

# Optimizing Multi-Electrode Array Design, Placement, and Stimulation Patterns Using a Multiscale Multimodal Modeling Framework

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Patterned electrical stimulation is the most widely used method of modulating or restoring brain activity e.g. deep brain stimulation and hippocampal cognitive prosthesis. However, given the difficulty and complications in implanting the multi-electrode arrays (MEAs) used to perform the electrical stimulations and the lack of a means to validate and verify the effects of the implanted system, there exists a need to be able to model the interactions that ultimately result in an electrically stimulated spatio-temporal pattern. Using such a model, the design and placement of the electrodes as well as the stimulation patterns may be optimized in order to construct an array that achieves the maximum desired effect. We have developed a multimodal approach combining an electric field admittance model and a multiscale model of the rat hippocampus in order to accomplish this goal. This approach allows us to model the interactions between the intracellular and extracellular dynamics of the system to accurately predict the response to electrical stimulation. Tissue conductance parameters that vary spatially according to the anatomy of the hippocampus have been implemented in the admittance model to predict the electric field spread due to a biphasic current pulse. Multi-compartmental neuron models have also been constructed and placed following the same anatomy with realistic morphologies, active and passive membrane properties, and anatomically-derived topography to model the response to the external electric field and the propagation of activity through a hippocampal slice. We have modeled the dentate gyrus in a hippocampal slice and are in the process of including the CA3 and CA1 regions with the overall goal to model the entire hippocampus. With this system, we are able to simulate multiple electrodes in user-defined orientations and investigate the resulting activity elicited by arbitrary stimulation patterns. As MEAs and stimulus patterns approach a finer level of spatial and temporal sophistication this modeling approach provides a useful tool for optimizing such arrays and maximizing the effectiveness of electrical stimulation-based therapy.

# Bridging Biomolecular Mechanisms to Multicellular Networks in a Multiscale Model of the Hippocampus Using Input-Output Modeling

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Experimental studies have repeatedly shown that even single protein mutations can significantly affect the behavior and performance of an animal in response to a task. In order to investigate how lower-level mechanisms can cascade into and affect high-level system behaviors, we have developed a multiscale modeling framework that incorporates detailed mechanistic models from the biomolecular level to the systems neural network level in order to study the rat hippocampus. However, embedding every instantiation of lower level models across successive scales would be computationally overwhelming and practically infeasible. To solve this problem, we have developed non-parametric, input-output models of the mechanistic models to bridge the levels of scale. Specifically, we have simulated broadband input-output data with EONS, a highly detailed, mechanistic synaptic model. Then the input-output data are used to build a surrogate Volterra model-based, non-linear dynamical model that captures the input-output transformational property of the mechanistic model with much simpler mathematical forms. The synaptic input-output models are inserted into multi-compartmental neuron models with realistic morphologies and active and passive membrane properties. Thus, the lower-level scale is converted into an input-output model that provides input to the next hierarchical level. Anatomically-derived topography is then used to specify the connectivity of the large-scale neuron population. Through this framework, we can create a more computationally efficient model while preserving the accuracy in order to capture the interactions across multiple scales and link changes at the protein level to systemic activity, and we have demonstrated the application of our hybrid mechanistic/input-output multiscale framework to a large-scale, biologically realistic, computational model of the rat hippocampus.