3-Dimensional Computational Model of Neural Activity in the Central Nucleus of the Amygdala During Pain

Carley Reith[1, 2], Rachael Neilan[1], Benedict Kolber[2]

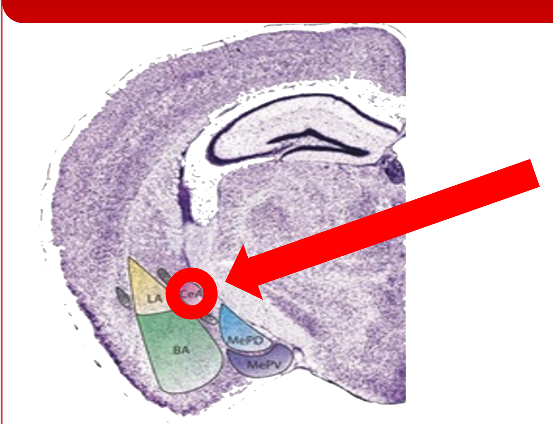
[1]Department of Mathematics and Computer Science, Duquesne University, Pittsburgh PA 15282

[2]Department of Neuroscience and Center for Advanced Pain Studies, University of Texas at Dallas, Richardson, Texas 75080

Abstract

The central nucleus of the amygdala (CeA) is a region of the brain important in pain processing. Neurons within the CeA expressing protein kinase c-delta (PKCδ) or somatostatin (SOM) have opposing roles in pain modulation. We created a 3-dimentional agent-based model (ABM) of these neuron populations and their connectivity in the CeA to predict system-level measures of pain. The model was programmed in Netlogo 3D, specialized software for designing and visualizing 3-D ABMs, and laboratory data was used to estimate model parameters. During the model's initialization, an ellipsoid is created to represent the CeA. Within the ellipsoid, 5000 agents representing individual neurons are created with cell-type specific properties and behaviors and a network of directed links between the neurons is established. During each model time step, neurons accrue damage based on the intensity of an external stimulus, and the firing rates of all neurons are updated. Inhibitory signals are sent between neurons via the network. If a neuron's incoming signals exceed a threshold, the neuron is silenced. At the end of each model time step, a system-level measure of pain is calculated as the difference in the cumulative firing rates of PKCδ and SOM neurons. Results demonstrate the ABM's ability to output both spontaneous and evoked pain in response to noxious stimuli. We continue to refine and adapt the ABM as new laboratory data emerges. Currently, we are enhancing the ABM to include a spatial domain that accurately reflects the topology of the CeA and its subregions.

Background



The central nucleus of the amygdala (CeA)

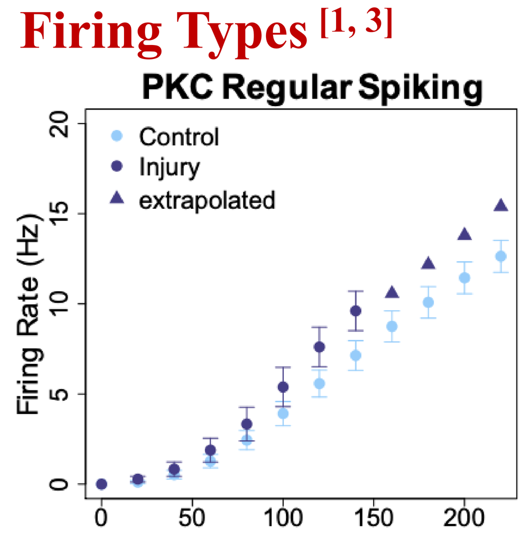
Two pain-related neuron populations in the CeA:

