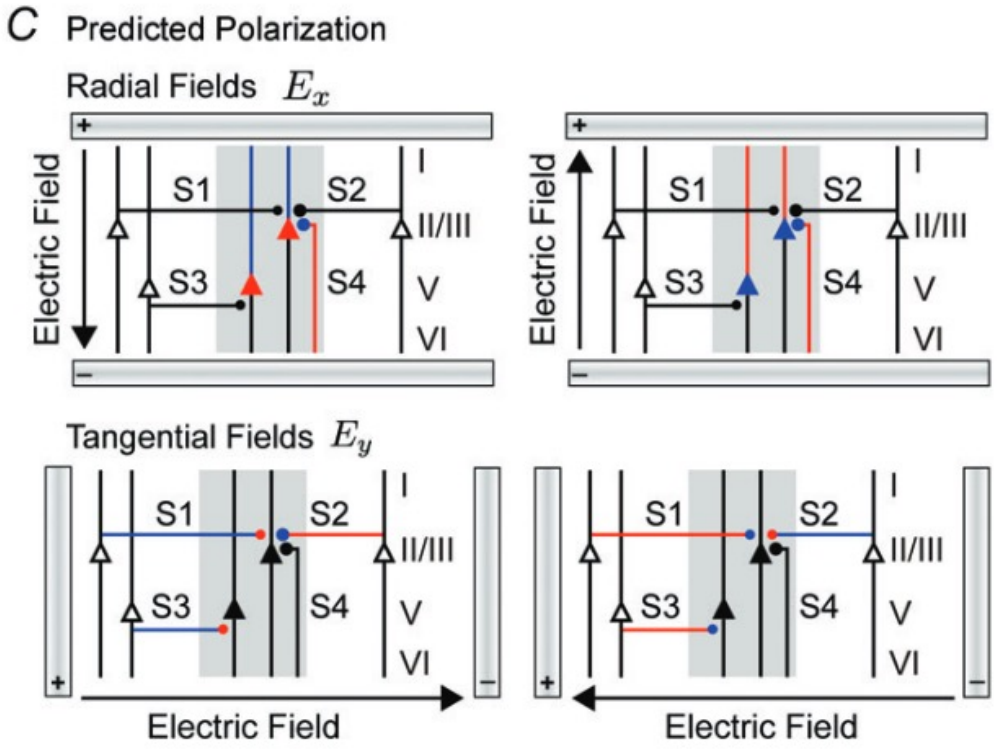
- **Model:** Point neuron(LIF), inhibition-dominated recurrent neural network
- **Assumption:** tDCS triggers a homeostatic response of the network involving growth and decay of synapses
- **Effect:** Anatomical connectivity among stimulated and nonstimulated neurons
- **Results**
  - The stimulated population eliminates excitatory synapses with the unstimulated population
  - New synapses among stimulated neurons are grown to form a cell assembly.
  - Strong focal stimulation tends to enhance the connectivity within new cell assemblies,
  - Repetitive stimulation with well-chosen duty cycles can increase the impact of stimulation even further.

