Krembil Centre for Neuroinformatics
Summer School 2021

Day 4

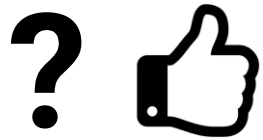
Simulating Brain Microcircuit Activity and Signals in Mental Health

Etay Hay

camh | Krembil Centre for Neuroinformatics

UNIVERSITY OF TORONTO

KCNI Summer School - Connect



(during sessions) Use the chat or the ask question!

virtually meet with us
in **gather.town**

You can return to the session and
re-watch the videos

Post session survey - tell us how the session went:

https://forms.gle/ji18qLMZEZ9L16Ln6

KCNISchool@camh.ca

CAMH Land Acknowledgement

CAMH is situated on lands that have been occupied by First Nations for millennia; lands rich in civilizations with knowledge of medicine, architecture, technology, and extensive trade routes throughout the Americas. In 1860, the site of CAMH appeared in the Colonial Records Office of British Crown as the council grounds of the Mississaugas of the New Credit, as they were known at the time.

Today, Toronto is covered by the Toronto Purchase, treaty No. 13 of 1805 with the Mississaugas of the Credit.

Toronto is now home to a vast diversity of First Nations, Inuit, and Métis who enrich this city.

CAMH is committed to reconciliation. We will honour the land through programs and places that reflect and respect its heritage. We will embrace the healing traditions of the Ancestors, and weave them into our caring practices. We will create new relationships and partnerships with First Nations, Inuit, and Métis and share the land and protect it for future generations.

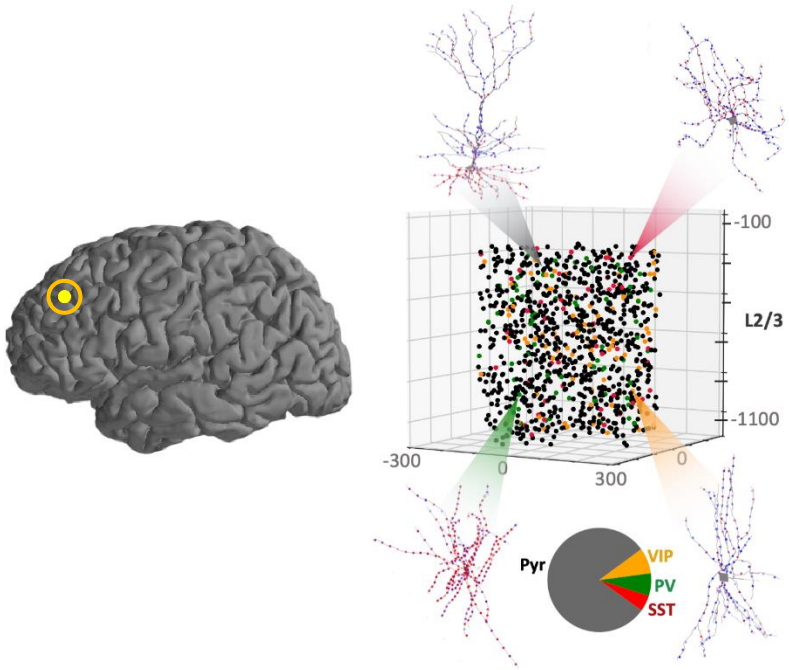
Day 4 - Synopsis

9:00 am - 10:30 am	*Simulating brain microcircuit activity in mental health* Etay Hay
10:45 am - 12:15 pm	*Simulating EEG from brain microcircuits in mental health* Etay Hay

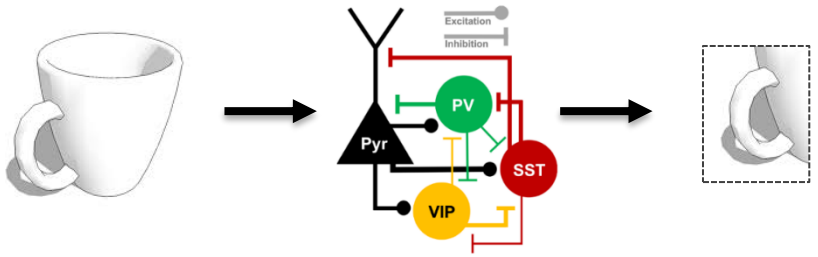
1:00 pm - 2:30 pm	*Tutorial – simulating and analyzing spiking from neurons and microcircuits* Frank Mazza
2:45 pm - 4:15 pm	*Tutorial – simulating and analyzing EEG signals from brain microcircuits* Frank Mazza

Cortical Microcircuits in Mental Health

Human Microcircuit Models

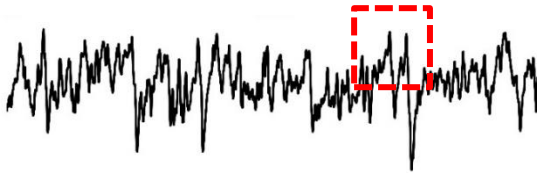


Mechanisms of Cortical Processing

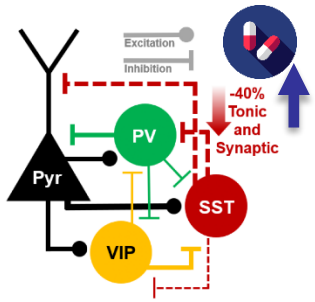


Diagnostic Biomarkers

Simulated EEG



Testing Pharmacology In Silico



Depression, Aging
Schizophrenia

Krembil Centre for Neuroinformatics
Summer School 2021

Day 4 – Session 1

Simulating brain microcircuit activity in mental health

Etay Hay

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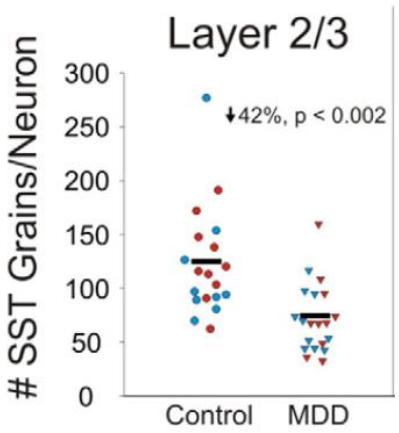
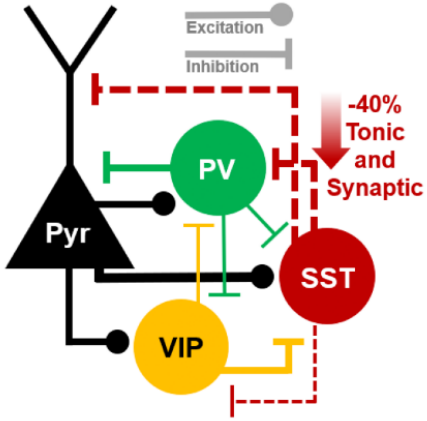
UNIVERSITY OF TORONTO

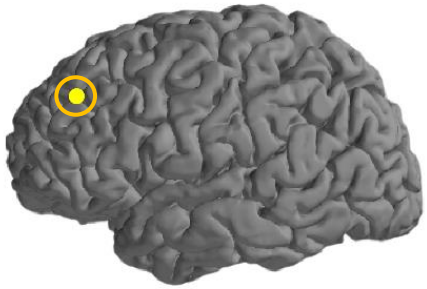
From Cellular Mechanisms to Brain Microcircuit Function

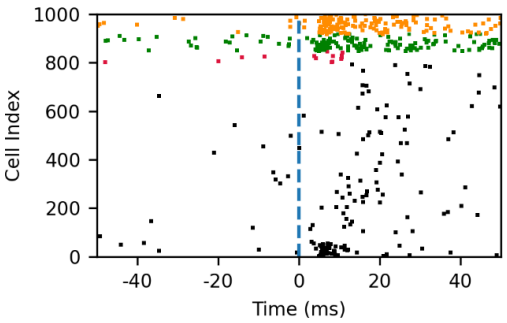
Gene Expression in Health and Depression



Brain Activity & Function



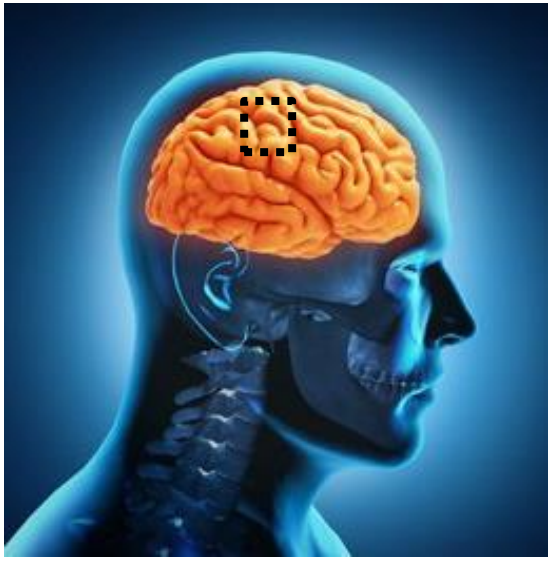




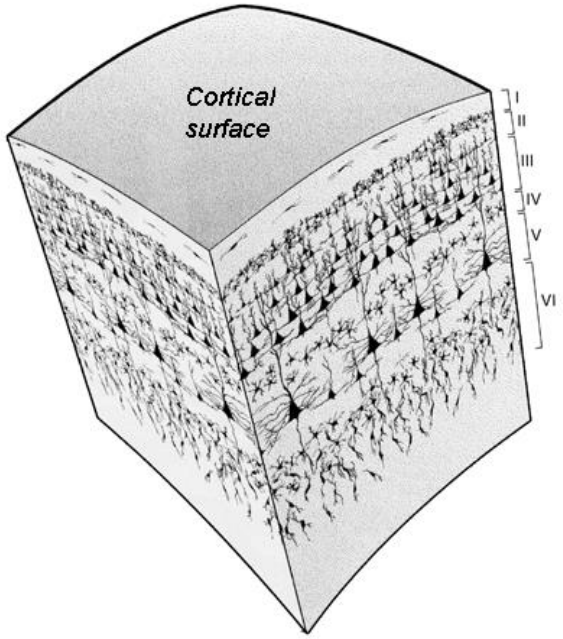
Stimulus Processing

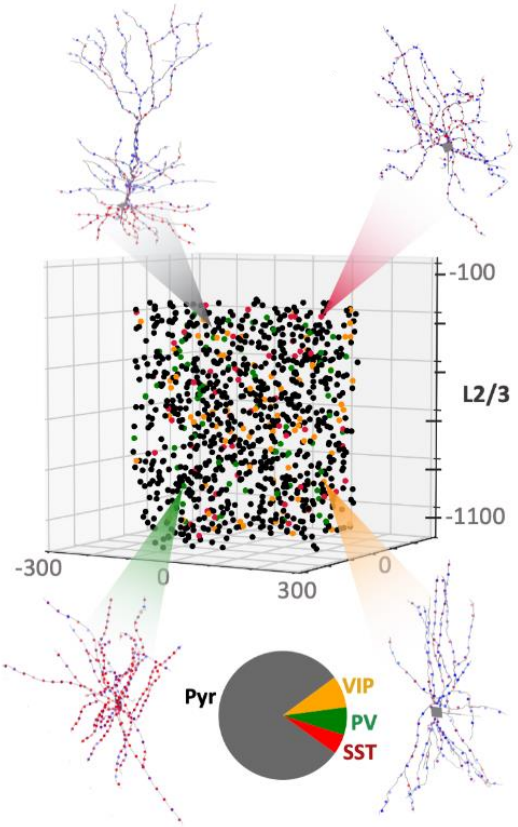
Cortical Microcircuits

Cerebral Cortex



Microcircuits



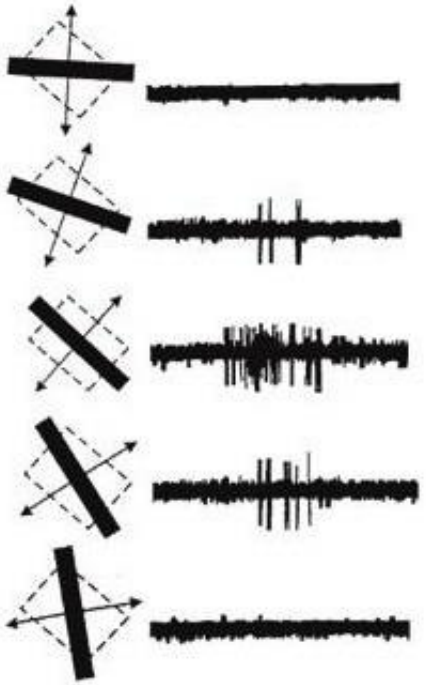


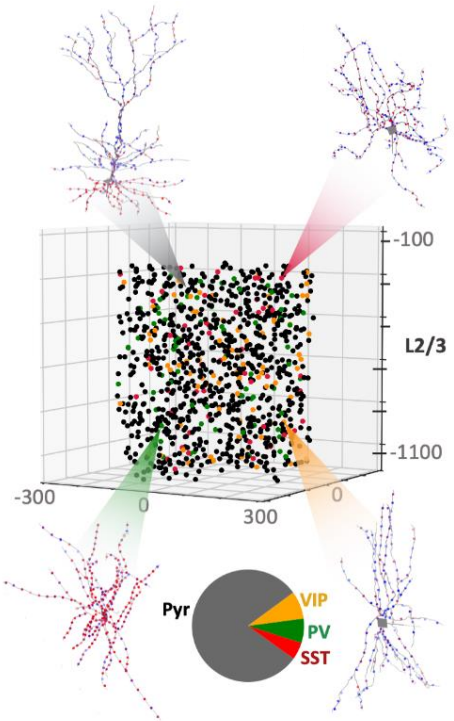
- ~30,000 neurons in a cortical column
- 3,000-7,000 neurons in each layer
- Distinct neuronal types and connectivity

Stimulus Processing in Neuronal Microcircuits

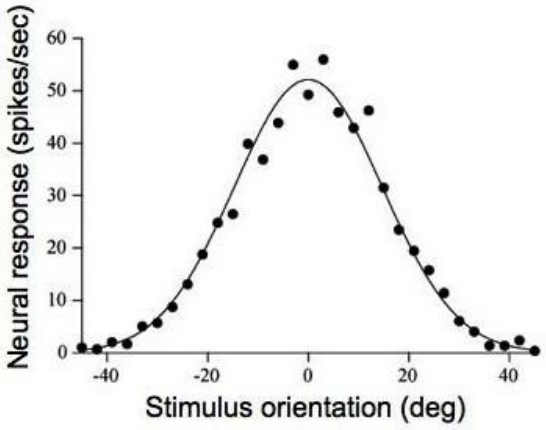
Stimulus Orientation

Neuron Response





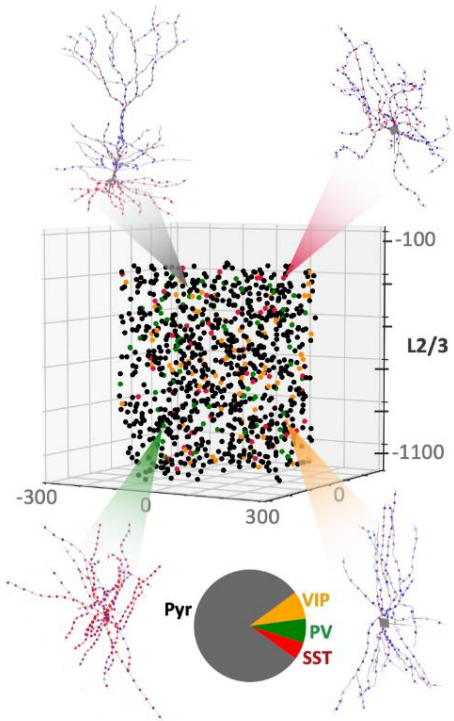
Feature Selectivity



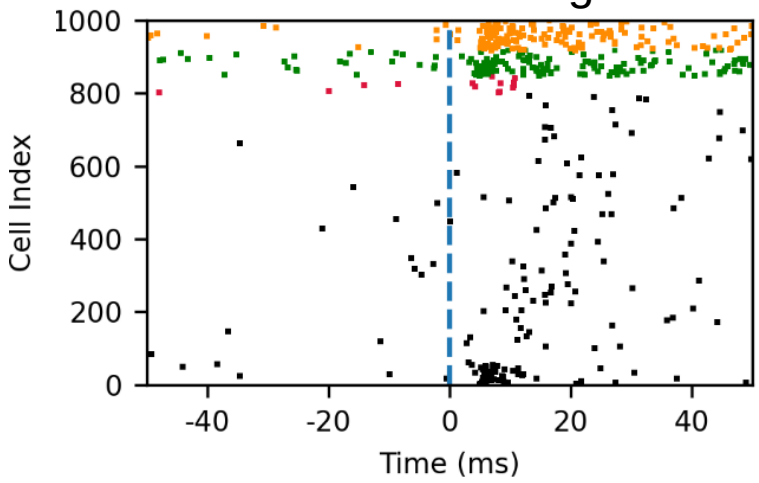
Hubel and Wiesel
(Nobel Prize)

Stimulus Processing in Neuronal Microcircuits

Feature Detection

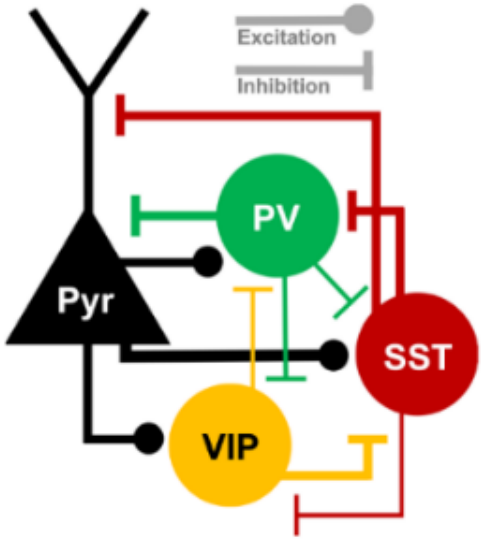


Baseline vs. Signal

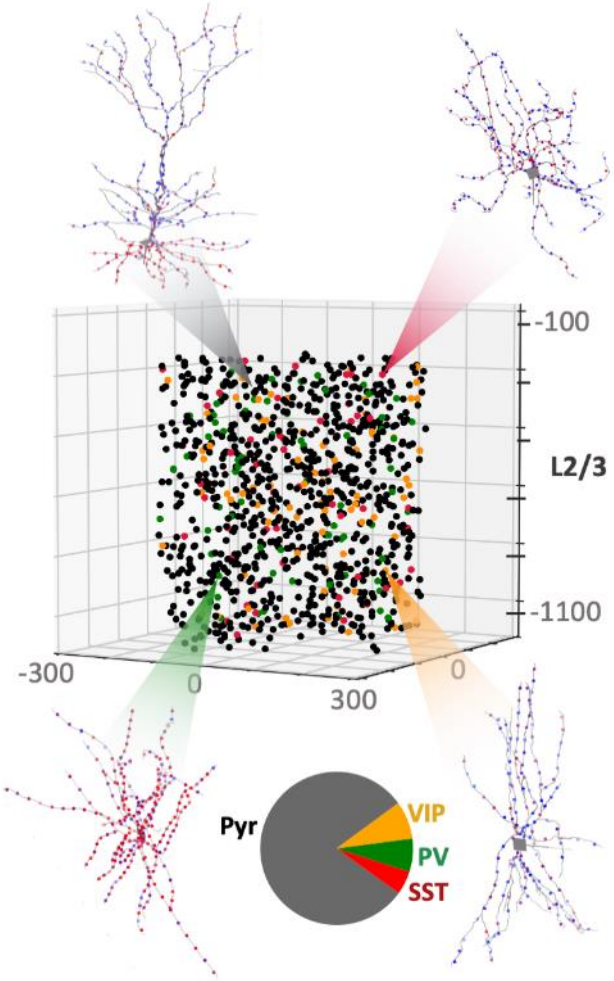


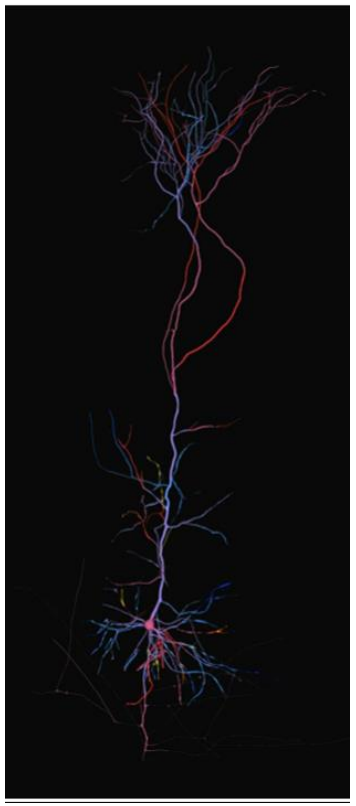
- Population coding
- Baseline (no signal) vs. response (signal)

Neuronal Microcircuit Properties



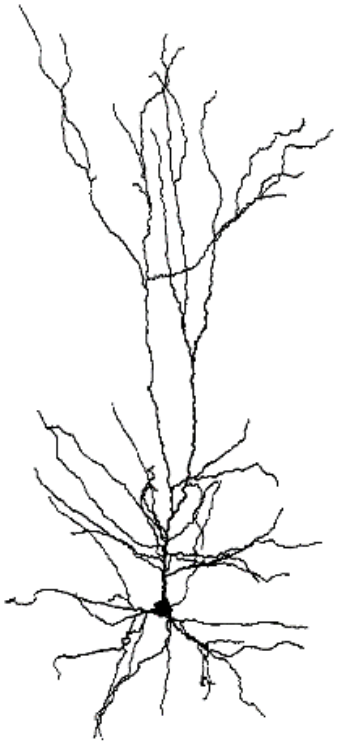
Circuit
Connectivity



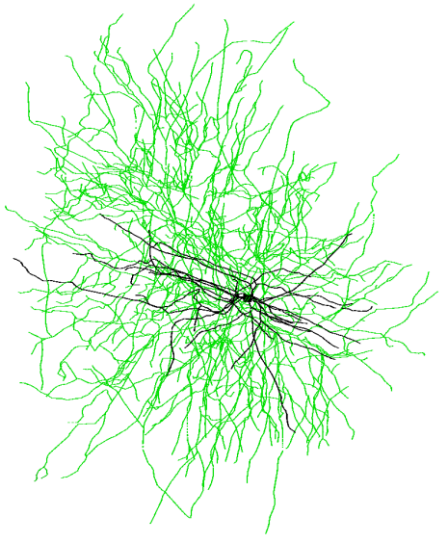


Neuronal
Electrophysiology

Neuron Types



Pyramidal Neuron



PV Interneuron

SST Interneuron

VIP Interneuron

Reconstructed human morphologies from:

