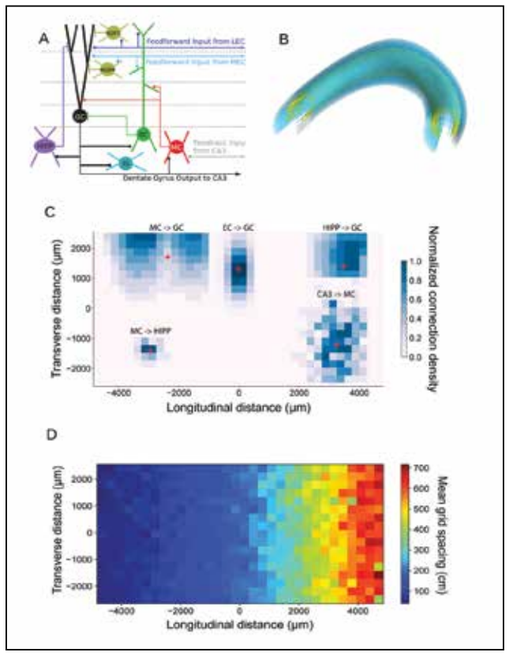
FULL-SCALE BIOPHYSICAL MODELING OF HIPPOCAMPAL NETWORKS DURING SPATIAL NAVIGATION

Allocation: NSF PRAC/8,150 Knh
PI: Ivan Soltesz[1]
Collaborators: Ivan Raikov[1], Aaron Milstein[1], Darian Hadjiabadi[1]

[1]Stanford University

EXECUTIVE SUMMARY

This work is the first attempt to fully understand how memories are formed in the brain by means of a detailed computational model of each neuron in the hippocampus, a brain area important for learning and memory. The computational capacity of Blue Waters allows the research team to rapidly conduct simulations of brain function at 1:1 scale, to observe and record the behavior of millions of model neurons, and to compare the results with experimental data. The researchers' model is capable of representing spatial location via the activation of a small number of neurons sensitive to a specific location, closely approximating the navigational system used by the brain. Further, the software infrastructure developed for this project is now allowing the team to explore several hypotheses about the formation of neural sequences as part of the process necessary for storing memory traces.



RESEARCH CHALLENGE

This 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, the research group's computational projects aim to construct the first-of-its-kind, full-scale, biophysically detailed computational models of the three major neuronal circuits within the mammalian hippocampus: the dentate gyrus, 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, the team proposes to utilize their full-scale models to study the mechanisms of abnormal dynamics that emerge in epilepsy.

METHODS & CODES

The principal simulation environment the researchers use is NEURON [1], http://www.neuron.yale.edu/neuron/, 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 message passing interface with near-linear scaling [3].

The representation of the geometric structure of neurons and their connectivity requires hundreds of gigabytes for each of the models, which has necessitated a parallel computational infrastructure for data management. Thanks to the Petascale Application Improvement Discovery program, the research team has 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.

The construction of biophysical models of neurons involves tuning a set of parameters in order to make the model neuron dynamics closely match experimental recordings of real neurons. Because of complex dendritic geometry and nonlinear ion channel dynamics, the model parameter space is enormous. The team has devised a multiobjective evolutionary optimization algorithm that varies ion channel distributions in order to fit the experimentally obtained electrophysiological properties of the target neuron type. This optimization method can be applied not only to models of diverse neuron types but also to a number of other problems ranging from the study of information processing in microcircuits to parameter tuning of large-scale network dynamics.

Figure 1: (A) Circuit structure of dentate gyrus model. (B) 3D anatomy and cell body distribution. (C) Distance-dependent connectivity structure between different neuron types. (D) Topological distribution of grid cell inputs with different spacing to dentate gyrus.

