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Topography-Dependent Spatio-Temporal Correlations in the Entorhinal-Dentate-CA3 Circuit in a Large-Scale Computational Model of the Rat Hippocampus

Gene J. Yu¹ [IEEE Student Member], Phillip J. Hendrickson² [IEEE Student Member], Dong Song³ [IEEE Member], and Theodore W. Berger⁴ [IEEE Fellow]

Department of Biomedical Engineering, Center for Neural Engineering, University of Southern California, Los Angeles, CA 90089, USA

Abstract

The correlation due to different topographies was characterized in a large-scale, biologically-realistic, computational model of the rat hippocampus using a spatio-temporal correlation analysis. The effect of the topographical projection between the following subregions of the hippocampus was investigated: the entorhinal to dentate projection, the entorhinal to CA3 projection, and the mossy fiber to CA3 projection. Through this work, analysis was performed on the individual and combined effects of these projections on the activity of the principal neurons of the dentate gyrus and CA3. The simulations show that uncorrelated input transmitted through the entorhinal-to-dentate or entorhinal-to-CA3 projection causes spatio-temporally correlated activity in the principal neurons that manifest as spike clusters. However, if the mossy fiber system provides uncorrelated input to the CA3, then the CA3 activity remains uncorrelated. When considering the transfer of correlation through the dentate, this analysis suggests that the mossy fiber system do not imbue any correlation to the activity as it propagates from the granule cells of the dentate to the CA3. With the spatio-temporal correlation analysis, the influence of each topographical projection on the transfer of correlation can be investigated as additional subregions and neuron types are added to the large-scale model.

I. INTRODUCTION

In the brain, the hippocampus plays a crucial role in memory and cognition, transforming short-term memory into long-term memory. This process occurs through a series of non-linear, spatio-temporal transformations as neural activity propagates through the hippocampal system. To study these transformations, we are developing a large-scale, biologically realistic, computational model of the rat hippocampus.

The topography between neural regions has been shown to affect the spatio-temporal transformation of activity as the activity propagates from the input region to the output region [1]. Topography refers to the organization of the structural connectivity that allows a

¹geneyu at usc.edu

²phendric at usc.edu

³dsong at usc.edu

⁴berger at usc.edu

group of neurons to communicate with another group. Pre-synaptic neurons send signals through their axons which connect to post-synaptic neurons through synapses. The locations where the axons are sent and the branching structure of the axons determine the spatial distribution of the topography.

Although the effects of different topographies have been shown to modulate spatio-temporal activity, a satisfactory method to characterize or quantify these modulations have yet to be developed. However, correlation may be an appropriate metric to perform this analysis. The spatially-distributed connectivity causes activity from a single neuron to simultaneously drive many neurons distributed in space resulting in a spatially and temporally synchronized excitation/inhibition. Given a particular topography, the shape of the spatio-temporal activation can change causing different spatio-temporal correlations in the post-synaptic population.

This work explores the spatio-temporal correlations that result from the different topographies that exist between the principal neurons of the entorhinal cortex (EC), dentate gyrus (DG), and CA3 of the hippocampus using the large-scale model. Perforant path projections to both the dentate gyrus and CA3 are investigated as well as the mossy fiber projection between the dentate granule cells and CA3 pyramidal cells (Fig. 1).

II. METHODS

A. Model Framework

Multi-compartmental models of the granule cells (GC) of the dentate and the CA3 pyramidal cells were modified from existing models that were written for the NEURON environment [2]. The GC model was based on Santhakumar's work, and the CA3 pyramidal cell model was based on Hemond's work [3][4]. Both models contain non-uniformly distributed active and passive membrane properties and realistic morphologies. The active membrane properties consist of voltage- and ion-dependent membrane channels including sodium channels, potassium channels, calcium-dependent potassium channels, and calcium channels. Morphologies for the GCs were generated using a modified version of L-NEURON, and the CA3 pyramidal cells consisted of a single morphology based on a CA3 pyramidal cell reconstruction [5]. A total of 100,000 GC and 33,000 CA3 pyramidal cell models were used in the simulations.

The entorhinal cortex, which provides input to the GCs and CA3 pyramidal cells, was divided into the lateral and medial entorhinal cortex (LEC and MEC). For all simulations, the EC neurons provided independently-generated, Poisson-distributed, inter-spike interval spike trains with a mean rate of 3 Hz to the dentate and CA3 and were synaptically coupled to the principal neurons there. A total of 66,000 MEC and 46,000 LEC neurons were instantiated for the simulations.

