Bridging Biomolecular Mechanisms to Multicellular Networks in a Multiscale Model of the Hippcampus 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.