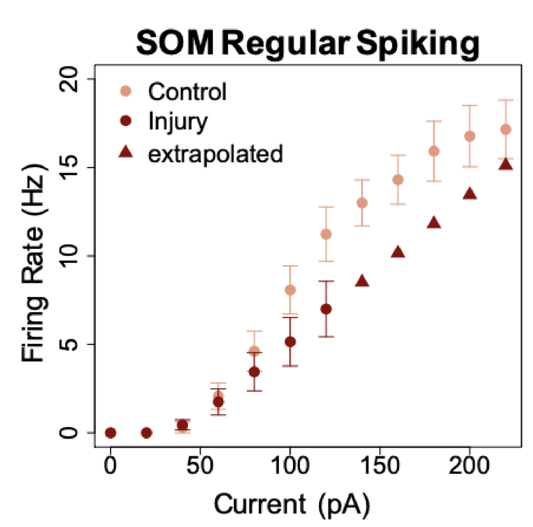
PKC-δ - increase pain. SOM – decrease pain.

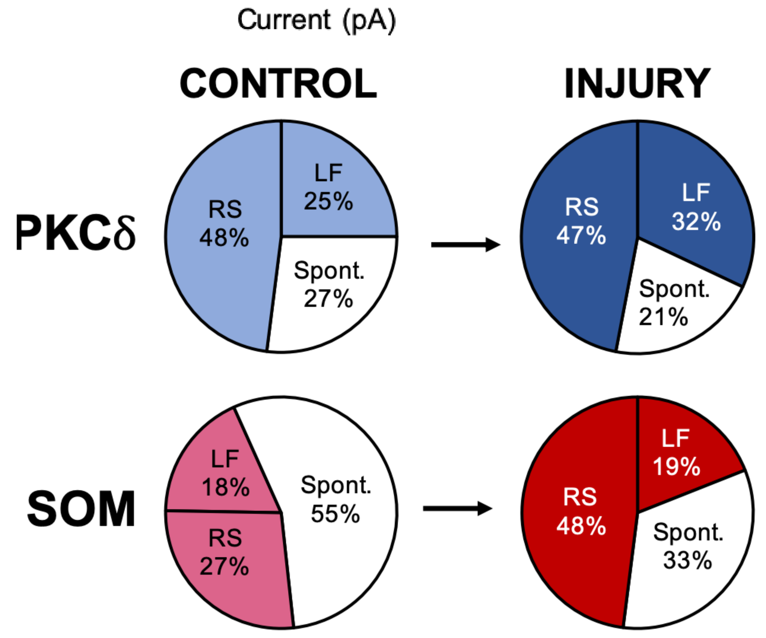
- **Quantity of Neurons**

PKC-δ: 682 (68%) SOM: 317 (32%)

- **Firing Types [1, 3]**







Proportions of regular spiking (RS), late firing (LF), and spontaneous (S) cells change during injury for SOM neurons only.

