Multiscale model of the spinal dorsal horn reveals changes in network processing associated with chronic pain

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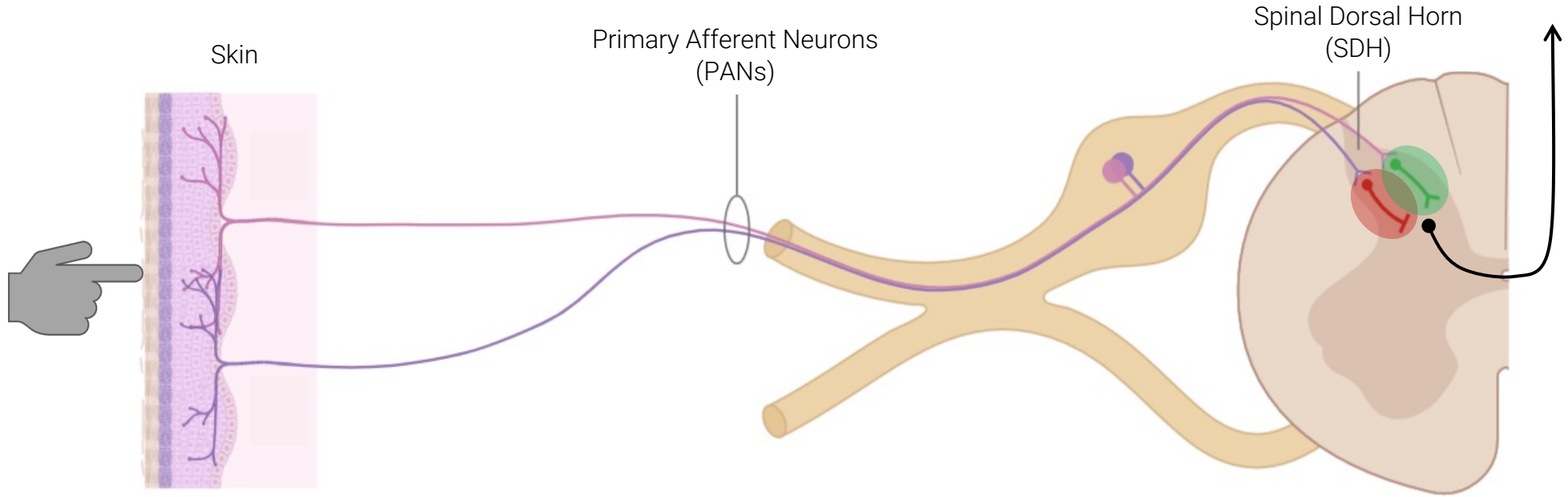
Sensory Processing

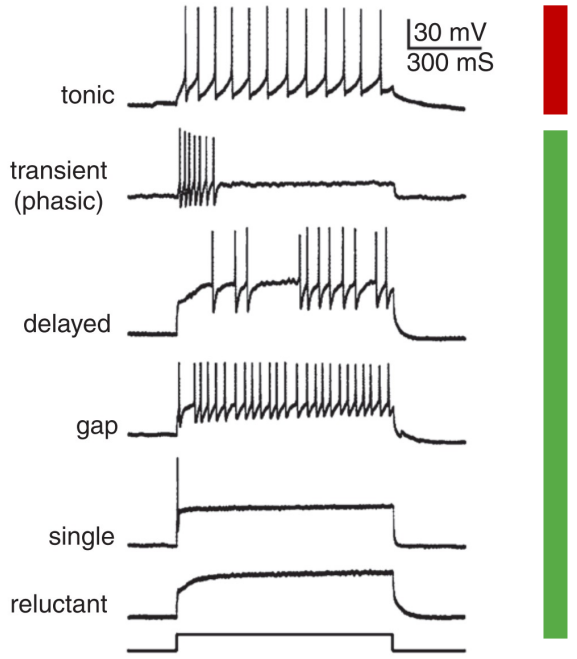
- Sensory processing begins when primary afferents carry touch signals to the spinal cord
- In the SDH signals are processed by interneurons before being relayed to the brain by projection neurons



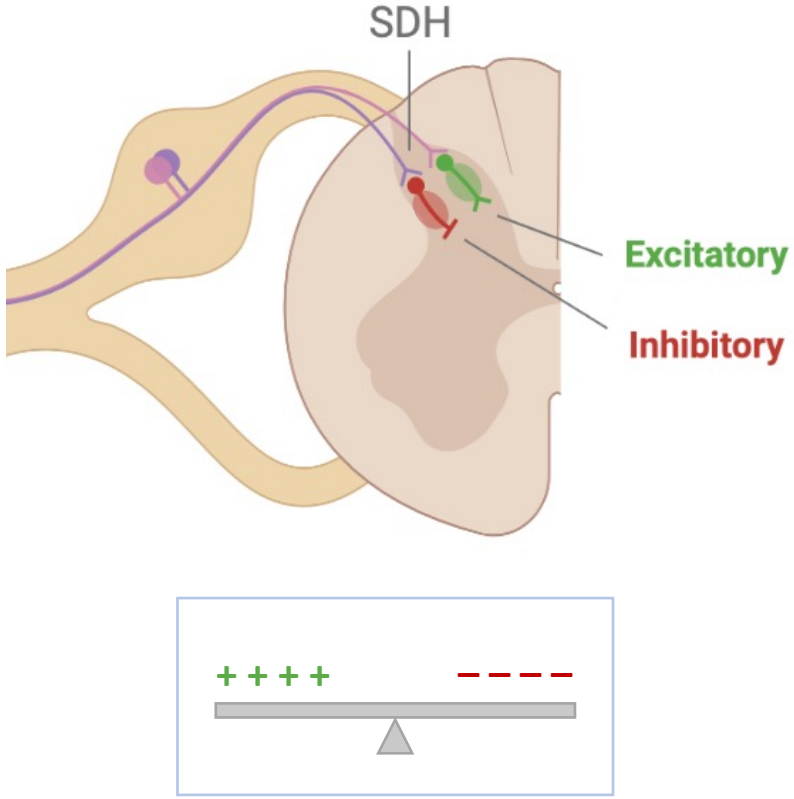
Spinal Dorsal Horn

- The SDH relies on multiple cellular- and circuit-level mechanisms to correctly process sensory input

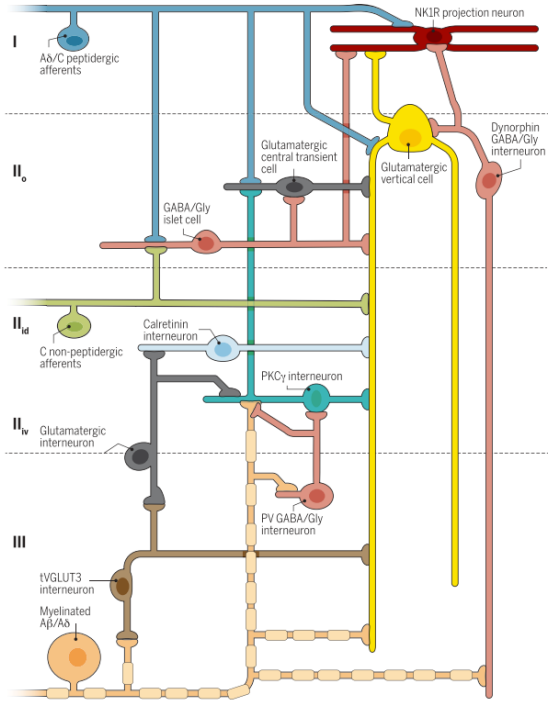
Cellular Mechanisms



Prescott & Ratté (2012)



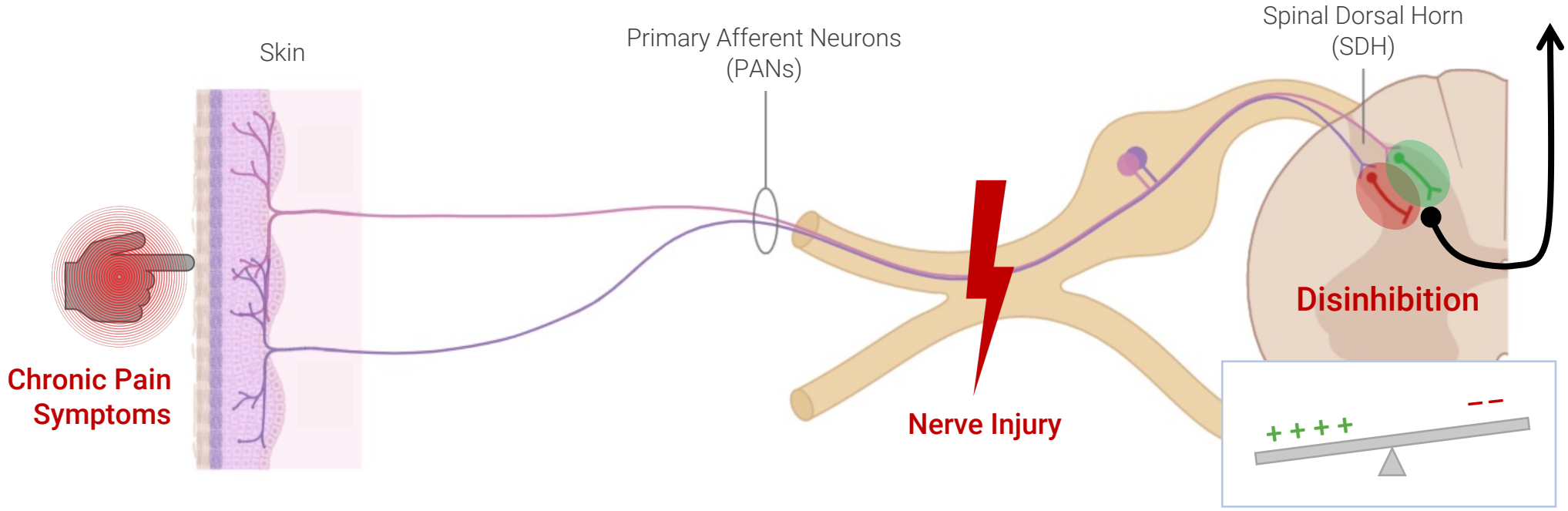
Circuit Mechanisms



Peirs & Seal (2016)

