Published in final edited form as:

Conf Proc IEEE Eng Med Biol Soc. 2016 August ; 2016: 1405–1408. doi:10.1109/EMBC.2016.7590971.

Place Field Detection Using Grid-Based Clustering in a Large-Scale Computational Model of the Rat Dentate Gyrus

Gene J. Yu¹ [IEEE Student Member], Dong Song² [IEEE Member], and Theodore W. Berger³ [IEEE Fellow]

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

Abstract

Place cells are neurons in the hippocampus that are sensitive to location within an environment. Simulations of a large-scale, computational model of the rat dentate gyrus using grid cell input have been performed resulting in granule cells that express multiple place fields. The typical method of detecting place fields using a global threshold on this data is unreliable as the characteristics of the place fields from a single neuron can be highly variable. A grid-based implementation of DENCLUE has been developed to calculate local thresholds to identify each place field. An adaptive binning algorithm used to smooth the rate maps was combined with the DENCLUE implementation to adaptively choose the size of the smoothing kernel and reduce the number of free parameters of the total algorithm. A sensitivity analysis was performed using the threshold parameter to demonstrate the robustness of using local thresholds as opposed to using a single global threshold in detecting the place fields resulting from the large-scale simulation. The analysis supports the use of applying local thresholds for place field detection and will be used to further investigate the role of granule cells in hippocampal function.

I. INTRODUCTION

Place cells are neurons in the hippocampus that reliably respond to a specific location within the environment [1]. Typically associated with memory formation, the discovery of place cells exposed a new facet to hippocampal function, the formation of a spatial map. The discovery of place cells within the hippocampus revealed a behavioural correlate through which the function of the hippocampus could be further investigated through the context of the spatial maps that it forms.

The canonical place cell, found within the CA3 and CA1 subfields of the hippocampus, has been commonly shown to exhibit a single place field, a finite, continuous region in the environment at which the neuron preferentially spikes, though multiple place fields can also be expressed. A significant finding that explained how place cells could form were the discovery of grid cells in the medial entorhinal cortex. Grid cells are neurons that have multiple place fields, and the place fields are arranged in a triangular lattice pattern

¹geneyu at usc.edu,

²dsong at usc.edu,

³berger at usc.edu

throughout the environment [2]. The finding was significant because the entorhinal cortex provides the major input to the hippocampus. In the classical definition of the trisynaptic pathway, input from the entorhinal cortex synapses with granule cells in the dentate gyrus. Granule cells synapse onto CA3 pyramidal cells, and CA3 pyramidal cells synapse onto CA1 pyramidal cells. The CA1 provides the output of the hippocampus. Various experimental and computational works have verified the requirement of grid cell input as well as other necessary mechanisms by which place cells can be formed [3], [4].

Less understood is the role that the dentate gyrus has in place cell formation. As an intermediate region between the entorhinal cortex and CA3, it is unclear how the dentate gyrus fits into the place cell framework. Granule cells in the dentate gyrus have been shown to exhibit multiple place fields similar to grid cells, but the place fields are distributed irregularly, lacking the triangular structure that is characteristic of grid cells [5]. By providing grid cell input to a large-scale, computational model of the rat dentate gyrus, the granule cell models were found to express multiple place fields as well. However, the place fields for a single neuron were not only distributed irregularly but had variable characteristics such as maximal firing rate.

Typical place field detection algorithms have used a global threshold to identify place fields which can affect the number of place fields detected and the resulting characteristics of the detected place fields. This work proposes a grid-based application of the DENCLUE clustering algorithm to calculate and apply local thresholds for place field detection. By combining an adaptive binning procedure used to smooth the rate maps with the DENCLUE algorithm, the number of free parameters used for the detection was reduced to a single parameter. A sensitivity analysis is also presented which shows the robustness of using local thresholds in contrast to global threshold methods in detecting place fields from the large-scale model.

