34th Annual International Conference of the IEEE EMBS
San Diego, California USA, 28 August - 1 September, 2012

Towards a Large-Scale Biologically Realistic Model of the Hippocampus

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Abstract— **Real neurobiological systems in the mammalian brain have a complicated and detailed structure, being composed of 1) large numbers of neurons with intricate, branching morphologies – complex morphology brings with it complex passive membrane properties; 2) active membrane properties – nonlinear sodium, potassium, calcium, etc. conductances; 3) non-uniform distributions throughout the dendritic and somal membrane surface of these non-linear conductances; 4) non-uniform and topographic connectivity between pre- and post-synaptic neurons; and 5) activity-dependent changes in synaptic function. One of the essential, and as yet unanswered questions in neuroscience is the role of these fundamental structural and functional features in determining "neural processing" properties of a given brain system. To help answer that question, we're creating a large-scale, biologically realistic model of the intrinsic pathway of the hippocampus, which consists of the projection from layer II entorhinal cortex (EC) to dentate gyrus (DG), EC to CA3, DG to CA3, and CA3 to CA1. We describe the computational hardware and software tools the model runs on, and demonstrate its viability as a modeling platform with an EC-to-DG model.**

I. Introduction

More than a century of observation and research has made it clear that real neurobiological systems in the mammalian brain have a complicated and detailed structure, being composed of:

1. Large numbers of neurons with intricate, branching morphologies. Complex morphology brings with it complex passive membrane properties,
2. Active membrane properties – nonlinear sodium, potassium, calcium, etc. conductances,
3. Non-uniform distributions throughout the dendritic and somal membrane surface of these non-linear conductances,
4. Non-uniform and topographic connectivity between pre- and post-synaptic neurons, and
5. Activity-dependent changes in synaptic function.

Despite the large volume of experimental work that has been done on various systems in the mammalian brain, one of the essential, and as yet unanswered questions in neuroscience is the role of these fundamental structural and functional features in determining "neural processing" properties of a given brain system. To help answer this question, we're in the process of creating a large-scale, biologically realistic model of the intrinsic pathway of hippocampus, which consists of the projection from layer II EC to DG, EC to CA3, DG to CA3, and CA3 to CA1. In the context of the model, "biologically realistic" means that we're including accurate and detailed morphologies for the major classes of neurons in the hippocampus, nonlinear, non-uniformly distributed membrane channels on each of the cells, topographically constrained connectivity, and activity-dependent synaptic plasticity.

Our goal with this model is to study the contribution of each of these factors to global hippocampal function. For example, how does the topology of the system, which places constraints on the connectivity between the various regions of the hippocampus, affect the signal processing capabilities of the system as a whole? How do the morphologies and biophysics of the various cell types contribute to overall system function? What role do the various types of system non-stationarities (i.e., synaptic plasticity) play in defining the system's capabilities? Why are so many cells required to achieve the system-level functionality of the hippocampus? A large-scale, biologically realistic model of the hippocampal system can give us insight into all of these questions.

This work represents a first-of-kind model of the hippocampus, and as such, incorporates several advances that either have not been included in other large-scale models, or that have not been included in simultaneously in one model:

1. Uniquely generated cells, both morphologically and biophysically. When it comes to defining individual cells in a systems-level model, common practices in the modeling community include creating simple artificial cells (such as the integrate-and-fire model), creating Hodgkin-Huxley (HH) type cells with reduced morphologies, and creating HH-type compartmental cells with detailed morphologies. In the majority of models, however, all cells of a certain type (CA1 pyramidal, for instance) are identical to every other cell of that same type; all cells are based off of a template. In our model, every primary hippocampal cell will have a uniquely generated morphology and set of biophysical parameters to reflect the fact that no cell in the brain is identical to any other cell.
2. Differing morphologies by cell location. It's not enough that every primary cell in the model be unique, as there are macro-level morphological changes within a given population of neurons, usually as a

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function of physical position within the given region. We take these location-based differences into account when generating cells.

3. Multiple types of synapse-level plasticity, including long-term potentiation/depression (LTP/LTD) and short-term plasticity, with augmentation and/or homeostasis as additional types of plasticity we may incorporate in the future.

4. Between-region topology/connectivity. Several detailed models of portions of the hippocampus exist, with dentate gyrus and CA1 being the most frequently selected regions for modeling. In most cases, those models incorporate topological constraints for the connectivity between the various cell types within that given region. Those constraints are often informed by the axonal spread of the input cells and/or the dendritic spread of the output cells. Because we are modeling the full intrinsic circuit of the hippocampus, we are able to additionally impose between-region topological constraints on connectivity.