Chronic Pain

- In chronic pain conditions there is abnormal processing of touch signals
- Improved clinical treatments are hindered by incomplete understanding of higher-level sensory processing



Problem: We need to investigate the network-level consequences of disinhibition

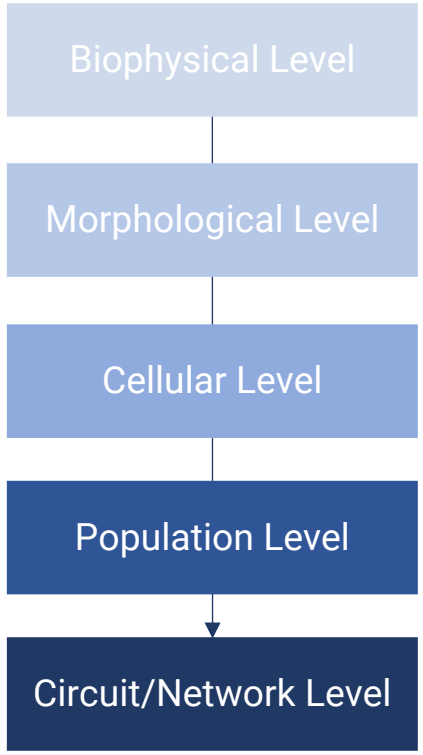
- Probing the SDH is difficult to do experimentally due to its immense complexity

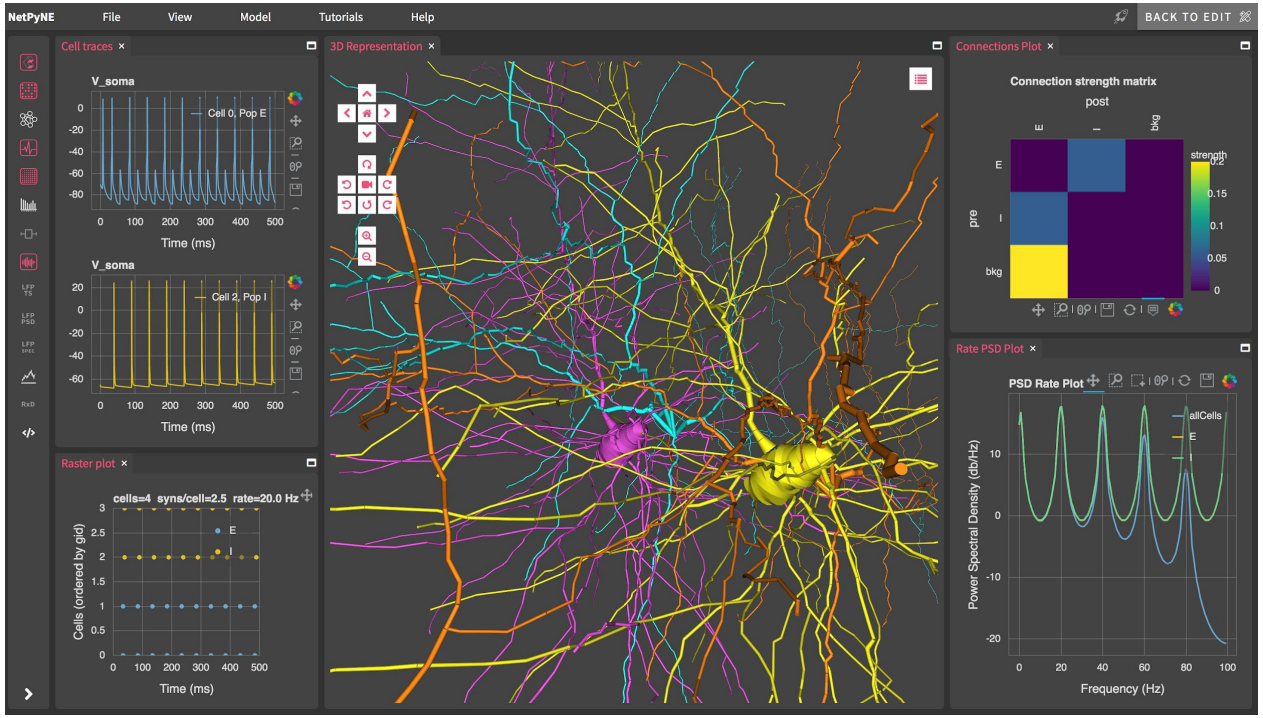
Solution: We built a multiscale model of the SDH and simulate disinhibition

- Link the molecular-, cellular-, and network-level properties underlying chronic pain

NetPyNE

- We developed the network using NetPyNE, a Python package that helps facilitate the development, simulation, and analysis of multiscale network models in NEURON

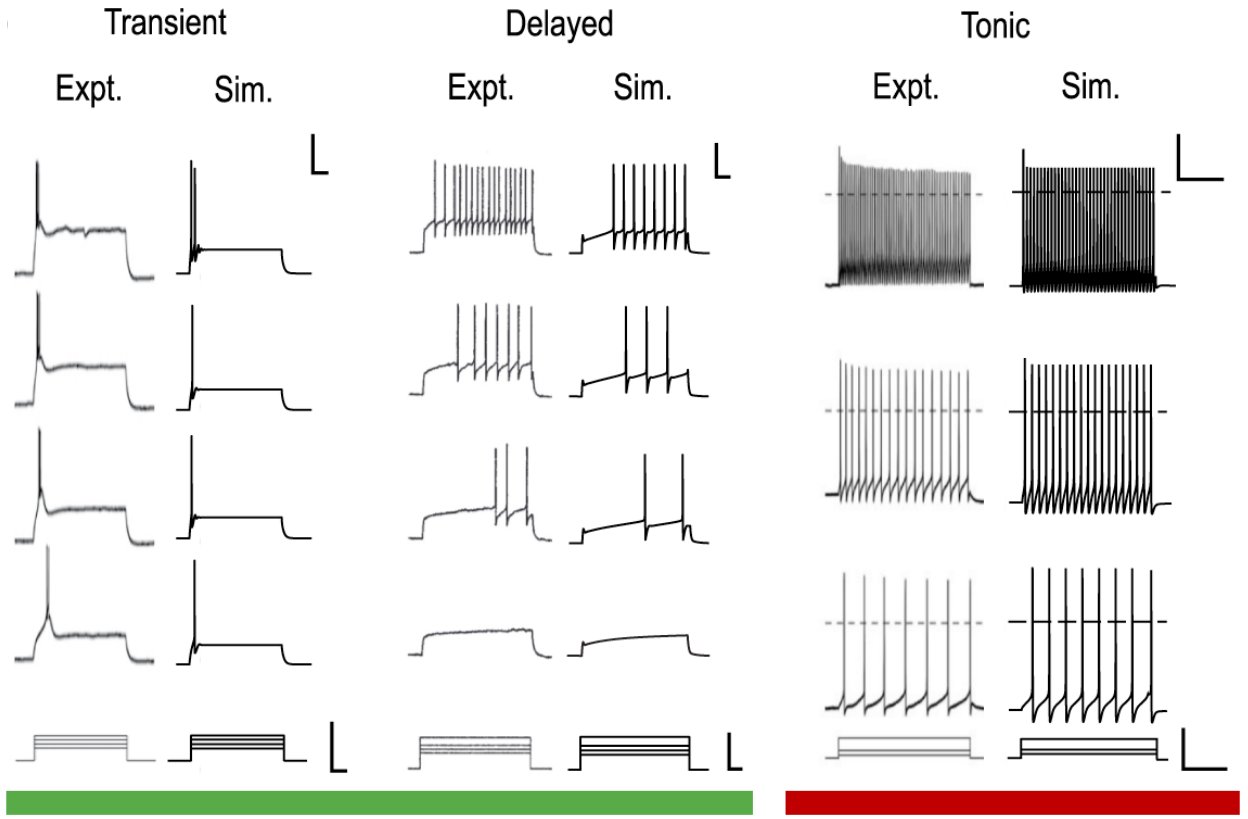




Dura-Bernal et al. (2019)