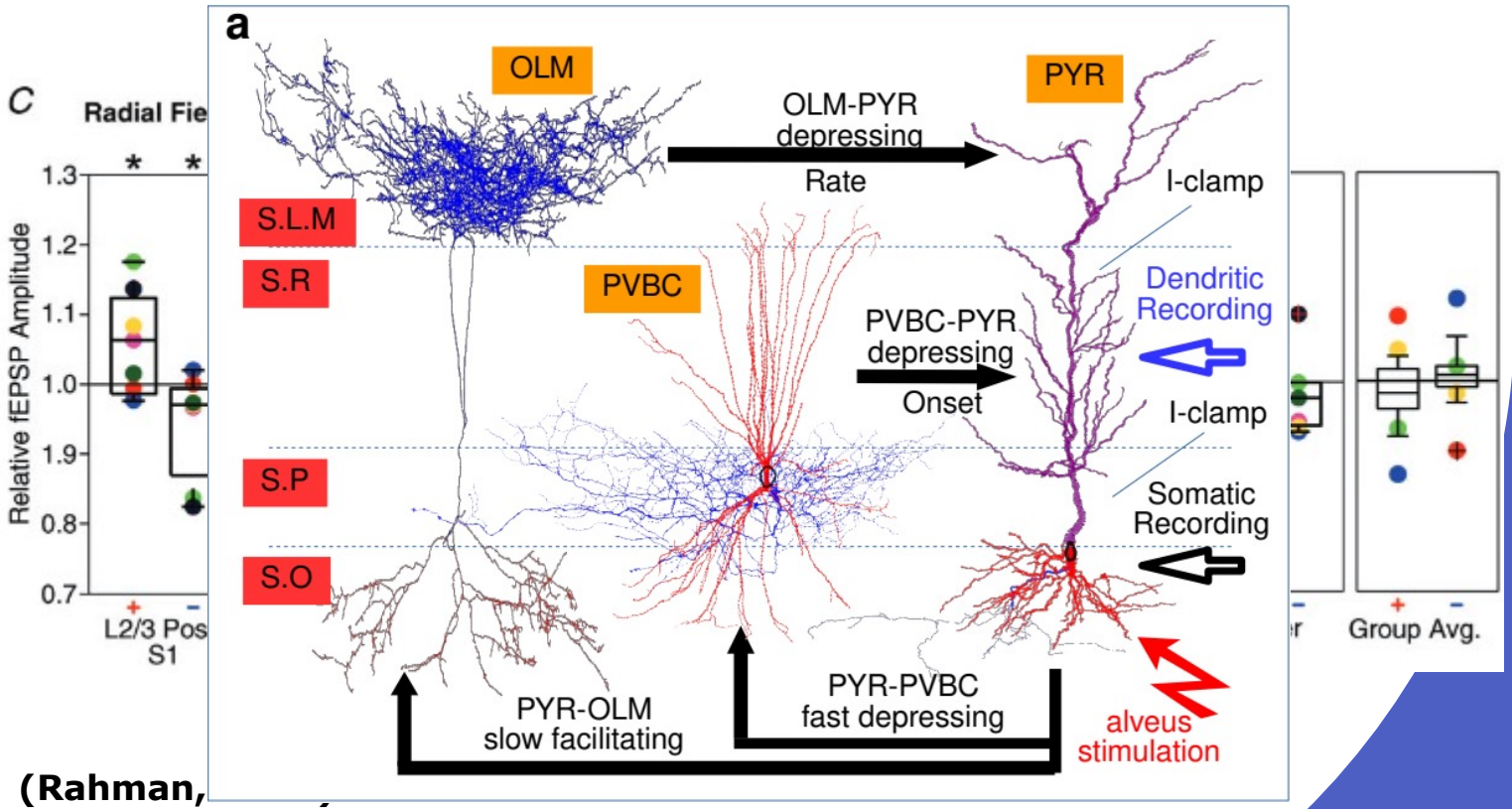


Lu H, Gallinaro JV, Rotter S. Network remodeling induced by transcranial brain stimulation: A computational model of tDCS-triggered cell assembly formation. Netw Neurosci. 2019 Sep 1;3(4):924-943. doi: 10.1162/netn_a_00097. PMID: 31637332; PMCID: PMC6777963.

More Neurons

- **Effects of DCS on a cortical columns or a neural network?**



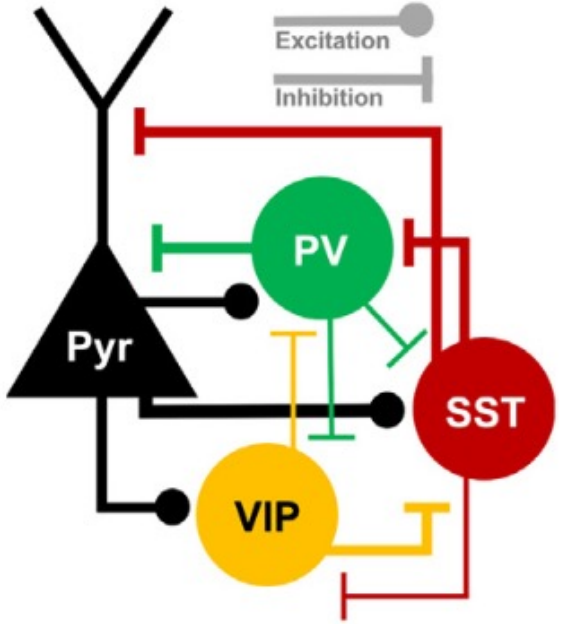


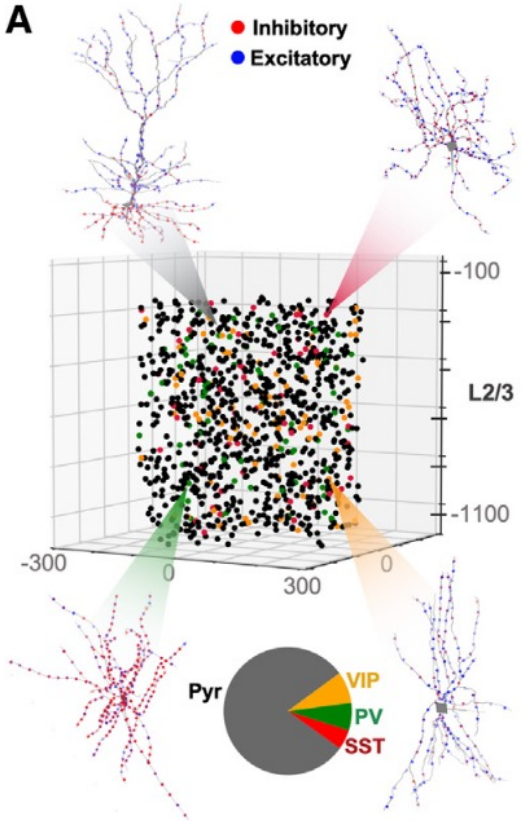
(Rahman,

(Ponzi, Accepted)

Model of human cortical L2/3 Microcircuits

- **Cortical processing depends on finely tuned excitatory and inhibitory connections in neural microcircuits**
  - Reduced dendritic inhibition from the somatostatin (SST) interneurons is associated with treatment-resistant depression and other disorders.
- **Microcircuits of cortical layer 2 and 3 of the human cerebral cortex**
- **Conclusions: (1) higher baseline activity, (2) reduced s-to-n ratio, and (3) increased false/failed detection of stimuli**





(Yao, 2021)

Project Flowchart

- **Preliminary Research Question: How would DC affect the baseline activity of difference neurons in the microcircuit?**