II. Methods

A. Hardware/Software

We run all simulations on our high-performance compute cluster consisting of 394 dual quad-core Intel-based nodes and 74 dual hexa-core Intel-based nodes, for a total of 4,040 processor cores. The system has 8.1 TeraB of distributed RAM, 73.1 TeraB of distributed disk space, and a maximum theoretical performance of 38.82 teraflops (Figure 1). All nodes are connected to a high-speed, low-latency 10G Myrinet networking backbone. These nodes are housed, maintained and monitored in facilities operated by the University of Southern California Center for High-Performance Computing and Communications. We utilize the MPI-enabled version of the NEURON simulation engine [1] to run all simulations, and use Python for model specification and data visualization/analysis [2].

B. Model components – Morphology

In order to generate unique morphologies for the primary cell types in the hippocampus, we use L-Neuron [3], a software tool based off of an algorithm first described by Dean Hillman [4], and rooted in Lindenmayer-systems. The Lindenmayer formalism is quite useful for describing anything with a branching structure, including trees, fractals, and dendrites. L-Neuron allows us to describe the fundamental morphological characteristics of a given cell type with a set of statistical distributions, and then create arbitrary numbers of unique dendritic trees by sampling, independently, from those distributions. Fundamental parameters for dendritic trees include soma diameter, initial stem diameter, branch path length (for both terminal and non-terminal branches), taper ratio, and bifurcation amplitude, among others. To generate unique dendritic trees for our granule cell models, we used the statistical distributions for the morphological parameters that Hillman measured [10] (see Table 1). We then import those morphologies into the NEURON environment as compartmental models, where we can then add the proper biophysics for the cells and the proper connectivity for the network. Figure 2 shows a sample of the granule cell morphologies we've generated using this methodology.

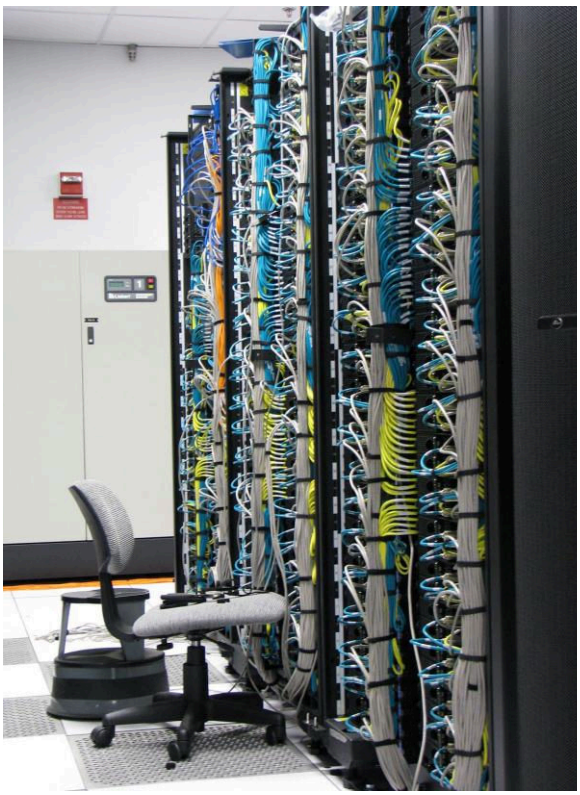

Figure 1: 4,040-CPU Beowulf cluster used to run simulations. NEURON running over MPI was used to run the simulations, with Python being used to specify the model and perform data visualization/analysis.

C. Biophysics

NEURON allows us to re-create the non-linear dynamics of voltage- and ligand-gated membrane channels, and then to insert those channels in varying densities into the membrane of our cell models. In this way, we are able to accurately simulate the non-uniformly distributed, non-linear active cellular mechanisms of all of the cells we will include in the large-scale model. For the population of granule cells, we used the same channel types, densities and distributions as Santhakumar et. al. [11], similarly partitioning each cell into a somatic, granule cell layer, inner third, middle third, and outer third area. Table 2 shows the values for the passive membrane parameters and the maximum conductances for the active channels in the somata of the granule cells. We added variability to the biophysical mechanisms by allowing them to randomly vary by up to +-5% from their default value.

