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

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EXECUTIVE SUMMARY

Our work is the first attempt to use a detailed computational model for each neuron in the hippocampus, a brain area important for learning and memory, to fully understand how memories are formed in the brain. The computational capacity of Blue Waters allows us to rapidly conduct simulations of brain function, to observe and record the behavior of millions of neuron models, and to compare the results with experimental data. We have developed methodological advancements to our models to allow unprecedented biological realism and increased computational efficiency, including software tools to manage large data sets on supercomputers and a novel method for model optimization, the process used to fit mathematical models of neurons to experimental data.

RESEARCH CHALLENGE

Our research aims to elucidate the mechanisms of sharp-wave ripples (SWRs), which are oscillatory events in the hippocampus that are required for memory consolidation and subsequent recall. To support this goal, our computational projects aim to construct full-scale, biophysically detailed computational models of the three major neuronal circuits within the mammalian hippocampus: the dentate gyrus (DG), CA3, and CA1. These models will be used to provide insight into the dynamical properties of hippocampal networks that produce the SWR-specific oscillatory patterns. Furthermore, we propose to utilize our full-scale models to study the mechanisms of abnormal dynamics that emerge in epilepsy or through radiation damage.

METHODS & CODES

The principal simulation environment we use is NEURON [1], which describes neurons in terms of membrane properties and geometric structure [2], and networks in terms of connections between neurons [3]. The biophysical dynamics of the neuronal membrane are described by differential–algebraic equations solved by an implicit integrator optimized for branched structures [1]. NEURON can be fully parallelized via MPI with near-linear scaling [3].

The representation of the geometric structure of neurons and their connectivity requires hundreds of gigabytes for each of our models, which has necessitated a parallel computational infrastructure for data management. Thanks to the Petascale Application Improvement Discovery program, we have developed a parallel I/O software substrate based on the HDF5 file format that allows the rapid generation and analysis of neuronal morphology and connectivity data according to user-specified rules about neuronal structure and distribution of connectivity in a 3D volume.

An important step in the development of biological neuronal network models is optimizing the neuronal cell models to fit experimentally observed biophysics. The corresponding objective

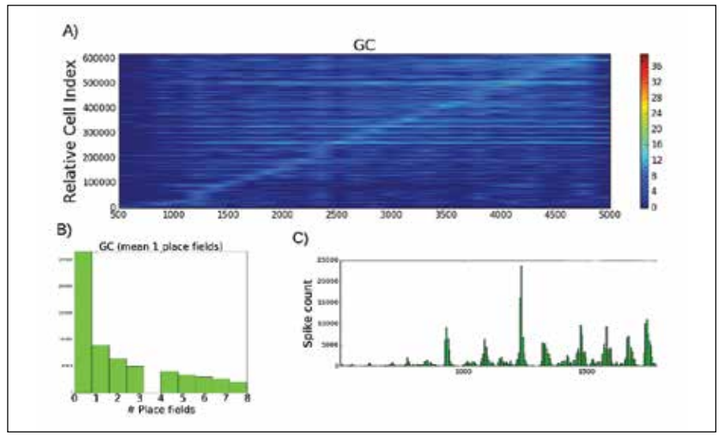

Figure 1: (A) Firing rate map of granule cells, ordered by peak firing rate. (B) Rhythmic population activity of the major cell types in the network. (C) Consistent with experimental observations, the granule cells in the model have a mean 1 place field and a log-normal distribution of number of place fields.

functions are highly nonconvex, resulting in poor performance by gradient-based approaches. We have developed a new optimization algorithm, "population annealing," that combines aspects of simulated annealing and genetic algorithms to achieve multiobjective optimization in parallel with fewer overall function evaluations (roughly 150 iterations with around 200 models per generation as compared to more than 500 iterations in previous genetic algorithm-based approaches).

