Published in final edited form as:

Conf Proc IEEE Eng Med Biol Soc. 2019 July ; 2019: 2977–2980. doi:10.1109/EMBC.2019.8856799.

Network Activity Due to Topographic Organization of Schaffer Collaterals in a Large-Scale Model of Rat CA1

Gene J. Yu [Student Member, IEEE], Zhicheng Feng, Theodore W. Berger [Fellow, IEEE]

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

Abstract

Connectivity between neural regions, particularly in the hippocampus, is seldom all-to-all or random, yet it is the predominant method by which connectivity is implemented in most models of neuronal networks. We have been developing a computational platform for simulating the trisynaptic circuit of rat hippocampus with which we have constructed a large-scale, biologically-realistic, spiking neuronal network model of the entorhinal-dentate-CA3 system. Using the model, we had demonstrated a non-trivial effect of topographic connectivity on network dynamics and function. In this work, we detail the introduction of the CA1 subregion to the large-scale model. Using anatomical data, we constrained the distribution of axon collaterals, i.e., Schaffer collaterals, projected from CA3 to CA1 and preserved the topographic organization of the projections. Using a simplified multi-compartmental model of CA1 pyramidal cells and a single compartment model of CA1 parvalbumin basket cells, that were connected with disinaptic feedforward inhibition and feedback inhibition, we demonstrate the network activity of the CA1 network given a topographic organization of Schaffer collaterals. From this introduction of CA1 to the large-scale model, we can then observe the successive transformation of spatio-temporal, spiking neural activity as it propagates through the trisynaptic circuit.

I. INTRODUCTION

The hippocampus is a brain structure that is crucial to the formation of episodic memory and has been, and continues to be, the site of intense study which has led to the generation of large amounts of information. However, a complete understanding that links the properties underlying the hippocampus to its total system function remains elusive. We have been developing a comprehensive computational platform that is able to integrate data and constrain parameters at various physical scales in order to construct a large-scale, biologically-realistic, spiking neuronal network model of rat hippocampus. We intend to model the full number of neurons and synapses within a single hemisphere of rat hippocampus through which lower level properties can be linked to system level function and emergent properties can be discovered. Another key aspect of the model is the use of anatomical data to preserve the topography of the connectivity between different hippocampal subregions.

geneyu@usc.edu.

*This work was not supported by any organization.

The development of the model follows the framework of the trisynaptic circuit in which information propagates through the hippocampus in a predominantly feedforward manner starting from the entorhinal cortical projection the dentate gyrus, the dentate gyrus to the CA3, and the CA3 to the CA1. The construction of the model has followed the same progression. Using our platform, we have completed a model of the entorhinal-dentate-CA3 system [1]–[5] and incorporated behaviorally relevant input via grid cell activity [6]. These studies have revealed the importance of anatomically-derived, topographic connectivity in determining spatio-temporal neural dynamics and, at a higher level, information encoding [3].

In this work, we will describe the addition of the CA1 subregion into the large-scale model. The CA1 is the final subregion of the hippocampal trisynaptic circuit and provides the output, communicating the transformations performed by the hippocampus to the larger circuit to which the hippocampus belongs, e.g., the hippocampal-diencephalic-cingulate network [7]. The CA1 is connected to the hippocampus through axons originating from CA3 pyramidal cells that are called Schaffer collaterals. The axons contribute to both ipsilateral and contralateral connections between CA3 and CA1 [8], [9], but the ipsilateral connections are the sole focus of this work as the mapping of the contralateral projections are less known. Due to the technical difficulty, there are few studies that investigate the anatomy of the Schaffer collaterals and the topography of the projections. Additionally, the available data are either qualitative, in that the presentations of the findings are – to a degree – subjectively reported, and/or are incomplete, in that the study did not include the full mapping across the entire septo-temporal and transverse axis of the CA3 and CA1 regions (see Fig. 1 and Fig. 2). To address these issues and incorporate a CA1 model into the existing large-scale neuronal network, we have developed a method of digitizing and quantifying the data to constrain the topography of the Schaffer collateral projection from the CA3 and CA1. Furthermore, we present the effect of this connectivity on the spatio-temporal dynamics of a CA1 network comprised of simplified compartmental models of CA1 pyramidal cells and CA1 parvalbumin-positive basket cells.