II. METHODS

A. Generating Grid Cell Activity

Grid cell activity was generated by creating rate maps defined by a formula created by Blair *et al.* that sums a set of cosines oriented at different angles to form vertices in a triangular lattice structure of a certain size and spacing

$$G(r, \lambda, \theta, c) = g \left(\sum_{k=1}^3 \cos \left(\frac{4\pi}{\sqrt{3}\lambda} u(\theta_k + \theta) \cdot (r - c) \right) \right), \quad (1)$$

where the $u(\theta_k) = (\cos(\theta_k), \sin(\theta_k))$ determines the relative orientations of the cosines with $\theta_1 = -30^\circ$, $\theta_2 = +30^\circ$, and $\theta_3 = +90^\circ$ [6]. The angle θ defines a global orientation of the rate map. Intervortex spacing is dependent on λ , and the spatial offset is defined with $c = (x_0, y_0)$. The gain function was set to be $g(x) = \exp[a(x - b)] - 1$ with $b = -\frac{3}{2}$. The size of the place fields is determined by the a parameter. Rate maps were normalized such that the minimum firing rate was 0.1 Hz and the maximum firing rate was 50 Hz.

The movement of a virtual rat in a 100 cm $\times$ 100 cm square environment was simulated by setting a random orientation and velocity (0–60 cm/s) that the rat would move for a random interval of time (0–1 second) at time steps yielding a sampling rate of 30 Hz. If the rat's vector would take it beyond the square environment, the orientation would be reflected by 90° from the boundary. A total of 1000 seconds of movement was generated.

The individually generated rate maps for each grid cell would use the virtual rat's position vector as input to calculate a firing rate profile for the grid cell. A heterogeneous Poisson process was used to create the spike times for the grid cells.

B. Large-Scale Model

The large-scale model represented 1/10th of the full scale of a single hemisphere of the rat hippocampus. The entorhinal cortex was composed of 4,600 lateral entorhinal cortical (LEC) cells and 6,600 medial entorhinal cortical (MEC) cells of which 80% of the MEC cells were grid cells. Non-grid cells independently generated spike times derived from a homogeneous Poisson process of 6 Hz, which was the mean firing rate of the grid cells.

The dentate gyrus was composed of 120,000 granule cells and 5,600 basket cells. Granule cells received an average of 1,950 inputs from LEC cells, 1,685 inputs from MEC cells, and 1,100 inputs from basket cells. Basket cells received an average of 180 inputs from LEC and MEC cells and 60 inputs from granule cells. Granule cells and basket cells were distributed throughout a flattened two-dimensional representation of the dentate gyrus. The network followed a topographic connectivity scheme in which the connection probability was dependent on the distance between the neurons, and the distribution of the granule cells and basket cell connection probabilities was described by a Gaussian distribution with standard deviations of 0.152 mm and 0.215 mm, respectively. The topographic projections between the entorhinal cortex and dentate gyrus and within the dentate gyrus and additional model parameters have been described in further detail in a previous work [7]. With this connectivity scheme, basket cells would provide both feed-forward inhibition to the granule cells via entorhinal input and feedback inhibition to the granule cells via granule cell inputs.

The granule cell and basket cell models were specified and simulated using the NEURON simulation environment [8]. The granule cell model was reduced from a previously published version to a 7-compartmental model representing a soma and 2 principle dendrites with 3 compartments each to allow the large-scale simulation to simulate 1,000 seconds in a reasonable amount of time [7]. Basket cells were 1-compartment models, and the active and passive membrane properties were derived from a previous work by Santhakumar *et al* [9].

C. Creating and Processing the Rate Map

The spiking activity of the granule cells was converted into a spatial firing map by dividing the 100 cm $\times$ 100 cm environment into square bins with side lengths of 2 cm and counting the number spikes that were elicited while the virtual rat was located in each bin. The amount of time it had spent in each bin was also computed and used to normalize the firing map calculate the mean firing rate for each bin, resulting in a rate map (Fig. 1). The spatial information (SI) of the granule cells was calculated to determine if the spiking of the granule cell contained any information on position. The SI score proposed by Skaggs *et al.* was

$$SI = \sum_i P_i \cdot \left(\frac{\lambda_i}{\lambda} \right) \cdot \log_2 \left(\frac{\lambda_i}{\lambda} \right), \quad (2)$$

where λ_i is the firing rate in the i^{th} bin, λ is the mean firing rate of the neuron, and P_i is the probability of being located in the i^{th} bin [10].

Granule cells with a SI of <0.5 bits/spike were eliminated from the analysis. Additionally, the spikes were shuffled relative to each other to create a rate map from the shuffled data, as described in [11]. The SI of the firing map of the shuffled map was computed, and the process was repeated 100 times. The SI of the original rate map was considered significant if it was greater than the shuffled SI with $p < 0.01$.

