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A Computational Perspective of Schizophrenia

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Introduction

The etiology of schizophrenia remains largely elusive, thus dampening the effectiveness of current treatment strategies. Abnormal neural migration and neurogenesis in the hippocampus have been suggested to be involved in schizophrenia (Jakob & Beckmann, 1994). A few approaches, including computational modeling, have investigated schizophrenia as a network disorder. Computational modeling uses mathematics to predict the behavior of biological systems based on the input of a set of parameters collected from laboratory experiments.

In this study, we constructed a computational model to explore the ramifications of additional PV neurons migrating to an aberrant location in the hippocampus and interfering with a closed-loop circuit between a preexisting PV neuron and 10 pyramidal neurons. Evidence suggests that PV neurons provide GABAergic input and oscillating gamma rhythmicity (30-80 Hz) to pyramidal neurons in the CA1 region of the hippocampus (Tukker et al., 2007). We predict that asynchronous release of action potentials from a migratory PV neuron will decrease the level of excitation and reduce the gamma-band activity in our closed-loop computational circuit. If this computational model can make an accurate prediction, it may serve to be a reliable tool to probe the direction of future research in not only schizophrenia, but in a wide range of mental afflictions.

Methods

Using the Neuron software developed by professors at Yale and Duke Universities, a computational model of 11 neurons was created to represent a closed-loop neural circuit located in the CA1 region of the hippocampus.

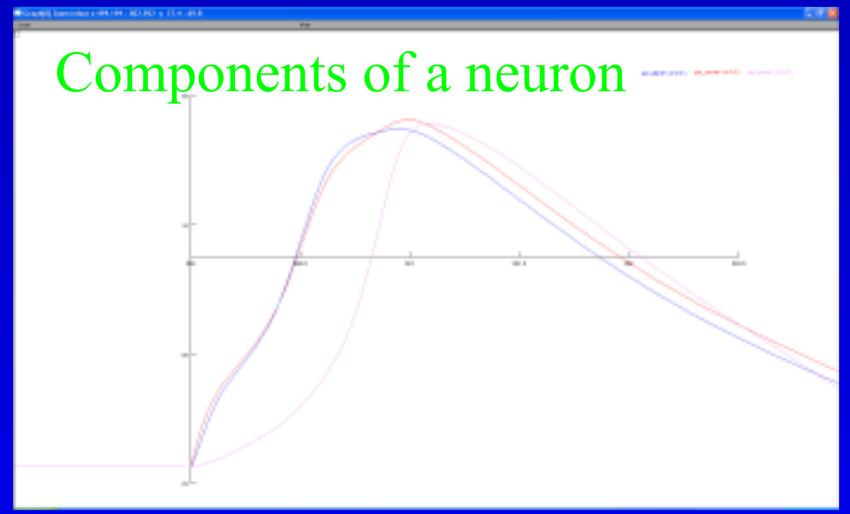
- The axon of 1 PV neuron (PV 1) was programmed to synapse with the dendrites of 10 pyramidal neurons.
- The 10 pyramidal neurons were set to receive random and continuous stimuli, collectively producing gamma-band activity (60Hz), to represent the input they would normally receive from other brain regions.
- A self-sustaining closed-loop system was created by having the axon of 1 pyramidal neuron (Pyramidal 1) synapse with the dendrite of PV 1.
- To represent a schizophrenia model, a second PV neuron (PV 2) was added with its axon synapsing with the dendrite of a pyramidal neuron in that same circuit (Pyramidal 2).
- PV 2 receives stimulation from an external neuron not part of the original circuit.
- This external neuron receives the same random and continuous stimuli as the 10 pyramidal neurons.

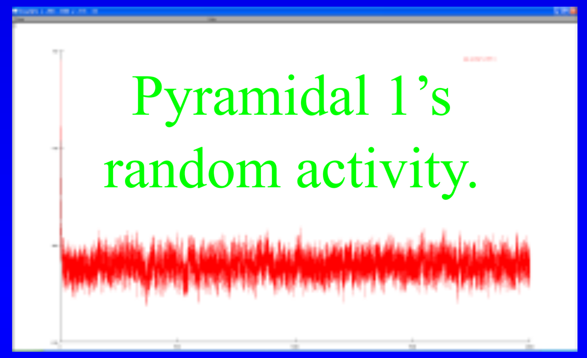
Data Analysis

Neuron displays a simulation of electrical activity recorded from the soma of each neuron programmed into the model. To aid in differentiating each neuron in this intricate ensemble, each neuron is color-coded.