D. Connectivity

Anatomical data is very important in the determination and implementation of the proper connectivity scheme for each of the regions in the intrinsic pathway of the hippocampus. Knowing the numbers and densities of cells in a given region, such as the dentate gyrus, allows us to properly place our cell models [6]. Knowing the axonal spread of the cells in the population of input cells, together

Variable	Disto. type	Mean	Std. Dev.	Min.	Max.
Soma Diameter	Gaussian	9	2	1	15
Number of Stems	Uniform			2	4
Stem initial diameter	Gaussian	1.51	0.79	0	5
Threshold Diameter for branching	Gaussian	0.49	0.28	0	5
IBF branch pathlength	Gaussian	10.7	8.4	0	50
Terminal branch pathlength	Gaussian	10.7	8.4	0	50
Daughter ratio	Uniform			1	2
Taper ratio	Gaussian	0.1	0.08	0.01	0.5
Rall power	Constant			1.5	1.5
Bifurcation amplitude	Gaussian	42	13	0	180
Bifurcation torque	Uniform			-180	180
Contraction	Uniform			0.75	1
Tree azimuth	Uniform			-180	180
Tree elevation	Gaussian	10	2	0	180
		42	2	0	180
		75	2	0	180

Table 1: Statistical distributions for the fundamental parameters governing the morphologies of the population of dentate granule cells.

with the dendritic spread of the cells in the output population allows us to calculate convergence and divergence values. And retrograde tracing experiments can help us identify which sub-populations on the input side project to which sub-populations on the output side [7]. Please refer to Yu *et al.* in these proceedings [5] for a much more detailed description about how we implemented topographically constrained connectivity for the projection from entorhinal cortex (EC) to the dentate gyrus (DG).

E. Activity-dependent Plasticity

In order to capture the activity-dependent changes in synaptic function, we have started by implementing plasticity rules on two different time-scales. Long-term potentiation (LTP) and depression (LTD) are implemented based on a spike-timing-dependent plasticity (STDP) rule. Our short-term plasticity implementation modifies a previously defined population-level deterministic model [9] to become a probabilistic release model that works at a single-synapse level. Both types of plasticity have been implemented and validated using the NEURON simulation engine. Please refer to Robinson *et al.* in these proceedings [8] for more detail about the implementation of both STP and STDP.

III. RESULTS

To demonstrate the viability of our cluster and accompanying software toolset as a modeling platform, we show preliminary simulation results from a 1/10th-scale EC-to-DG model that features unique granule cell morphologies, non-uniformly distributed membrane channels, inhibitory feedback from basket cells, topologically constrained connectivity, and variable spike timing (Figure 3). To

Mechanism (Soma)	Value
C_m, [μF/cm^2]	1
R_a, [Ωcm]	210
Leak Conductance [S/cm^2]	0.00004
Sodium [S/cm^2]	0.12
Delayed Rectifier K (slow) [S/cm^2]	0.006
Delayed Rectifier K (fast) [S/cm^2]	0.016
A-Type K [S/cm^2]	0.012
L-Type Calcium [S/cm^2]	0.005
N-Type Calcium [S/cm^2]	0.002
T-Type Calcium [S/cm^2]	3.7E-05
Ca-dependent K (SK) [S/cm^2]	0.001
Ca & Voltage-dependent K (SK) [S/cm^2]	0.0006

Table 2: Passive parameters and maximum conductances for the channels in the dentate granule cell somata.

simulate 1 second of biological time required approximately 6,500 CPU hours (1 CPU hour = 1 hour on a single CPU core) for the 100,000 granule cells, 11,200 EC cells, and 1,000 basket cells that composed the model – that leaves us enough unused computational capacity to grow the model to the size of the full rat hippocampus.

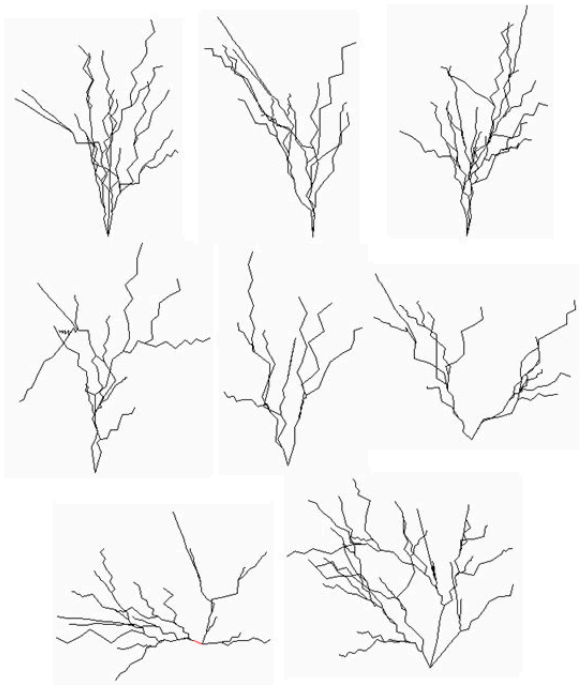

Figure 2: Sample of 8 granule cell morphologies generated using L-Neuron.