- **Morphology [2]**

PKC-δ

- Fewer, longer connections

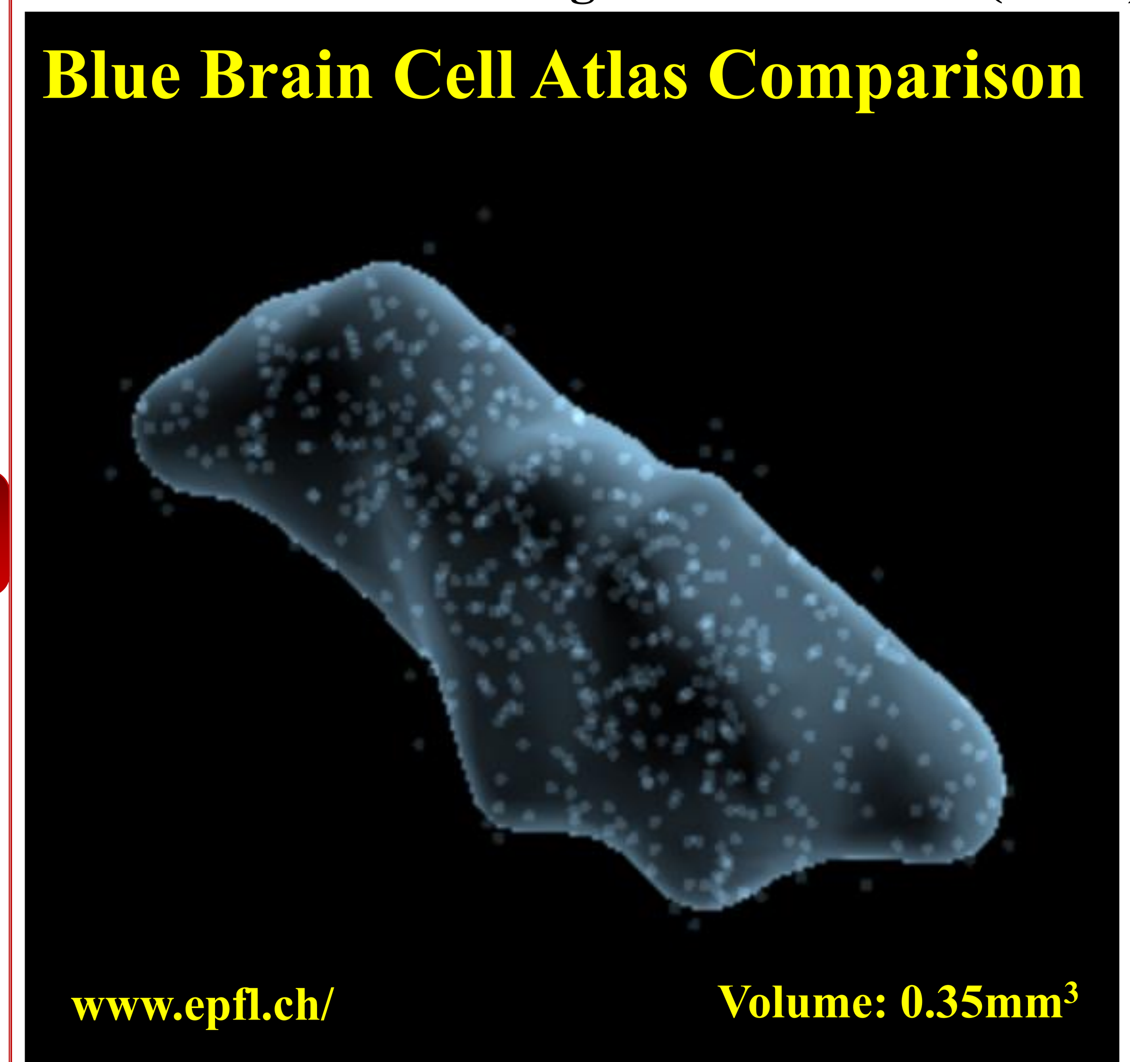
SOM

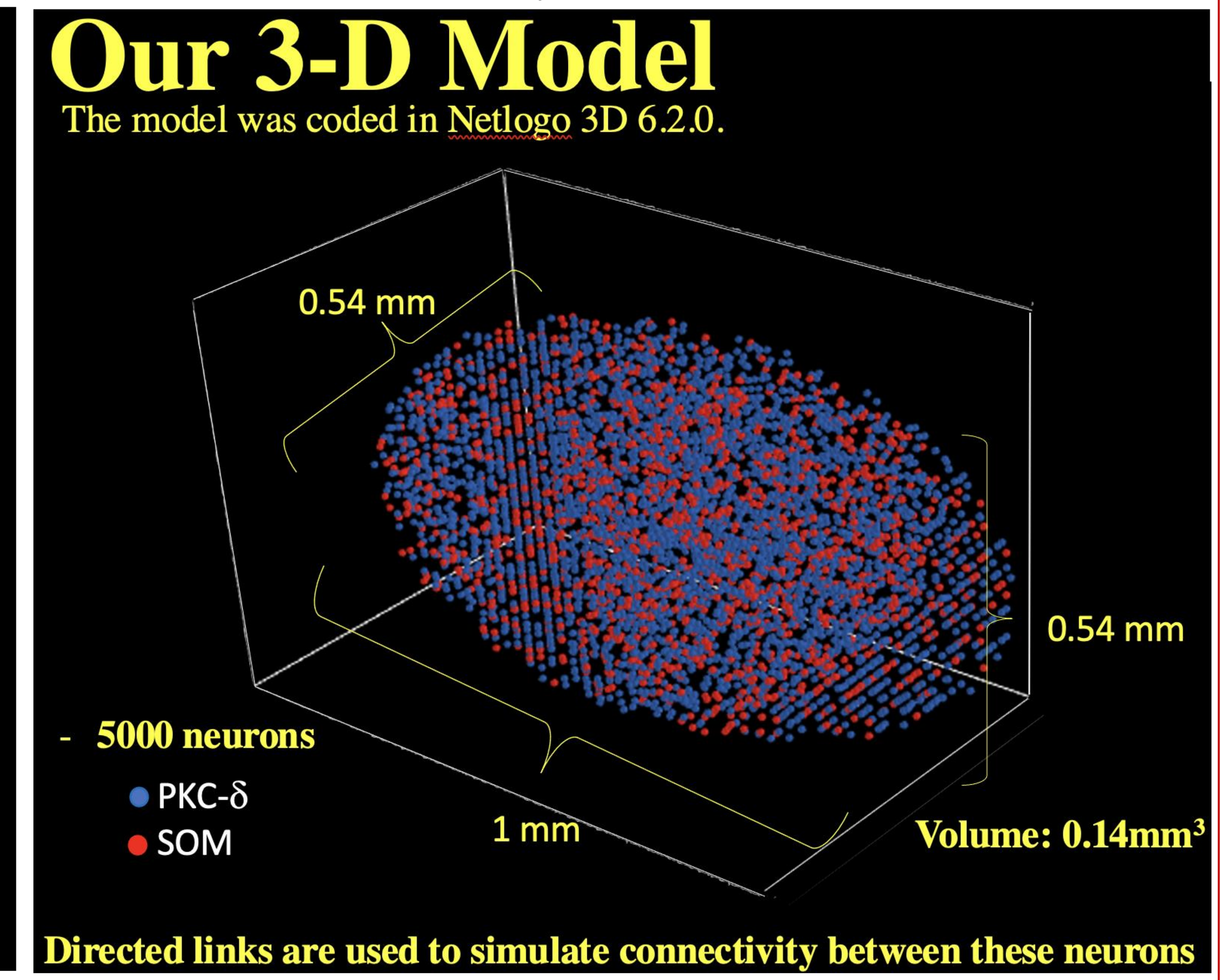
- More, shorter connections

Agent-Based Computational Model