The connectivity of the neuron models was determined using anatomical constraints, and the specific implementation of the connectivity has been reported previously [6][7] (Fig. 2). In both the DG and CA3, the MEC and LEC neurons had axons that extended longitudinally following a Gaussian distribution with a standard deviation of 0.167 mm. The axons were

distributed uniformly in the transverse direction. In the CA3, the first third of the CA3, corresponding to the CA3c, did not receive any EC input. The mossy fibers followed a transverse trajectory in the CA3 for the first two-thirds before turning in a temporal direction for the last third.

The dentate gyrus was divided into an infrapyramidal and suprapyramidal blade. The infrapyramidal GCs received an average of 1,253 and 1,479 inputs from the MEC and LEC, respectively. The suprapyramidal GCs received 2,117 and 2,417 inputs from the MEC and LEC, respectively. The CA3 pyramidal cells, not within the first third, received an average of 1,800 inputs from LEC and 1,800 inputs from the MEC. The CA3 pyramidal cells further received an average of 70 inputs from the mossy fibers.

The effect of each topographical projection on the spatio-temporal correlation of the population was investigated by isolating each projection to look at their individual effects and by systematically adding projections to look at interactions. In one set of simulations, the monosynaptic, or direct, activation of dentate and CA3 via EC alone was considered. In another simulation, the disynaptic activation of the CA3 via the EC was studied. EC input would excite GCs through the perforant path projection, and the GC activity would propagate through the mossy fiber projection to excite the CA3 pyramidal cells. This activation is considered disynaptic because the activity must traverse two synapses before reaching CA3. A fourth simulation looked at the combined monosynaptic and disynaptic activation of the CA3 via the EC.

Similar to how the EC provided broadband input to the dentate and CA3, the GCs were isolated and modelled as spike generators for two simulations to investigate how the mossy fiber projections shape the spatio-temporal correlation. In one simulation, the GCs alone provided uncorrelated input to the CA3 via the mossy fibers. In another simulation, both the EC and GCs provided uncorrelated input to the CA3 through their respective pathways. In this simulation, the EC did not drive GC activity. Each simulation reproduced 10 seconds of real time.

B. Calculating Spatio-Temporal Correlation

An average spatio-temporal correlation was calculated by taking a uniform random sample of 10,000 neurons of a given cell type. The spike trains of these cells were discretized using a bin size of 5 ms, where each bin indicated the number of spikes that were fired in that bin, and the normalized pairwise cross-correlation was computed between every unique neuron pair combination. The cross-correlations were then sorted and binned based on the spatial distance between the neuron pairs using a bin size of 0.5 mm. The measure represents the average of how the cross-correlation between a neuron and its neighbours changes as a function of distance from the neuron and time.

III. RESULTS

When the CA3 was monosynaptically stimulated by the EC alone, the CA3 responded with clusters of activity as seen in the EC activation of the GCs (Fig. 3A). The longitudinal-temporal correlation shows a longitudinal correlation that approximately matches the height

of each cluster. The temporal component is high within a time lag of 10 ms from the center followed by a period of anti-correlation (likely the refractory period) before returning to a baseline correlation.

When the CA3 was stimulated using uncorrelated, random activity from the GCs, the CA3 responded with random activity (Fig. 3B). The spatio-temporal correlation shows that there was little correlation between any neuron pair on any axis. This is in contrast to the EC projection which causes spatio-temporally correlated activity although the input was uncorrelated. This can be attributed to the low convergence of the mossy fiber pathway and the lack of spatial overlap between mossy fibers.

The combination of uncorrelated EC input and uncorrelated dentate input to the CA3 resulted in seemingly clustered and aperiodic activity. However, the longitudinal-temporal correlation revealed a decaying periodicity in time (Fig. 3C).

In figure 4A, the GC activity due to monosynaptic EC input is shown. During the disynaptic activation of the CA3, it is this dentate activity that is used as input to the CA3. The resulting CA3 activity has regions that start near the same locations and times as the GC clusters but are stretched out in time, appearing as a temporally smoothed version of the GC clusters (Fig. 4B). This is reflected in the longitudinal-temporal correlation where the temporal width of the correlation is larger in the CA3 than the dentate.