ALLEN BRAIN ATLAS
DATA PORTAL

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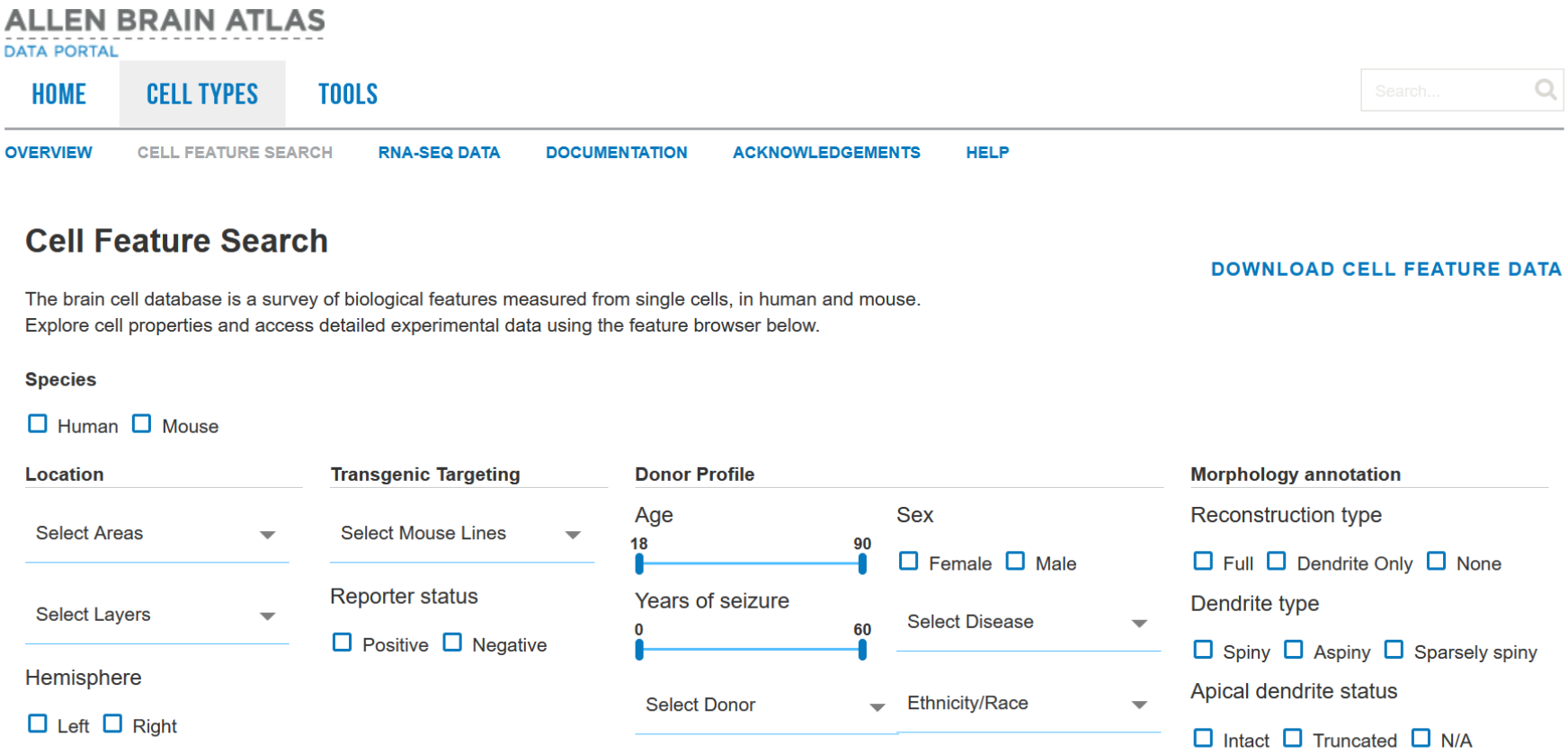
Allen Brain Database



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Allen Brain Database

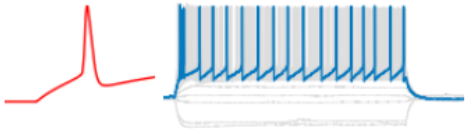
Results: 2333 of 2333 cells

Human cell id: 643625553

PLP Layer 5 aspiny

Donor: 29 yrs, Male

Disease state: epilepsy



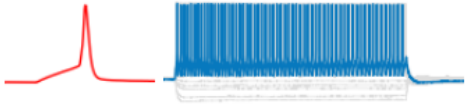
Electrophysiology ›

Human cell id: 643584386

PLP Layer 5 aspiny

Donor: 29 yrs, Male

Disease state: epilepsy



Electrophysiology ›

Human cell id: 643575207

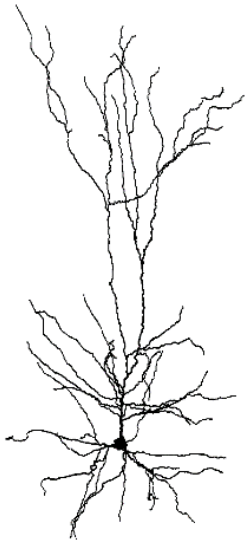
PLP Layer 3 aspiny

Donor: 29 yrs, Male

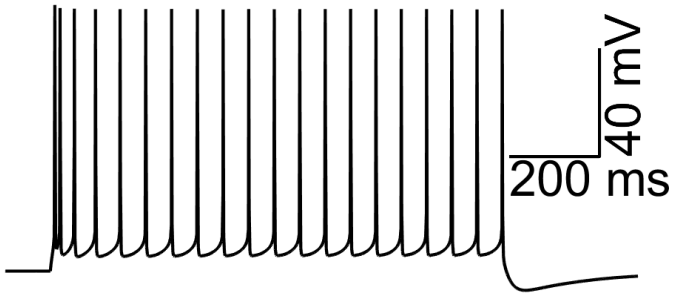
Disease state: epilepsy

Electrophysiology › Morphology ›

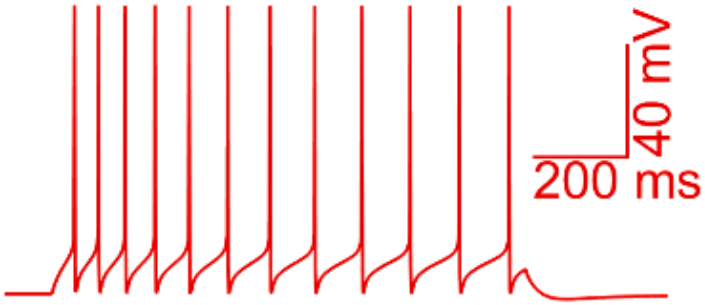
Neuronal Firing and Gain



Model Human Pyramidal Neuron

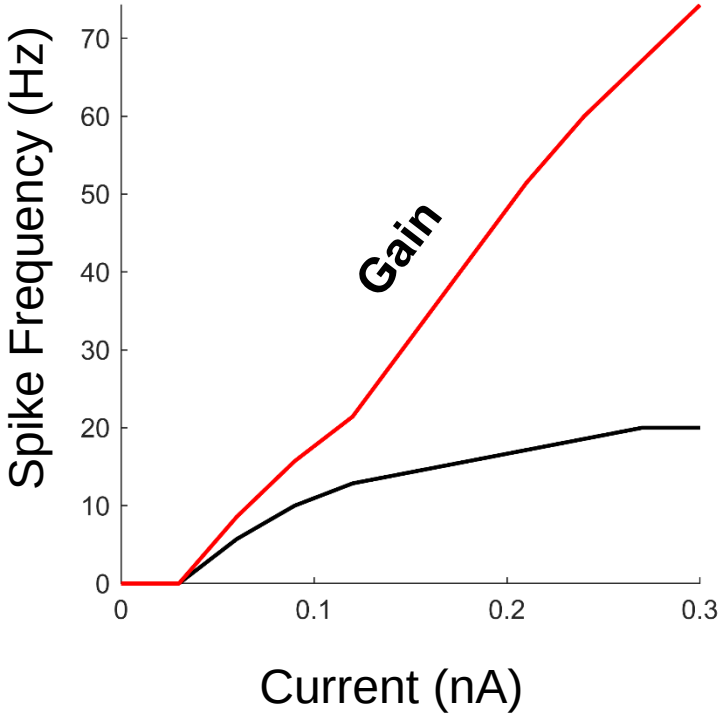


Model Human SST Interneuron

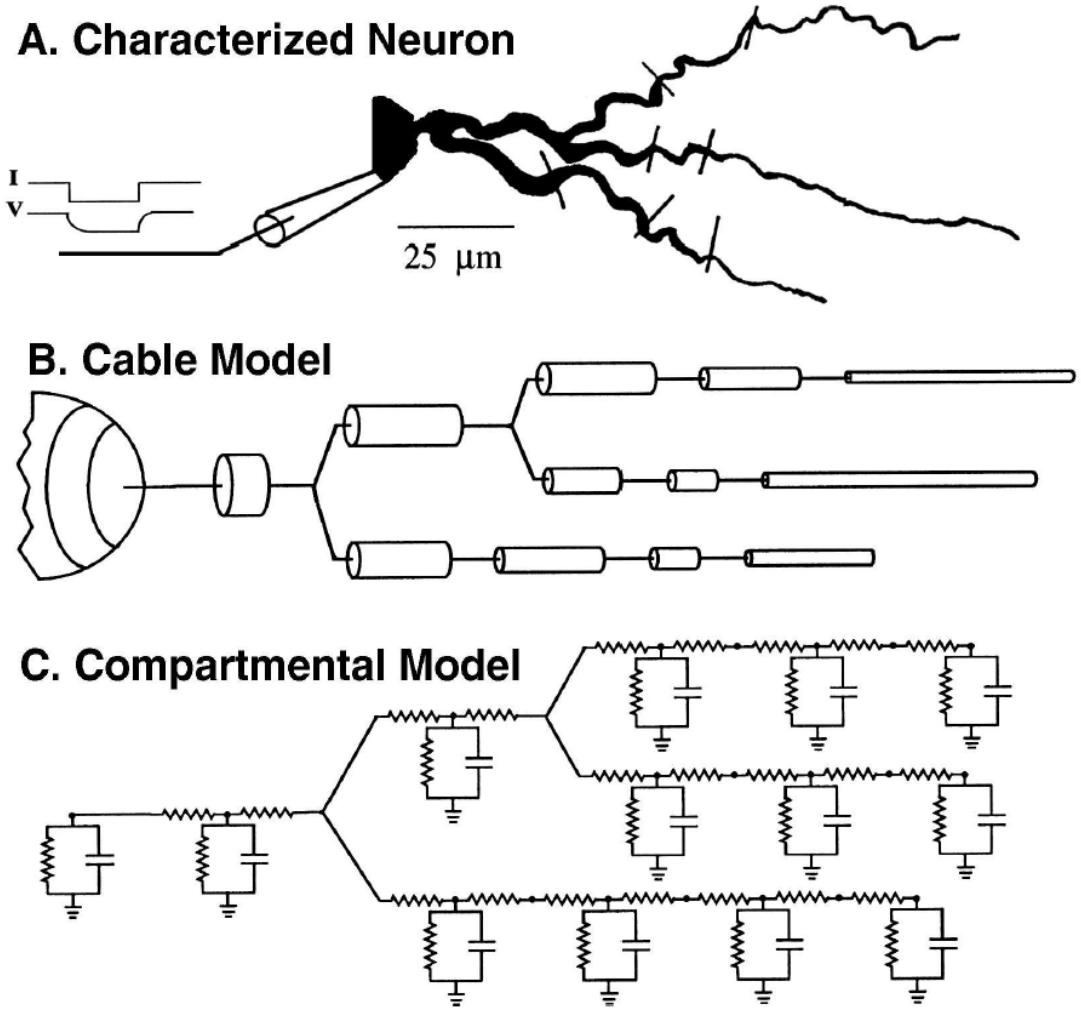


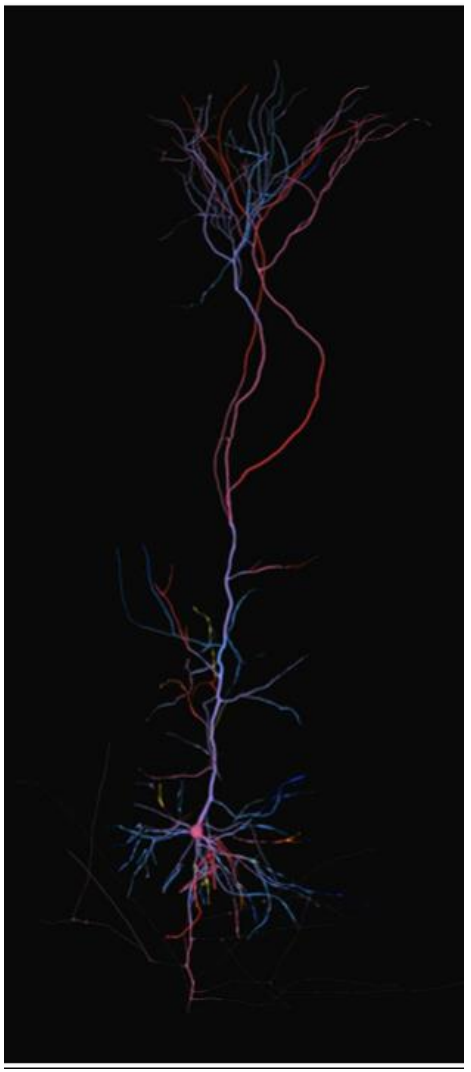
I_{stim}

Frequency-Input Curve



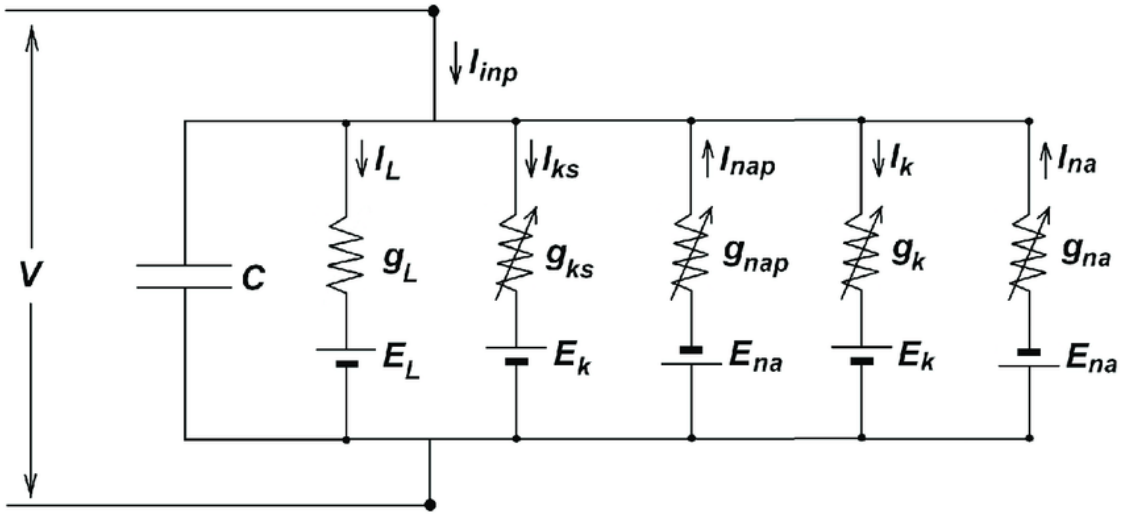
Biophysical Models

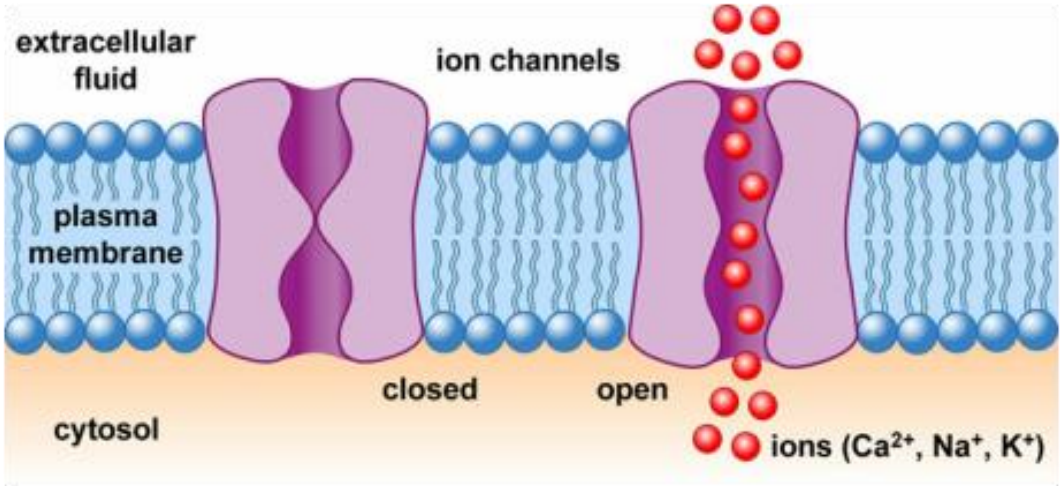


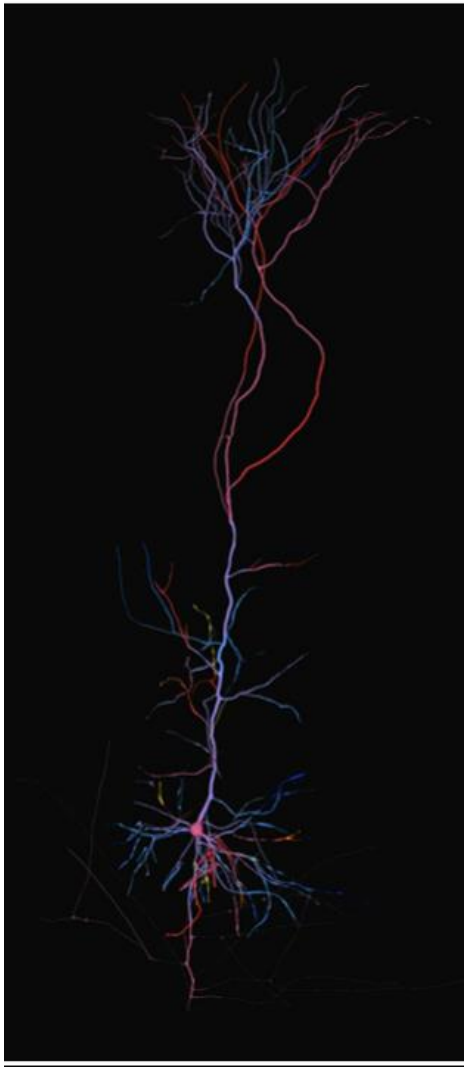


Simulated in *NEURON*

Membrane Currents





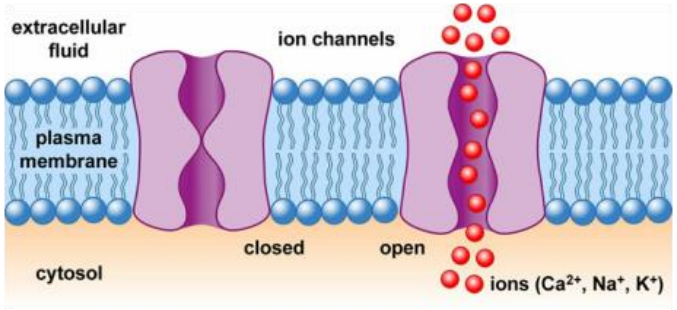


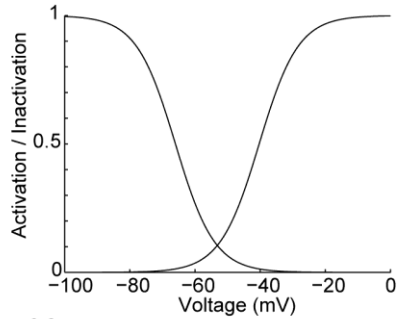
Ion Channel Models

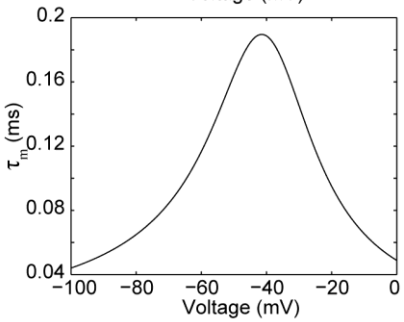
$$I = \bar{g} \cdot m^x \cdot h^y (V - E)$$

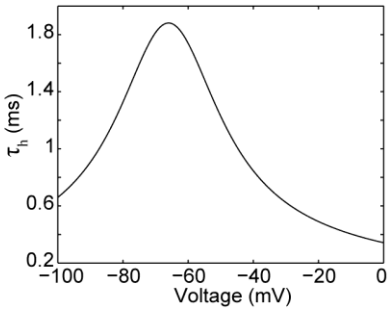
$$\frac{dm}{dt} = \frac{(m_\infty - m)}{\tau_m}$$

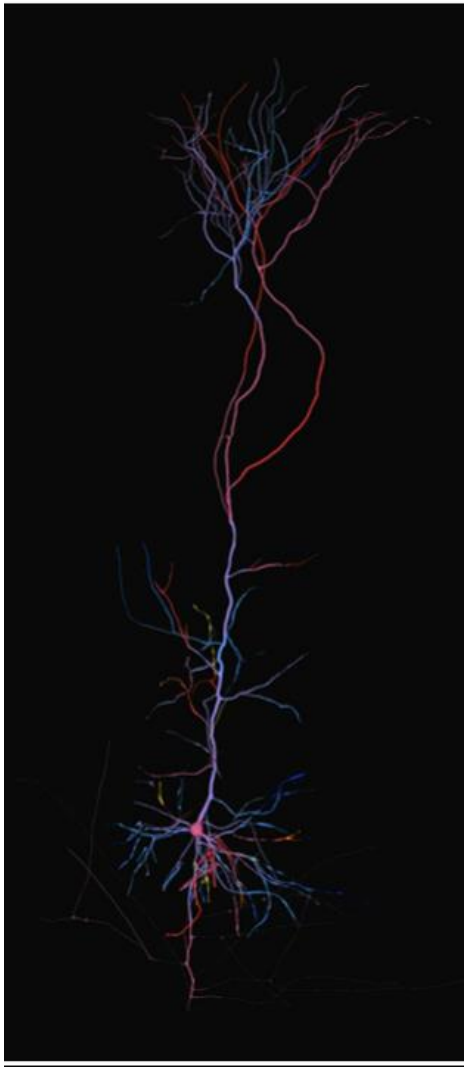
$$\frac{dh}{dt} = \frac{(h_\infty - h)}{\tau_h}$$





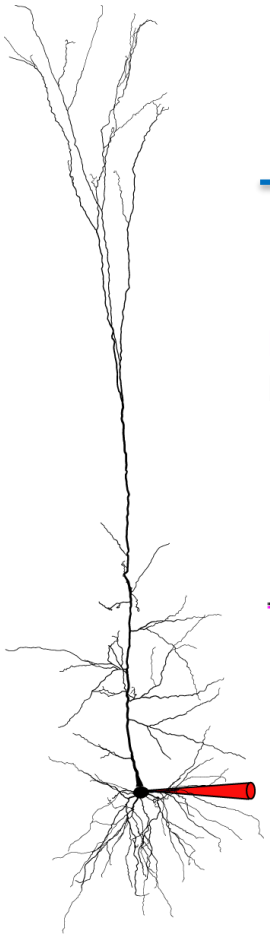


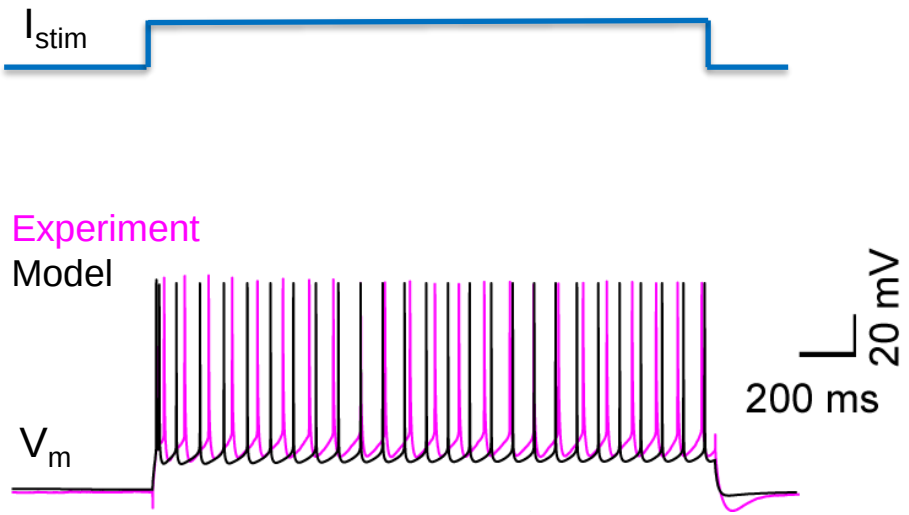




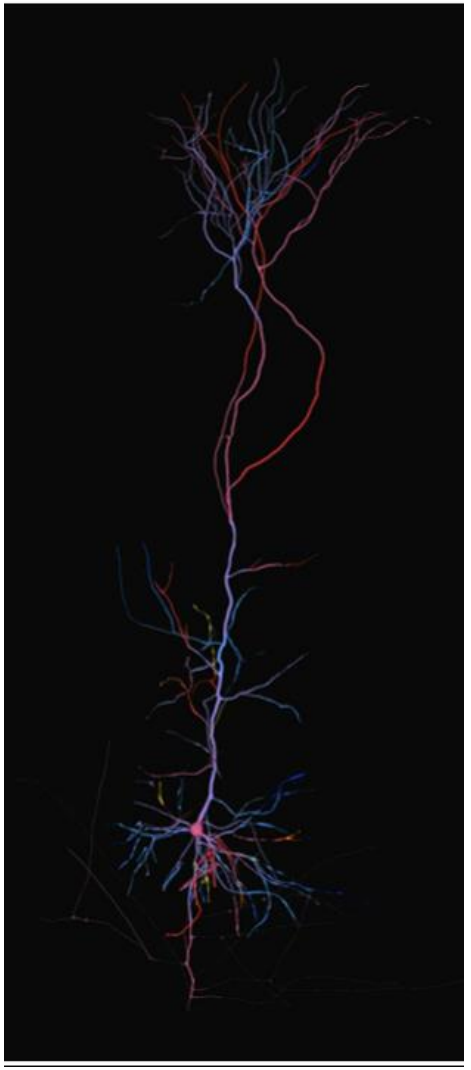
Hodgkin & Huxley (Nobel Prize)