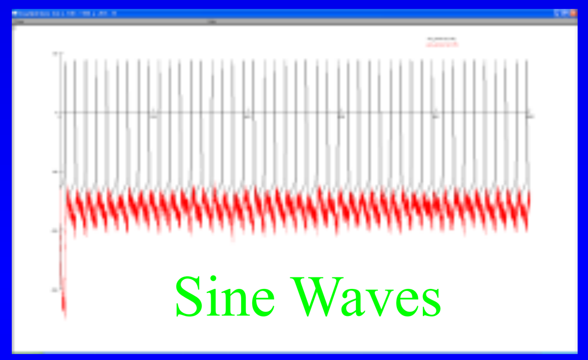
Results

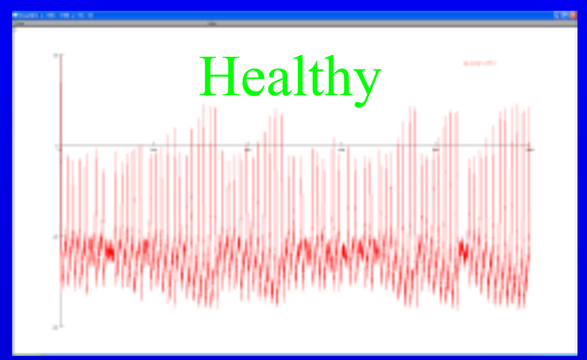
All of the components of a neuron were established. As the soma is stimulated with an IClamp once, the soma (red) increases voltage first and the axon (purple) increases voltage last. There is also evidence of backpropagation as the voltage changes in the dendrite (blue).