II. METHODS

A. Parameterizing the Spatio-Temporal and Transverse Distribution of Schaffer Collaterals in CA1

The most complete study of the CA3 projection onto CA1 was performed by Ishizuka et al., 1990 [8]. In their work, horseradish peroxidase was injected into CA3 pyramidal cells that were located at nine separate septo-temporal and transverse sections of the CA3 which resulted in the ipsilateral labeling of their axon collaterals both within the CA3 and the CA1. The data presented the resulting septo-temporal and transverse distributions of the axon collaterals in the CA1, features important to understanding the topographic projection of the Schaffer collaterals, which have yet to be repeated in rat with more advanced techniques. To use the data to constrain our model of connectivity, there were three issues that needed to be addressed: The axonal distributions in CA1 were reported qualitatively with two levels of axonal density, the CA1 brain regions for each experiment had different shapes, and the experiments did not span the entire CA3 region.

We developed a workflow for digitizing the data, standardizing the data, fitting the distributions to a parameterized equation that could vary as a function of CA3 pyramidal cell location, and re-mapping the data to a chosen CA1 map (Fig. 1B). The methods were based on our previous work which applied the technique to extract CA3 associational connectivity [5]. In the digitizing step, masks were drawn over the published figures to label the entirety of the CA1 region, to obtain the map boundaries, and the density levels of the axon collaterals. In the standardization step, a standard space with dimensions much greater than the original data (10,000 x 10,000 pixels) was chosen to ensure the subject map boundaries would be preserved. The ratios between the rows and columns of the individual subject space maps and the standard map were obtained to redraw the data in a standard space. In the parameterization step, the parameters for a modified two-dimensional skew normal equation was optimized using the least-squares method.

$$\phi(x) = \frac{1}{\sqrt{2\pi}} e^{-\frac{x^2}{2}} \quad (1)$$

$$\Phi(x) = \frac{1}{2} \left[1 + \operatorname{erf} \left(\frac{x}{\sqrt{2}} \right) \right] \quad (2)$$

$$f(x) = \frac{2}{\omega} \phi \left(\frac{x - \xi}{\omega} \right) \Phi \left(\alpha \left(\frac{x - \xi}{\omega} \right) \right) \quad (3)$$

$$x' = x \cdot \cos(\theta) + y \cdot \sin(\theta) \quad (4)$$

$$y' = -x \cdot \sin(\theta) + y \cdot \cos(\theta) \quad (5)$$

$$f(x, y) = \frac{4}{\omega_x \omega_y} \phi \left(\frac{x' - \xi_x}{\omega_x} \right) \Phi \left(\alpha_x \left(\frac{x' - \xi_x}{\omega_x} \right) \right) \phi \left(\frac{y' - \xi_y}{\omega_y} \right) \Phi \left(\alpha_y \left(\frac{y' - \xi_y}{\omega_y} \right) \right) \quad (6)$$

Equation (1) is the probability distribution function of a normal distribution, (2) is the cumulative distribution function of a normal distribution, and (3) describes a skew normal function where α controls the skew, ξ , is an offset, and ω is the standard deviation. An additional parameter θ was used to control the rotation of the function. Equation (6) shows the final two-dimensional skew normal function.

The dimensions of the standard map were reduced to 250 x 250 pixels for the optimization to decrease computational time. Afterwards, the parameters were linearly interpolated as a function of septo-temporal location within the CA3 to estimate the shape of the axon distribution between the available data. The parameters were then extrapolated beyond the locations covered by available data by using the slope of the parameters obtained by the linear interpolation. In all cases, the slope needed to be multiplied by a scalar factor to

reduce the magnitude of the slope so that the skew normal functions did not return abnormal values and so that the mode of the function remained within the CA1 map boundaries.

B. CA1 Network Model

A simplified but multi-compartmental model of CA1 pyramidal cells published by Marasco et al. was used to test the effect of topographic connectivity on network activity [10]. The number of synapses that each CA1 pyramidal cell received were estimated by multiplying the synaptic densities and total dendritic lengths within the stratum radiatum and oriens as reported in [11]. Additionally, the heterogeneity of the morphology of CA1 pyramidal cells along the septo-temporal axis was incorporated to vary the amount of synaptic input available to a CA1 pyramidal cell as function of its position [12]. The minimum and maximum numbers of synapses in the stratum radiatum were calculated to be 19,000 and 14,800, for the dorsal and ventral CA1 respectively. The numbers of synapses in the stratum oriens were 13,500 and 10,500, respectively. The morphology of CA1 pyramidal cells were found to be relatively homogeneous along the transverse axis. The CA1 pyramidal cells were then distributed along septo-temporal axis according to volumetric data published in [13]. The network size was 38,000 CA1 pyramidal cells which is one-tenth of the full number of neurons as reported by [14].