When the CA3 is stimulated both disynaptically by the EC via the GCs and monosynaptically by the EC, the CA3 output again changes drastically (Fig. 4C). The output is composed of non-uniformly distributed epochs of periodic activity. The longitudinal-temporal correlation shows a periodicity, but the correlation switches from being periodic with a positive correlation to periodic with a negative correlation.

IV. DISCUSSION

This series of large-scale simulations make it evident that topography influences the basic spatio-temporal transformations that occur between neural regions. The spatio-temporal correlation measure used in this work is able to capture the average correlations that a neuron in the DG or CA3 has in relation to its neighbouring neurons across time and space under different topographical conditions. In particular is the contrast in the effects of the entorhinal projection and the mossy fiber projection. Independently generated, Poisson random spike trains propagated through the entorhinal projection resulted in spatio-temporally correlated activity in both the dentate gyrus and CA3. However, when input with the same properties was propagated through the mossy fibers to the CA3, no correlation was present in the CA3 activity.

The structural connectivity that is topography, however, only provides a static view of how spatio-temporal patterns are propagated in the hippocampus. Activity-dependent processes such as long-term potentiation are able to modulate the strength of these connections and imbue non-stationarities to neural networks. It is the next challenge to investigate how both topography and plasticity interact to shape the spatio-temporal patterns that make up the neural code.

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References

1. Yu, GJ.; Hendrickson, PJ.; Robinson, BS.; Song, D.; Berger, TW. The role of topography in the transformation of spatiotemporal patterns by a large-scale, biologically realistic model of the rat dentate gyrus. 35th Annual International Conference of the IEEE EMBS; 2013;
2. Carnevale, NT.; Hines, ML. The NEURON book. Cambridge, UK: Cambridge University Press; 2006.
3. Santhakumar V, Aradi I, Soltesz I. Role of mossy fiber sprouting and mossy cell loss in hyperexcitability: A network model of the dentate gyrus incorporating cell types and axonal topography. Journal of Neuroscience. Jan; 2005 93(1):437–453.
4. Hemond P, Epstein D, Boley A, Migliore M, Ascoli GA, Jaffe DB. Distinct classes of pyramidal cells exhibit mutually exclusive firing patterns in hippocampal area CA3b. Hippocampus. Apr; 2008 18(4):411–424. [PubMed: 18189311]
5. Hendrickson, PJ.; Yu, GJ.; Robinson, BS.; Song, D.; Berger, TW. Toward a Large-Scale Biologically Realistic Model of the Hippocampus. 34th Annual International Conference of the IEEE EMBS; 2012;
6. Yu, GJ.; Robinson, BS.; Hendrickson, PJ.; Song, D.; Berger, TW. Implementation of topographically constrained connectivity for a large-scale biologically realistic model of the hippocampus. 34th Annual International Conference of the IEEE EMBS; 2012;
7. Yu, GJ.; Song, D.; Berger, TW. Implementation of the excitatory entorhinal-dentate-CA3 topography in a large-scale computational model of the rat hippocampus. 36th Annual International Conference of the IEEE EMBS; 2014;

Fig. 1.

Overall structure of the rat hippocampus and the classical trisynaptic loop. The EC provides the majority of the input to the hippocampus through the DG. The DG synapses with the CA3, and the CA3 provides input to the CA1. The CA1 forms the output of the hippocampus.

Fig. 2.

Examples of the entorhinal projections to the dentate and CA3 and the mossy fiber projection to the CA3. A single entorhinal cortex synapses with all of the granule cells and CA3 pyramidal cells shown in green. A single granule cell mossy fiber follows a characteristic trajectory, contacting much fewer CA3 pyramidal cells than the EC.

Fig. 3.

Raster plots and spatio-temporal correlations of simulations using uncorrelated, random EC and GC input to the CA3. The left column contains raster plots depicting the spatio-temporal location of action potentials as dots. The middle column shows the longitudinal-temporal correlation, and the right column shows the longitudinal-transverse correlation. A) CA3 activity due to monosynaptic activation via EC. B) CA3 activity due to uncorrelated GC input via the mossy fibers. C) CA3 activity due to the combined excitation via uncorrelated, random EC and GC input.

Fig. 4.

Raster plots and spatio-temporal correlations of simulations using monosynaptic and disynaptic EC input to the CA3. The left column contains raster plots. The middle column shows the longitudinal-temporal correlation, and the right column shows the longitudinal-transverse correlation. A) GC activity due to monosynaptic activation via EC. B) CA3 activity due to disynaptic EC activation. C) CA3 activity due to the combined input of the EC and GCs.