Neuron Simulations





Ion channel densities optimized using Genetic Algorithms



Simulated in *NEURON*

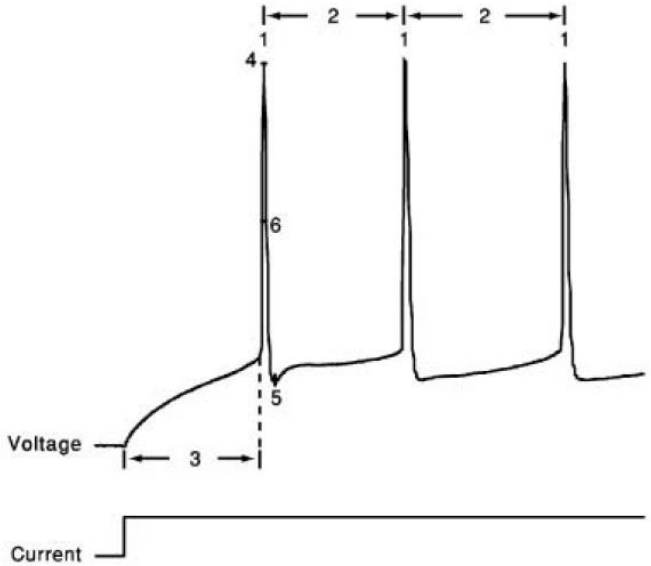
Electrophysiological Features

Spike height, width

Spike rate

Adaptation

Latency

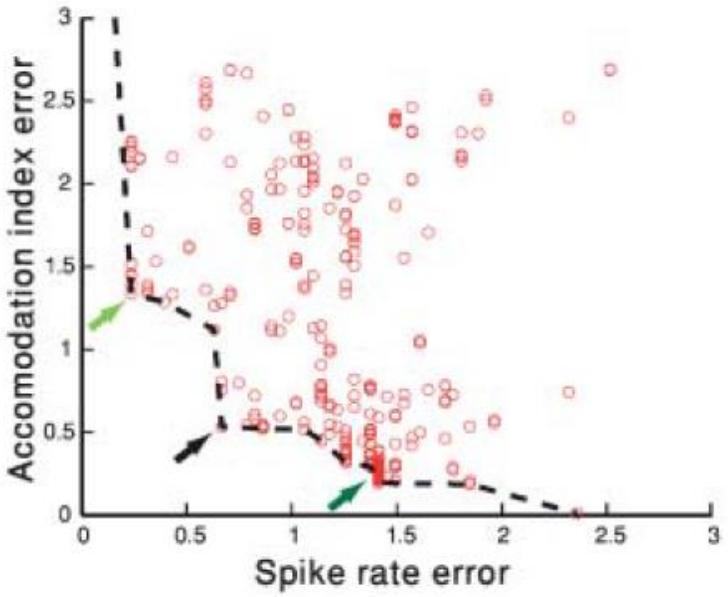


Multi-Objective Optimization

- Objectives: electrophysiological features
- Non-dominance
- Pareto-front

Green models do not dominate each other

Black model doesn't dominate green models



Genetic Algorithm Optimization

1. Population of N models

	Na_T	Ca_{HVA}	K_T	K_P
Model 1	0.5	0.01	0.1	0.3
Model 2	0.2	0.05	0.5	0.5
…				
Model N	0.1	0.1	0.2	0.2

Channel density

Genetic Algorithm Optimization

2a. Mutation with some probability

	Na_T	Ca_{HVA}	K_T	K_P
Model 1	0.5	0.01	0.1	0.3
Model 2	0.2	0.05	0.5	0.5
…				
Model N	0.1	0.1	0.2	0.2

	Na_T	Ca_{HVA}	K_T	K_P
Model 1	0.5	0.01	0.1	0.3
Model 2	0.18	0.05	0.75	0.5
…				
Model N	0.1	0.1	0.2	0.2

Genetic Algorithm Optimization

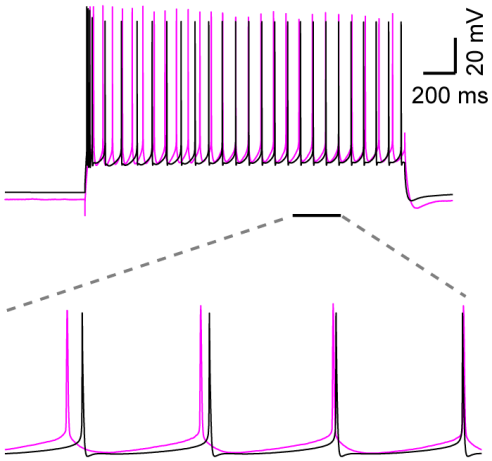
2b. Crossover between models

	Na_T	Ca_{HVA}	K_T	K_P
Model 1	0.5	0.01	0.1	0.3
Model 2	0.18	0.05	0.75	0.5
…				
Model N	0.1	0.1	0.2	0.2

	Na_T	Ca_{HVA}	K_T	K_P
Model 1	0.5	0.05	0.75	0.3
Model 2	0.18	0.01	0.1	0.5
…				
Model N	0.1	0.1	0.2	0.2

Genetic Algorithm Optimization

3. Evaluate model fitness



	Na_T	Ca_{HVA}	K_T	K_P	Fitness (SD)	
Model 1	0.5	0.05	0.75	0.3	0.8	✓
Model 2	0.18	0.01	0.1	0.5	4.4	✗
…						
Model 2N	0.1	0.1	0.2	0.2	1.1	✓

Genetic Algorithm Optimization

4. Select N <u>best</u> models as next generation

	Na_T	Ca_{HVA}	K_T	K_P	Fitness (SD)
Model 1	0.5	0.05	0.75	0.3	0.8
~~Model 2~~	~~0.18~~	~~0.01~~	~~0.1~~	~~0.5~~	~~4.4~~
…					
Model 2N	0.1	0.1	0.2	0.2	1.1

5. Iterate until model fitness is satisfactory (converges within experimental variability)

Genetic Algorithm Optimization

- Useful for optimizing biophysical models
  - Complex solution space
  - System with unclear learning rule

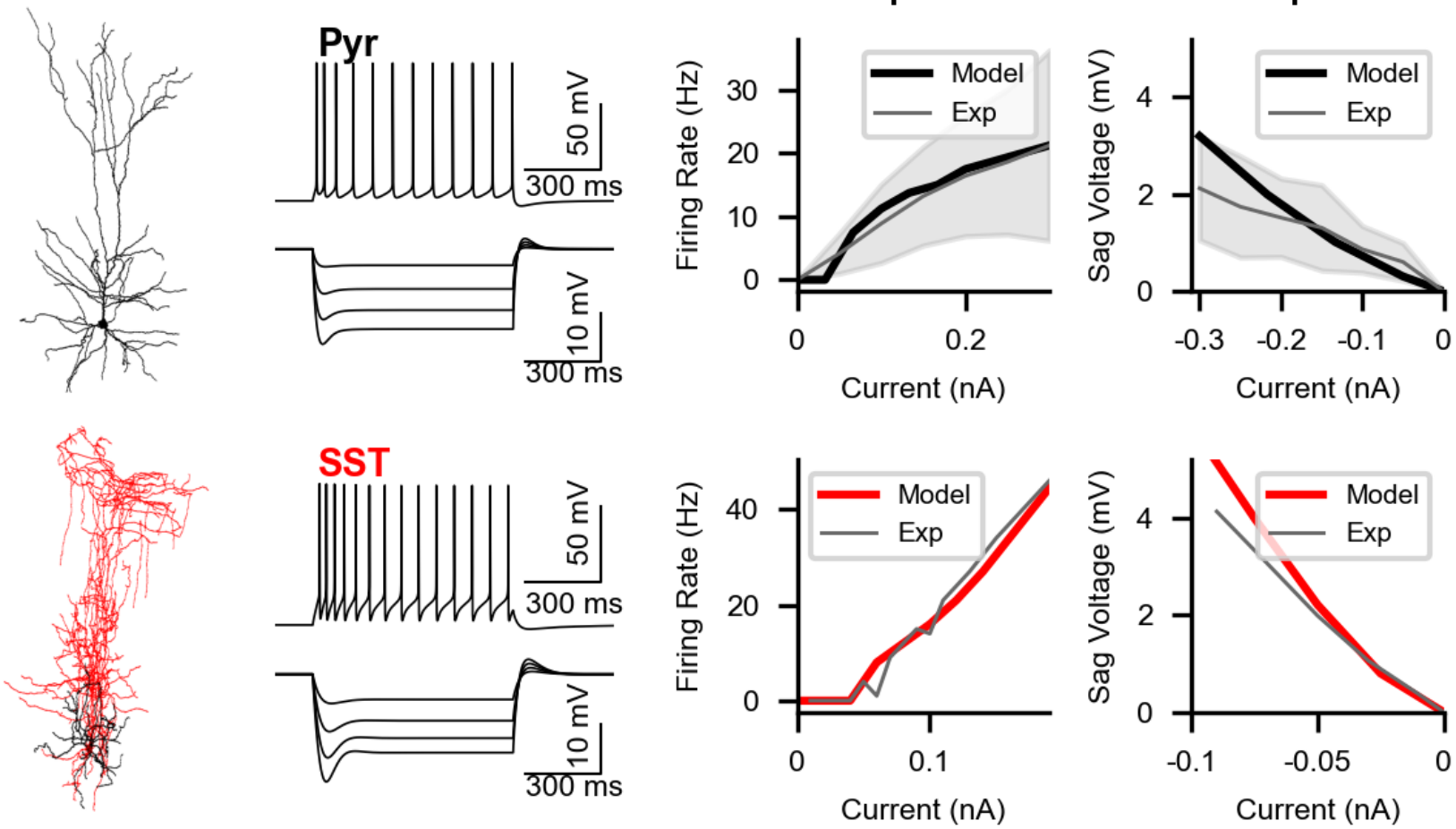
- Optimality not guaranteed but convergence is often good

- Parallel computing

- BluePyOpt available

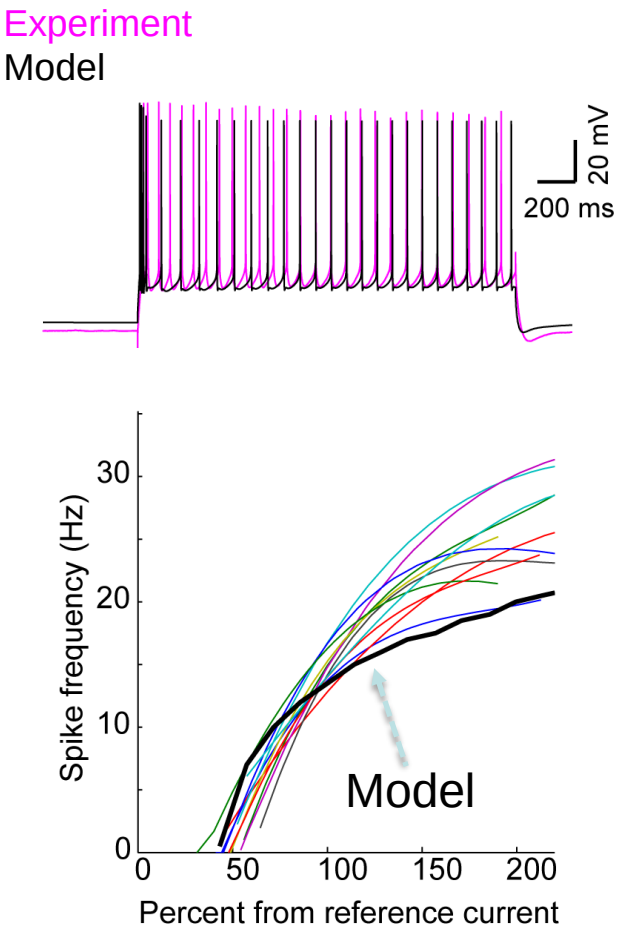
SciNet, NSG, BlueGene

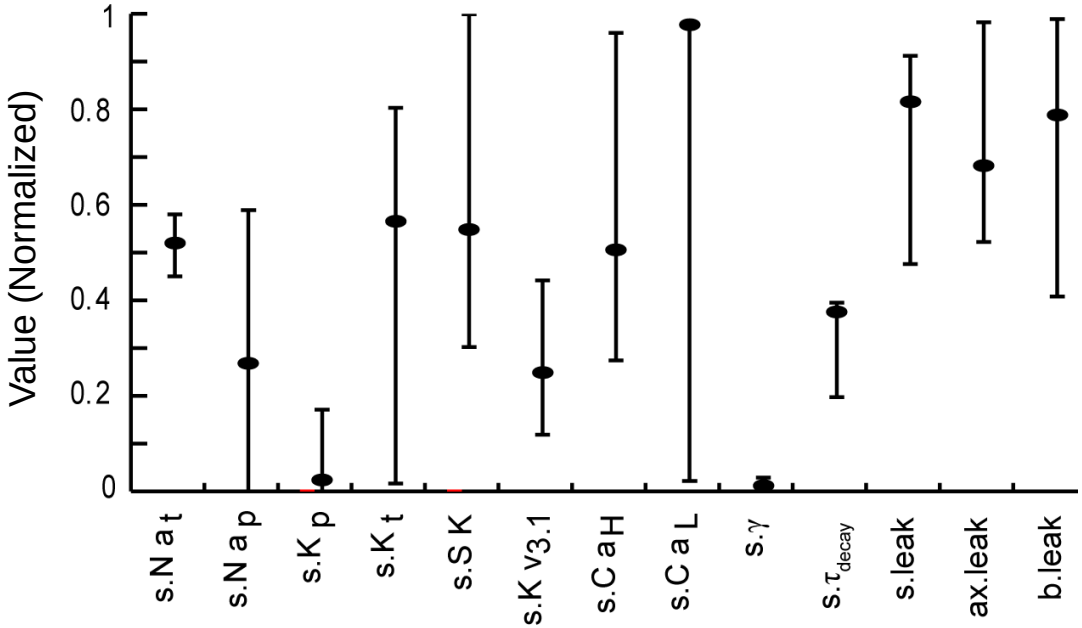
Models of Neuronal Firing



(Yao et al, 2021)

Biophysical Mechanisms

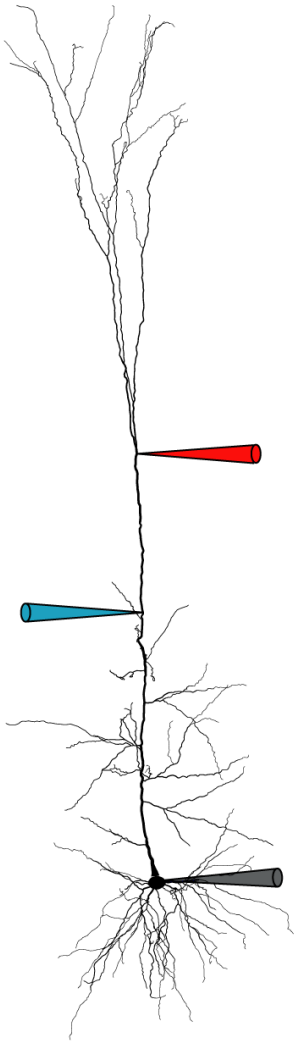




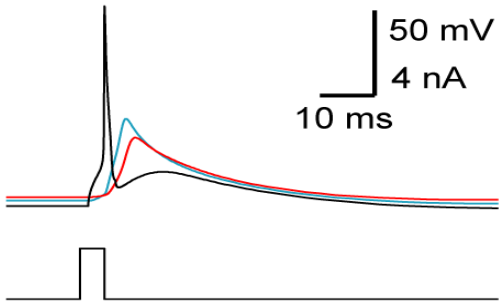
Parameter ranges from ~150 models for somatic firing

(Hay et al, 2011)

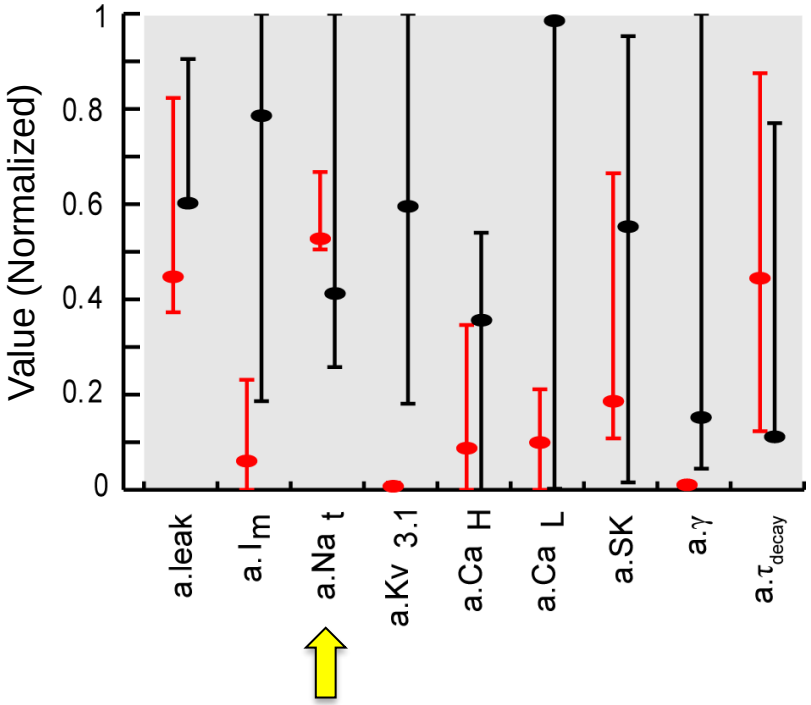
Biophysical Mechanisms



Backpropagating spikes



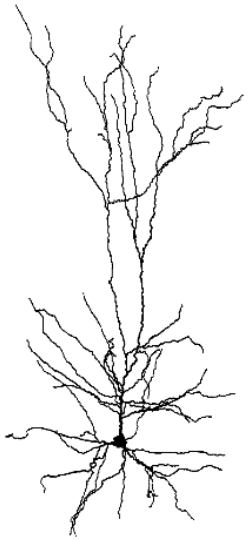
~150 models for somatic spiking
vs.
~900 models for dendritic spiking

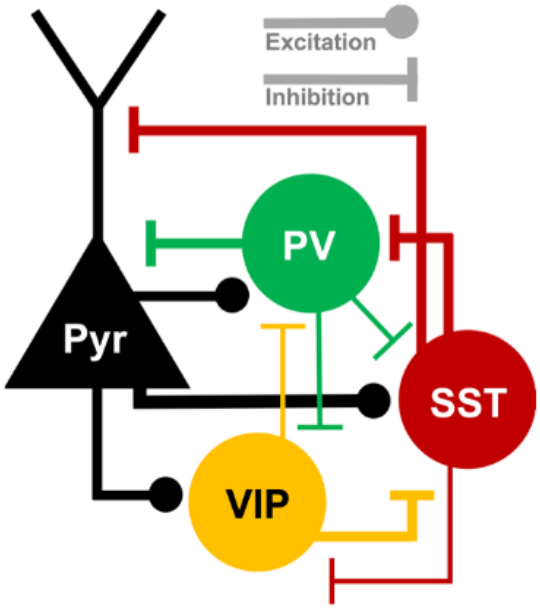


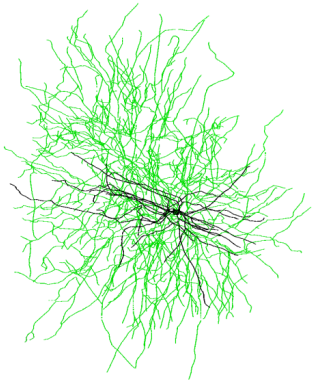
Dendritic Na^+ conductance in backpropagating spikes

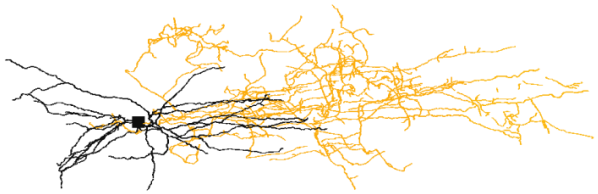
(Hay et al, 2011)