Parvalbumin basket cells were also represented using a single compartment model as described in [2]. They contribute to a disinaptic feedforward inhibition circuit via activation by the Schaffer collaterals in the stratum radiatum and oriens followed by the subsequent inhibition of CA1 pyramidal cells. They also contribute, in a diminished capacity, toward feedback inhibition of CA1 pyramidal cells. They received 8800 and 3700 excitatory synapses from the Schaffer collaterals in the stratum radiatum and oriens, respectively (see [15]) and 22 synapses from the CA1 pyramidal cells (see [16]). CA1 pyramidal cells received between 70 and 130 inhibitory synapses from the basket cells [15].

AMPA receptors were the only excitatory synaptic receptor included in this initial work, and their conductance was modeled using a double exponential equation. GABA_A receptors mediated the inhibitory synaptic current. The network was simulated using NEURON and Python [17].

III. RESULTS

A. Topographic Organization of Schaffer Collaterals

The results of the optimized parameters compared to the original data are shown in Fig. 2. For each injection, the skew normal distributions were able to capture the general shape and spread of the original data and preserve the relation between the mode of the axon distribution within the CA1 and the CA3 pyramidal cell's proximodistal origin, i.e., CA3 pyramidal cells located proximally to the dentate gyrus project axons to distal locations in the CA1, and CA3 pyramidal cells located distally to the dentate gyrus project axons to proximal locations within the CA1 (see Fig. 1A) [8].

The interpolated and extrapolated parameters and examples of the distributions generated by these parameters are shown in Fig. 3. The parameters for the original data are denoted with

orange dots, and the extrapolated parameters for the boundaries are denoted in red. For CA3c, an additional point needed to be inserted to ensure that the skew normal function behaved in a stable manner. In CA3a the slope for Y Offset needed to be inverted near the temporal pole for the same reason.

B. CA1 Network Activity

The CA1 network was driven with 3 Hz random Poisson inter-spike interval trains to approximate a broadband frequency input for each CA3-CA1 synapse which is a common technique for system identification. Contrary to the clustered activity seen in the dentate gyrus [1], the CA1 pyramidal cells responded with irregularly shaped bands of activity with a mean firing rate of 16.3 Hz (Fig 4). Based on previous work [1], the bands are likely due to the large septo-temporal spreads of the Schaffer collateral axons and may represent long overlapping clusters.

IV. DISCUSSION

The results shown in this manuscript represents a preliminary investigation into the role of the Schaffer collateral topography in affecting spatio-temporal dynamics. In future work, the propagation of activity beginning at the dentate gyrus will be investigated and additional CA1 circuit elements will be included.

Acknowledgment

Work supported by NIH Grant U01 EB025830 and ONR Grant N00014-13-1-0211. Computation for the work was supported by the University of Southern California Center for High-Performance Computing and Communications (www.usc.edu/hpcc).

REFERENCES

- [1]. Hendrickson PJ, Yu GJ, Song D, and Berger TW, "A million-plus neuron model of the hippocampal dentate gyrus: Critical role for topography in determining spatiotemporal network dynamics," *IEEE Trans. Biomed. Eng.*, vol. 63, no. 1, pp. 199–209. 2016. [PubMed: 26087482]
- [2]. Hendrickson P, Yu G, Song D, and Berger T, "Interactions between Inhibitory Interneurons and Excitatory Associational Circuitry in Determining Spatio-Temporal Dynamics of Hippocampal Dentate Granule Cells: A Large-Scale Computational Study," *Frontiers in Systems Neuroscience*, vol. 9 p. 155, 2015. [PubMed: 26635545]
- [3]. Yu GJ, Bouteiller J-MC, Song D, and Berger TW, "Axonal Anatomy Optimizes Spatial Encoding in the Rat Entorhinal-Dentate System: A Computational Study."
- [4]. Yu GJ, Hendrickson PJ, Song D, and Berger TW, "Topography-dependent spatio-temporal correlations in the entorhinal-dentate-CA3 circuit in a large-scale computational model of the Rat Hippocampus," in *Proceedings of the Annual International Conference of the IEEE Engineering in Medicine and Biology Society, EMBS*, 2015, vol. 2015-Novem.
- [5]. Yu G, Song D, and Berger TW, "Implementation of the excitatory entorhinal-dentate-CA3 topography in a large-scale computational model of the rat hippocampus," in *2014 36th Annual International Conference of the IEEE Engineering in Medicine and Biology Society, EMBC 2014*, 2014.
- [6]. Yu GJ, Bouteiller JC, Song D, and Berger TW, "Decoding Position to Analyze Spatial Information Encoding in a Large-Scale Neuronal Network Model of Rat Dentate Gyrus," in *2018 40th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC)*, 2018, pp. 6137–6140.