RESULTS & IMPACT

We have recently completed the first of its kind, full-scale, anatomically and physiologically constrained model of the CA1 subregion of the hippocampus [4], which contains 300,000 pyramidal cells and 30,000 inhibitory interneurons. We are in the process of tuning the physiological properties of our full-scale model of the dentate gyrus (DG) subregion that is likewise anatomically and physiologically constrained. The DG model contains one million granule cells with unique generated realistic dendritic morphologies depending on its position in the DG volume [5], 30,000 mossy cells, and approximately 20,000 inhibitory interneurons. Simulations of the DG network model thus far can reproduce an important phenomenon in the hippocampus—the formation of "place cells," which are neurons that encode the physical location of an animal during spatial navigation [6] (Fig. 1).

A necessary major technical innovation has been the development of synapse models that can capture the characteristic process of activity-dependent synaptic saturation, which prevents uncontrolled increase of synaptic conductance and excessive neural firing and plays a crucial role in information transfer between neurons. Previous models have implemented saturation by maintaining unique state variables for each connection, which results in excessive memory use. We have implemented an efficient scheme that tracks the activity of each connection, yet permits use of shared state variables between connections, which results in an approximately three-fold reduction of simulation runtime of our models on Blue Waters (Fig. 2).

Our approach to modeling neuronal networks with realistic cellular diversity and spatial topography provides a detailed understanding of how information propagates in the brain, and how the diverse oscillatory dynamics of brain networks emerge. Thus far, it has not been possible to investigate these parameters with reduced-scale models, where network dynamics are potentially strongly distorted [7]. Furthermore, particular types of high-frequency oscillations are the hallmark of focal epilepsy and are hypothesized to have a causal role in the initiation of seizures, yet these oscillatory patterns have proven difficult to replicate in prior computational models. Altogether, our software infrastructure for large-scale neuronal modeling offers a pioneering methodology for rapidly developing, validating, and measuring the information-processing capabilities of realistic, biophysically detailed networks of millions of neurons.

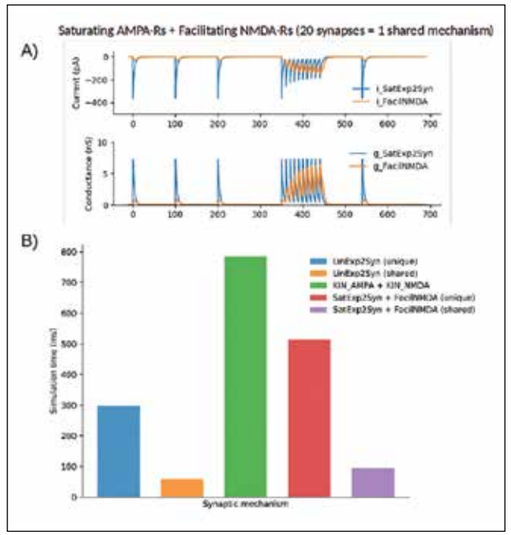

Figure 2: Synaptic mechanisms for full-scale simulations. (A) Biophysically realistic postsynaptic responses of two major types of synapses, a saturating AMPA and facilitating NMDA receptor. (B) Simulation performance: simplified exponential rise and decay LinExp2Syn; physiologically detailed KIN_AMPA and KIN_NMDA; saturating and facilitating mechanisms optimized for connection sharing SatExp2Syn and FacilNMDA.

WHY BLUE WATERS

Our research requires the simulation of behaviorally relevant brain activity on the scale of tens of seconds. In our first year of using Blue Waters, 10-second simulations of our models took 14 to 19 hours to run on 1,024 Blue Waters CPU nodes. Thanks to the PAID program and the technical expertise of Blue Waters' staff, we have reduced the runtime to three or six hours on 1,024 or 2,048 nodes, respectively. Only Blue Waters can permit longer simulations of the eventual combined hippocampal model. The important discoveries revealed by our simulations underscore the essential need for public petascale computing resources such as Blue Waters.

PUBLICATIONS & DATA SETS

Raikov, I., A. Milstein, I. Soltesz, Determinants of sparse population coding in a computational model of the rat dentate gyrus. *Society for Neuroscience*, Washington, D.C., 2017.

Milstein, A., et al., Place field translocation by bidirectional behavioral time-scale synaptic plasticity. *Computational and Systems Neuroscience (Cosyne)*, Denver, Colo., 2018.