Microcircuit Connectivity

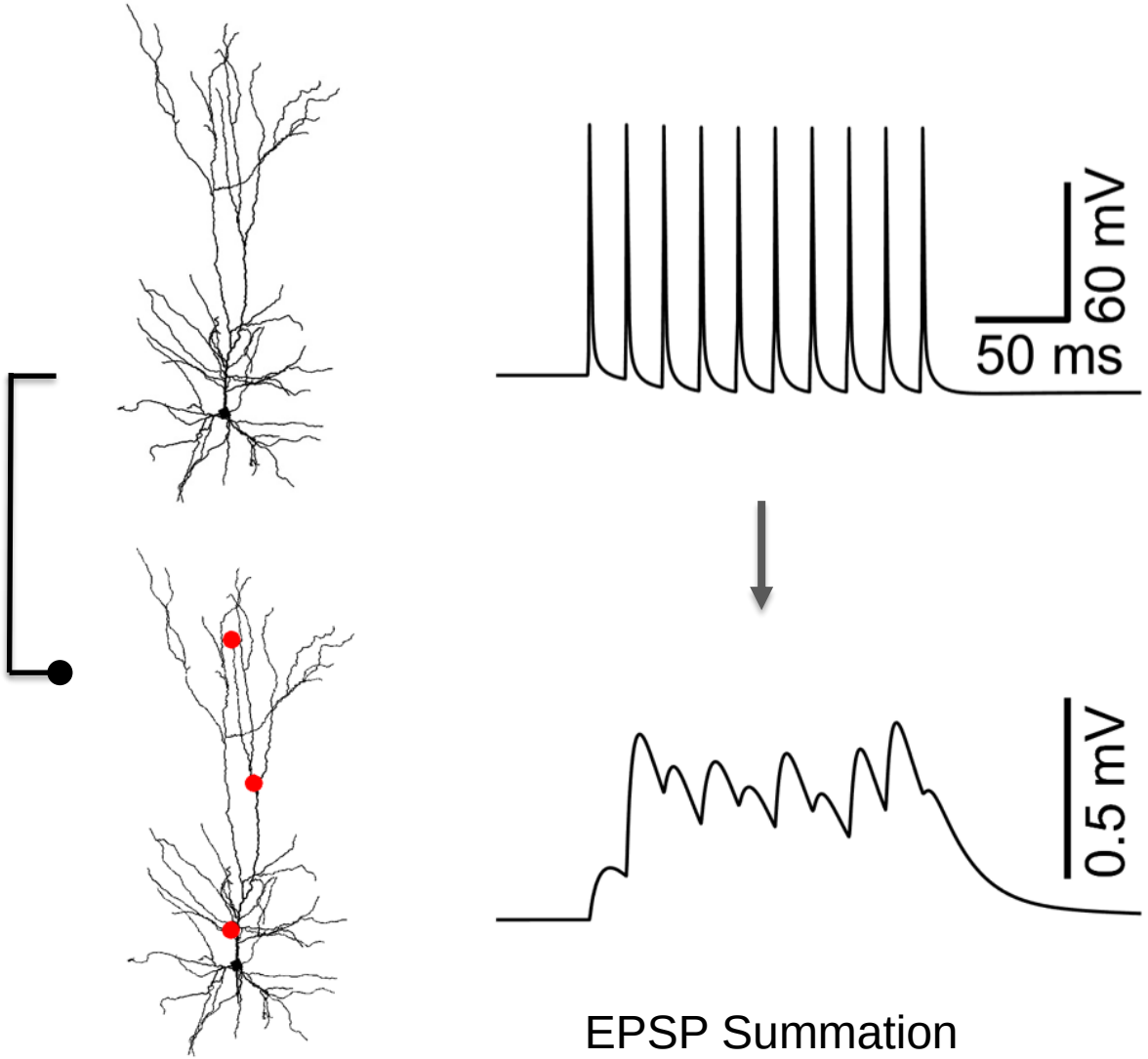








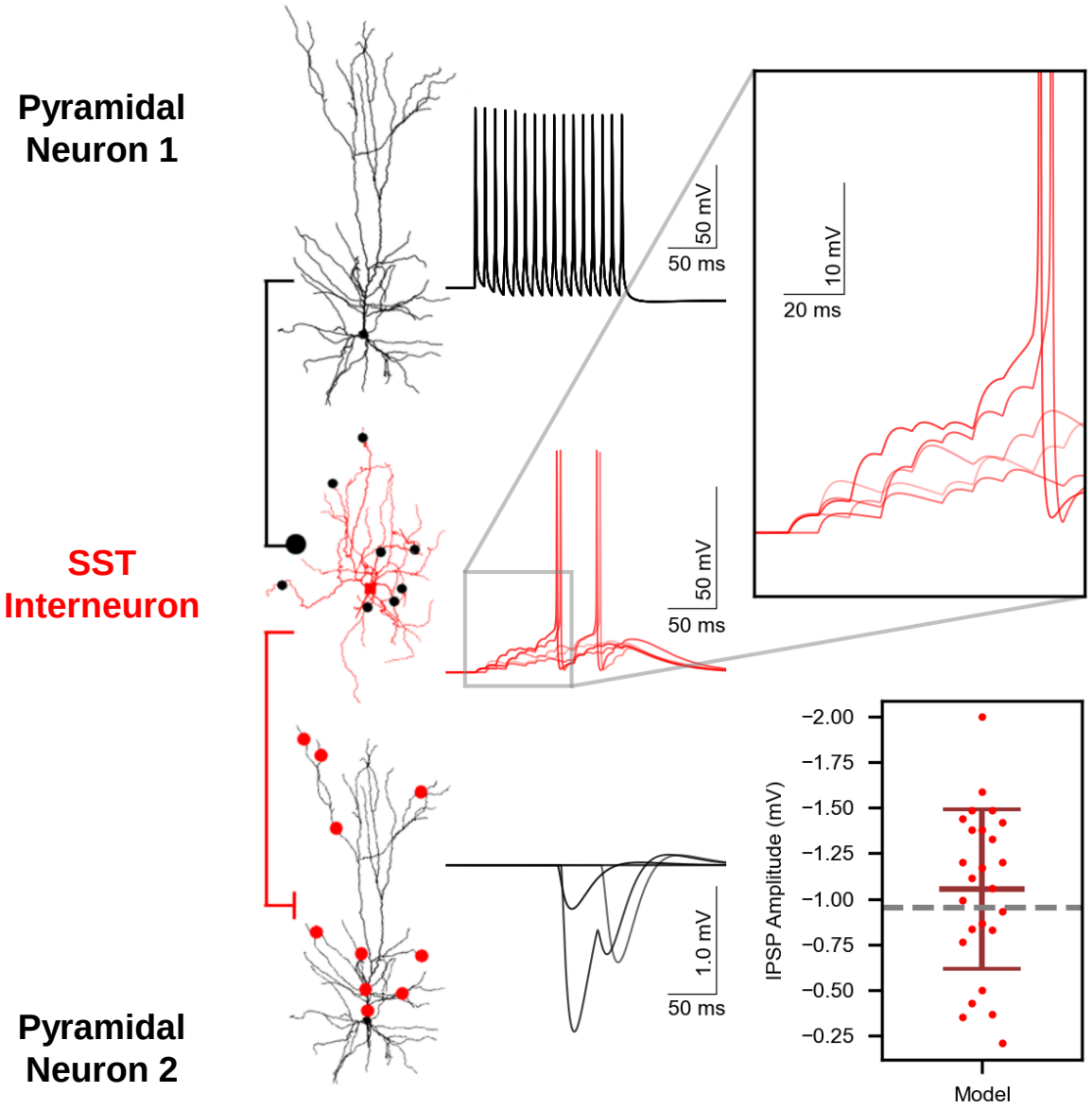
Excitatory Connections



EPSP Summation
(Short-term Dynamics)

(Yao et al, 2021)

Lateral Inhibition

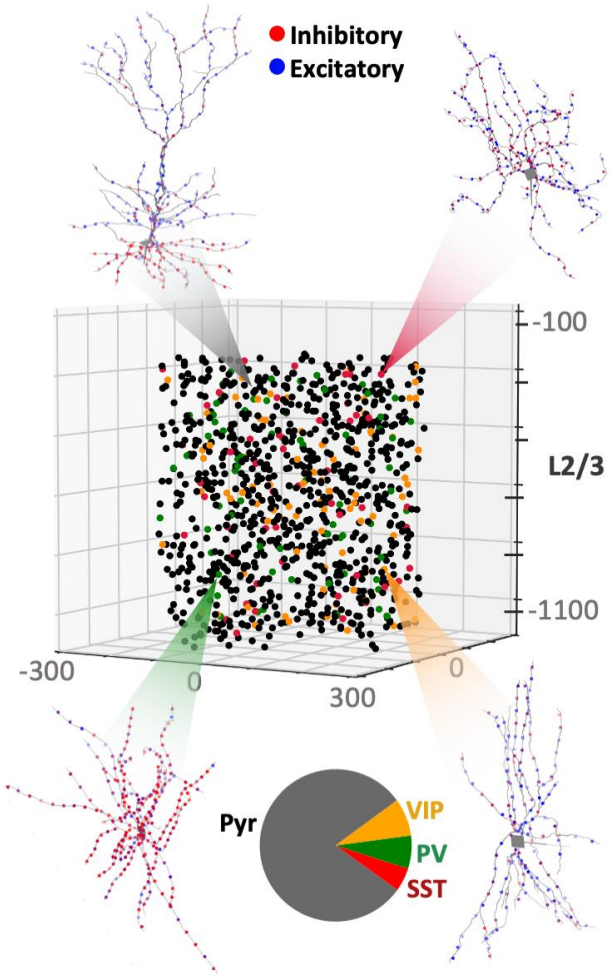


Facilitating Summation

(Yao et al, 2021)

Microcircuit Models – cell proportions

Cortical Layer 2/3 Microcircuit Models

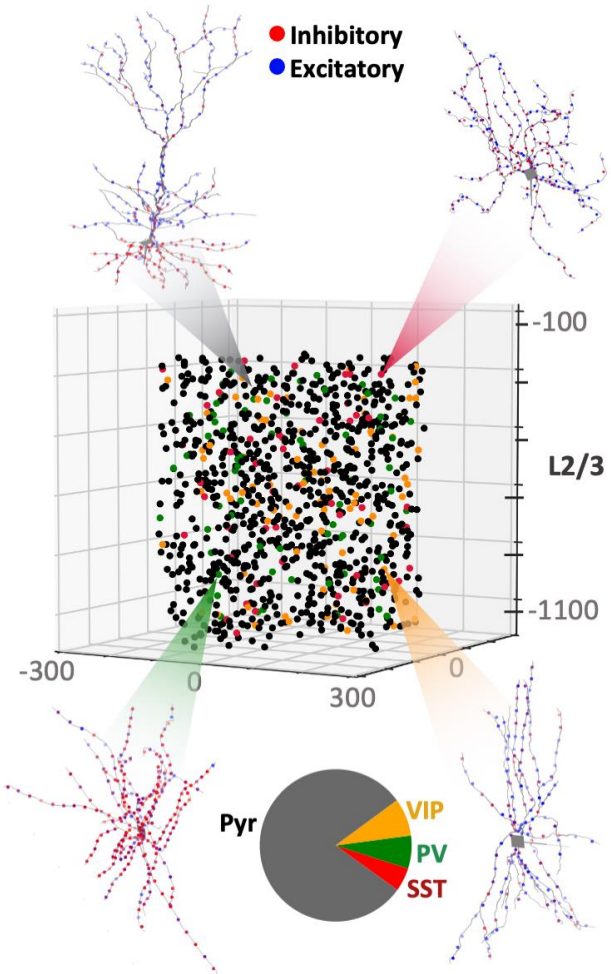


- 20% interneurons in somatosensory microcircuits
- 30% interneurons in prefrontal microcircuits
- Slightly higher % in human vs. mice

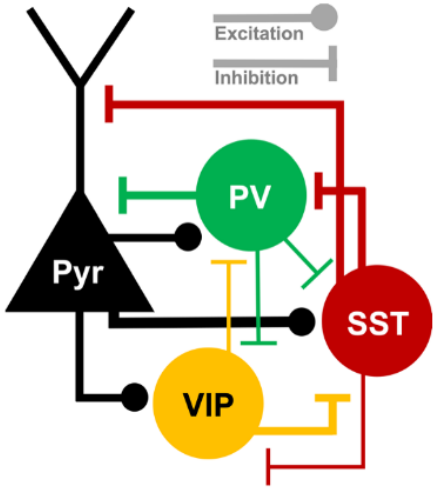
(Yao et al, 2021)

Microcircuit Models – connectivity

Cortical Layer 2/3 Microcircuit Models



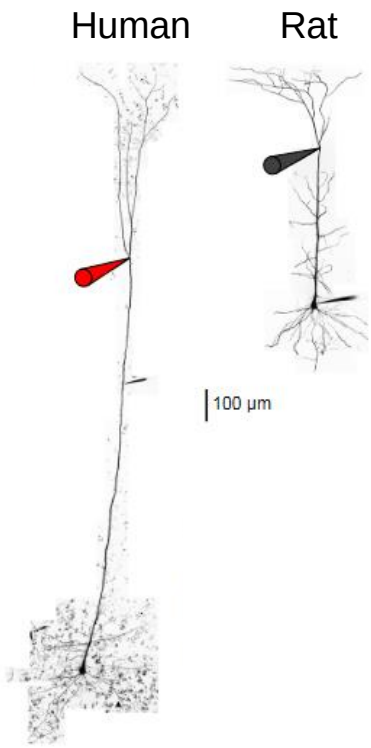
- Pyr→Pyr, p = 0.15 (literature)
- Type-specific probabilities
  (Allen Brain, Blue Brain)



(Yao et al, 2021)

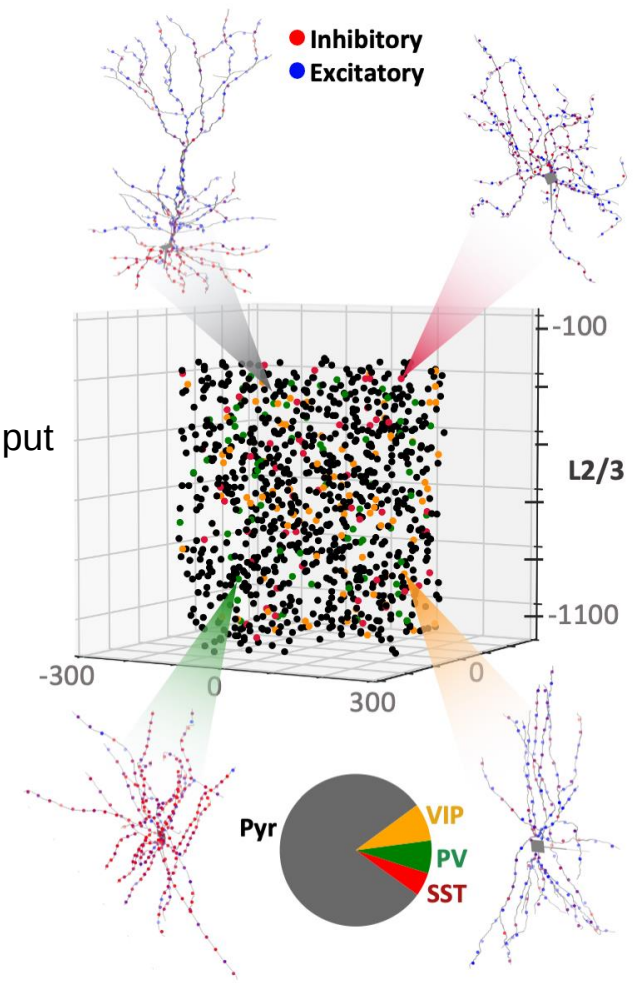
Human vs. Rodent Cortical Microcircuits

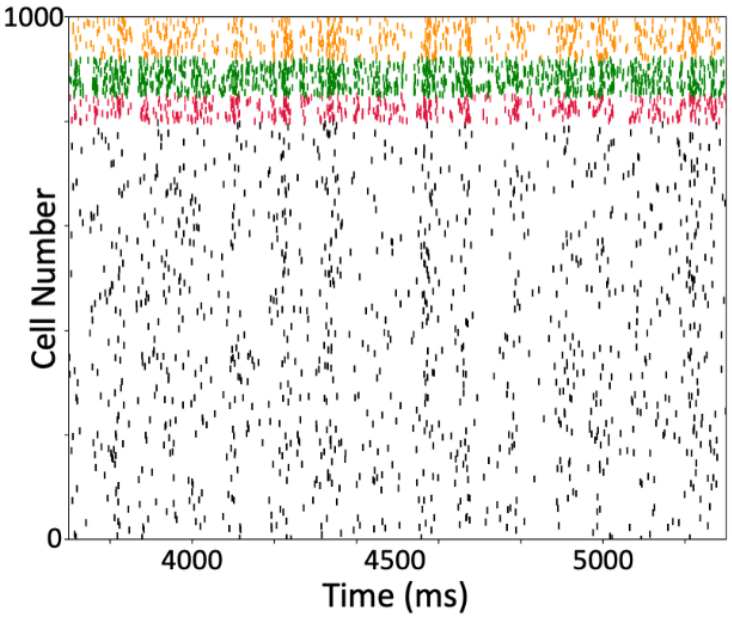
- Larger neurons
  – altered input integration
- Stronger inhibitory synapses
- Larger layer dimensions
  - altered EEG contributions?
- Model prediction power for human disorders

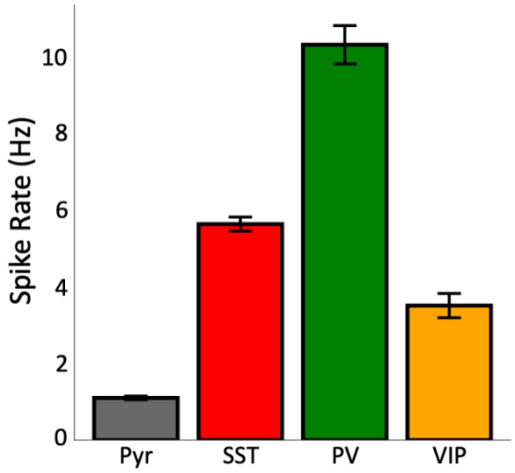


Simulating Baseline Microcircuit Activity

Background input (random)





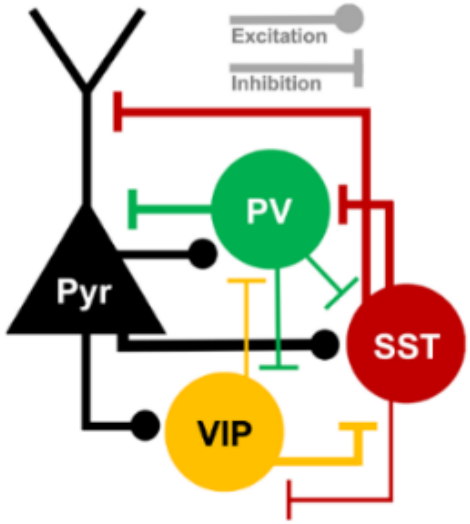


Model reproduces baseline rates across neuron types

(Yao et al. 2021)

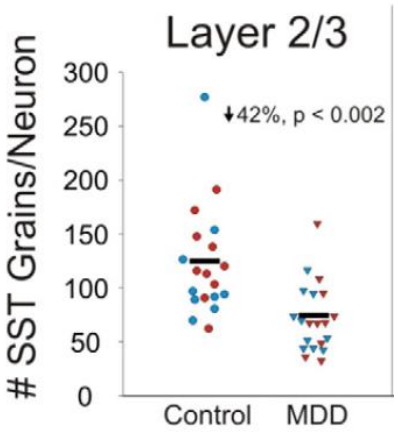
Altered Inhibition in Depression

- MDD – major depressive disorder (depression)
- Leading cause of disability worldwide
- 66% of patients resistant to SSRI treatment
- Altered inhibition associated with treatment-resistant depression



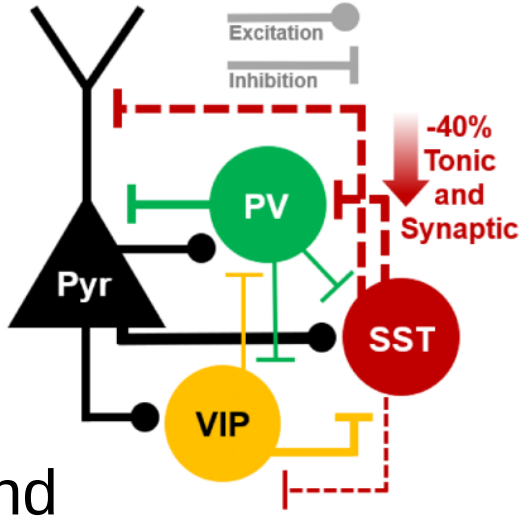
Reduced SST Inhibition in Depression

SST Expression in SST⁺ Interneurons



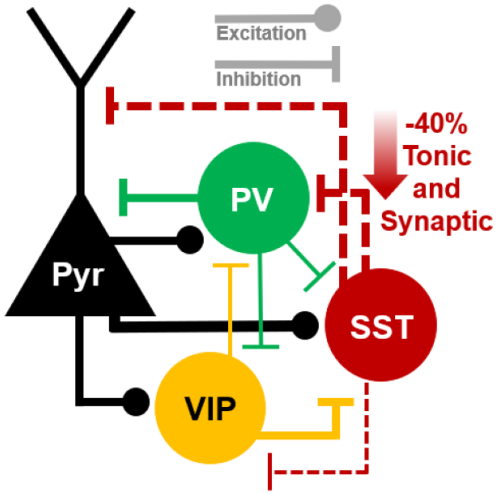
SST Interneuron

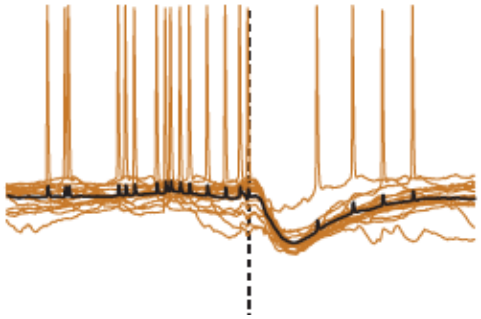
(Seney et al. 2015)



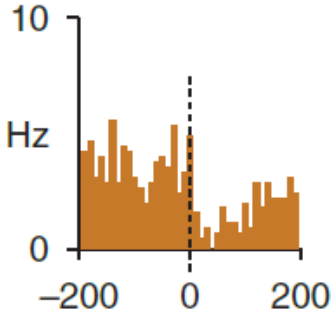
- Postmortem tissue, healthy vs. depression
- ~40% reduction across layers
- Supported by pharmacological (prevot 2019) and optogenetic (Fee 2021) studies in rodent models

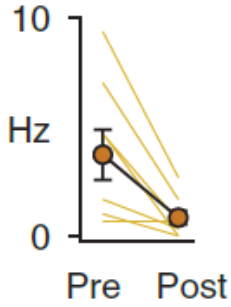
SST - Baseline vs Response





(stimulus)

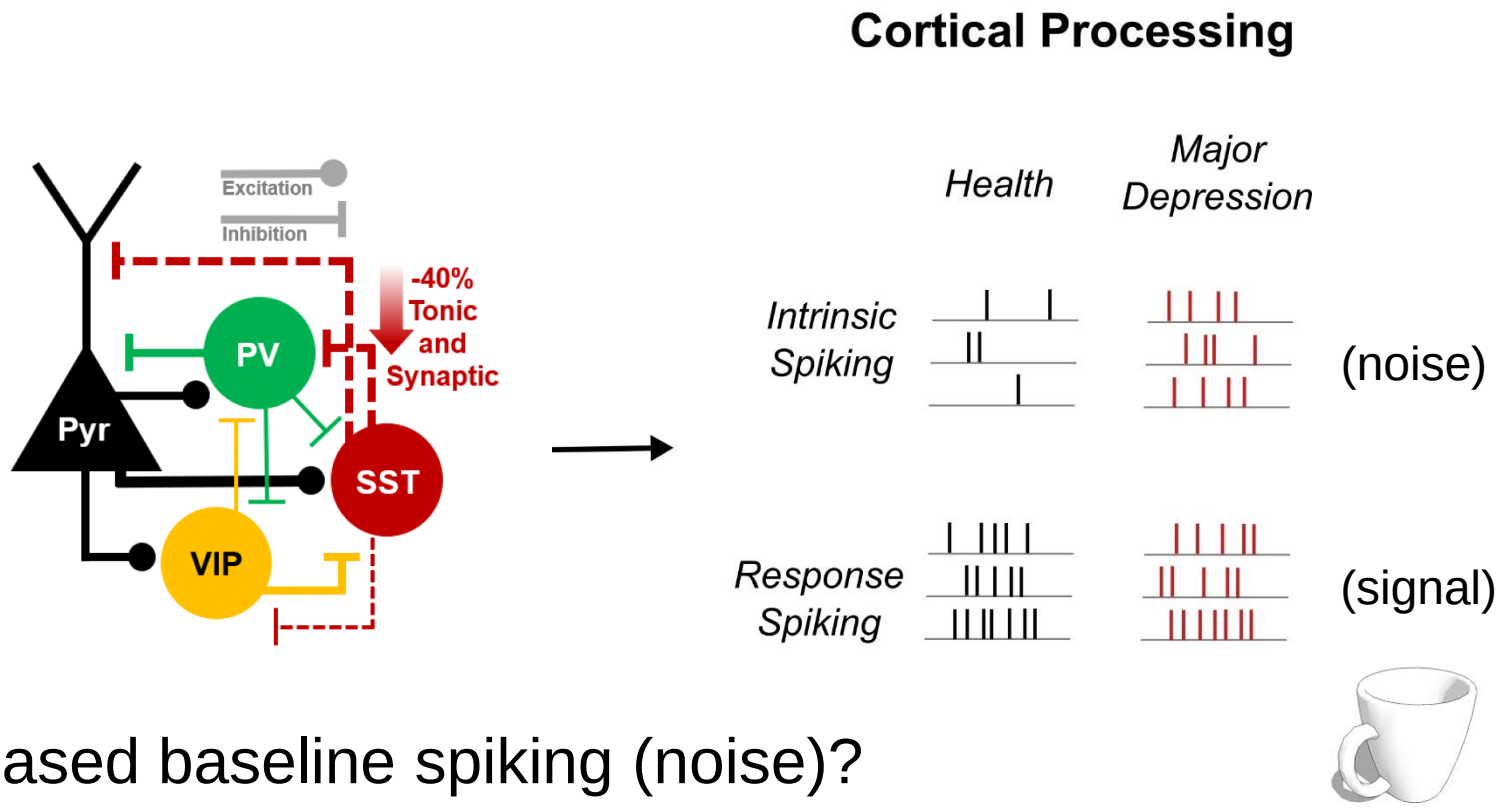




Gentet et al. 2012

- SST interneurons mediate baseline inhibition
- Silent during early response

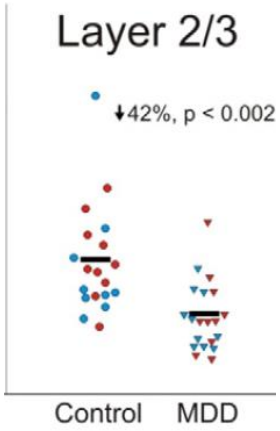
Reduced SNR in depression?

