DATA-DRIVEN, BIOLOGICALLY CONSTRAINED COMPUTATIONAL MODEL OF THE HIPPOCAMPAL NETWORK AT FULL SCALE

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EXECUTIVE SUMMARY

We have extensively validated a first-of-its-kind 1:1 scale, strictly biological data-driven computational network model of the CA1 region of the rodent hippocampus. The model spontaneously generates theta oscillations, which occur in the brain during locomotion and spatial navigation. Theta oscillations are critical to the formation of episodic memory, which associates events with places. We have simulated a large number of perturbed network configurations in order to determine the range of parameters and conditions that are necessary and sufficient for the emergence of the theta oscillations. In addition, we have conducted initial simulations that mimic realistic spatial information input from the entorhinal cortex, which is the principal source of information for the hippocampus. These results confirm that our computational models are capable of replicating major dynamic phenomena in the hippocampus and provide a stepping stone to modeling cognitive processes associated with the hippocampus such as episodic memory.

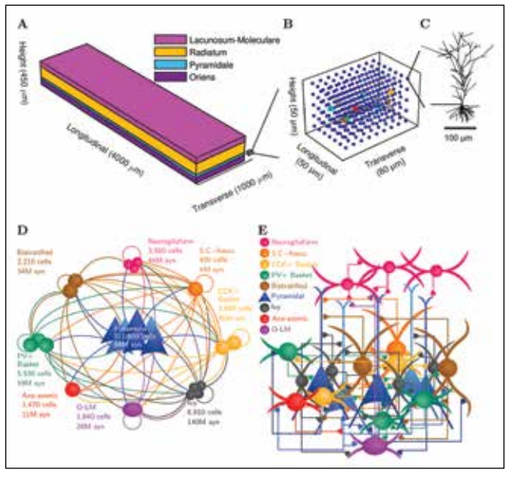

Figure 1: Structure of the CA1 network model. (A) The model network has dimensions identical to the rat hippocampus, (B) model cell bodies laid out in their respective layers, (C) detailed morphology and synapse placement for each model neuron, (D) illustration of the connectivity types, (E) the characteristics of each connection are constrained by experimental data.

RESEARCH CHALLENGE

The main goal of the project is to study the mechanisms that govern the emergence of characteristic oscillatory behavior in the hippocampal network and its implications for information processing using 1:1 scale biophysical computational models that are closely based on electrophysiological, morphological, and imaging data. The hippocampal circuits that store and recall information are comprised of diverse cell types, each exhibiting distinct dynamics and complex patterns of synaptic connectivity. Thus, even highly specific experimental perturbations of a single component of these neuronal circuits can have highly nonlinear and counterintuitive effects on their internal dynamics and output. Our computational models offer a framework to integrate knowledge and quantitatively predict how each element of a neuronal network is expected to respond to specific perturbations. Our computational models completed so far represent a major milestone in the development of large-scale, anatomically and biophysically realistic models of the brain, which allow for the generation and testing of hypotheses concerning synaptic and network mechanisms of behaviorally relevant oscillations with unparalleled biological realism and precision.

METHODS & CODES

Our principal simulation environment is NEURON 7.4 [1]. NEURON is designed to simulate neuronal models that are described in terms of the membrane properties and geometric structure of neurons [2], and supports computationally efficient representation of connections among neurons in a network [3].

NEURON is formulated around the notion of continuous cable "sections" that can be connected together to form any kind of branched cable. A section can be assigned properties that vary continuously with position along its length. User-defined biophysical properties of membranes, such as ion channel dynamics, are described in terms of differential equations, kinetic schemes, and sets of simultaneous equations. These model descriptions are compiled to C, so that membrane voltage and gating states can be computed efficiently using an implicit integration method optimized for branched structures [2]. NEURON is very well supported and has been used in more than 1,532 publications as of September 2014 and can be fully parallelized [2]. NEURON includes an introspective interpreter for simulation code (HOC or Python) that is flexible and supports a wide range of model description paradigms.