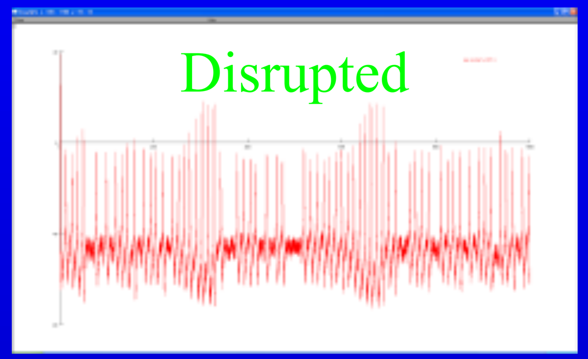


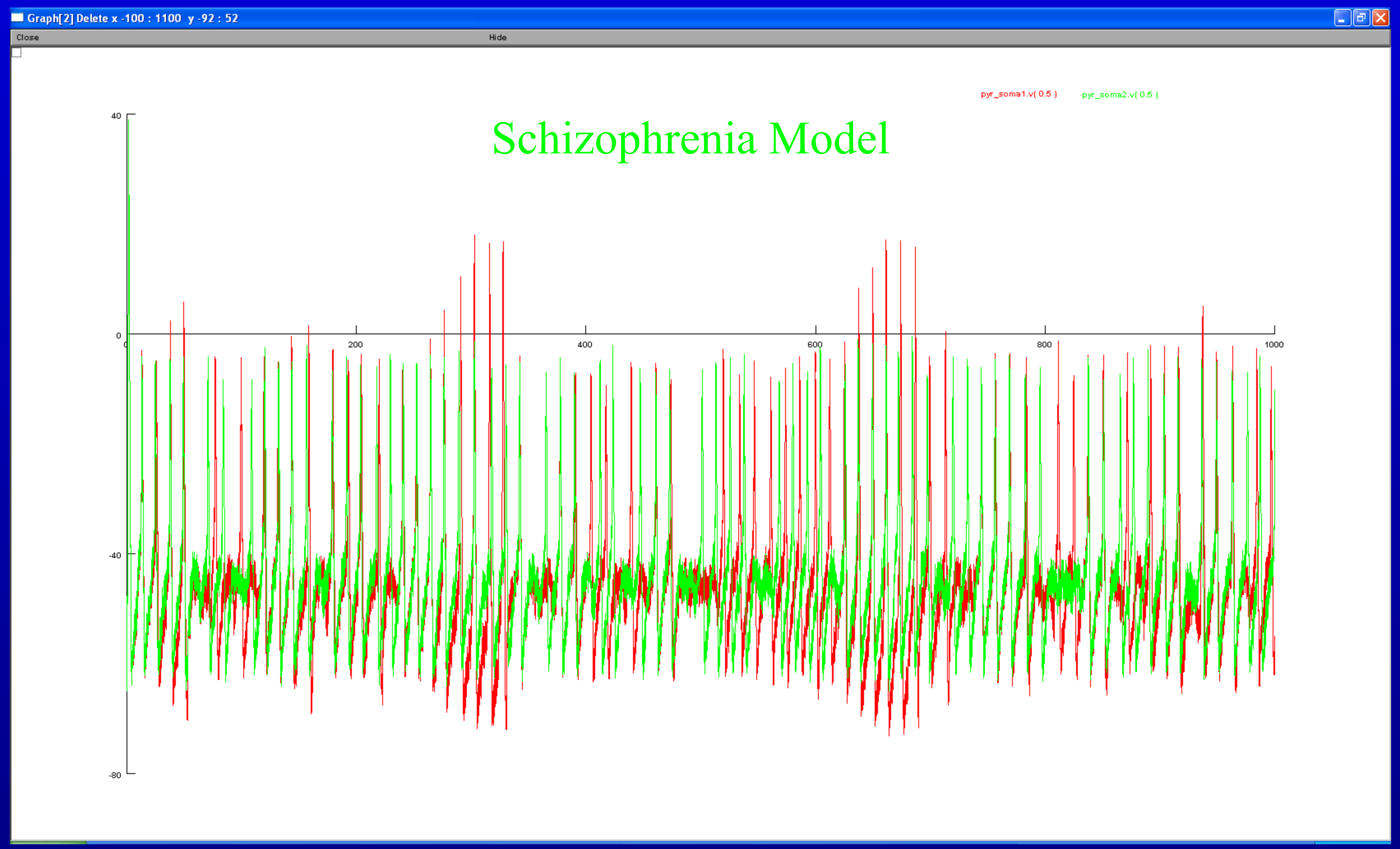
Pyramidal 1's (red) random activity transforms into sine waves when receiving input from PV 1.





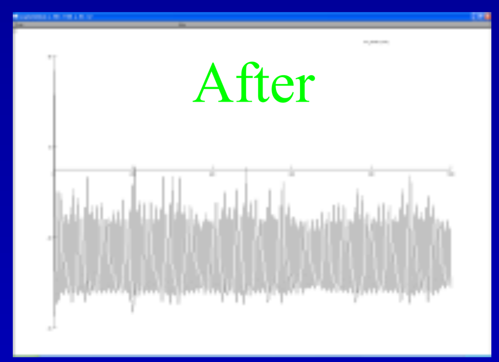
When PV 2 is added to the network, Pyramidal 1 (red) experiences more frequent and longer duration low peak voltage moments.





The asynchrony between Pyramidal 1 (red) and Pyramidal 2 (green) in the recurrent network is evident when PV 2 synapses with Pyramidal 2.

No apparent difference can be observed with PV 1 activity when PV 2 is added to the network.



Conclusion

Over the course of the summer, we constructed a computational model of a closed-loop circuit in the hippocampus and tested a possible mechanism involved in schizophrenia.

- Based on previous laboratory data, we designed a computational model of a healthy hippocampal circuit with gamma-band activity (60Hz)
- The insertion of an additional PV neuron decreased the level of excitation and reduced the gamma-band activity, exemplifying the indirect affect an additional PV neuron has on all of the pyramidal neurons in the circuit
- Apparent asynchronous behavior is noted in the pyramidal neuron that is directly connected to the additional PV neuron. This asynchronous behavior is consistent with in vivo data of schizophrenia
- The accuracy of the simulation can be improved by inputting biological parameters obtained in the laboratory, including sodium channel conductance and axon/dendrite lengths.

Future research could investigate these shortcomings and a more developed computational model can be designed to reevaluate

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