- [7]. Bubb EJ, Kinnavane L, and Aggleton JP, "Hippocampal–diencephalic–cingulate networks for memory and emotion: An anatomical guide," *Brain Neurosci. Adv.*, vol. 1, p. 23982128177234432017.
- [8]. Ishizuka N, Weber J, and Amaral DG, "Organization of intrahippocampal projections originating from CA3 pyramidal cells in the rat," *J. Comp. Neurol.*, vol. 295, no. 4, pp. 580–623, 1990. [PubMed: 2358523]
- [9]. Li X-G, Somogyi P, Ylinen A, and Buzsáki G, "The hippocampal CA3 network: An in vivo intracellular labeling study," *J. Comp. Neurol.*, vol. 339, no. 2, pp. 181–208, 1994. [PubMed: 8300905]
- [10]. Marasco A, Limongiello A, and Migliore M, "Fast and accurate low-dimensional reduction of biophysically detailed neuron models," *Sci. Rep.*, vol. 2, p. 928, Dec. 2012. [PubMed: 23226594]
- [11]. Megias M, Emri Z, Freund TF, and Gulyás AI, "Total number and distribution of inhibitory and excitatory synapses on hippocampal CA1 pyramidal cells," *Neuroscience*, vol. 102, no. 3 pp. 527–540, 2001. [PubMed: 11226691]
- [12]. Dougherty KA, Islam T, and Johnston D, "Intrinsic excitability of CA1 pyramidal neurones from the rat dorsal and ventral hippocampus," *J. Physiol.*, vol. 590, no. 22, pp. 5707–5722, 2012. [PubMed: 22988138]
- [13]. Ropireddy D, Bachus SE, and Ascoli GA, "Non-homogeneous stereological properties of the rat hippocampus from high-resolution 3D serial reconstruction of thin histological sections," *Neuroscience*, vol. 205, pp. 91–111, 2012. [PubMed: 22245503]
- [14]. West MJ, Slomianka L, and Gundersen HJG, "Unbiased stereological estimation of the total number of neurons in the subdivisions of the rat hippocampus using the optical fractionator," *Anat. Rec.*, vol. 231, no. 4, pp. 482–497, 1991. [PubMed: 1793176]
- [15]. Gulyás AI, Megias M, Emri Z, and Freund TF, "Total Number and Ratio of Excitatory and Inhibitory Synapses Converging onto Single Interneurons of Different Types in the CA1 Area of the Rat Hippocampus," *J. Neurosci.*, vol. 19, no. 22, p. 10082 LP–10097, Nov. 1999. [PubMed: 10559416]
- [16]. Deuchars J and Thomson AM, "CA1 pyramid-pyramid connections in rat hippocampus in vitro: Dual intracellular recordings with biocytin filling," *Neuroscience*, vol. 74, no. 4, pp. 1009–1018, 1996. [PubMed: 8895869]
- [17]. Carnevale NT and Hines ML, *The NEURON Book*, 1st ed New York, NY, USA: Cambridge University Press, 2009.

Figure 1.

(A) Cartoon depiction of the anatomy of the hippocampus and (B) the parameterization process to fit the axon distributions. (A) A cross-section of the hippocampus reveals the trisynaptic circuit (left). Anatomists have created a two-dimensional, flattened representation of the hippocampus by unfolding the dentate gyrus and the CA regions (middle). The CA3 is divided on the transverse axis based on the proximodistal distance from the dentate gyrus (right). Ishizuka et al., performed injections at different septo-temporal and proximodistal locations within the CA3 region to reveal their projections within the CA1 region. (B) The original Ishizuka data was digitized into separate colors and then converted into standard space. In the standard space, a two-dimensional, skew normal distribution was fit to the data. Finally, the distribution was converted back into subject space.

Figure 2.

Two-dimensional, skew normal fits to original data. The maps are organized by the location of the injected CA3 pyramidal cell neuron. The original data is presented on the left-side in two colors. The fits are presented on the right.

Figure 3.

Interpolated and extrapolated parameters of the skew normal distributions as a function of septo-temporal position within the CA3. The parameters based on the original data are denoted with orange dots. Extrapolated parameters at the boundaries and additional points that needed to be inserted (see the CA3c column) for the skew normal function to be stable are denoted by red dots.

Figure 4. Raster plot activity of CA1 pyramidal cells. Each black dot indicates the generation of an action potential by a CA1 pyramidal cell model at a particular septo-temporal location and time. A 3 Hz random Poisson inter-spike interval train was used to drive the CA1 network starting at time 0.