

Synaptic Integration of Entorhinal Cortical inputs to Dentate Gyrus Granule Cells: A Multiscale Computational Model for Investigating Hippocampal Response to Electrical Stimulation

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Recent advancements in neuroprosthetic systems and brain-computer interfaces present significant potential for recording and electrically stimulating the hippocampus, a brain region that is critical for the formation of long-term memory, thereby offering new opportunities for understanding its role, but also modulate and possibly enhance and restore its function. However, these advances are accompanied by considerable challenges due to the intricate architecture of neural tissue and the incomplete understanding of how electrical stimulation interacts with the hippocampal network. To address these challenges, we have developed a detailed computational model based on a rat hippocampal network that replicates its intricate architecture and integrates electrical stimulation via simulated neighboring electrodes.

Previous work (Bingham et al., 2018) introduced a computational model that simulates the effects of electrical stimulation on a 400 μm thick rat hippocampal slice. Building on this foundation, our model expands upon their work, offering an accurate depiction of the septal-to-temporal extent of the dentate gyrus, with a focus on axonal projections from entorhinal cortex onto their corresponding granule cell (GC) neurons and their dendritic structures. The simulation process consists of two stages: (1) generating a 3D model of hippocampal tissue with its associated resistivity to calculate the electric field distribution created by bipolar electrode stimulation; (2) utilizing this field data to stimulate the neurons within the tissue. The electric field distribution is determined using the admittance method (AM), while the neuronal network simulations are conducted in the NEURON platform. Notably, the resulting model incorporates detailed 3D reconstructions of the rat dentate gyrus derived from thin histological sections (Ropiredy and Ascoli, 2012). It also features a network model of the dentate gyrus that includes GCs and axon arbors from the entorhinal cortex (EC), connected to the GCs via the perforant path, with realistic axon arbor configurations generated using the Ruled-Optimum Ordered Tree System (ROOTS) algorithm (Bingham et al., 2020).

Using this multi-scale computational model, we investigated the effect of synaptic connectivity between myelinated EC axons and GCs. Our findings reveal that a minimum of 1600 synapses from both medial and lateral EC axons is required to initiate action potentials in GCs. Furthermore, we have explored various electrical stimulation parameters to identify the minimum current required to activate GCs. Our results indicate that a current amplitude of 500 μA (1 ms cathodic-first biphasic pulse) applied at the infrapyramidal blade is sufficient to activate GCs.

In addition, exploration of different electrode positions, such as the crest, suprapyramidal and infrapyramidal blade, highlights the significant influence of stimulation parameters and electrode placement on the spatial dynamics of GC activation. These insights contribute to a deeper understanding of the relationship between stimulation configurations and neural activation patterns, highlighting the merit of the proposed model to optimize electrode placement and configuration or to identify the most effective stimulation parameters, while providing critical insights into the neural responses elicited by electrical stimulation.