Glial ensheathment of inhibitory synapses drives hyperactivity and increases correlations

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Abstract:
Recent evidence highlights the active role of glial cells, such as microglia and astrocytes, in modulating neuronal dynamics through regulating neurotransmitter concentrations, ion buffering, and releasing neuroactive compounds. A notable recent study found that during and after anesthesia, microglia target inhibitory synapses for ensheathment, disrupting neurotransmitter flow between pre- and postsynaptic terminals. In this work, we develop computational models and mathematical frameworks to explore the effects this ensheathment has on neuronal dynamics.
We first extend a microscale synaptic cleft model to examine how varying strengths of synaptic ensheathment influence synaptic communication. Our findings align with prior work, showing that ensheathment accelerates synaptic transmission but reduces its strength. However, the previous model underestimates glial cells' ability to switch off synaptic connections. We integrate our updated model into a large network of exponential integrate-and-fire neurons with highly heterogeneous synaptic parameters determined by glial proximity. We extend linear response theory to account for this heterogeneity and use it to analyze not only network firing rate distributions but also noise correlations across excitatory neurons. Despite significant heterogeneity in the system, we find that our mean-field approximation accurately captures network statistics found in the spiking simulations.
Our model reproduces a key experimental finding, namely that increases in glial ensheathment of inhibitory synapses can lead to hyperactivity. It also makes the testable prediction that this ensheathment leads to significant increases in the power spectrum of the

excitatory population across a range of task-relevant frequencies. These results suggest that glial-driven synaptic plasticity is an underappreciated mechanism cortical circuits use to modulate recurrent dynamics.