Objective: Design a 3-dimensional computational model of PKC-δ and SOM neurons in the CeA for the purpose of predicting pain.

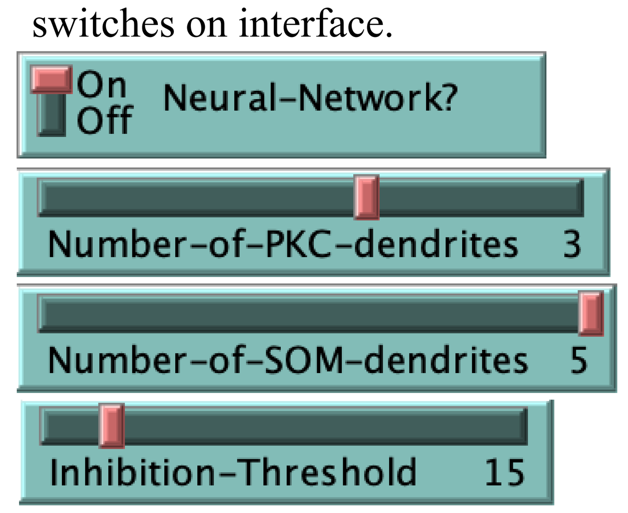
Methods: We used an **agent-based model (ABM)** to simulate neural activity in the CeA.