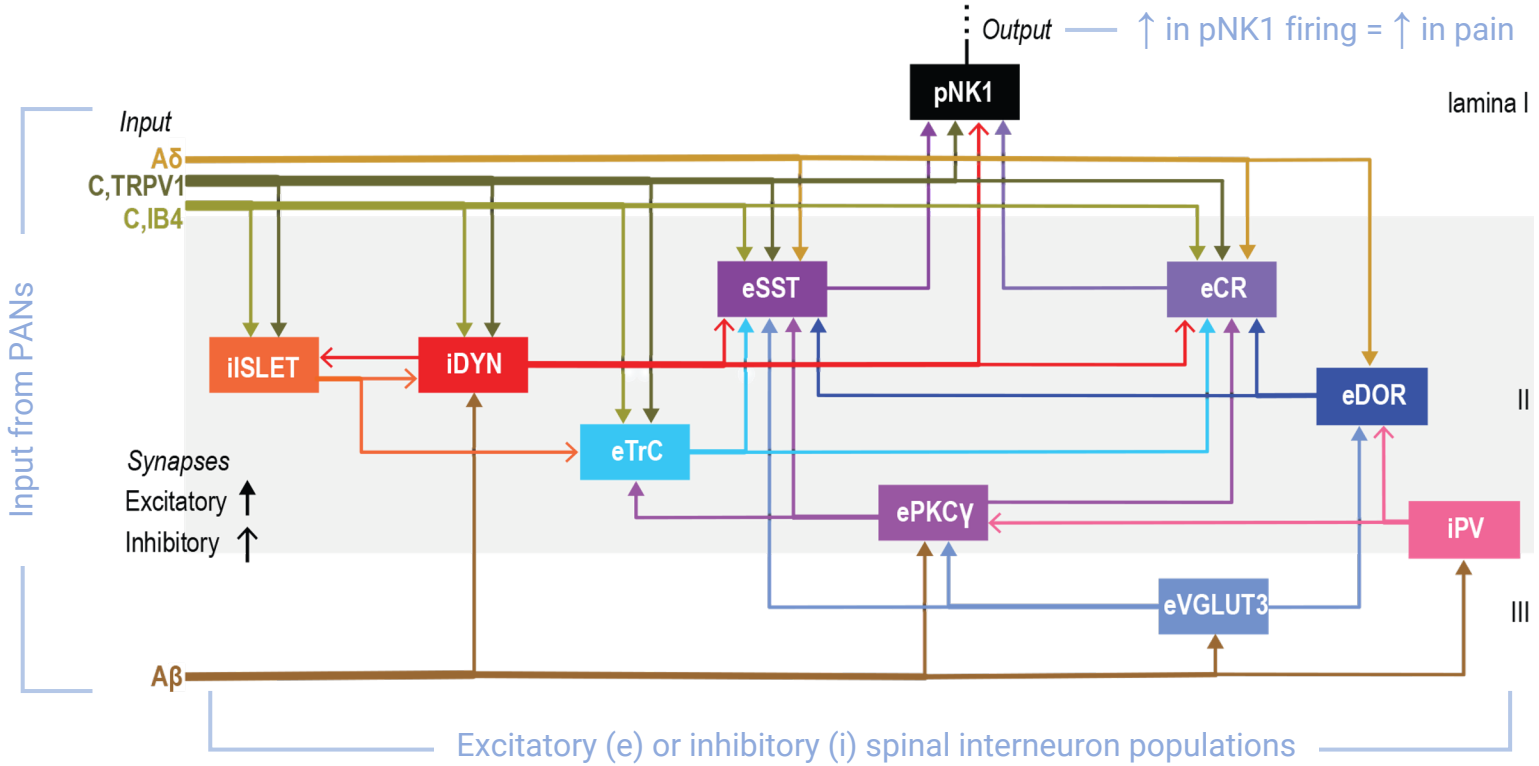
Spinal Neuron Models

- Conductance-based models were tuned to match electrophysiology recordings from spinal neurons



Circuit Connectivity

- The model circuit was designed based on experimentally-derived SDH connectivity



Experimentally dissected using:

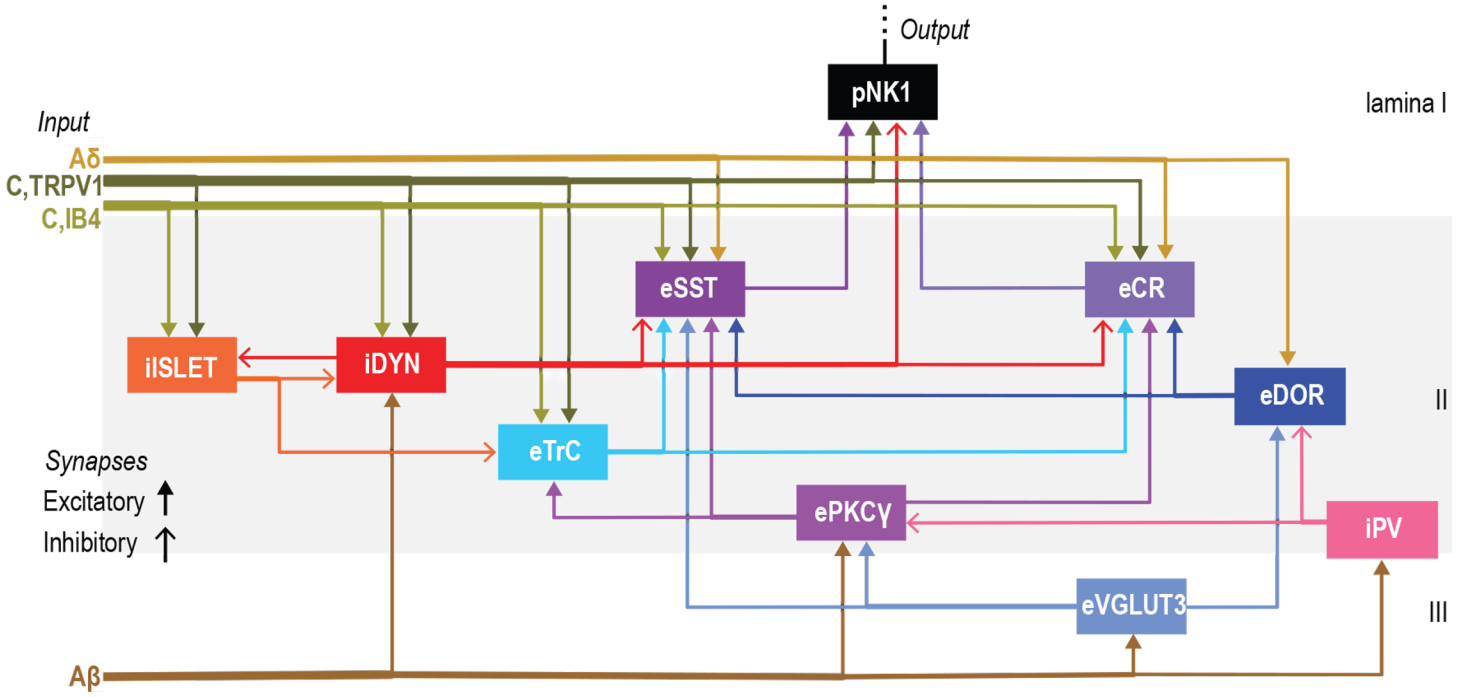
- Paired recordings
- Genetic labeling
- Optogenetics
- Ablation studies

Circuit Connectivity

- Variability in circuit output (e.g. across pNK1 spike trains) is influenced by…

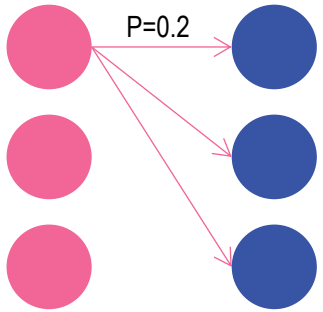
1

Input modeled as Poisson processes



2

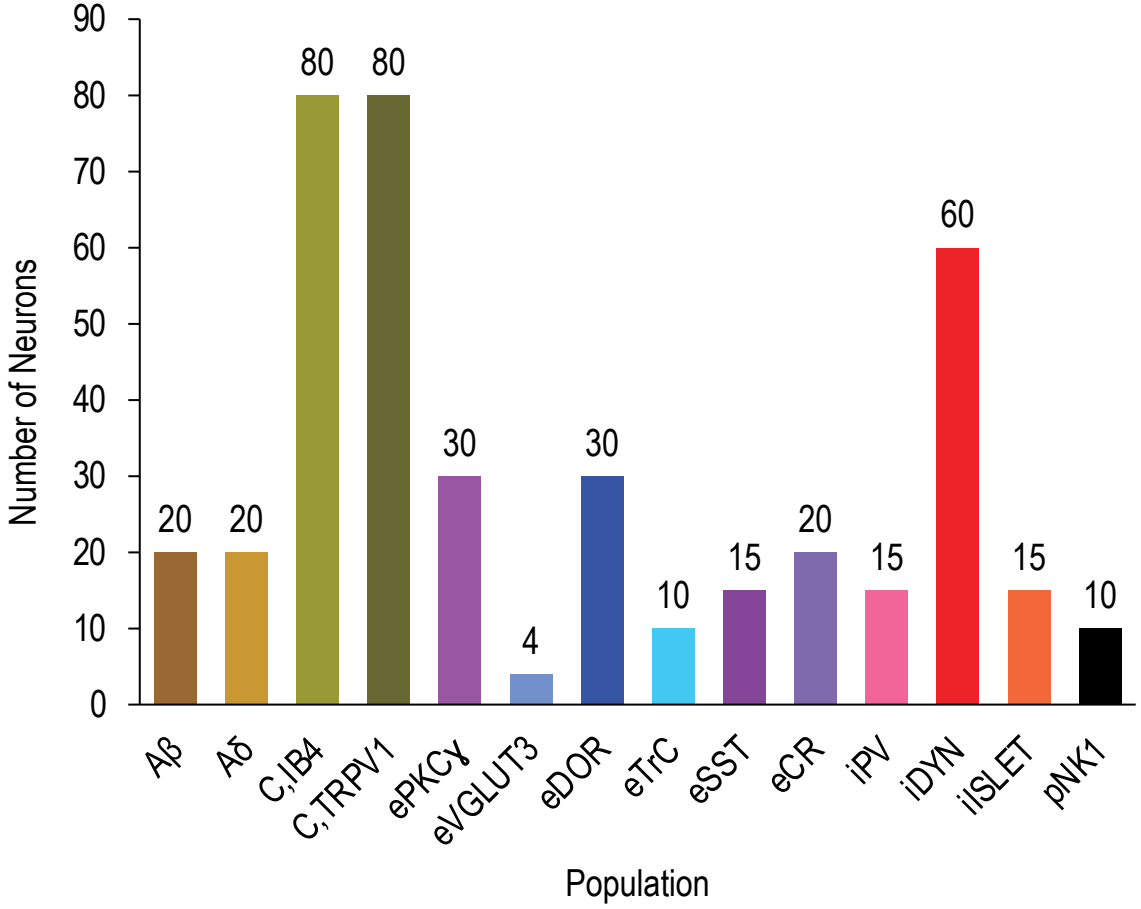
Connectivity isn't all-to-all, it is probabilistic



Presynaptic neuron has a 20% probability of connecting to a postsynaptic neuron

Population Size

- A total of 409 neurons were simulated across 15 different populations.
- Numbers of neurons in each population were mainly approximated from immunohistochemical data.
- The number of neurons were scaled down to 20% to reduce computing load.