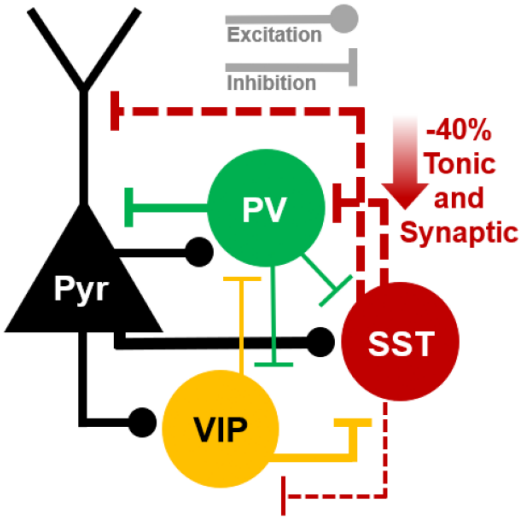


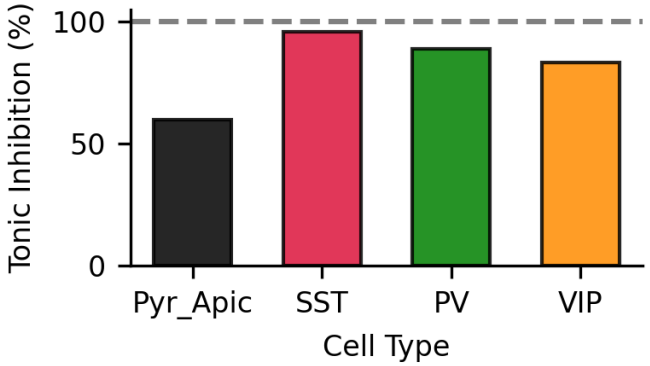
- Increased baseline spiking (noise)?
- Reduced signal-to-noise ratio, detection quality?
- May play a role in rumination

Depression Microcircuit Models

SST expression data

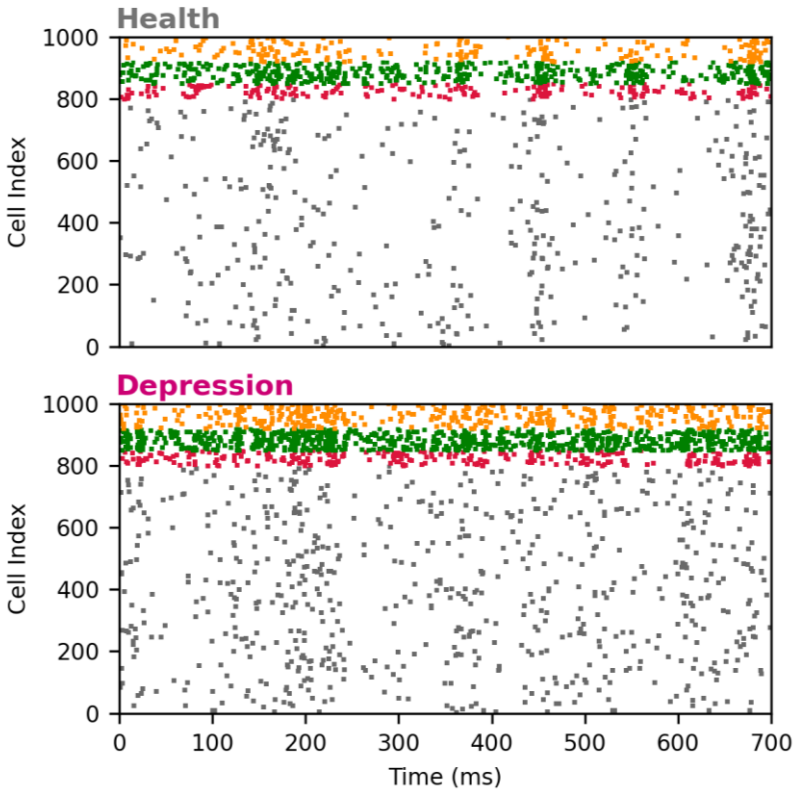


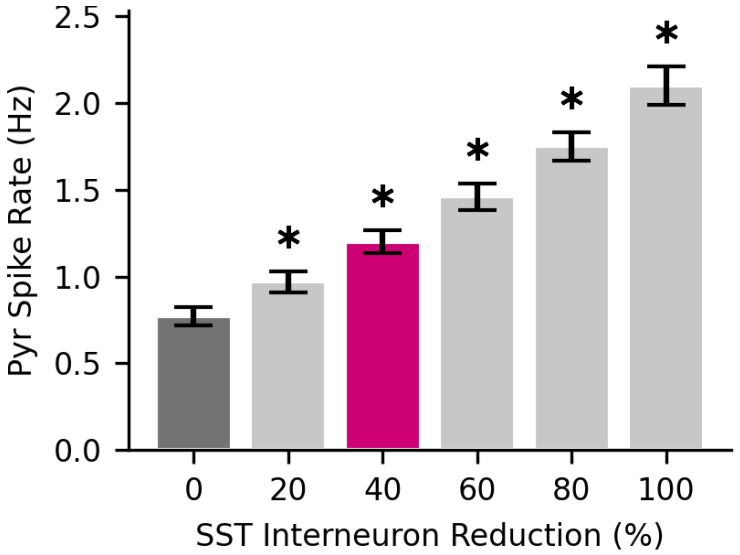




(Yao et al. 2021)

Increased Baseline Activity in Depression Microcircuits

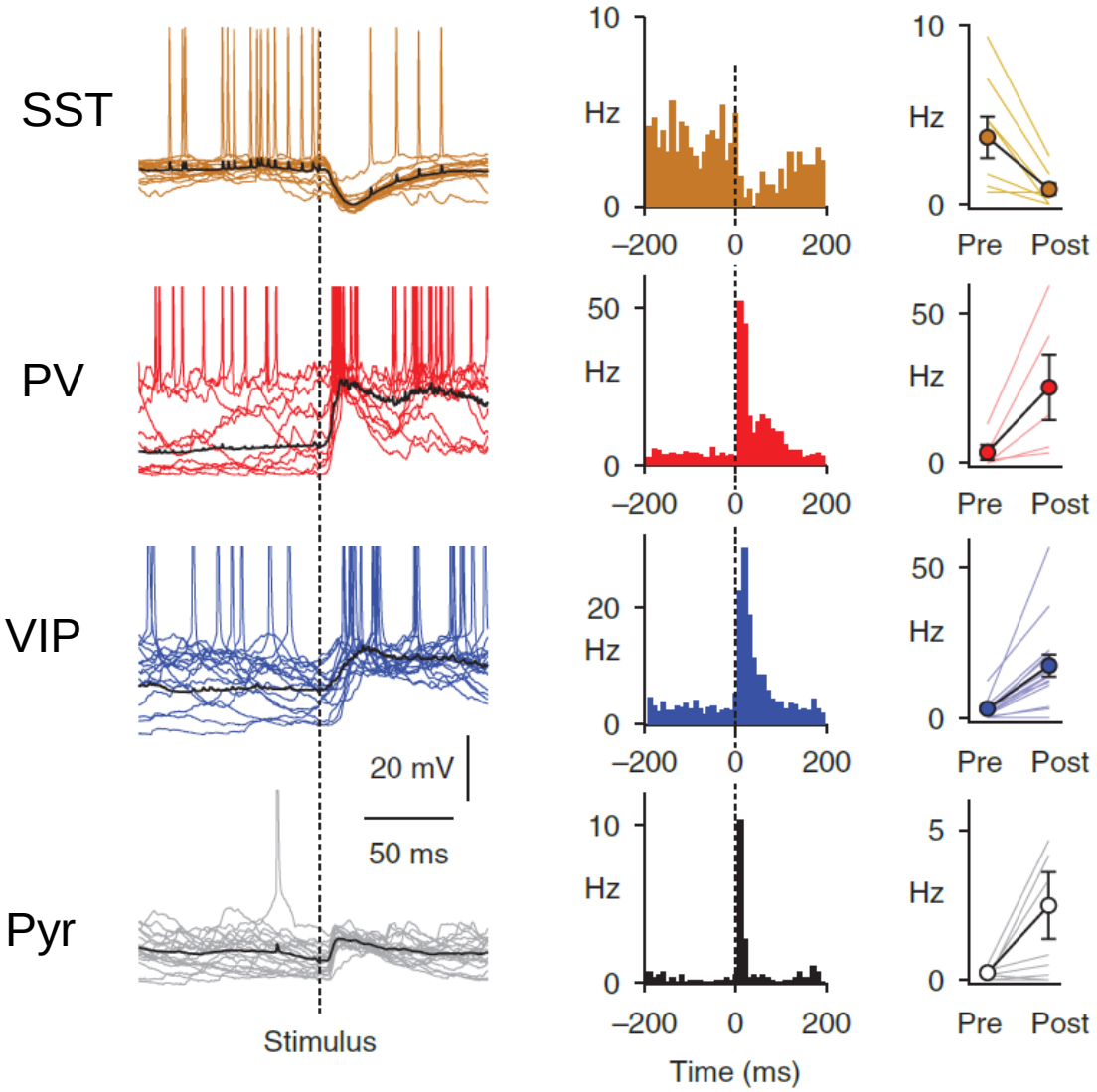




~50% increased firing in depression

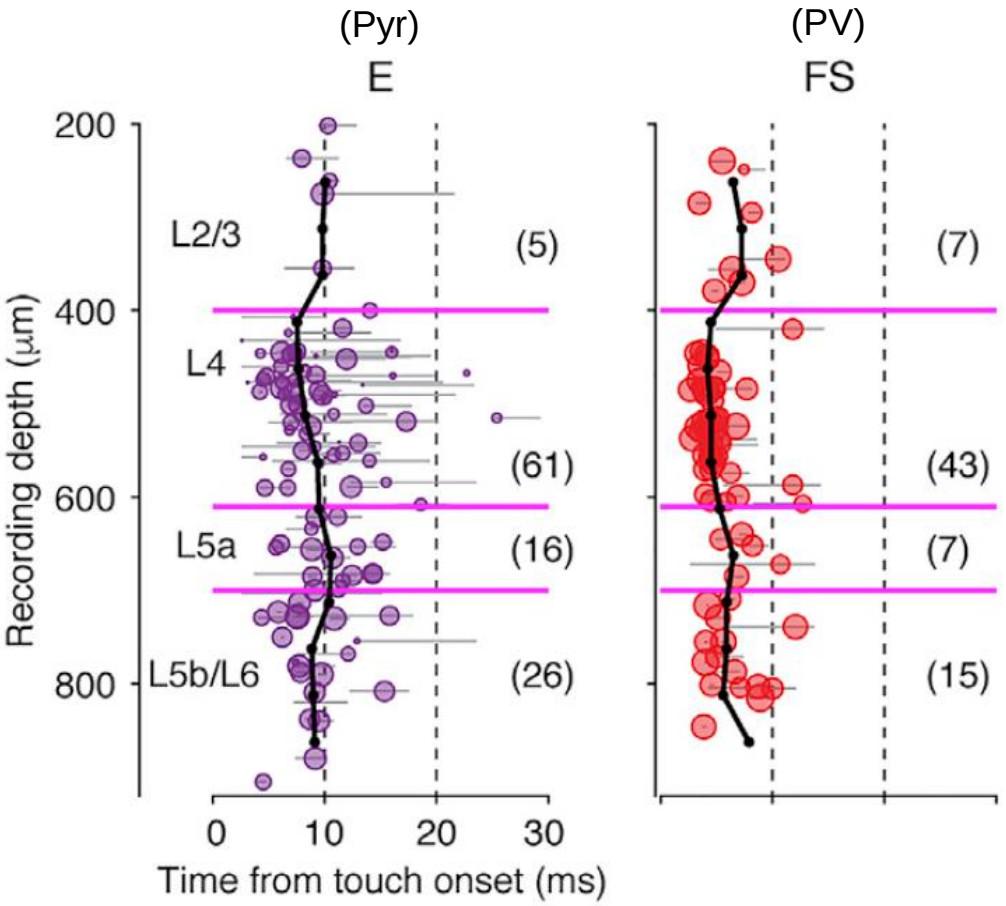
(Yao et al. 2021)

Baseline vs Response Activity



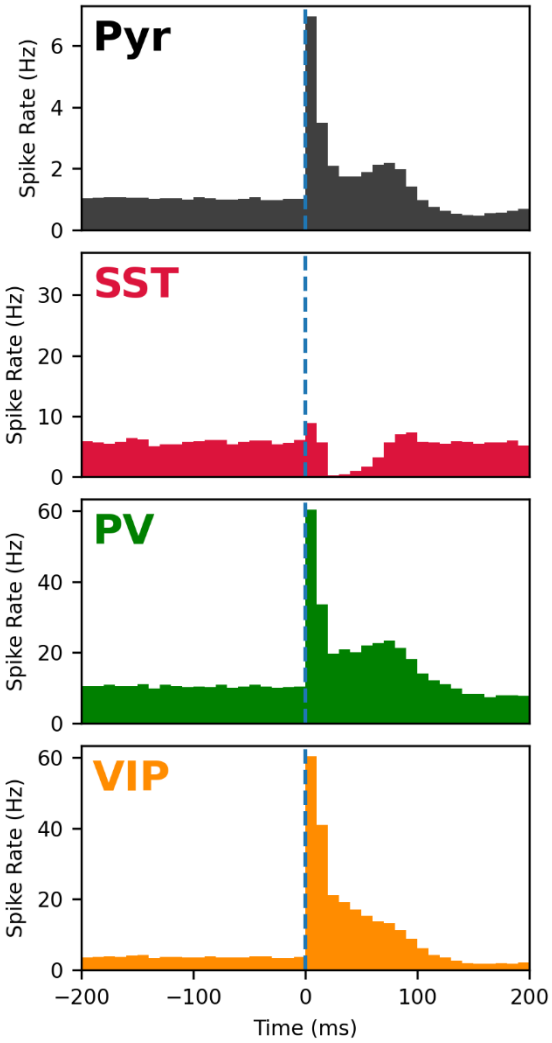
Gentet et al. 2012

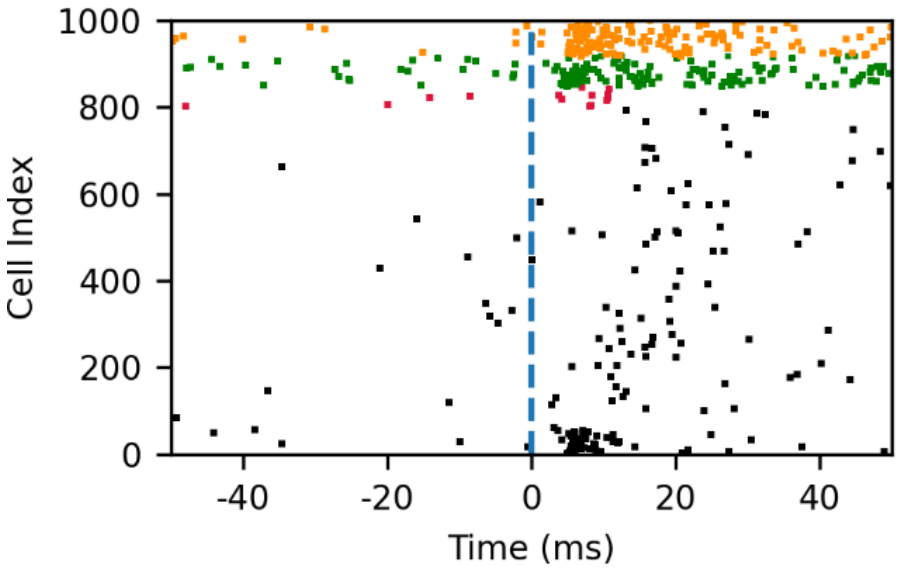
Response Latency



Yu et al. 2019

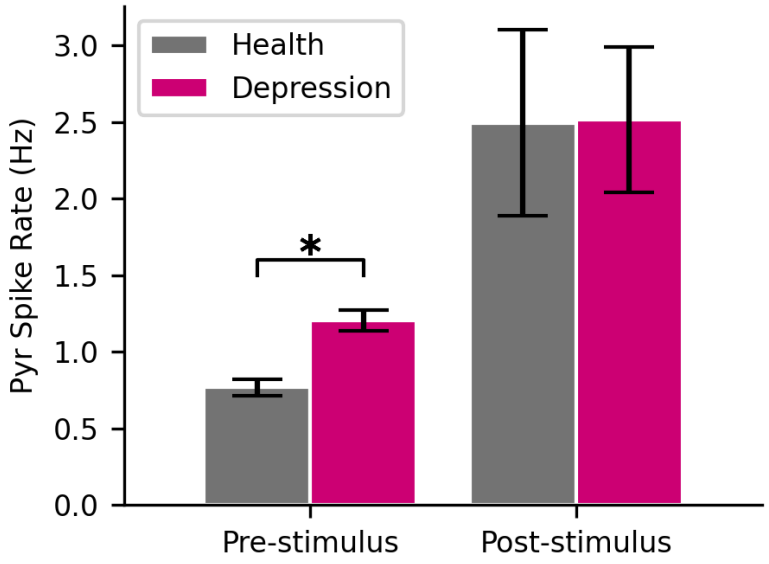
Simulating Microcircuit Response

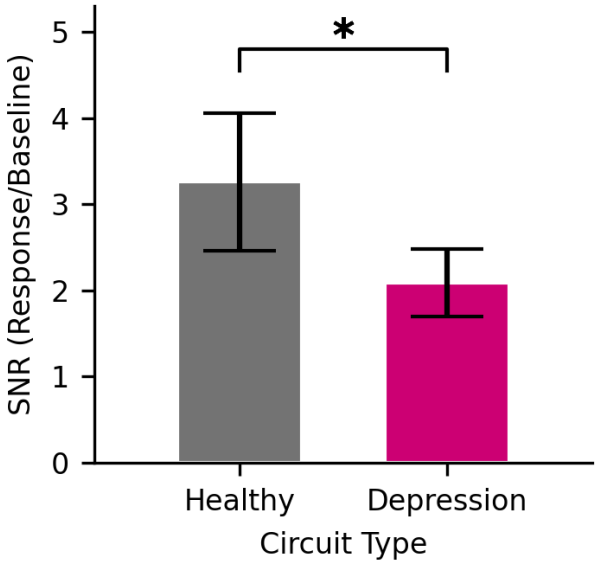




(Yao et al. 2021)

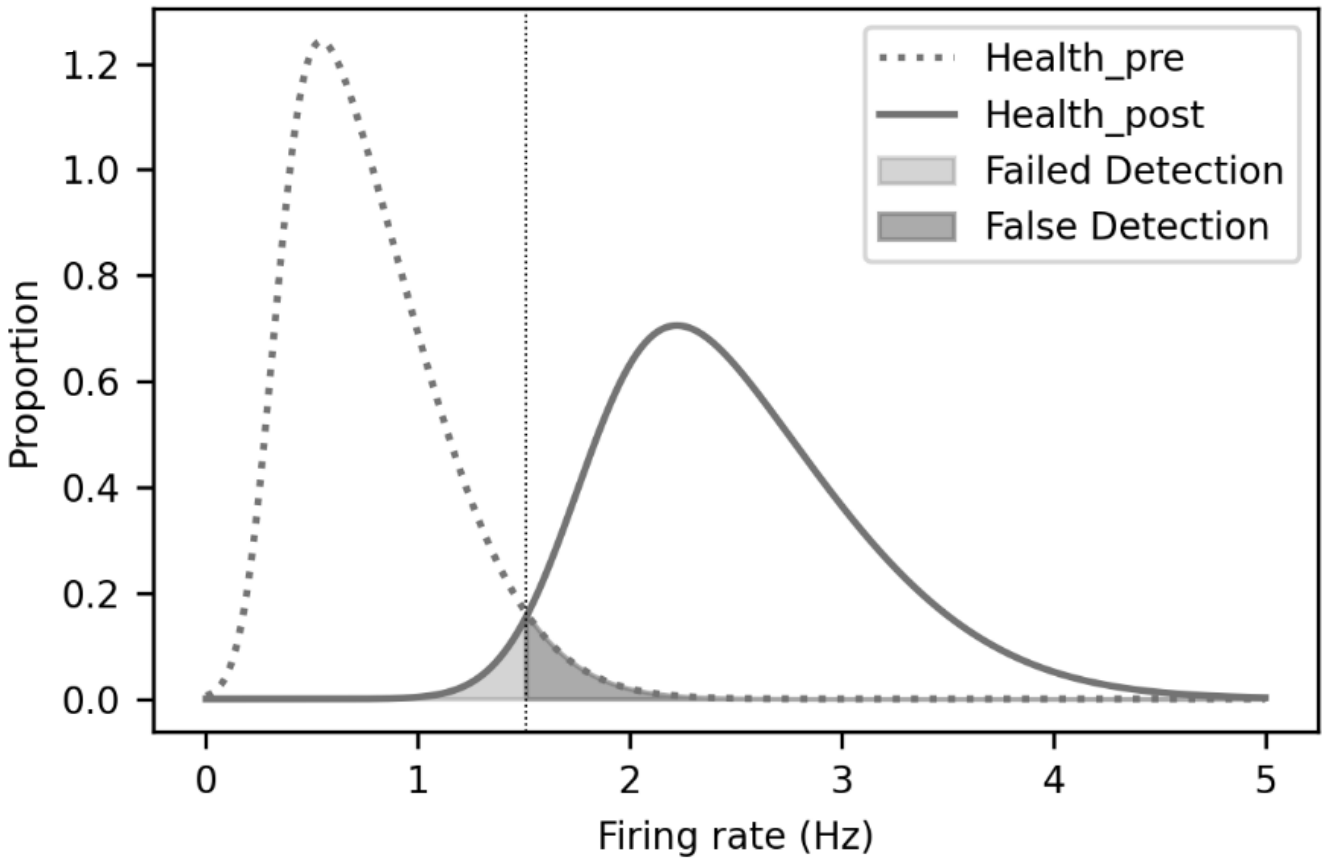
Reduced Cortical SNR in Depression





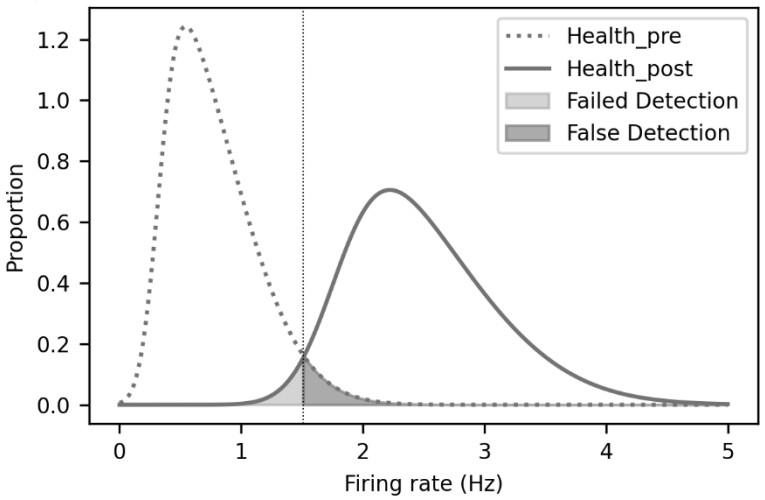
(Yao et al. 2021)