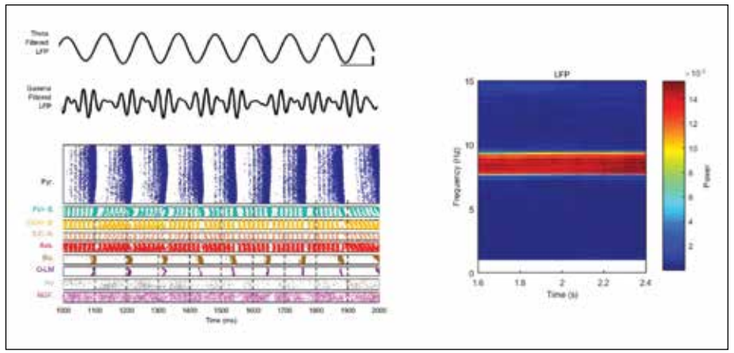

Figure 2: Oscillatory network activity of the CA1 model. (A–B) Local field potentials (LFP) generated by the model, filtered at (A) theta (5–10 Hz) or (B) gamma range (25–40 Hz) show clear oscillatory activity. (C) Neuronal spike times generated by the model. (D) Spectrogram of LFP shows the stability and intensity of the theta oscillation.

RESULTS & IMPACT

We have made major advances toward achieving our aims. Specifically, we have extensively validated a first-of-its-kind 1:1 scale, strictly biological data-driven computational network model of the CA1 region of the rodent hippocampus. The model spontaneously generates theta oscillations, which occur in the brain during locomotion and spatial navigation. In addition, we have studied large numbers of perturbed network configurations in order to determine the range of parameters and conditions that are necessary and sufficient for the emergence of the theta oscillations. Furthermore, we have advanced our technique for generating biologically realistic dendritic trees and applied it toward constructing a 1:1 scale model of the dentate gyrus (DG), another major hippocampal region and a key component of our modeling efforts. We have conducted a number of control simulations to validate the dynamic behavior of this model and tuned its synaptic parameters so that its spatial coding properties are consistent with recently published experimental results. These advances, which have never been achieved in computational neuroscience before, are critical for ensuring that our computational models have capabilities for processing spatial information that are comparable with those of the rodent hippocampus.

The CA1 model that we have completed during the project period is capable of spontaneous generation of theta and gamma oscillations, replicating published studies. In addition, we have analyzed the firing patterns of each neuron type in the network. Next, we have conducted extensive work on perturbing various network and neuronal parameters to determine the relative contributions of each component to the generation of biophysically relevant oscillations. The model neurons exhibited firing patterns relative to the global network oscillations that are consistent with recently published experimental data. This is a major advance that indicates that the characteristic firing patterns of hippocampal neurons are possibly a function of the intrinsic network wiring.

Furthermore, we have tested whether theta rhythm was differentially sensitive to the contribution of each inhibitory neuron type, as well as the intrinsic properties of each interneuronal type by respectively muting the output of different neuron classes or configuring all neuron models with the same electrophysiological profile. Theta oscillations were not apparent in any of these perturbed configurations and, therefore, these results indicate, for the first time, that interneuronal diversity itself is an important factor in the emergence of biophysical oscillations in the CA1 network.

WHY BLUE WATERS

In order to simulate realistic spatial navigation and formation of place cells, the simulations must be long enough to reflect the brain's changing representation of space during locomotion. A typical behavioral experiment with animals running on a linear track has a duration of tens of seconds, and therefore our simulations must have a minimum duration of 10 seconds in order to be comparable to behavioral experiments. Simulations of our CA1 model of 10 seconds of physical time took 14 hours to run on 1,024 Blue Waters nodes. It would not have been practical or affordable to conduct simulations of such scale on other publicly or commercially available computational platforms. Our research plans require the ability to run even longer simulations of the combined hippocampal model, and for those only Blue Waters can provide the necessary computational capacity.

PUBLICATIONS AND DATA SETS

Bezaire, M., et al., Interneuronal mechanisms of hippocampal theta oscillations in a full-scale model of the rodent CA1 circuit. *eLife*, 5:e18566 (2016), DOI: 10.7554/eLife.18566.

Bezaire, M., I. Raikov, K. Burk, D. Vyas, and I. Soltesz, Computational model of CA1 network on ModelDB, accession number: 187604.

Bezaire, M., I. Raikov, K. Burk, D. Vyas, and I. Soltesz, Simulation results from full scale and rationally reduced network models of the isolated hippocampal CA1 subfield in rat on CRCNS.