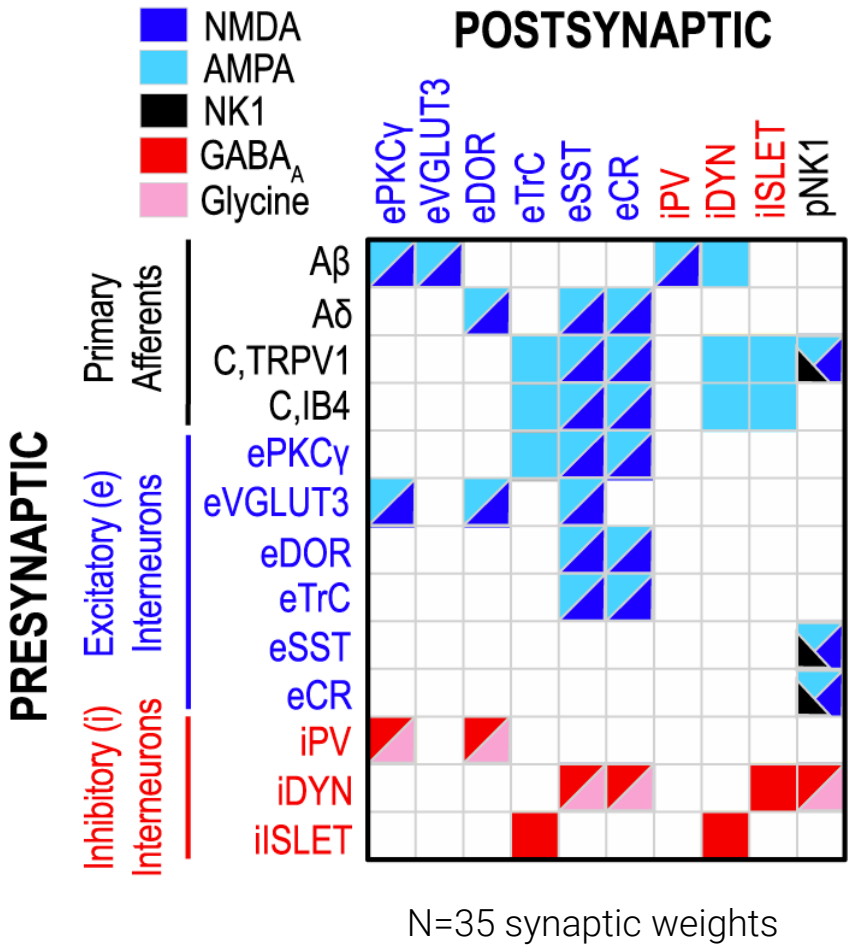
(Le Bars et al. 2001, Häring et al. 2018)

Synapse Models

- Excitatory synaptic transmission was mediated by AMPA, NMDA, or NK1 receptors.
- Inhibitory synaptic transmission was mediated by $GABA_A$ or glycine receptors.
- Synapses were modeled using Exp2Syn and scaled by a synaptic weight.

$$I_{syn} = g_{syn} \times (V - E_{ion})$$

$$g_{syn} = weight \times \left(e^{\frac{-t}{\tau 2}} - e^{\frac{-t}{\tau 1}}\right)$$

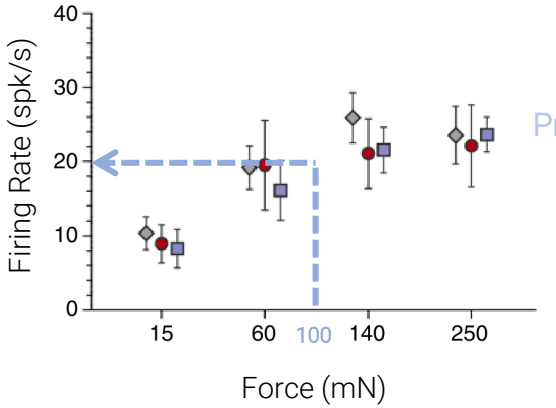


N=35 synaptic weights

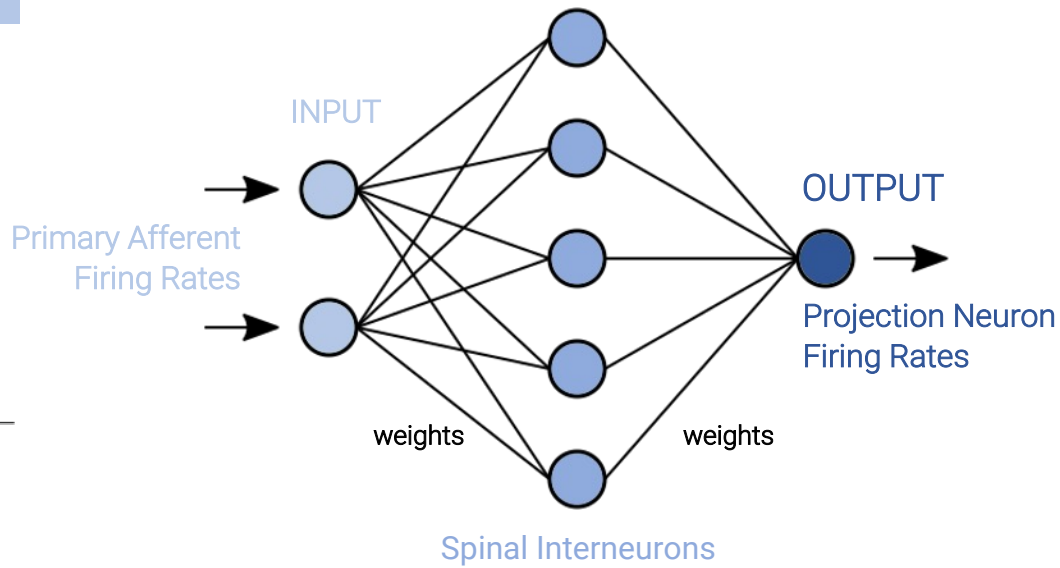
Fitting the Model to Experimental Data

- Synaptic weights were optimized so that primary afferent input produced projection neuron output in response to the same experimental stimulation.

Example: Pressure (100 mN)

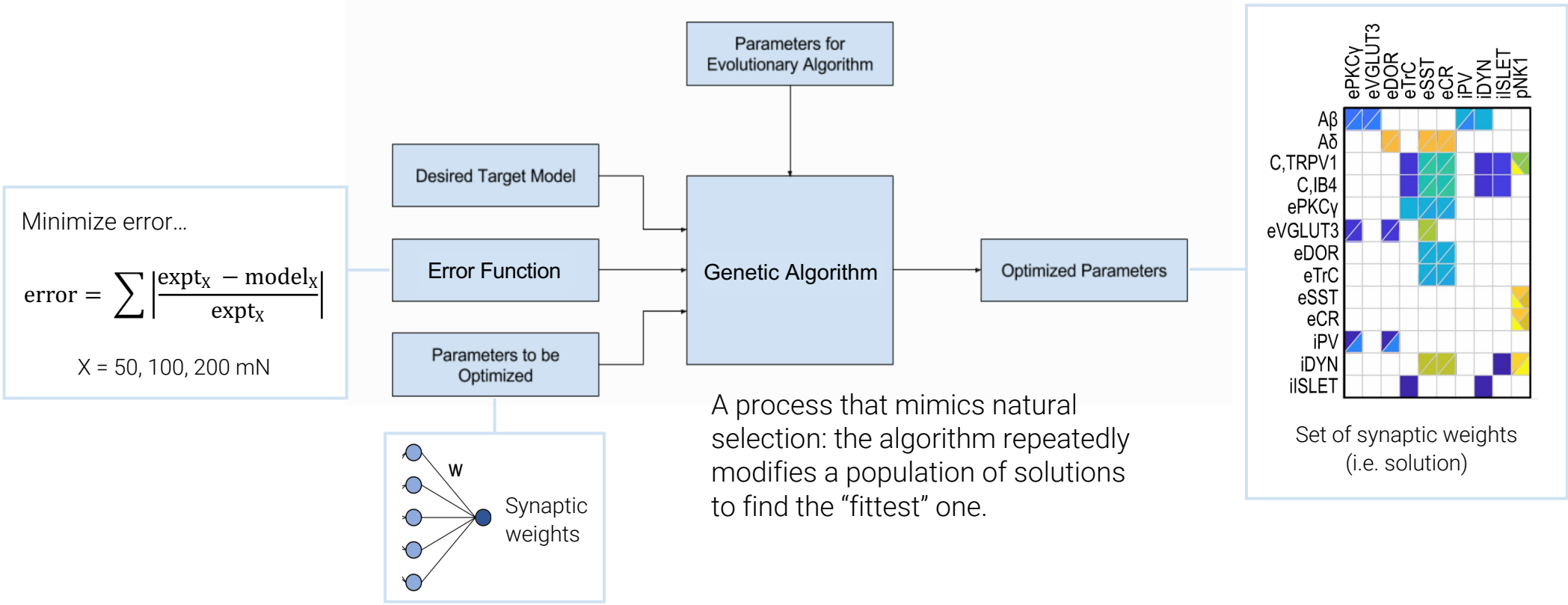


Walcher et al. (2018)