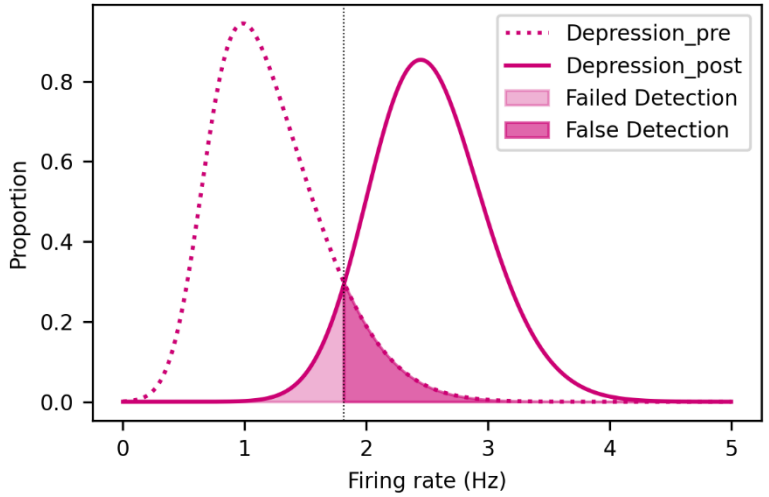
Failed/False Stimulus Detection

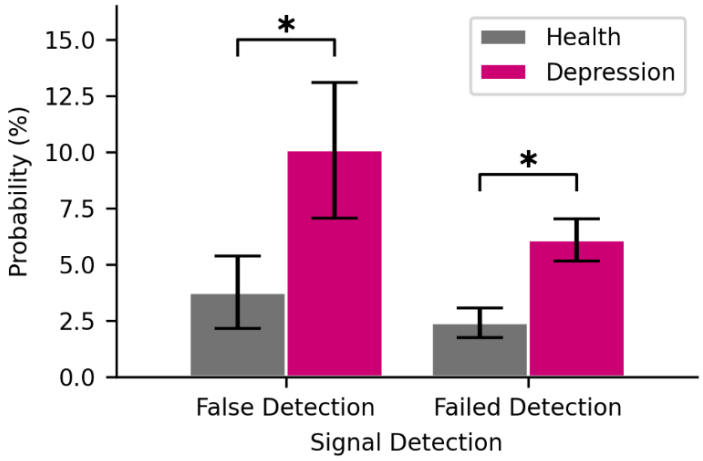


(Yao et al. 2021)

Failed/False Detection in Depression







(Yao et al. 2021)

Measurable Deficits

CPT parameters (mean ± S.D.) of controls and unmedicated depressed patients and differences in CPT performance between both groups

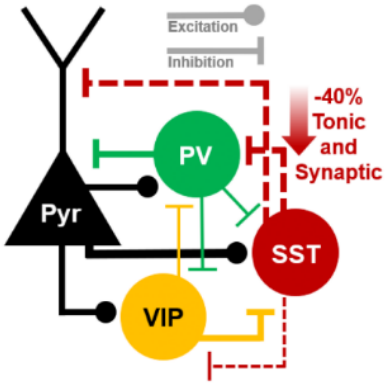
	Controls ($n = 73$)	Depressed patients ($n = 43$)	Delta	P-value
Reaction time (ms)	405.7 ± 50.3	448.1 ± 48.2	−42.4	< 0.05[a]
Omission errors (n)	0.19 ± 0.54	7.26 ± 10.98	−7.07	< 0.001[b]
Commission errors (n)	1.00 ± 1.39	2.35 ± 2.90	−1.35	< 0.05[b]

Similar deficits seen in continuous performance test (CPT) in depression (visual attention)

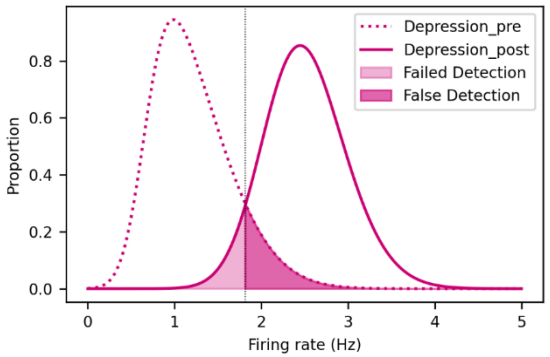
(Koetsier et al, 2002)

Modeling Brain Microcircuits
Applications in Mental Health

- Establish target mechanisms for new treatments



- Improve patient stratification



Krembil Centre for Neuroinformatics
Summer School 2021

Day 4 – Session 2

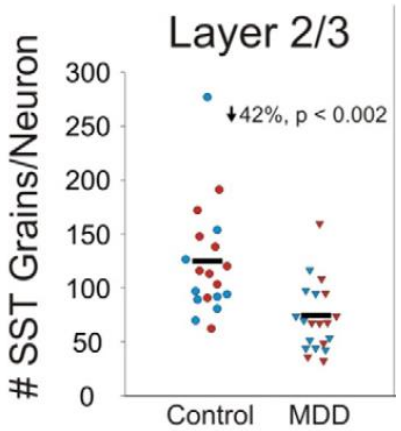
Simulating EEG from brain microcircuits in mental health

Etay Hay

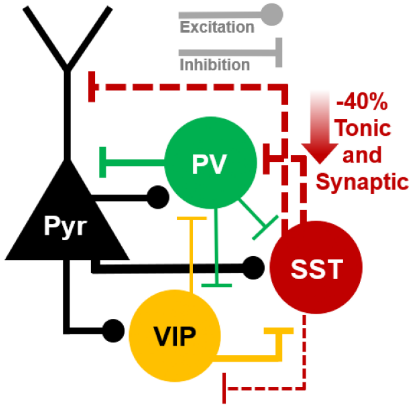
camh | Krembil Centre for Neuroinformatics
UNIVERSITY OF TORONTO

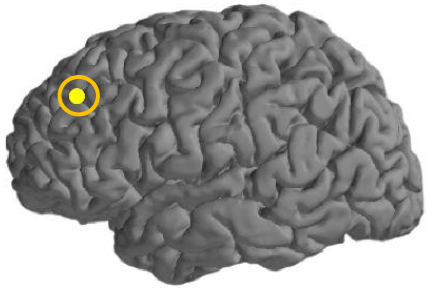
From Cellular Mechanisms to Brain Microcircuit Signals

Altered Mechanisms in Depression

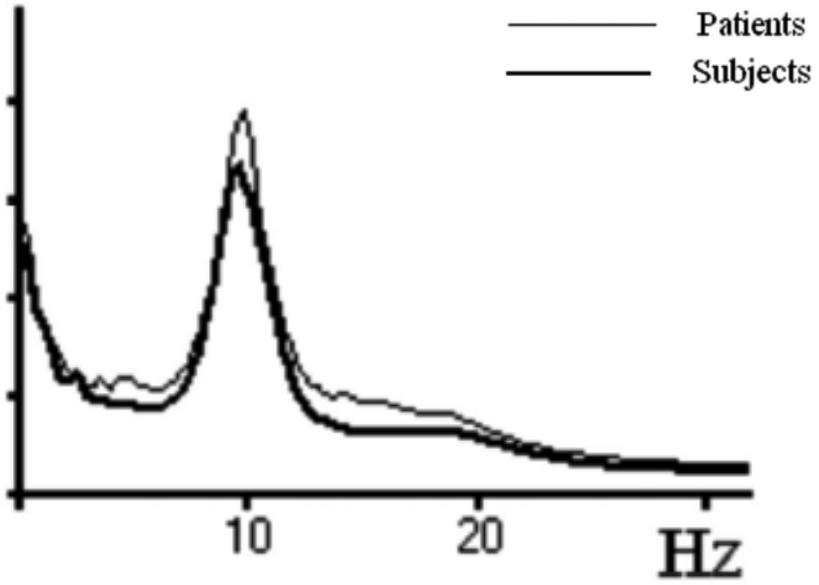


EEG Biomarkers?





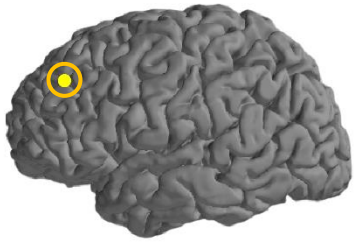
EEG Biomarkers in Depression



- Increased spectral power in early Depression
- EEG - cost-effective, temporal resolution

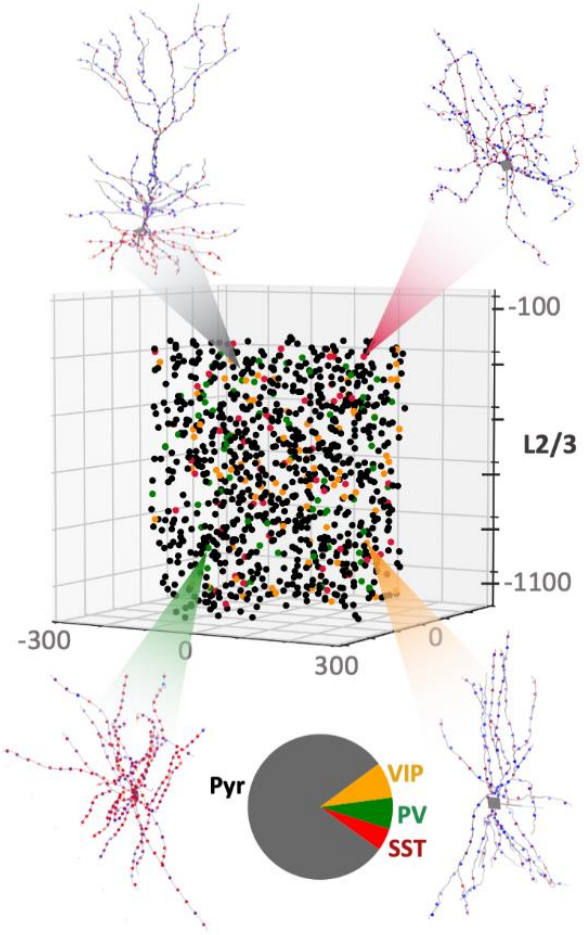
(Grin-Yatsenko et al, 2009)

Simulating EEG Signals

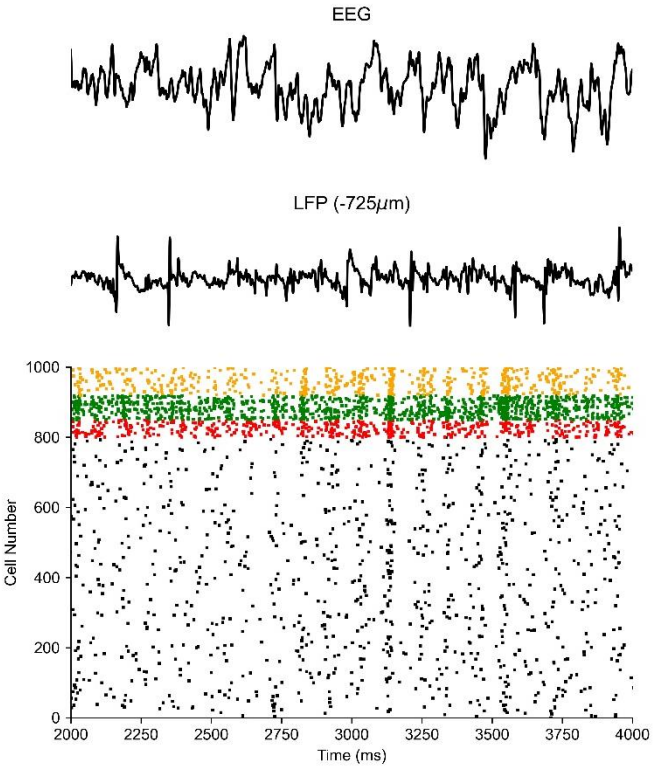


Simulated in LFPy and NEURON

3D Microcircuit Model

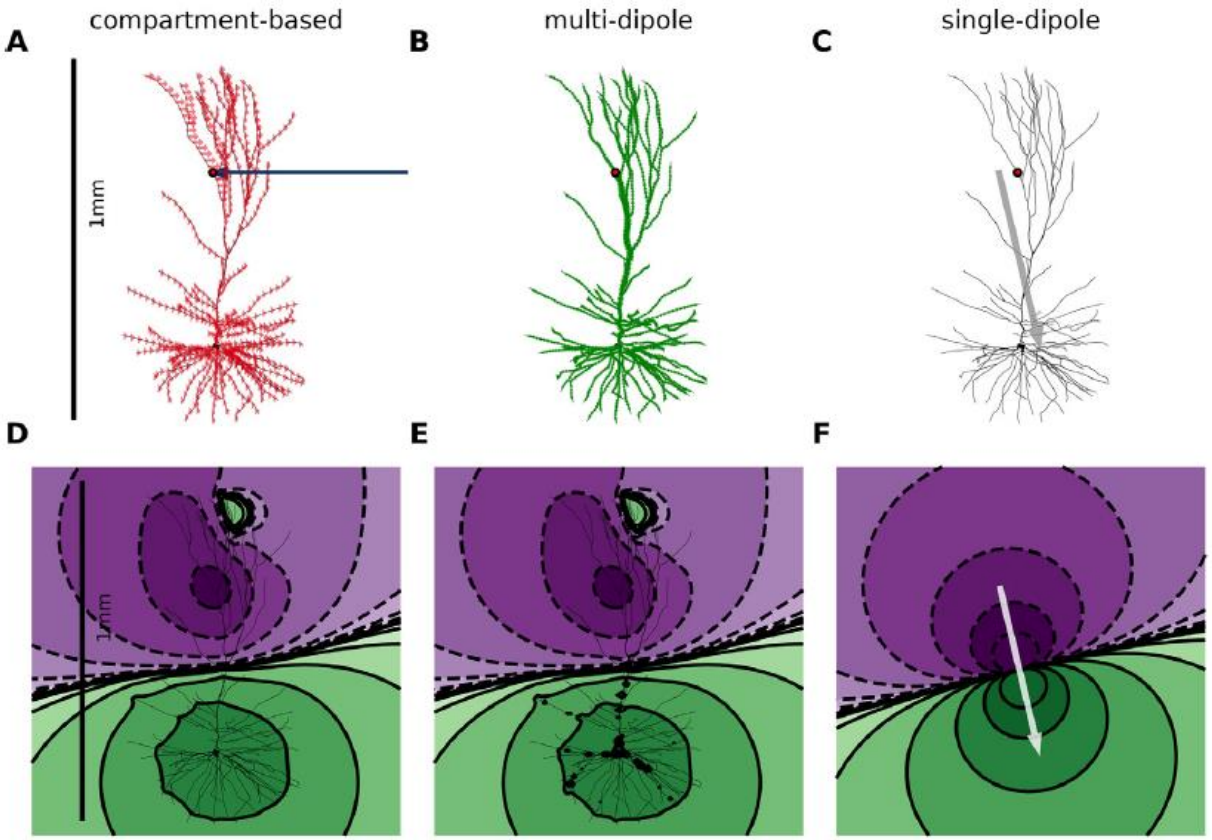


Simulated EEG and LFP



(Mazza et al. 2021, in preparation)

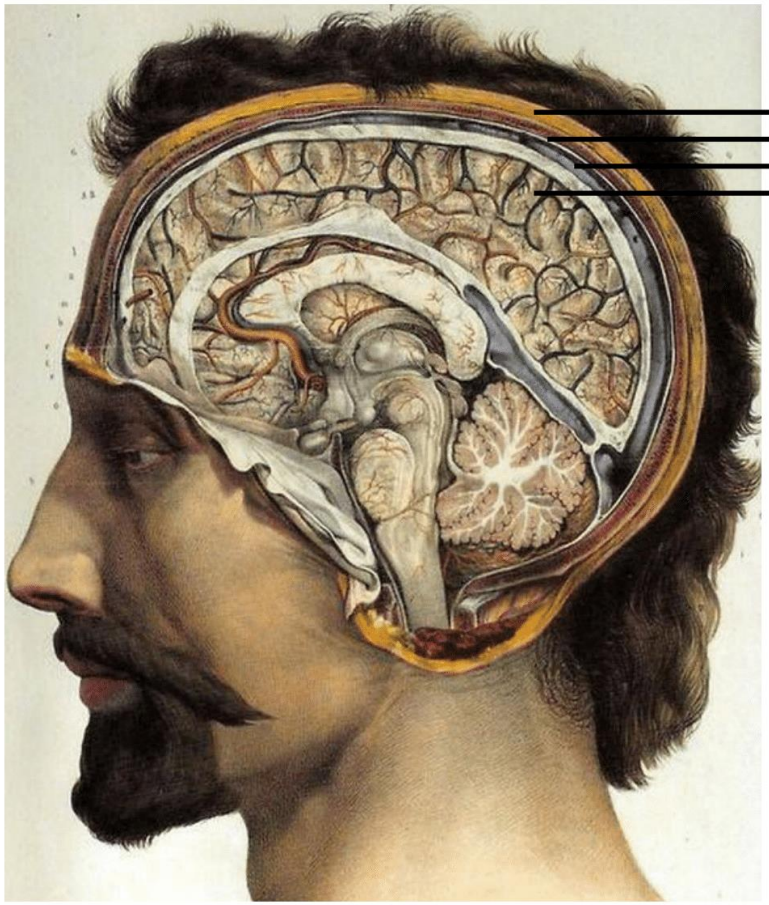
EEG Calculation

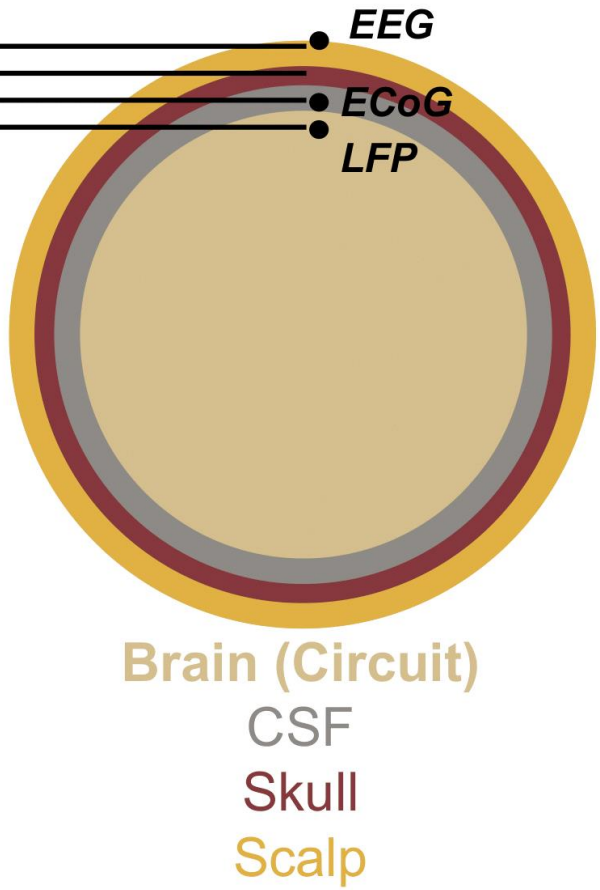


(Naess et al, 2021)

- Multi-compartmental EEG from neuron ~ single dipole
- LFPy tool – forward calculation

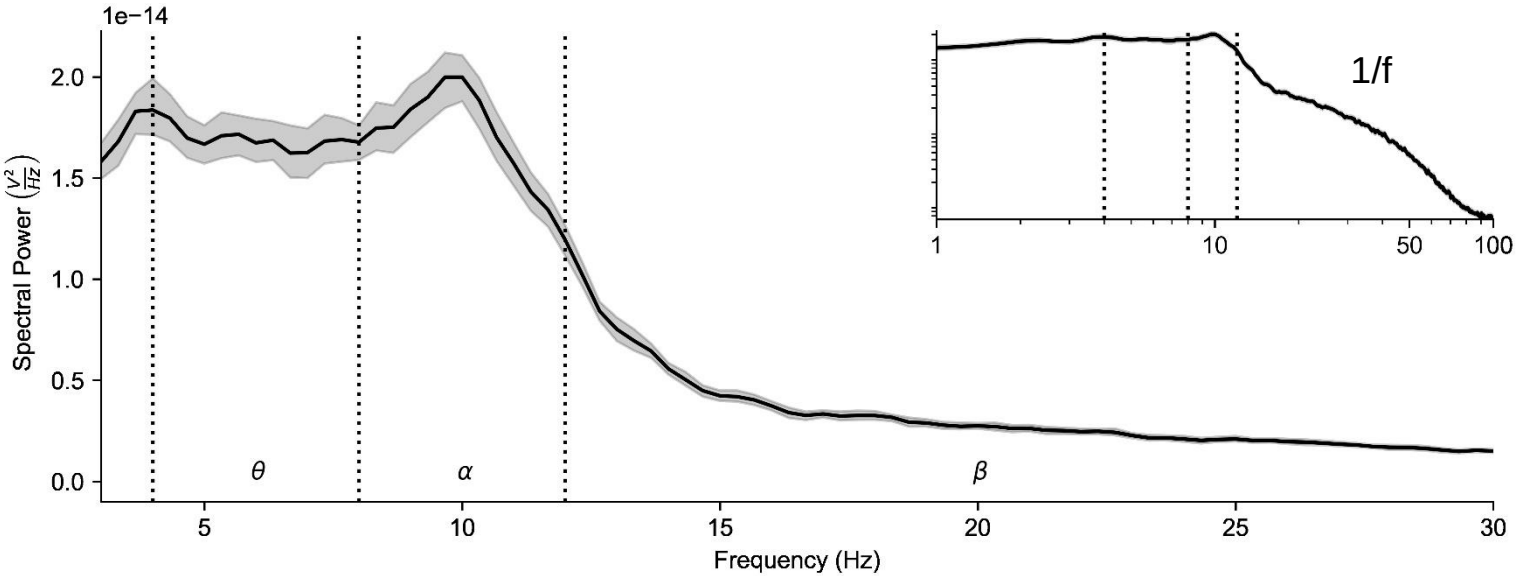
Four Sphere Head Model





Resting EEG Properties

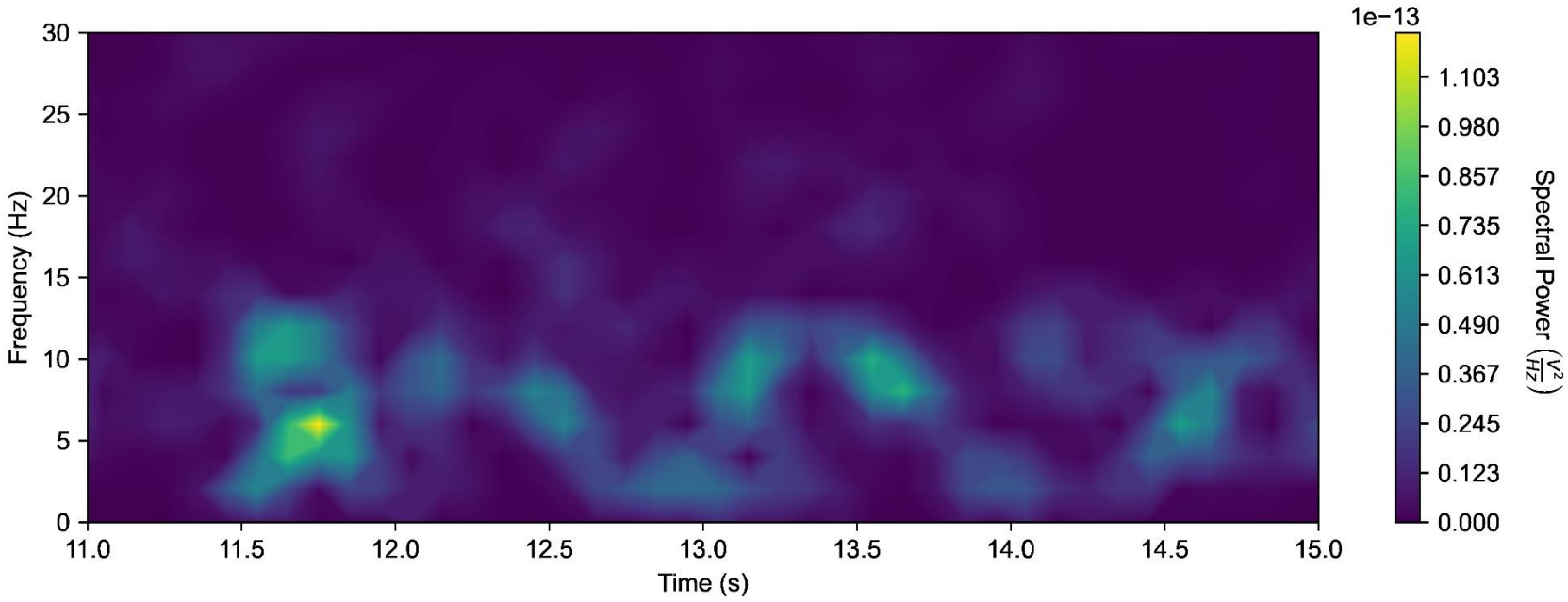
Microcircuit Model Validation



- Power spectral density (PSD)
- Theta and Alpha (4 – 12 Hz) peak power
- Log 1/f relationship