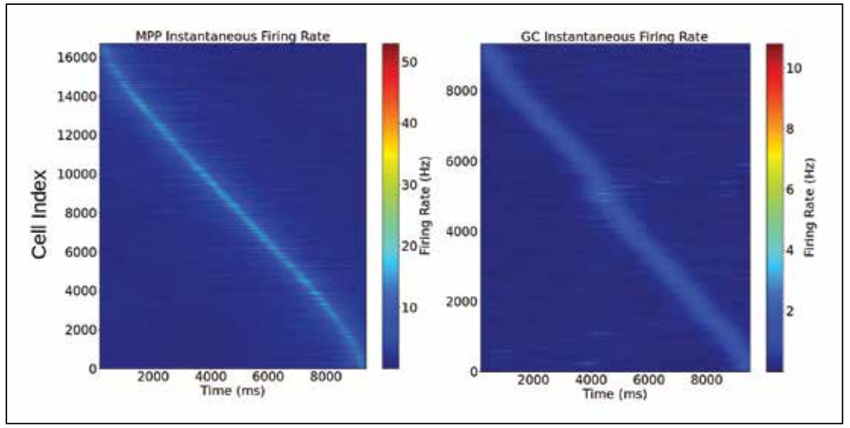


Figure 2: (A) Firing rate map of simulated spatial inputs to dentate gyrus model. (B) Firing rate map of granule cells, ordered by peak firing rate. Consistent with experimental observations, the granule cells in the model exhibit highly sparse activity, with approximately 1% active cells on a given trajectory.

RESULTS & IMPACT

The research team has made significant progress in developing a biophysically detailed, full-scale model of the rodent hippocampus comprised of realistically diverse cell types, cell-type-specific connectivity, and nonuniform distributions of synaptic input strengths. The researchers have constructed a full-scale model of the input layer to the hippocampus, the dentate gyrus (DG), to generate sparse, selective, and sequential population activity that matches *in vivo* experimental data [4,5]. The DG model has also served as the prototype to develop general software infrastructure to specify, simulate, optimize, and analyze large-scale biophysically detailed neuronal network models and is scalable across tens of thousands of processors. The team is extending the DG model to include CA3 and CA1 [6] and will release their modeling framework as a general open-source tool to construct models of any brain region at any level of scale and detail.

The DG model now contains over 1.2 million model cells and receives its principal input from stimulus patterns designed to mimic the spatial information content provided to the hippocampus by the entorhinal cortex. The neuronal synapses include NMDA receptors, which have a characteristic nonlinear transfer function. The researchers have found this biophysical property to be critical for a highly sparse subset of granule cells to fire at high rates within their place fields while maintaining essentially zero firing rate out of field, despite receiving a constant barrage of excitatory inputs. The team has been able to use their model to test a prominent theory that a log-normal distribution of synaptic weights combined with lateral feedback inhibition is sufficient to generate singly peaked place fields when being driven by multiply peaked gridfield inputs from the medial entorhinal cortex [7]. The model now also contains a back-projection from CA3 pyramidal cells to DG, which is the first step toward creating an interconnected model of the hippocampus. The back-projection will enable testing of a theory of SWR-related memory replay that posits that interactions between CA3 and DG are required for proper sequence generation [8].

WHY BLUE WATERS

The brain is one of the most complex systems studied by science. Computational modeling of the brain presents challenges in terms of both the mathematical complexity of neuronal dynamics and the large number of neurons and other cells that are part of the nervous system. This project requires the simulation of behaviorally relevant activity of approximately 2% of the total number of neurons in the rodent brain; but even then, such simulations have only been possible on Blue Waters, where producing seconds of simulated brain activity currently takes tens of hours on thousands of processors. Blue Waters has been indispensable in enabling the research team to simulate the brain at a biologically realistic anatomical scale and a behaviorally relevant timescale.

PUBLICATIONS & DATA SETS

I. Raikov and I. Soltesz, "Data-driven modeling of normal and pathological oscillations in the hippocampus," in *Multiscale Models of Brain Disorders*, Vassilis Cutsuridis, Ed. New York, NY, U.S.A.: Springer Nature, 2019.