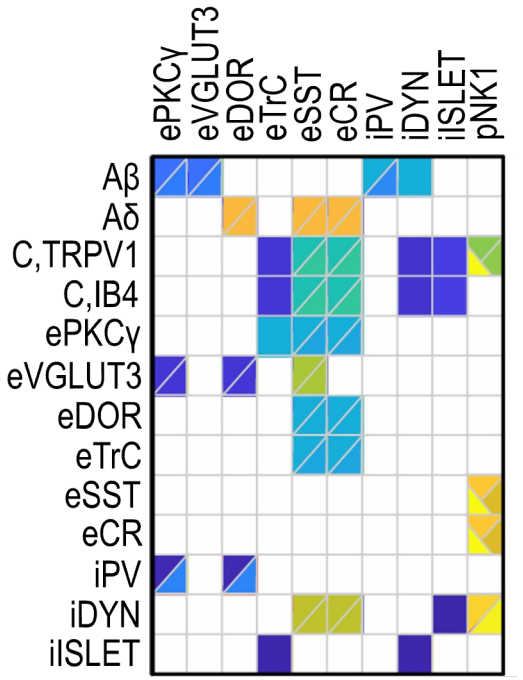


Optimizing Synaptic Weights

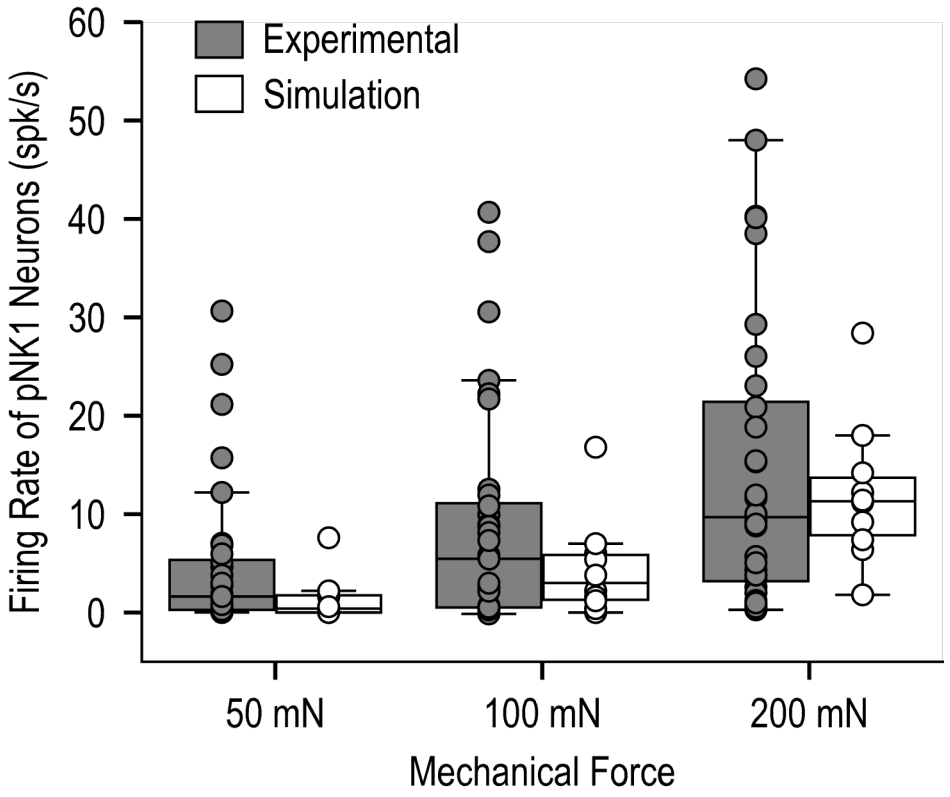
- We optimized the 35 synaptic weights using a genetic algorithm



Result 1: The SDH model reproduces experimental responses to mechanical stimulation across multiple intensities



An example set of synaptic weights from the GA



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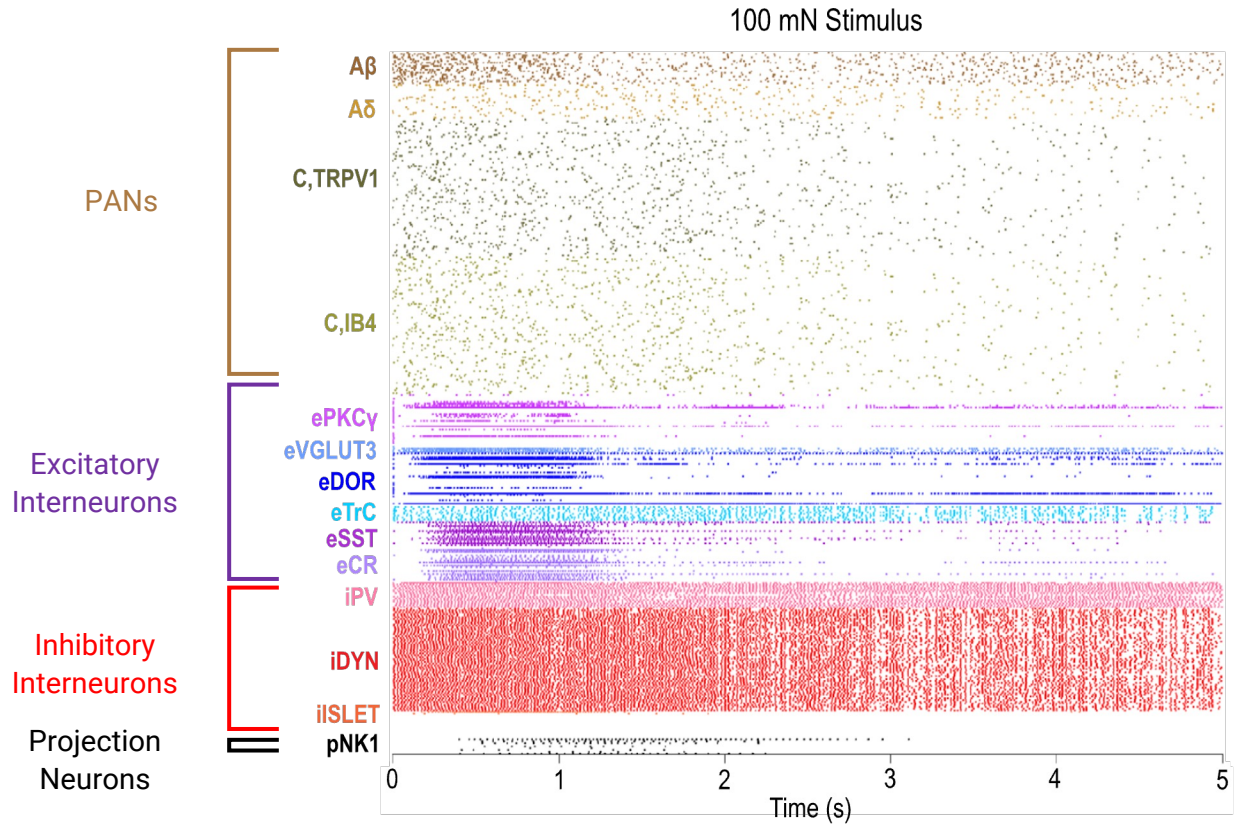
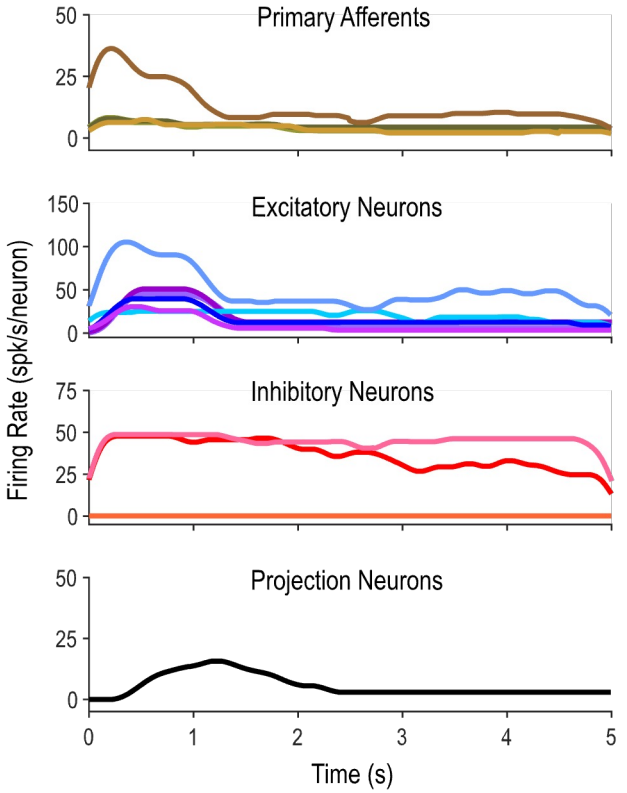
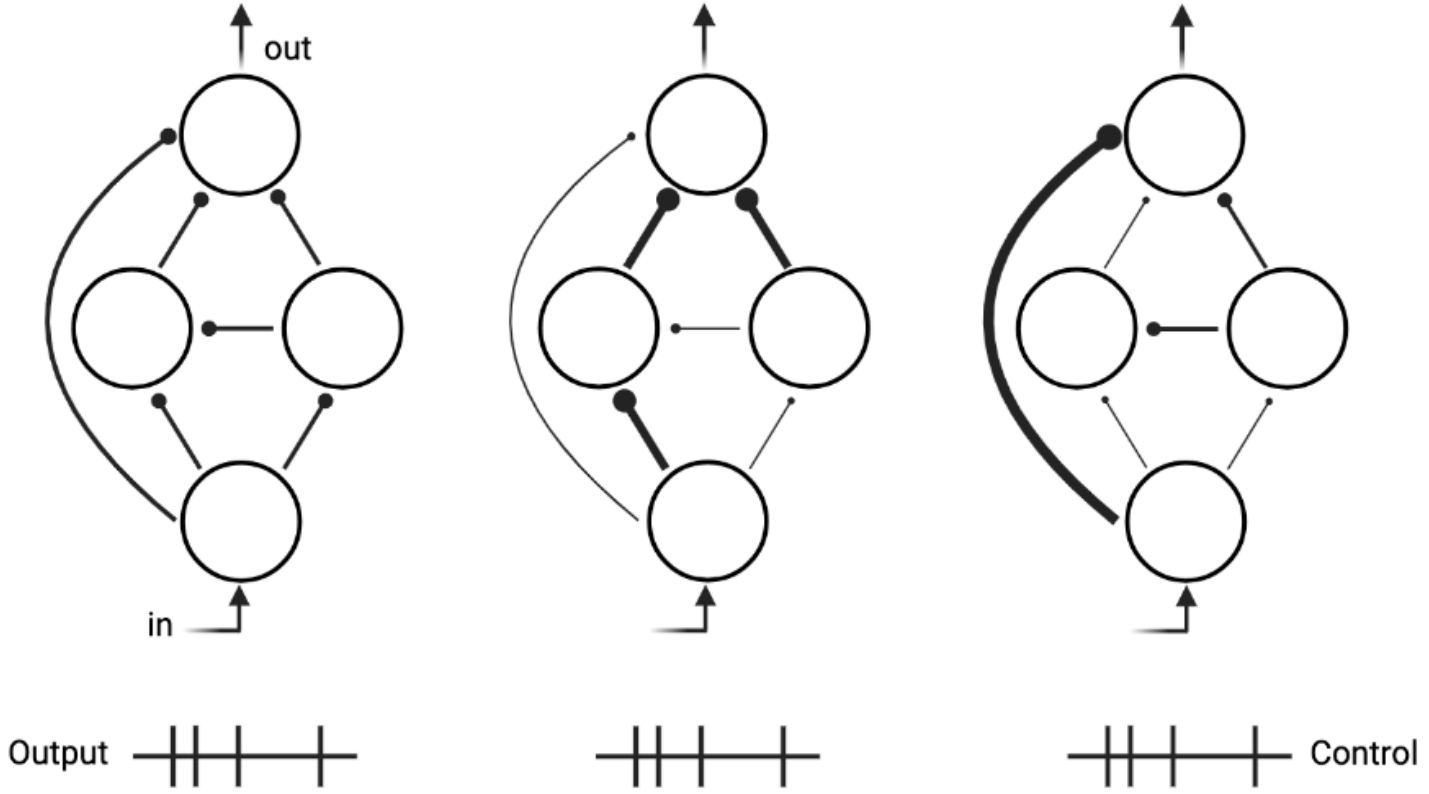
Ex. Model response to 100 mN…