(Mazza et al. 2021, in preparation)

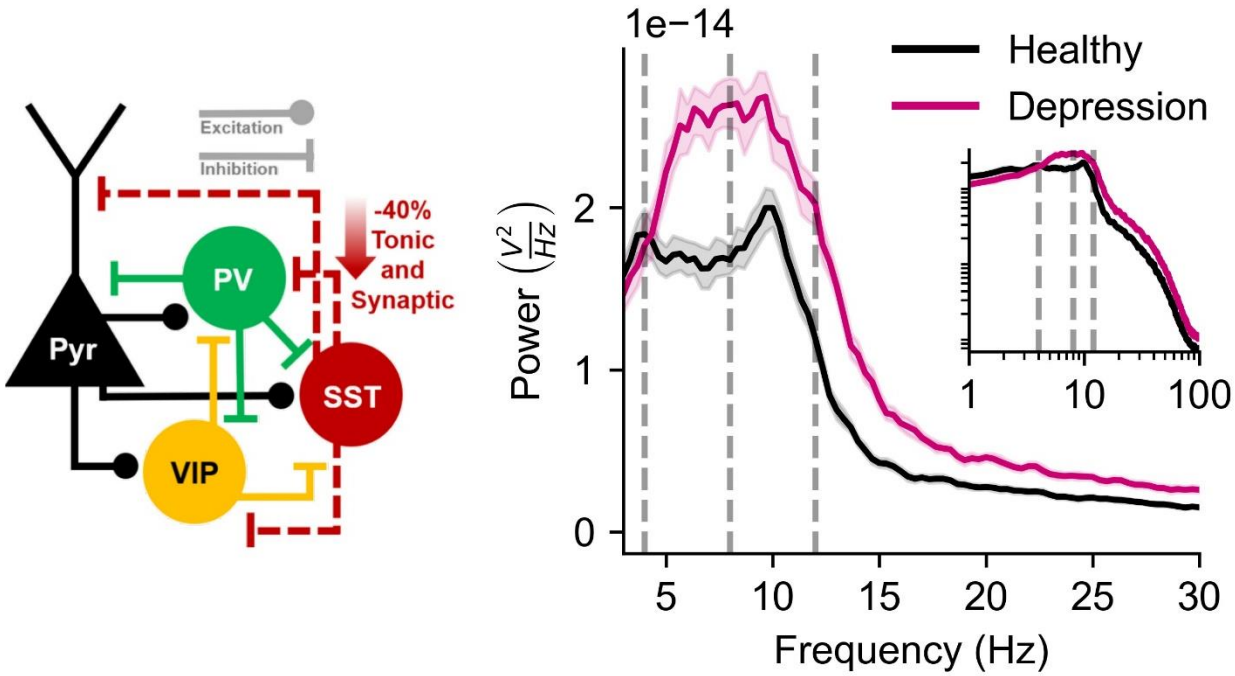
Microcircuit EEG Oscillations



- Spectrogram – frequency power in time
- Theta and Alpha (4 – 12 Hz) events
- In line with human *in-vivo* resting EEG

(Mazza et al. 2021, in preparation)

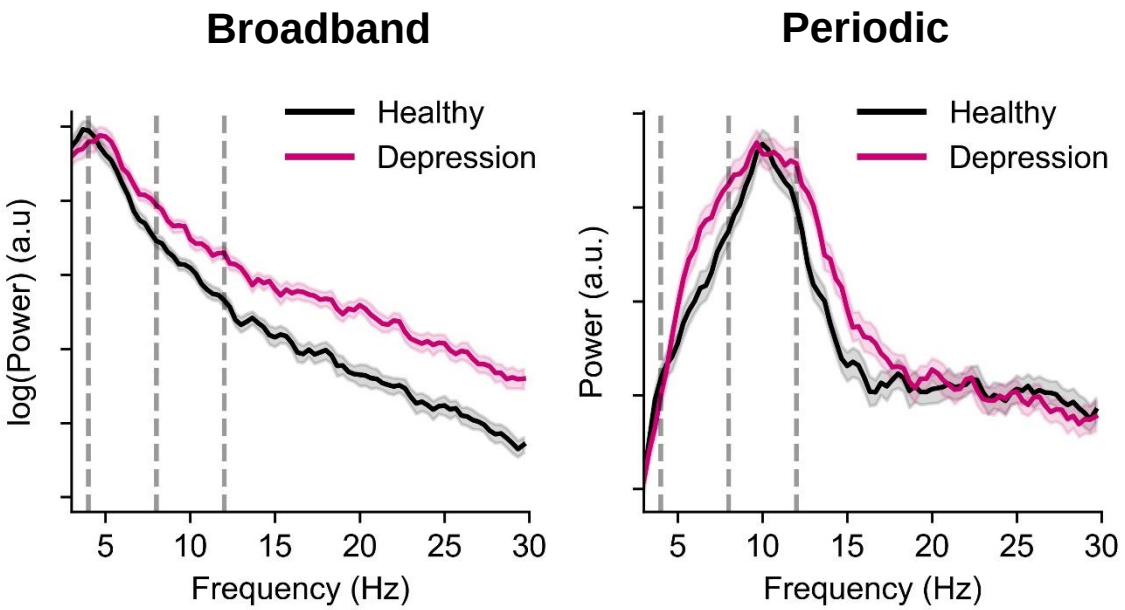
Simulated EEG in Depression



- Increased spectral power in depression
- Periodic vs. Broadband?

(Mazza et al. 2021, in preparation)

EEG Changes in Depression



- Increased broadband power
- Increased Theta (4 – 8 Hz) peak power
- Biomarkers of reduced SST inhibition

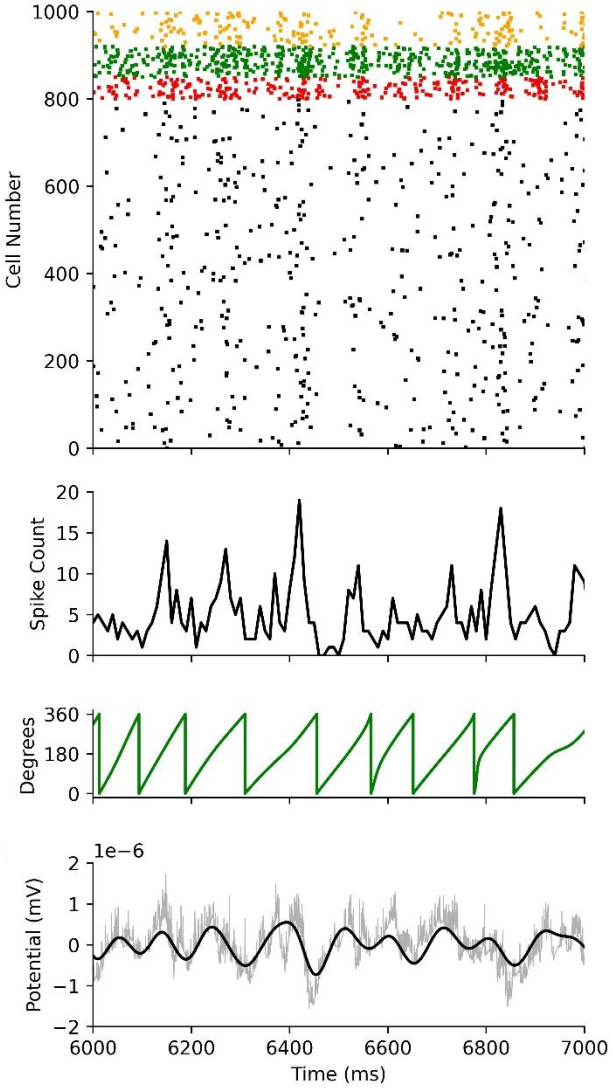
(Mazza et al. 2021, in preparation)

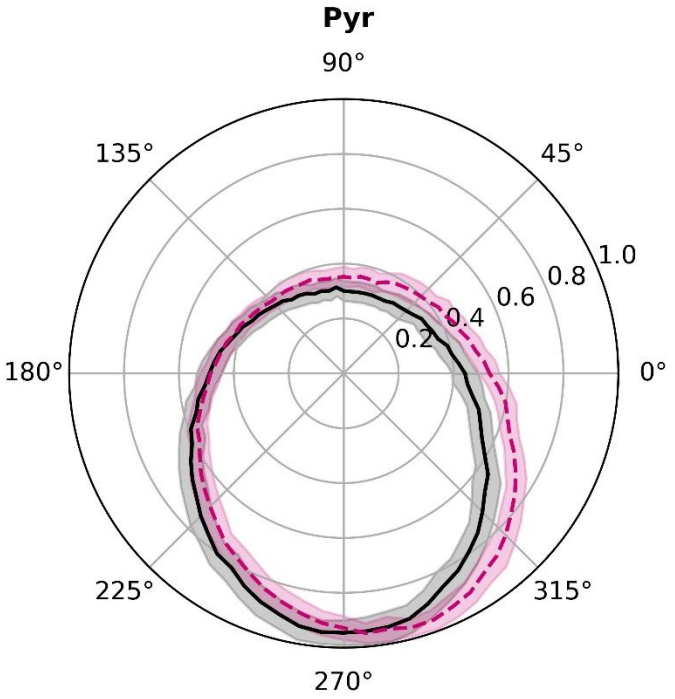
Spiking Phase Preference

Neuronal Spikes

Phase

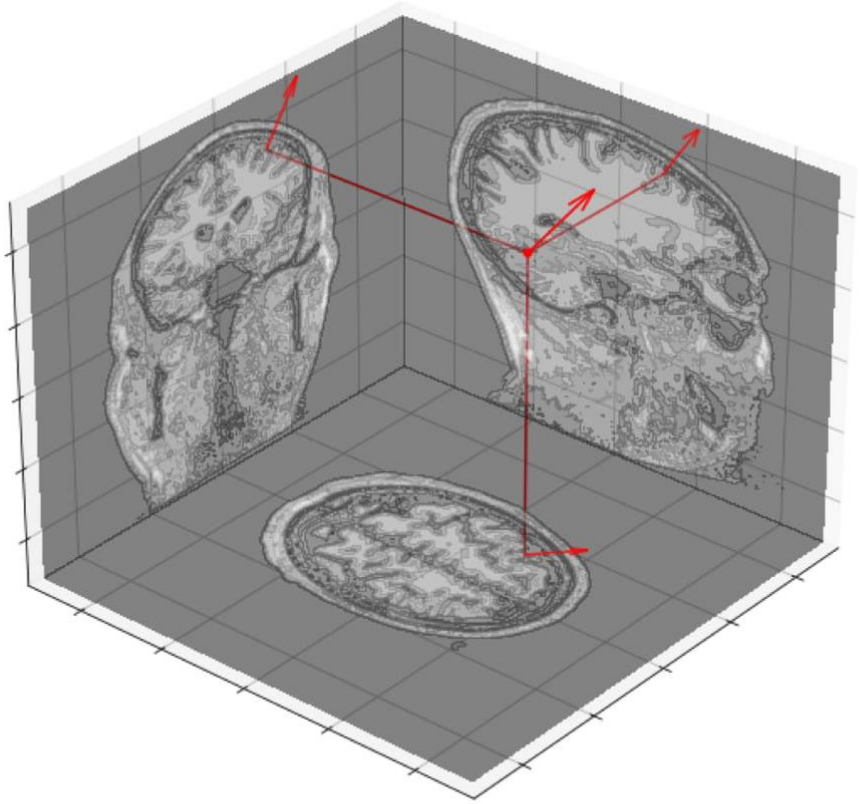
EEG





(Mazza et al. 2021, in preparation)

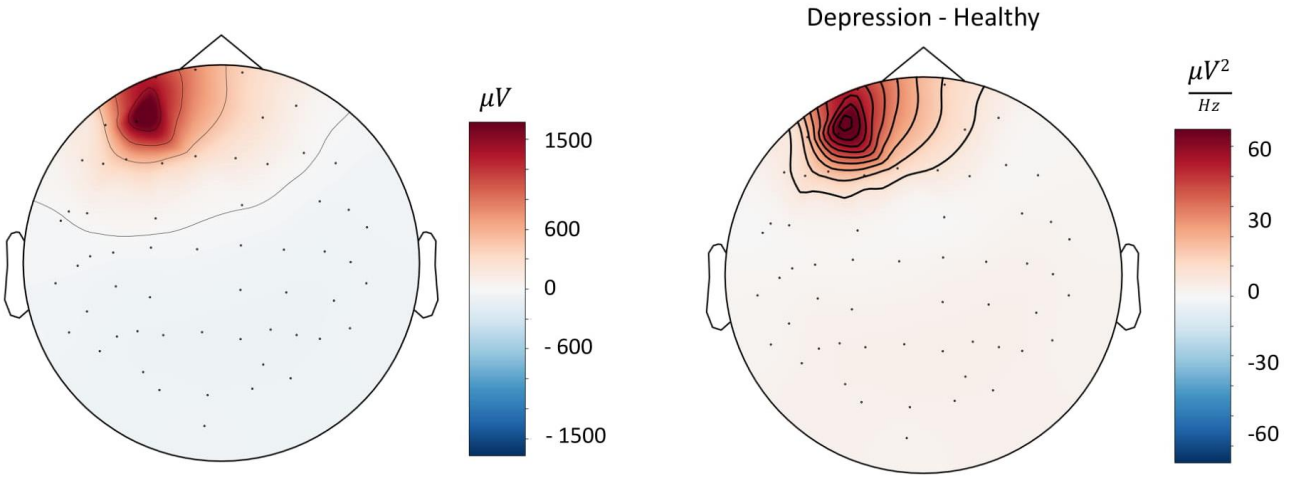
EEG – Realistic Head Model



- Place dipole in dlPFC (in MNE)
- Account for brain curvature

(Mazza et al. 2021, in preparation)

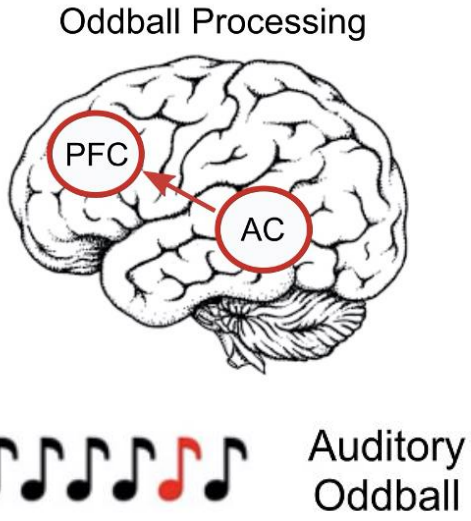
EEG – Realistic Head Model



- Microcircuit signal is local (few mm)
- Asymmetric spatial spread

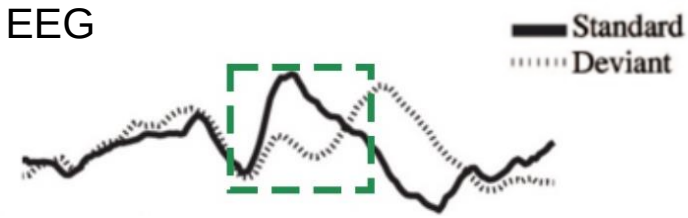
(Mazza et al. 2021, in preparation)

EEG Biomarkers - Schizophrenia



Standard tone

Deviant (oddball) tone

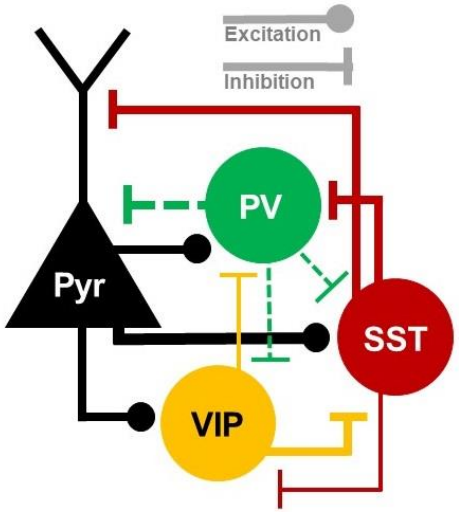


Mismatch Negativity (100 - 200 ms)

- PFC activity – processing deviation
- Mismatch negativity reduced in SCZ

Microcircuit Mechanisms in Schizophrenia

- Altered PV inhibition implicated
- Multiple mechanisms
  - NMDA input
  - PV output
- Schizophrenia subtypes?

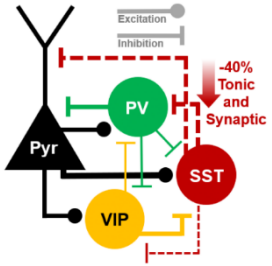


In Silico EEG Biomarkers

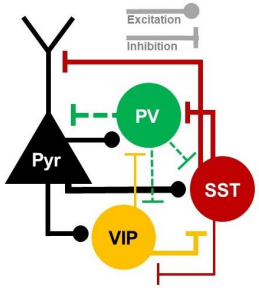
Applications

- Link EEG to disease mechanisms

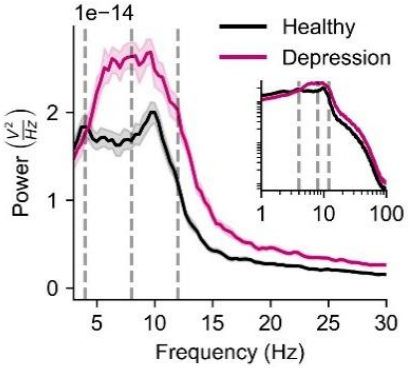
Depression



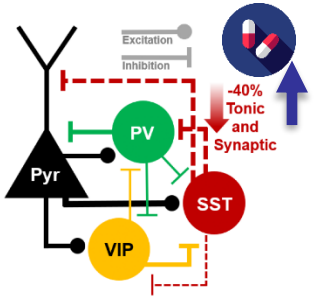
Schizophrenia



- Improve patient stratification



- Monitor new pharmacology



Further Topics
In
Cortical Microcircuit Modeling

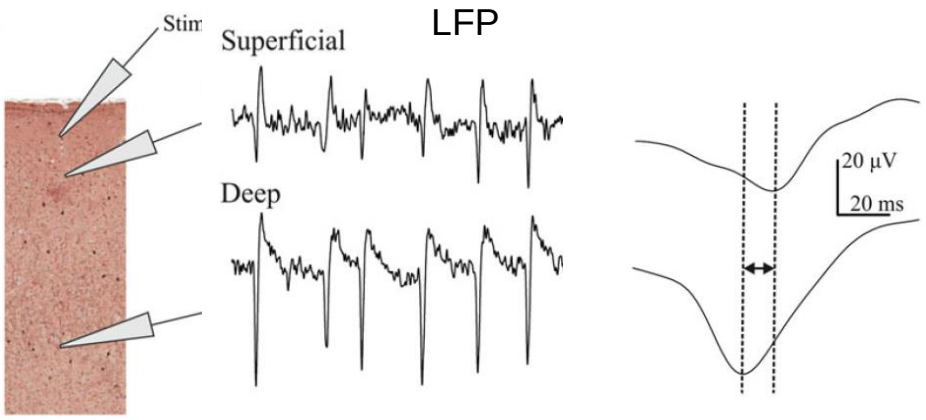
Etay Hay

camh | Krembil Centre for Neuroinformatics

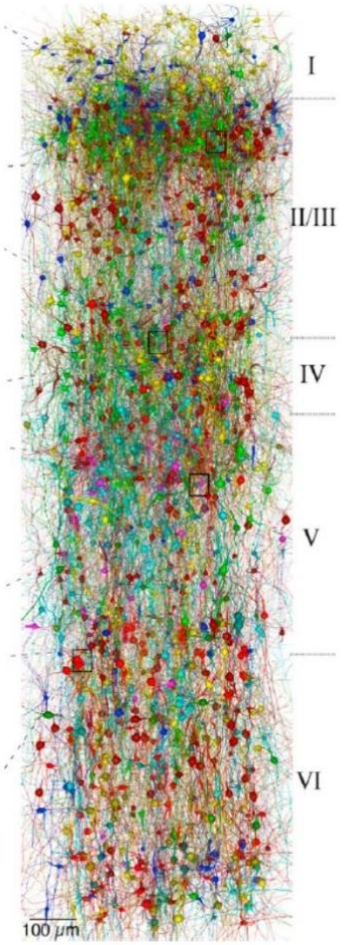
UNIVERSITY OF TORONTO

Multiple Cortical Layers

- Processing hierarchy
- Layer specific disease changes
- Oscillatory dynamics

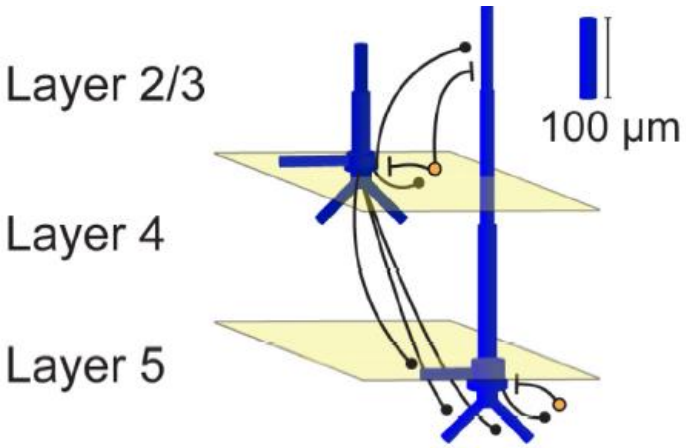


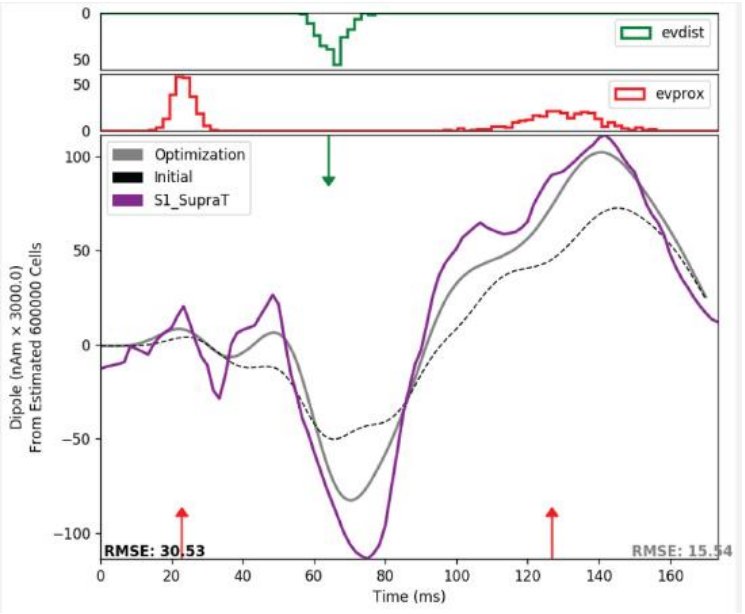
(Florez et al, 2015)