The rate map was then smoothed using an adaptive binning procedure also proposed by Skaggs *et al.* where the value of the bin was calculated by expanding a circle around the point until the following criterion was met

$$N_{spikes} > \frac{\alpha}{N_{occ}^2 r^2}, \quad (3)$$

where N_{spikes} is the number of spikes counted within the circle, N_{occ} is the number of samples within the circle, r is the radius of the circle in bins, and α is a scaling parameter, which was set to be 1.0×10^8 (Fig. 1) [10]. The value within the bin is $r_s \cdot \frac{N_{spikes}}{N_{occ}}$ where r_s is the temporal sampling rate. This technique optimizes a trade off between the number of available samples and the spatial resolution. The radius sufficient to satisfy the inequality was stored to be used during the place field detection process. The subsequent steps are performed on the smoothed rate maps after the adaptive binning procedure was applied.

D. Grid-Based Clustering with DENCLUE

DENCLUE was developed by Hinneburg and Gabriel as a clustering algorithm that imposes a density, or influencing, kernel on each data point and computes a local gradient that each data point follows to arrive at a local maximum (density attractor) [12]. Data points that converge to the same local maximum are considered to belong to the same cluster. To simplify the computation of the algorithm, the clustering was performed on the binned data rather than the individual points. The bins that belonged to the same attractor bin were considered a cluster, a place field. A Gaussian density kernel was assumed, and the standard deviation of the density kernel for a particular bin was set to be the radius used by the adaptive binning procedure for that bin. The only free parameter for the entire procedure is the α parameter from Eq. 3 that is used during the adaptive binning procedure.

E. Defining the Place Field

A place field was defined to be a set of contiguous bins with a minimum area of 200 cm². After all of the place fields were identified, the background activity was characterized by computing the mean and standard deviation of the rates of the bins that were not considered part of a place field. The mean rates of the place fields were calculated, and if the mean rate of a place field was not significantly greater than the background rate with a level $p < 0.01$, it was rejected as being a place field.

III. RESULTS

Three methods were applied in detecting place fields. In the first method, a global threshold is applied by calculating the maximum firing rate in the rate map and using a proportion of the maximum rate as the threshold. In the second method, a global threshold is applied, but the amplitude of the rate map, the difference between the maximum and minimum rate, is calculated, and a proportion of the amplitude is used as the threshold. In the third method, a local threshold is computed by calculating the amplitude of each place field and using a proportion of each amplitude as a threshold. These methods were applied to all granule cell rate maps using proportions of 0.1 through 0.9 at increments of 0.1. The average number and the average area of the detected place fields per granule cell were calculated. An example of how the differing threshold methods affect place field detection for the same rate map in Fig. 1 are shown in Fig. 2.

The means and standard deviations of the detected number of place fields and place field area per granule cell were computed for each method (Fig. 3). The place field areas were normalized by the total area of the environment that the virtual rat traversed (10,000 cm²). Furthermore, the means and standard deviations of the above quantities were computed across all thresholds for a given method, and the coefficient of variation was calculated using those metrics (Fig. 3).

IV. DISCUSSION

By visual inspection, it is evident that the rate map in Fig. 1 has multiple place fields. However, the peaks detected by the different methods vary greatly. Fig. 2 demonstrates some immediate problems with the global maximum as a threshold. At low thresholds, no place fields are detected because the entire rate map can be classified as a single place field. Depending on the difference between the maximum and minimum values, a low threshold could include every bin until the threshold surpasses the minimum. At high thresholds, two cases are possible. A single, small place field corresponding to the tip of the highest peak in the rate map is detected, or no place field is detected because the tip of the highest peak does not satisfy the minimum size required to be considered as a place field.

Using a global amplitude as a threshold takes the range of values into consideration which prevents cases where all bins are classified as a single place field. At the middle threshold region, this method begins to exclude all place fields except for the one with the highest peak. At higher thresholds, the single peak does not meet the size requirements and is excluded. These two results highlight the major disadvantages of using global metrics to

detect place fields. If the peak of the place fields are variable, then threshold values that are too high can exclude place fields. If the threshold is too low, place field detection is too coarse, and the entire rate map is classified as a single place field

The local amplitude method has a wider range of threshold values at which the number of detected fields are the same, demonstrating its robustness. Global methods used the requirement that the identified place fields be separated by at least one bin to be considered separate place fields, but the DENCLUE method is able to identify and separate discrete place fields regardless of whether they are directly contacting each other. This is demonstrated in Fig. 2 where at threshold 0.2, the DENCLUE method identified 8 separate place fields although a majority of the place fields appear contiguous. Finally, the coefficient of variation for the local amplitude method is the lowest indicating that the metrics that are calculated show the least variability relative to the mean, regardless of the threshold value that is used.

