

Effect of Bipolar Electrode Location and Stimulation Parameters on Dentate Gyrus and Downstream Hippocampal Network Response: A Computational Study

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The hippocampus is one of the most studied regions of the brain due to its critical role in memory formation, spatial navigation, and emotional regulation. Located in the medial temporal lobe, it has been subjected to extensive recording and electrical stimulation to deepen our understanding of its anatomy and function, and evaluate the hippocampal input-output spatio-temporal dynamics in both health and disease. However, the effect of electrode placement and various stimulation parameters on hippocampal network response are not fully characterized. To address this, we propose to develop a computational model that comprises the entorhinal cortex (EC) axons and the granule cells they project to within the dentate gyrus (DG), a key region of the hippocampus, and investigate their response to electrical stimulation.

We first developed a 3D model of DG with two bipolar electrodes and one ground electrode. The bipolar electrodes, each with a diameter of 100 μm and separated by 500 μm , are positioned at the center of the septo-temporal extent, within the granule cell layer. The EC axons are located within the half of the DG adjacent to the positive electrode. The ground electrode is placed distal to the DG to simulate the configuration of a ground electrode positioned on the skin or scalp. We then used the admittance method (AM) to calculate the three-dimensional voltage distributions in and around the DG. Then, we reconstructed the EC axonal morphologies and granule cells, which form the initial components of the trisynaptic hippocampal network and further propagates to the downstream hippocampal regions CA3 and CA1. To do so, a detailed model of EC axonal morphologies and their synaptic connections to granule cells (GC) in DG was developed using the anatomical map by Gaarskjaer (1978), which includes measurements of length and neuron density across both the suprapyramidal and infrapyramidal blades of the DG.

The morphologies of the granule cells were generated using statistical data obtained from NeuroMorpho.org. We then utilized high-resolution serial histological sections (Ropireddy, 2012) to reconstruct the granule cell layer and create a 2D-to-3D map, which enabled the conversion of 2D coordinates obtained from Tamamaki and Nojyo (1993) into a 3D coordinate system. Finally, the 3D coordinates were realistically connected to generate the axonal arbors using the Ruled-Optimum Ordered Tree System (ROOTS) algorithm (Bingham, 2020). The EC axons were then assigned biophysical properties based on established experimental evidence. In total, we reconstructed approximately 60,000 EC axons and 600,000 granule cells, representing over 50% of the entire DG septo-temporal extent. We applied current-clamp stimuli to the bipolar electrodes, generating voltage distributions using AM in and around the DG; these voltages were then passed onto the NEURON simulation platform to simulate the response of EC axons and the granule cells. Series of current clamp simulations were run with varying current amplitudes using a fixed (1 ms) duration, and EC axons and GC responses were recorded, allowing us to quantify the activation profile as a function of current amplitude for the surrounding EC axons, as well as the downstream granule cells they project to.

Future work will extend these investigations to other stimulation parameters (e.g., stimulation duration, electrode insertion depth) and will expand the hippocampal model to include the downstream CA3 and CA1 subregions. These results present a use-case of the computational platform to guide the identification of stimulation parameters for a given desired outcome. The model thus constitutes an ideal testbed to investigate the effects of electrical stimulation, its parameters as well as electrodes placement on hippocampal tissue response, thereby facilitating the determination of optimal parameters ranges to illicit a specific desired response.