(Markram et al, 2015)

Simpler Neuronal Microcircuits



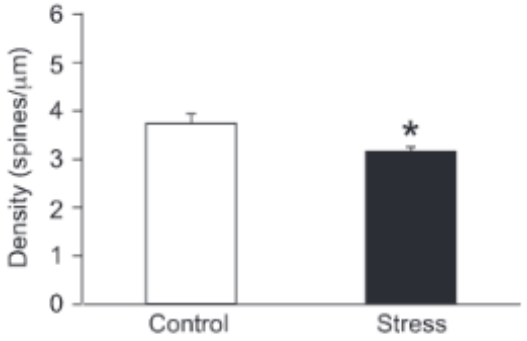


- Faster simulations/fitting
- Fewer parameters
- Useful for explorations
- Approximate EEG
  - Pyr neurons main contributors to signal

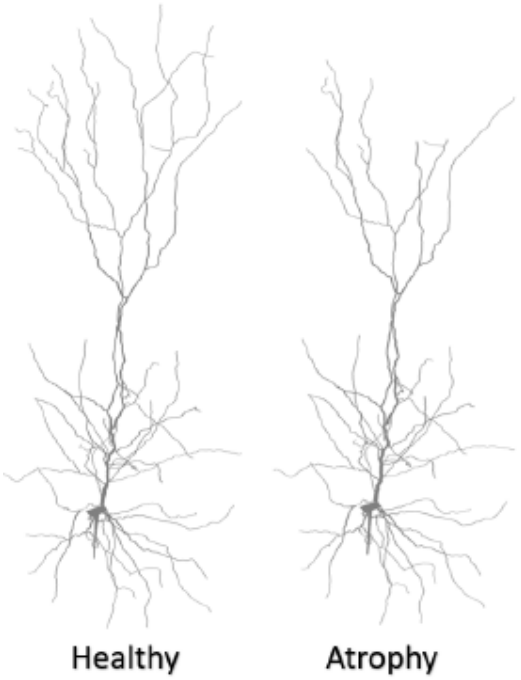
HNN tool
(Neymotin et al, 2020)

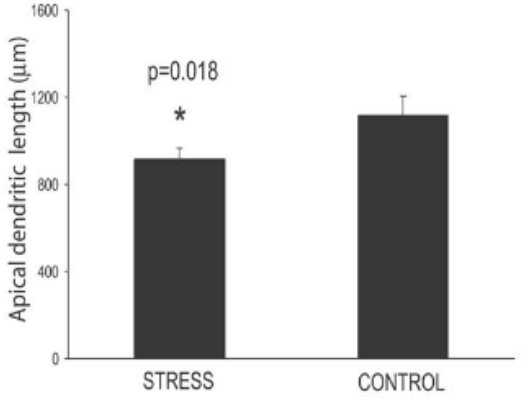
Multiple Disease Mechanisms

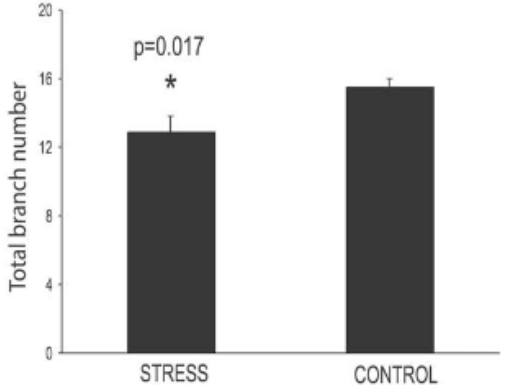
- Cell loss
- Synapse loss
- Cell atrophy



(Radley et al, 2006)

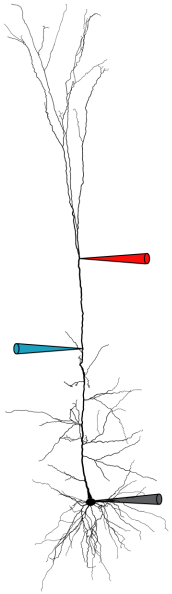






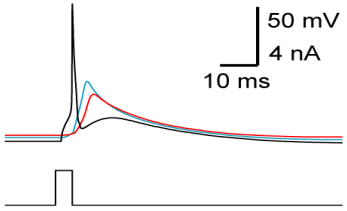
(Radley et al, 2004)

Other Dendritic Properties

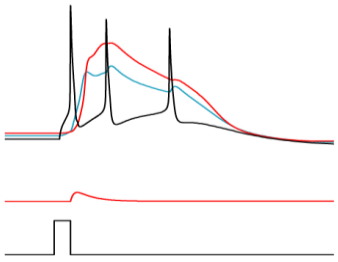


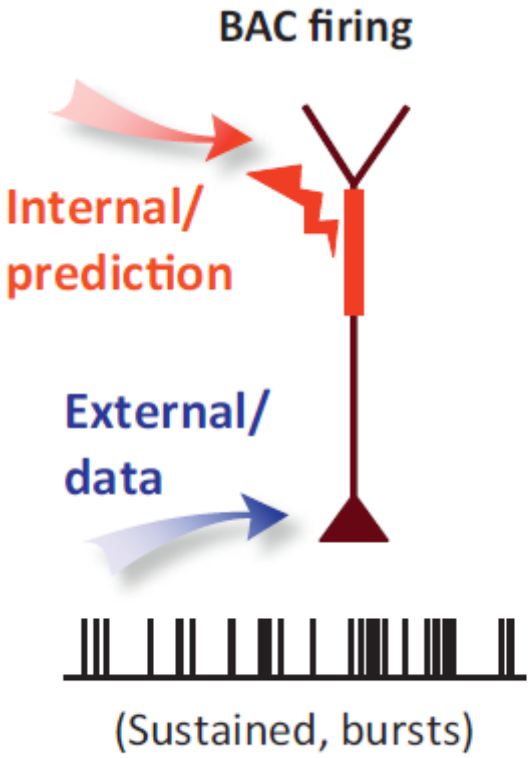
(Hay et al, 2011)

Backpropagating spikes



Calcium spike firing

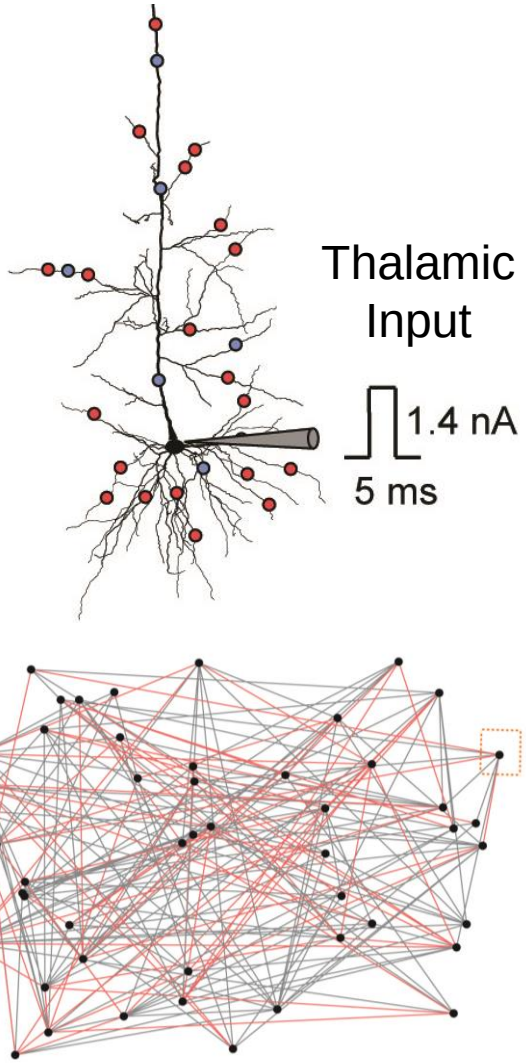


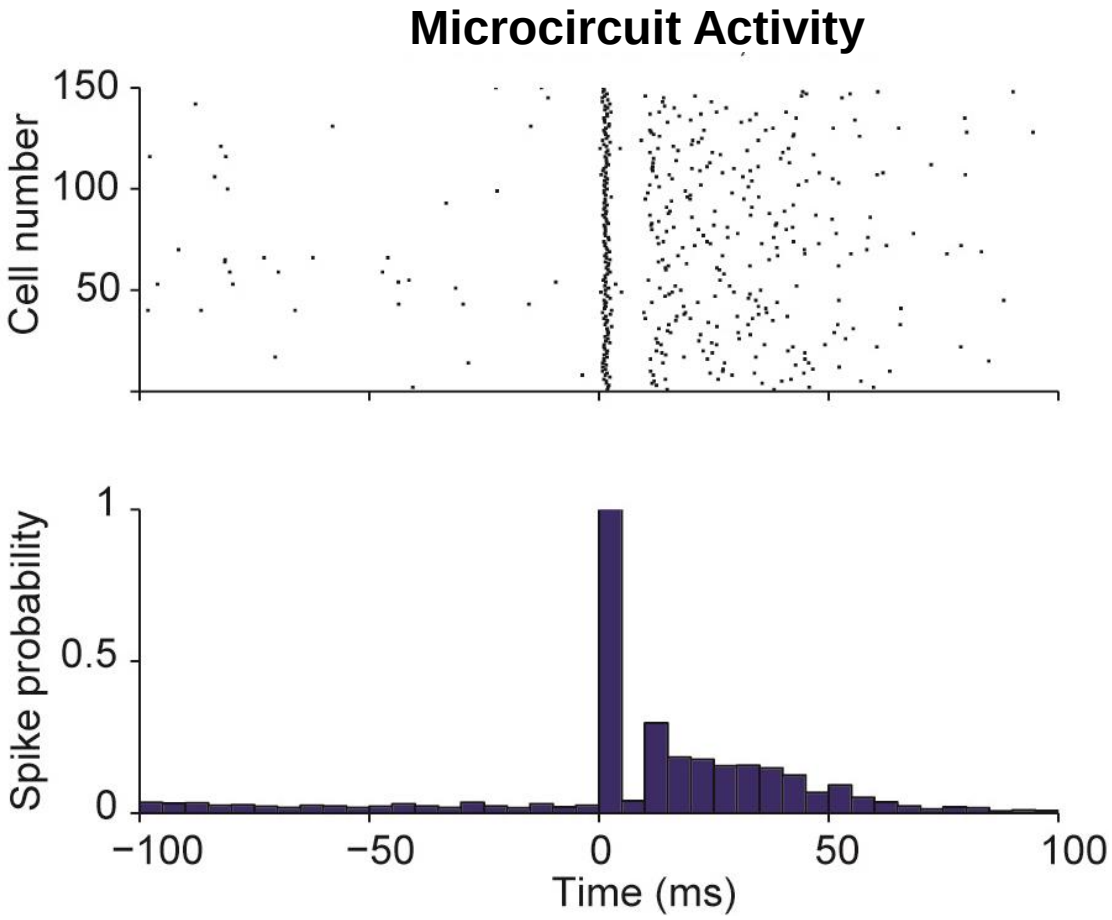


(Larkum, 2013)

- Data in human neurons is scarce
- Similar dendritic backprop spikes
- Different dendritic calcium spikes
- Relevant to SST inhibition in depression

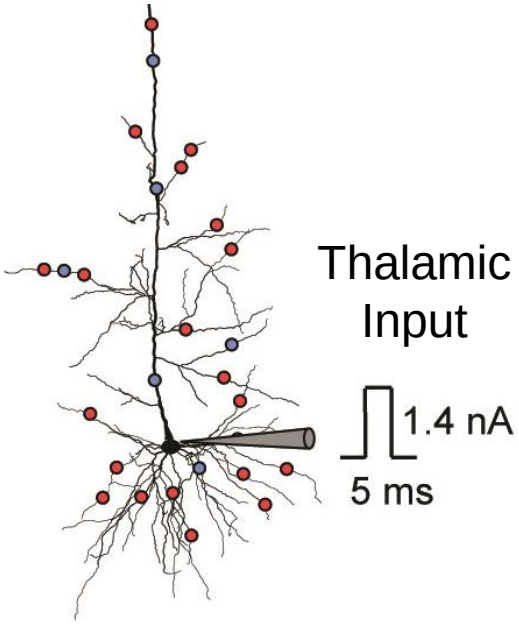
Modeling Other Brain Deficits

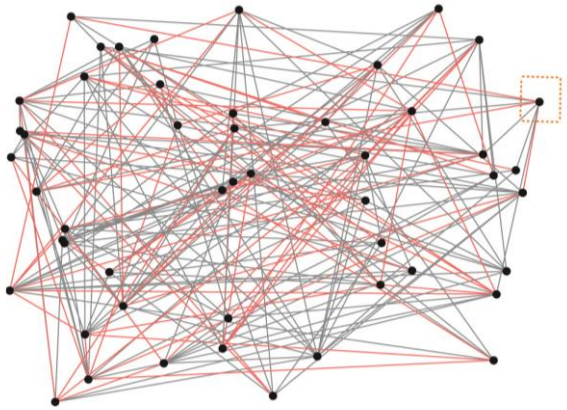




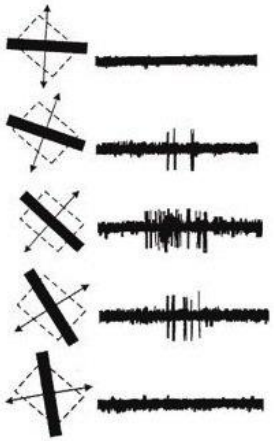
(Hay and Segev, 2015)

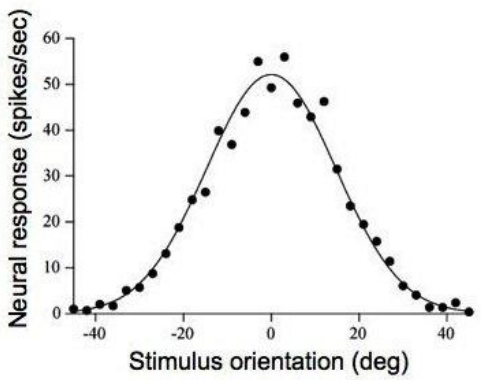
Modeling Other Brain Deficits





Tuning Curves



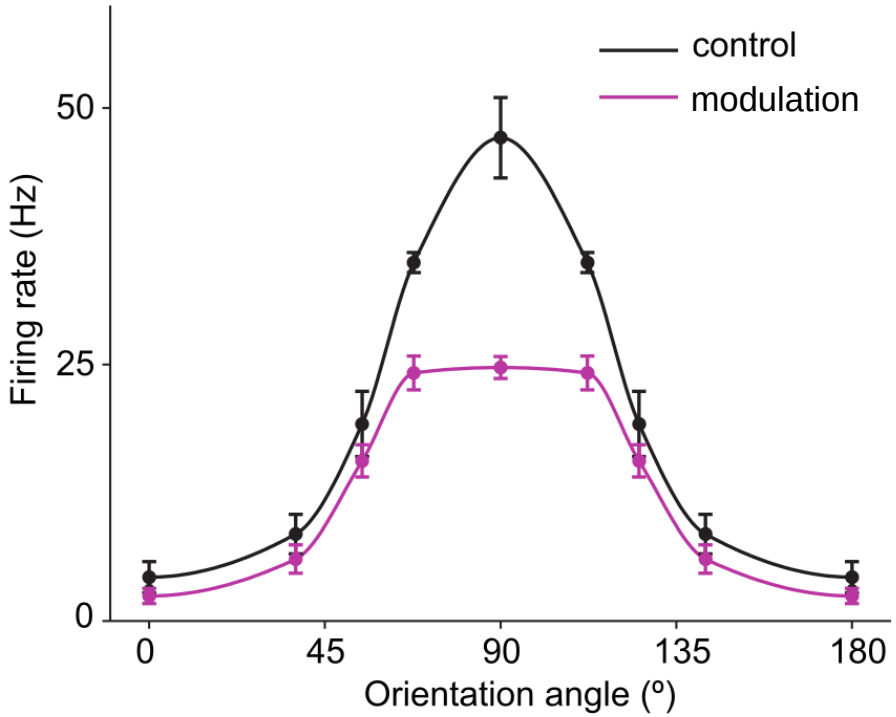


- Different amplitude of thalamic input for different orientations
- Different Microcircuit response rates

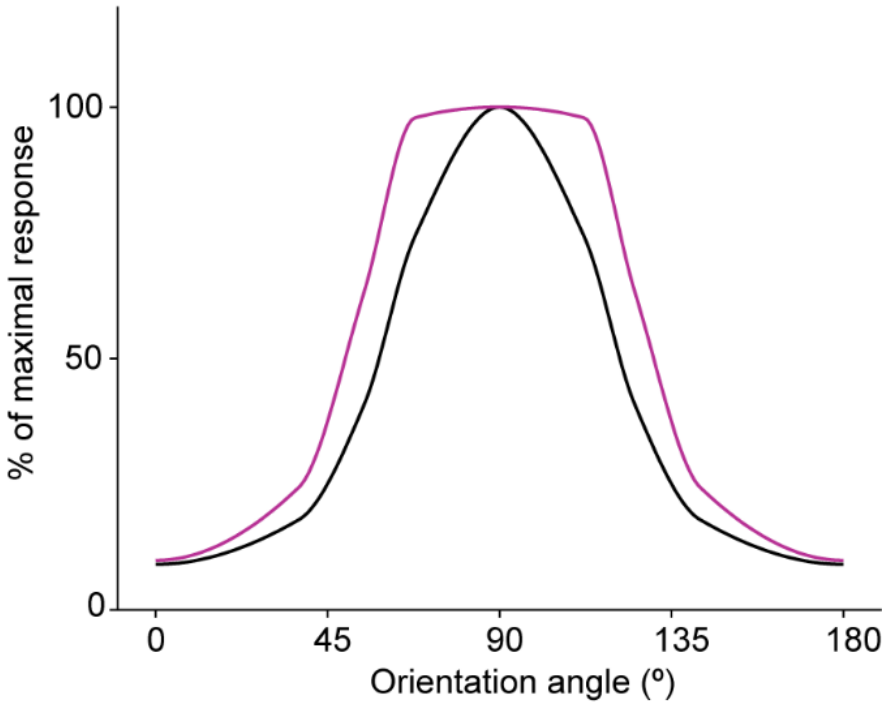
(Hay and Segev, 2015)

Modeling Other Brain Deficits

Response Amplitude



Tuning (Selectivity)

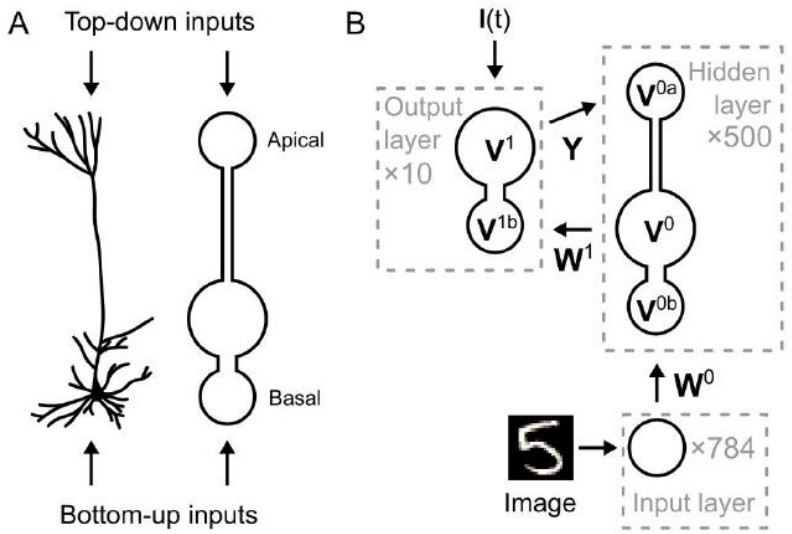


Sensory Stimulus

(Hay and Segev, 2015)

Modeling Other Brain Deficits

- Rumination?
- Memory
- Mood?
- Deep learning useful

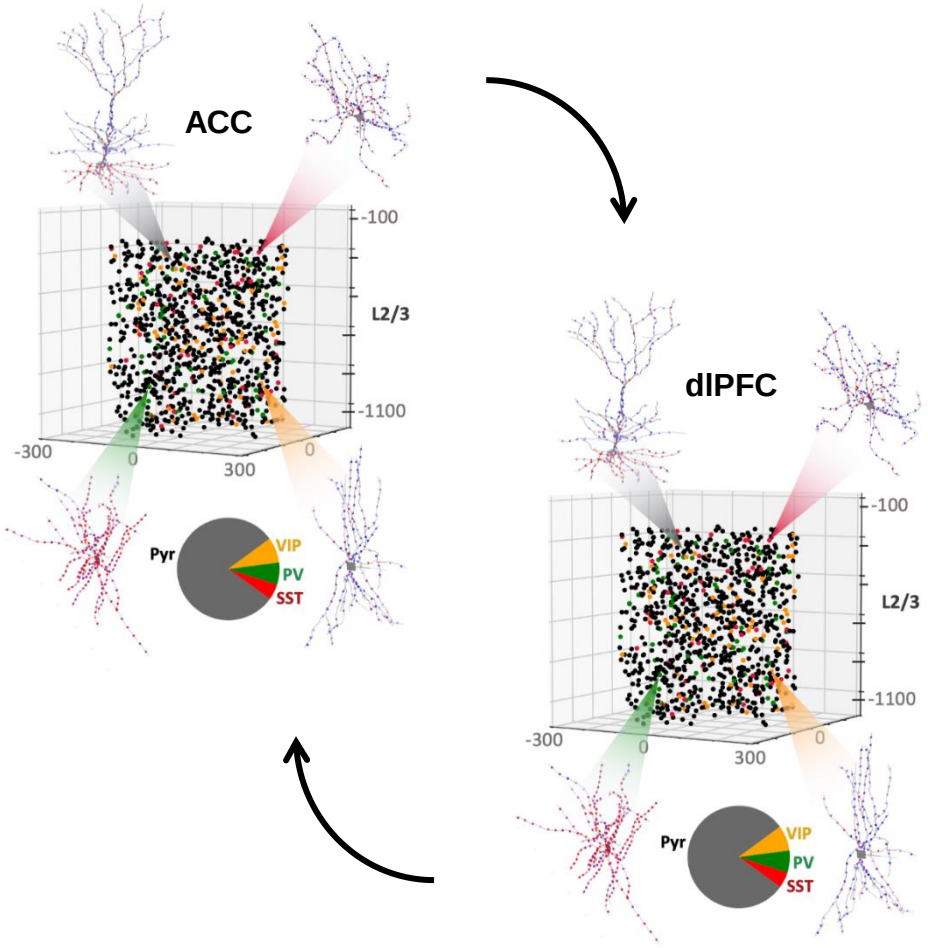


(Guerguiev et al, 2017)

Multi-regional Interactions

- PFC vs. ACC in depression

(Northoff and Sibille, 2014)



Day 4 – Next Session

1:00 pm - 2:30 pm	*Tutorial – simulating and analyzing spiking from neurons and microcircuits* Frank Mazza
2:45 pm - 4:15 pm	*Tutorial – simulating and analyzing EEG signals from brain microcircuits* Frank Mazza

- Check school github for binder or docker instructions
- Assistance available in Gathertown