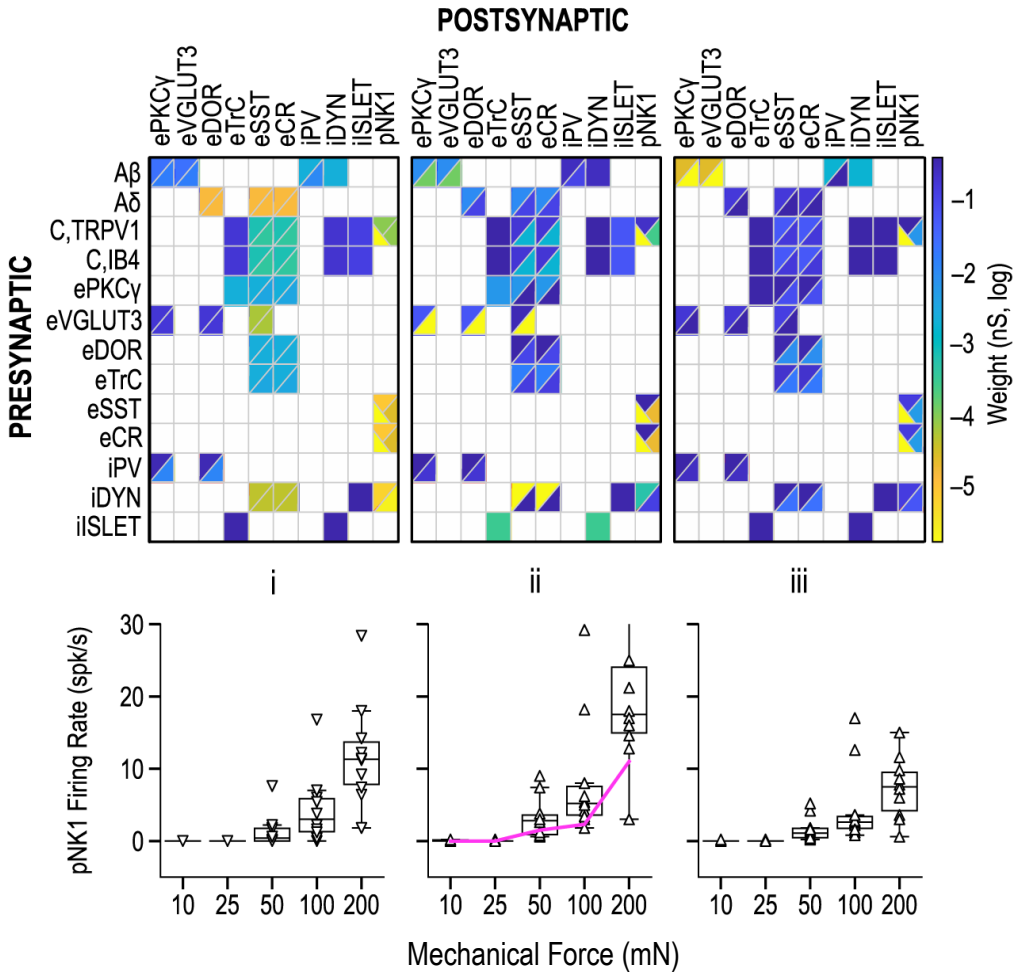
Result 2: Disparate combinations of synaptic weights produced equivalent circuit function, revealing **degeneracy** in the SDH



Degeneracy → Different mechanisms that give rise to similar/nearly identical behaviour

Adapted from Marder et al. (2015)

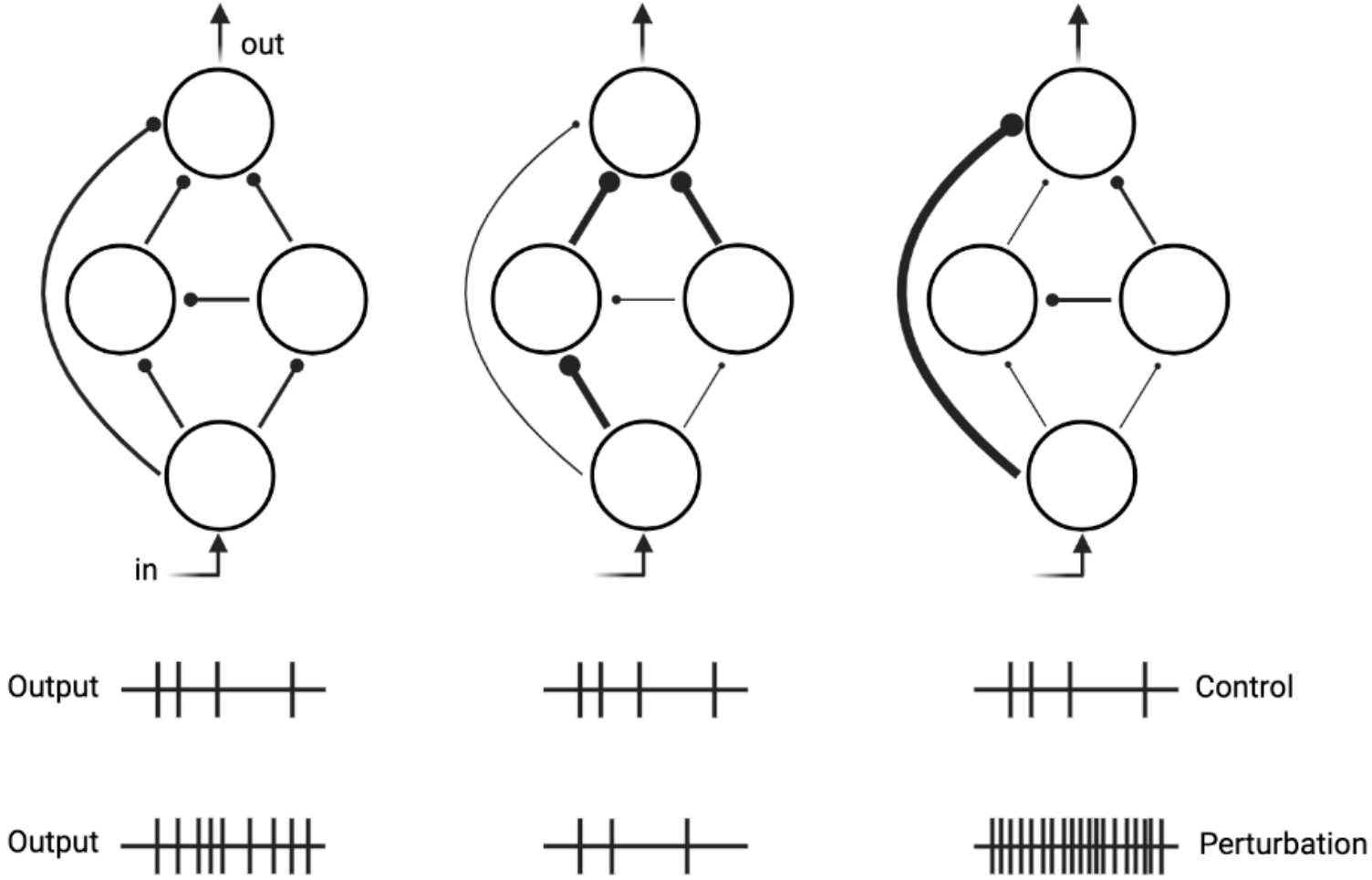
Result 2: Disparate combinations of synaptic weights produced equivalent circuit function, revealing **degeneracy** in the SDH