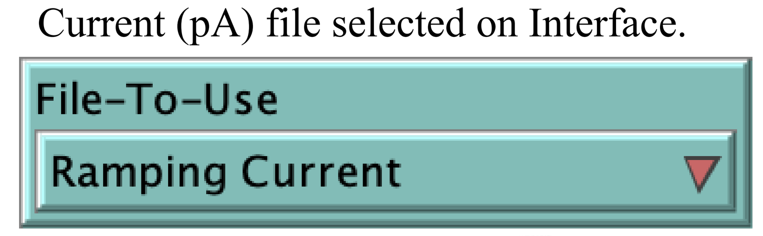


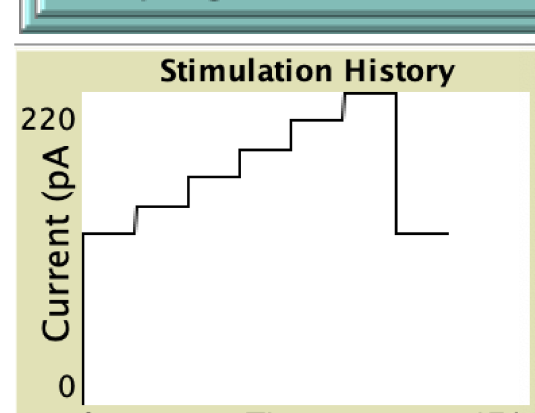
Model Initialization:

- Each neuron is assigned
  - random location
  - expression type (PKC-δ or SOM)
  - firing type (RS, LF, S)
  - other variables relating to damage accumulation
- Neural Network created based on sliders and switches on interface.



- Current (pA) file selected on Interface.



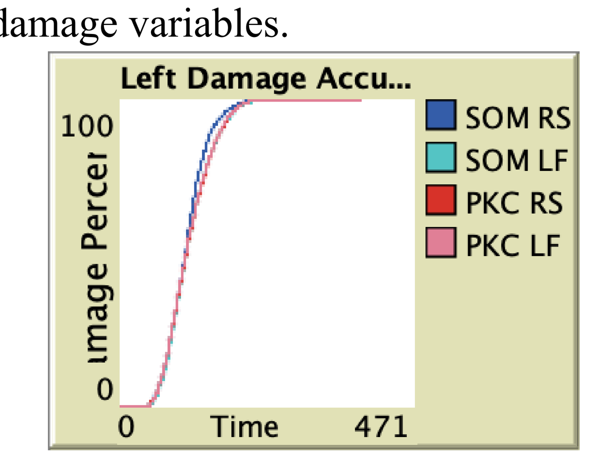


Current (pA) Output Graph on interface

Model Procedures:

At each time step

1. Each neuron's damage level (d) is updated depending on each neuron's current damage variables.



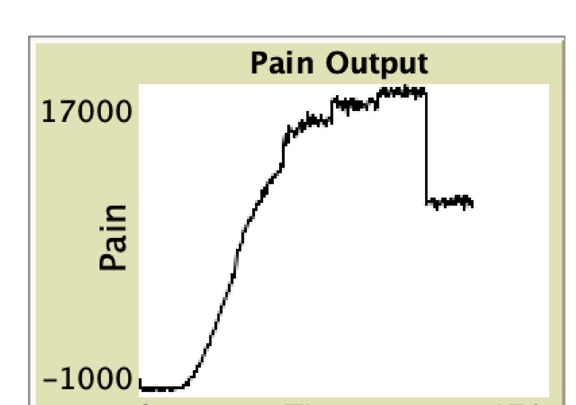
Damage Accumulation Output Graph on Interface

2. Each neuron's firing rate (FR) is stochastically updated using distributions estimated from lab data.

Firing rates are calculated using a linear combination of distribution X (from lab experiments on uninjured mice) and distribution Y (from lab experiments on injured mice).

$$FR = \frac{100 - d}{100} * X + \frac{d}{100} * Y$$

3. If neural network is turned on, neurons send inhibitory signals through directed links. For each neuron, if sum of incoming signals exceeds 15 Hz, then neuron is silenced (FR = 0).
4. System-level measure of pain (P) is calculated as difference in the cumulative firing rates of PKC neurons and cumulative firing rates of SOM neurons.