The sensitivity analysis demonstrates the robustness of the local amplitude method in detecting place fields (Fig. 3). The choice of threshold should minimize the slope in either direction for all of the relevant metrics. The data suggests a threshold value of 0.3 times the local amplitudes to be relatively stable. This parameter will be used for the ongoing investigation of place field formation in the dentate gyrus such as the effect of the local circuitry on granule cell place fields.

ACKNOWLEDGMENT

Work supported by NIH Grant U01 GM104604, NIBIB Grant P41 EB001978, 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).

This work was not supported by any organization

References

- [1]. O'Keefe J, "Place units in the hippocampus of the freely moving rat," *Experimental Neurology*, vol. 51, no. 1, pp. 78–109, 8 1976. [PubMed: 1261644]
- [2]. Hafting T et al., "Microstructure of a spatial map in the entorhinal cortex," *Nature*, vol. 436, pp. 801–806, 8 2005. [PubMed: 15965463]
- [3]. Miller VM and Best PJ, "Spatial correlates of hippocampal unit activity are altered by lesions of the fornix and entorhinal cortex," *Brain Research*, vol. 194, no. 2, pp. 311–323, 8 1980. [PubMed: 7388617]
- [4]. de Almeida L et al., "The input-output transformation of the hippocampal granule cells: From grid cells to place fields," *J. Neurosci*, vol. 29, no. 23, pp. 7504–7512, 6 2009. [PubMed: 19515918]
- [5]. Jung MW and McNaughton BL, "Spatial selectivity of unit activity in the hippocampal granular layer," *Hippocampus*, vol. 3, no. 2, pp. 165–182, 4 1993.
- [6]. Blair HT et al., "Scale-invariant memory representations emerge from Moiré interference between grid fields that produce theta oscillations: A computational model," *J. Neurosci*, vol. 27, no. 12, pp. 3211–3229, 3 2007. [PubMed: 17376982]
- [7]. Hendrickson PJ et al., "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, 1 2016. [PubMed: 26087482]
- [8]. Carnevale NT and Hines ML, *The NEURON Book*. Cambridge, UK: Cambridge University Press, 2006.

- [9]. Santhakumar V et al., "Role of mossy fiber sprouting and mossy cell loss in hyperexcitability: A network model of the dentate gyrus incorporating cell types and axonal topography," J. Neurophysiology, vol. 93, no. 1, pp. 437–453, 1 2005.
- [10]. Skaggs WE et al., "Theta phase precession in hippocampal neuronal populations and the compression of temporal sequences," Hippocampus, vol. 6, no. 2, pp. 149–172, 1996. [PubMed: 8797016]
- [11]. Neunuebel JP and Knierim JJ, "Spatial firing correlates of physiologically distinct cell types of the rat dentate gyrus," J. Neuroscim vol. 32, no. 11, pp. 3848–3858, 3 2012. [PubMed: 22423105]
- [12]. Hinneburg A and Gabriel H-H, "DENCLUE 2.0: Fast clustering based on kernel density estimation," in Advances in Intelligent Data Analysis VII, Berthold MR, Shawe-Taylor J, and Lavra N, Eds. Springer Berlin Heidelberg, 2007, pp. 70–80.

Fig. 1.

Example of a rate map generated by a granule cell. The left panel contains the raw data, and the right panel was smoothed using adaptive binning. The red areas indicate the locations in the environment that granule cell preferred to fire, indicating potential place fields.

Fig. 2.

Demonstration of the variability of the detected place fields due to changes in the threshold parameter. The top row varies the global maximum. The middle row varies the global amplitude. The bottom row varies the local amplitude using the DENCLUE algorithm.

Fig. 3.

The mean and standard deviation of the place field areas and number of detected place fields per granule cell for each threshold. The top row contains the detected number of place fields for each threshold method, and the bottom row contains the mean place field area. The right-most column computes the overall mean and standard deviation of the respective quantities with the coefficient of variation listed at the top of the bar plots. The place field area was normalized by the total area of the environment (10,000 cm²).