Different combinations of synaptic weights produce…

…equivalent responses to normal touch

Result 2: Disparate combinations of synaptic weights produced equivalent circuit function, revealing **degeneracy** in the SDH



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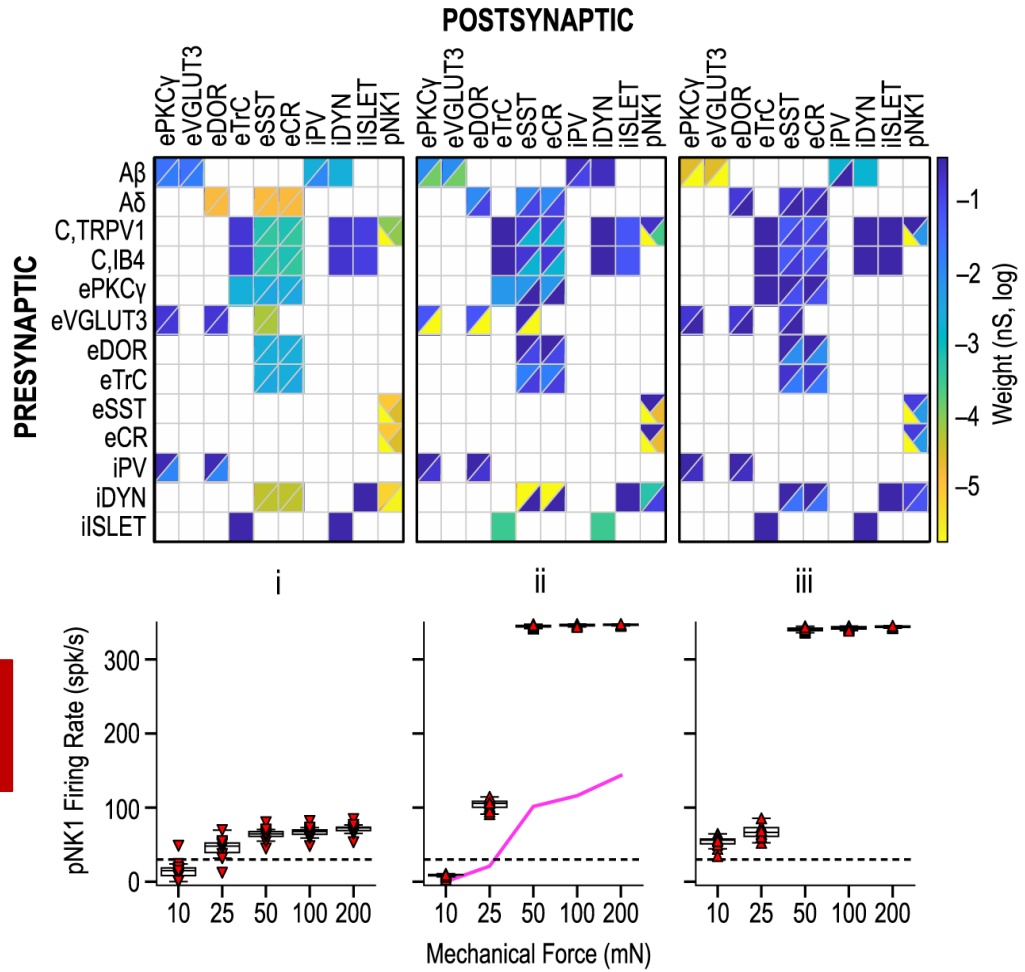

Inhibitory Receptor Block (wGABA/wGlycine=0)

Different combinations of synaptic weights produce…

…different responses to pathological disinhibition

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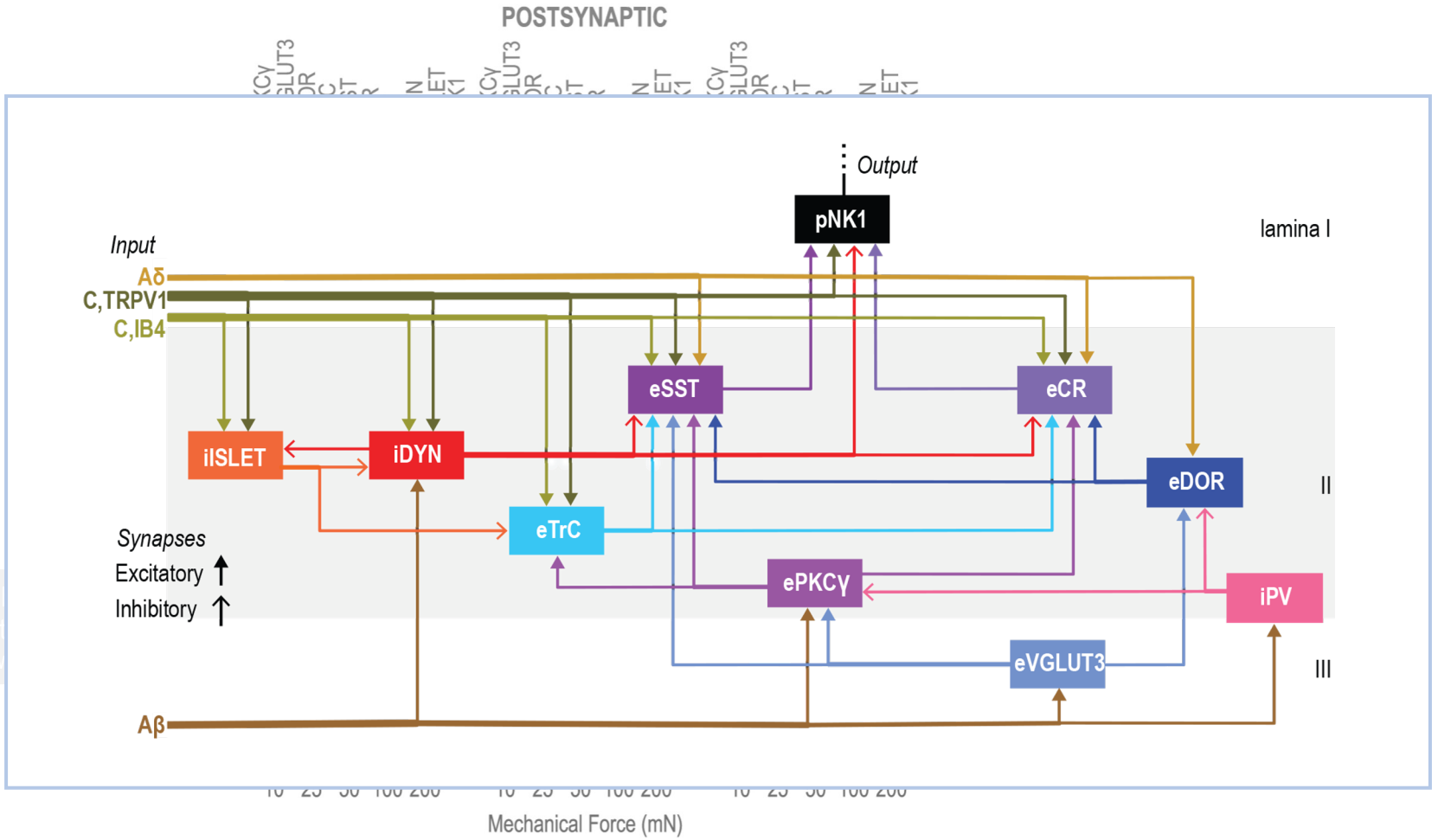

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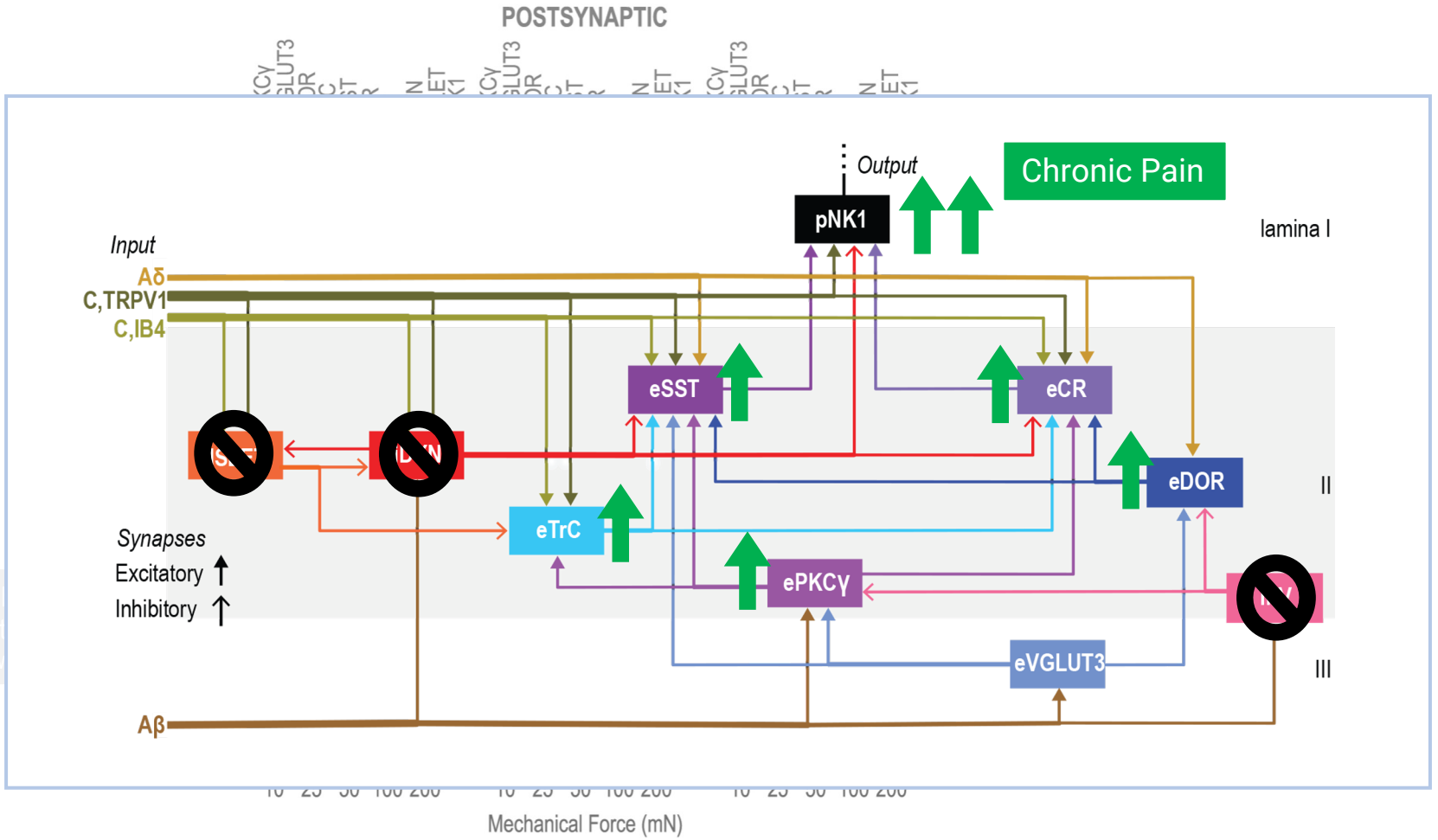