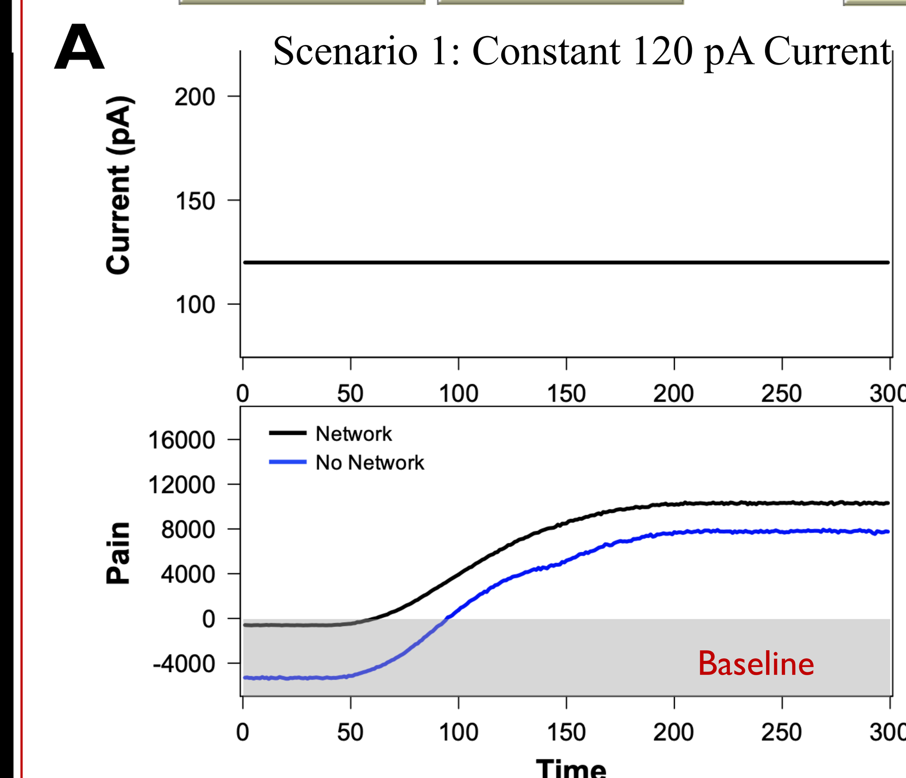
Pain Output Graph on Interface

$$P = \sum_{Type=PKC-\delta} \frac{d}{100} FR - \sum_{Type=SOM} FR$$

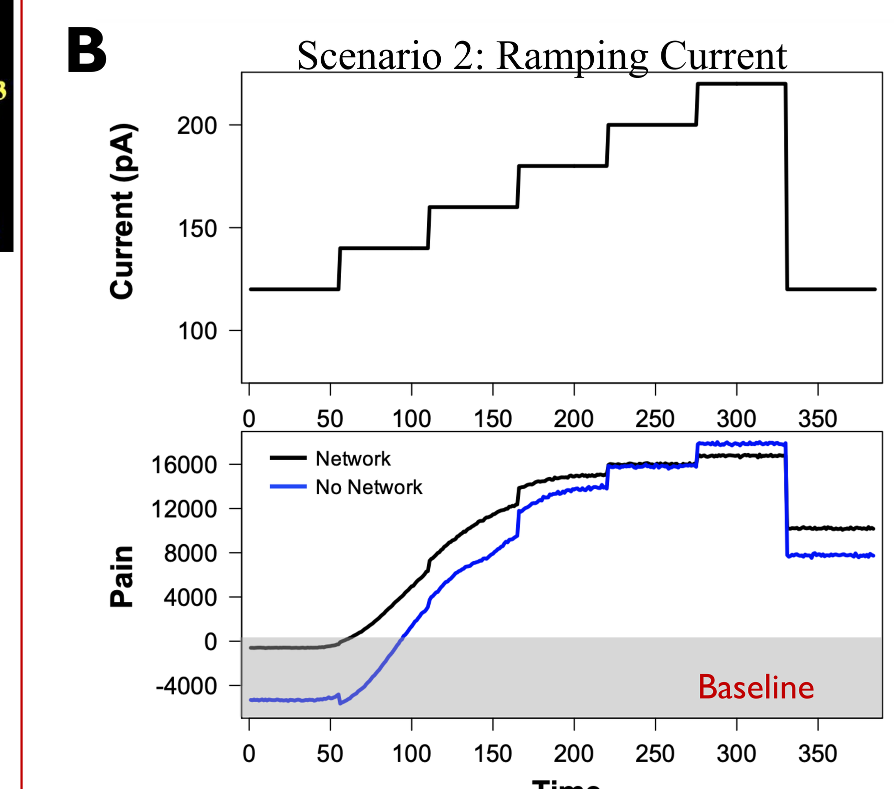
Results

The model's neural network preserves key connectivity properties.

% SOM->SOM	% PKC->SOM	Mean SOM link length (μm)
51.975	10.284	62.998
% SOM->PKC	**% PKC->PKC**	**Mean PKC link length (μm)**
14.95	20.52	122.549



Model output replicates both (A) spontaneous and (B) evoked pain



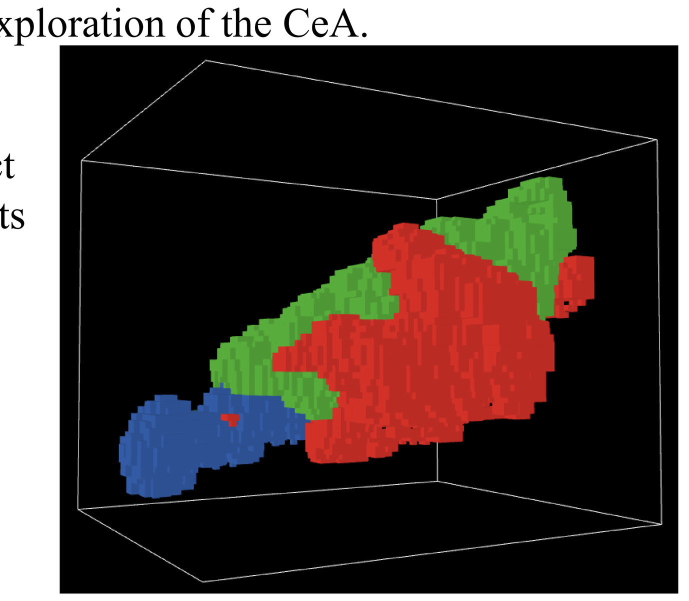
Neural network results in increased pain values except at high currents

Conclusion

- A computational model of the CeA was constructed and accurately represents the pain output and neural activity observed in the laboratory.
- Model contributes to the ongoing exploration of the CeA.

Next Steps:

- Refine model to capture the correct anatomical shape of the CeA and its sub-nuclei.



Spatial domain indicating the subnuclei of the CeA

(blue = lateral, green = medial, red = capsular)

Acknowledgment and Funding:

We thank Dr. Yarimar Carrasquillo (National Institute of Complementary and Alternative Health) for wet-lab data. Funding for CR was provided by R01 DK115478 (BJK and RN).

References:

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