IV. DISCUSSION AND FUTURE WORK

Initial simulations with the model indicate that many, if not all of the model features we implemented are important. As

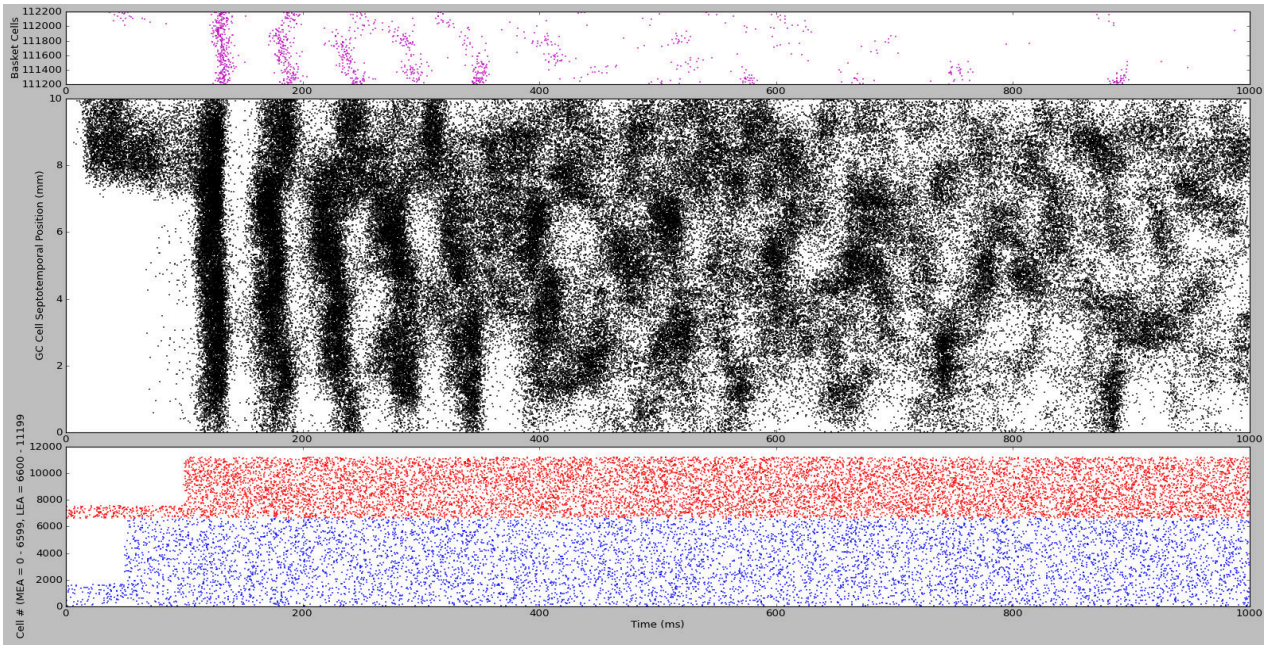

Figure 3: Simulation results from model with 100,000 unique dentate granule cells, 6,600 medial entorhinal cortical (MEA) cells, 4,600 lateral entorhinal cortical (LEA) cells, and 1,000 basket cells. Topology/connectivity was biologically based, with sub-regions of the MEA & LEA projecting to sub-regions of the dentate gyrus. Spike timing was variable. The spatio-temporal clustering of spikes in the 2nd half of the simulation is noteworthy, considering the uniform nature of the input.

a raster plot of the spike data shows (Figure 3), we see very interesting and non-uniform patterns of granule and basket cell activity emerge, even when the input from EC is uniform (the inter-spike interval follows a Poisson distribution). This shows that the model system is performing non-linear spatiotemporal signal processing to the input, even though the input is not biologically realistic. We still need to develop metrics to measure the amount of clustering occurring in the data, and we want to look at the response of the network to biologically-inspired inputs, and we plan to add additional hippocampal regions (CA3, CA1) to the network. We refer you to Gene *et al.* in these proceedings for more detailed results outlining the contributions of the topographically constrained connectivity to the signal processing capabilities of the system [5].

In summary, though the results of the model simulation are still fairly preliminary, we've seen that the system performs interesting and non-linear signal processing, even in the presence of a uniform input. With such a detailed model, we hope to be able to quantify the contribution of each of these features to that non-linear transformation.

ACKNOWLEDGMENT

Computation for the work described in this paper was supported by the University of Southern California Center for High-Performance Computing and Communications (www.usc.edu/hpcc).

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