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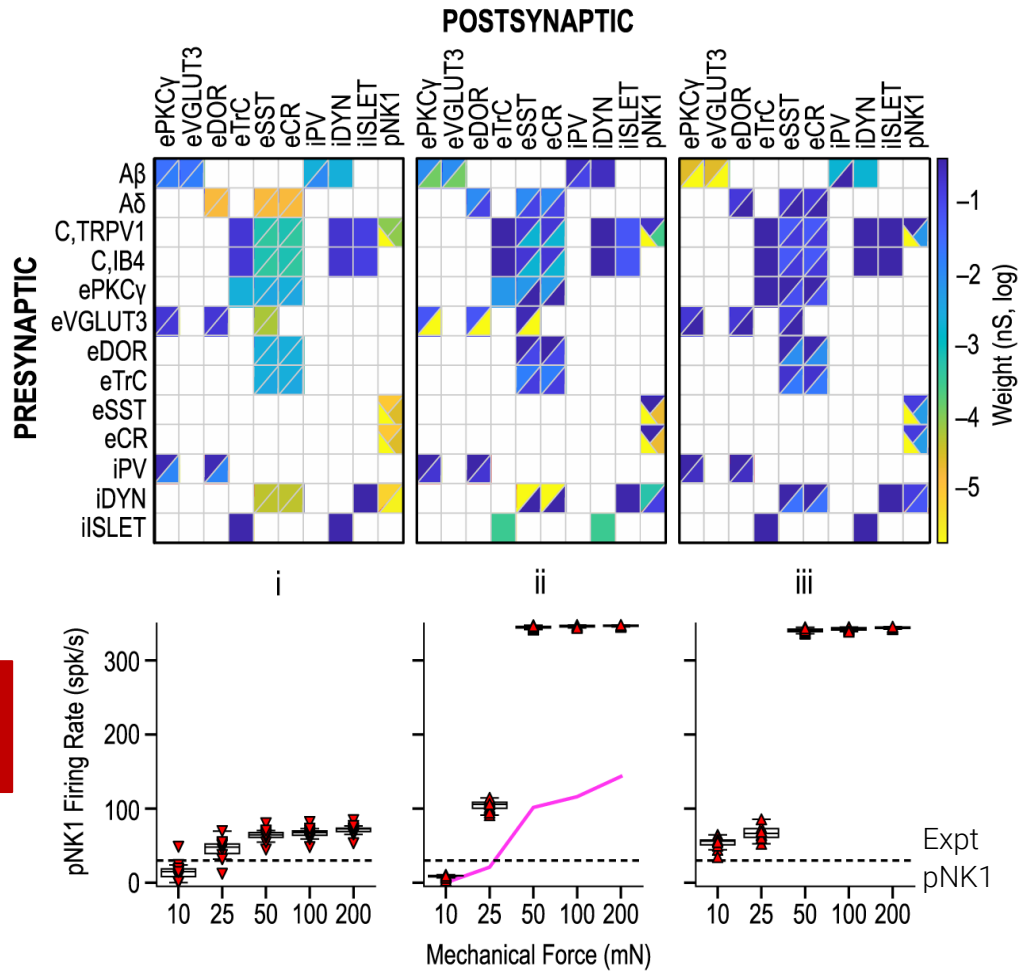


Inhibitory Receptor Block (wGABA/wGlycine=0)

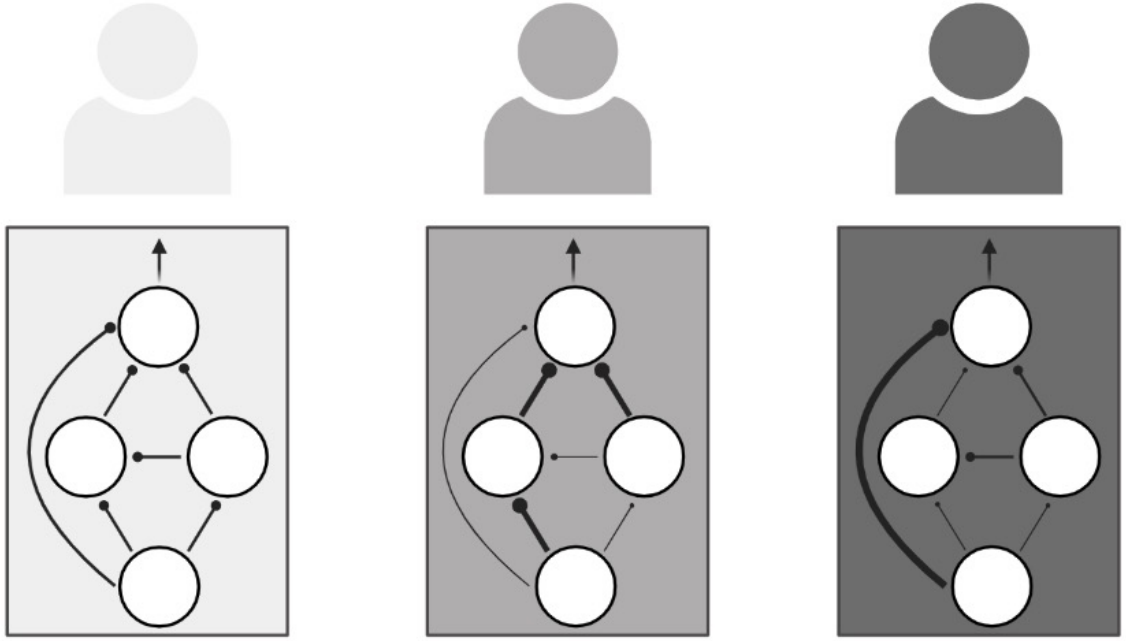
Different combinations of synaptic weights produce…

…different responses to pathological disinhibition

Also serves to validate the model!

Implications for Degeneracy in SDH

- Degeneracy in spinal circuit wiring may underlie heterogenous responses of different circuits to pathological insult or therapeutic intervention.



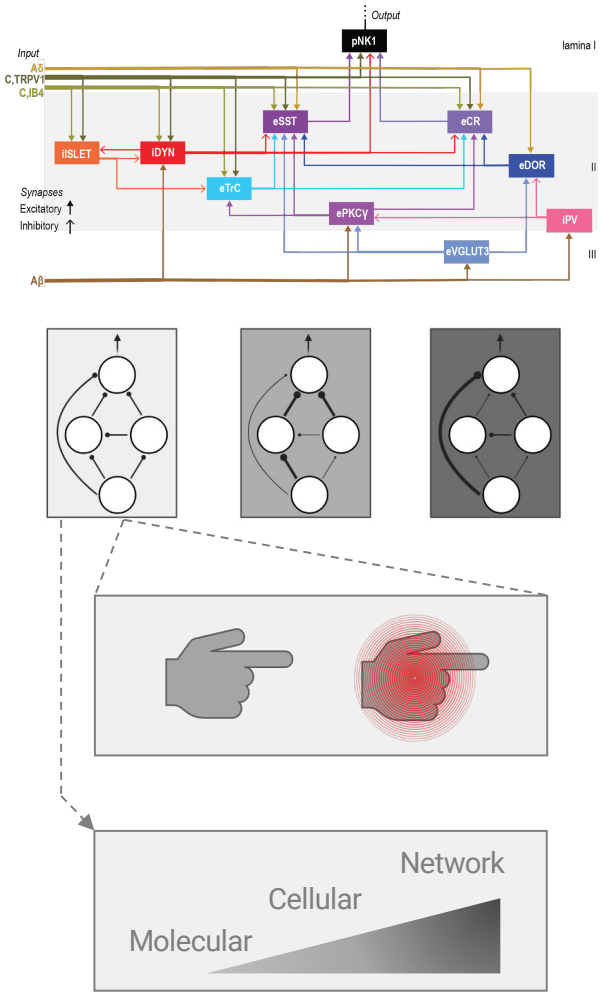
Summary & Conclusions

We have built a data-driven, multiscale model of the SDH circuit

Optimization of the model revealed circuit-level degeneracy in the SDH

Top model reproduces experimental data under normal and pathological conditions

The model provides a new tool for testing hypotheses *in silico*



Thank you!

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Dr. Salvador Dura-Bernal

SUNY Downstate, New York, US

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SCAN ME

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CIHR IRSC