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Community structure embedded in neuronal network

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Abstract– The way in which brain structure constrains the brain's functional activity is one of the critical questions in the field of neuroscience. In this research, first, we reconstructed causal interactions among neurons from the hippocampus using spike trains, which were recorded on a 512 electrode array system. Next, we separated the network structures by using several community detection analysis techniques, and extracted the subgroups of neurons communicating with each other. As a result, we could compare the estimated separation line and the structural dividing lines among Dentate Gyrus (DG), CA3, CA1 hippocampal regions. In this paper, we show the primitive result.

In the main conference, I will also talk about the advanced result and discuss how it relates to the concept of *Neuronal Avalanches* [1].

1. Introduction

Neurons connect and interact with each other through spike firings. A critical and important area where neuroscience is advancing today is how the spatial pattern of firing activity of the network is constrained by the structural network of the brain.

Researchers in the field of macroscopic neural activity have been attracted to this question. The spatial pattern of correlated whole brain activity recorded by fMRI, when participants are not performing any cognitive task, is called Default Mode Network (DMN). Recently, Hagman et al. measured the macroscopic brain structural connectivity by using Diffusion Spectrum Imaging (DSI). Honey and Sporns also showed that the structural connectivity could predict the connectivity of DMN [2, 3].

We assumed that specific features of microscopic neuronal connectivity reconstructed from spike train data would also show a clear correspondence to structural connectivity as previous researchers had observed in macroscopic connectivity. For testing this hypothesis, first, we provided a new analysis technique for reconstructing the causal interactions from neuronal spikes recorded by a 512 electrode array [4, 5, 13]. Secondly, we separated the networks into several groups by using community detection analysis. Finally, we compared the estimated neuronal networks with cell-distributions of dyed hippocampus substructures. As a result, in the test data, we succeeded in estimating the separation lines among neuronal groups of DG, CA3, and CA1 regions of the hippocampus.

This result suggests that the structural network and partition strongly constrains the causal interaction of spontaneous activity.

2. Method

2.1. Data acquisition

All neural tissue from animals was prepared according to guidelines from the National Institutes of Health and all animal procedures were approved by the Indiana University Animal Care and Use Committee. Organotypic cultures were prepared following the method of [14], as previously described [15]. Briefly, brains from postnatal day 1 (P1)–P3 Sprague Dawley rat pups (Harlan) were removed under a sterile hood and placed in chilled Gey's balanced salt solution for 1 h at 8°C. After 30 min, half the solution was changed. Brains were next blocked into ~5 mm3 sections containing hippocampus and surrounding cortex. Blocks were then sliced into coronal sections with a thickness of 450 μm. Each slice was placed on a small circular cutout of permeable membrane (Millipore, Billerica, MA) that was then placed on top of a larger membrane that spanned a culture well. Culture medium consisted of HBSS (Sigma; H9394) 1:4, Mega cell medium (Sigma; M4067) 2:4, horse serum (Sigma; H1270) 1:4, and 4 mm glutamine, with penicillin/streptomycin 1:100 volume of media (Sigma; P4083). Slices were maintained at an interface between medium below and atmosphere above. The plates of wells were constantly maintained at 37°C in humidified atmosphere with 5% CO_2. After 3 weeks the cultures were then gently placed on a microelectrode recording array by lifting the small circular cutout of membrane with tweezers. Each culture was placed tissue side down, with the membrane facing up. We attempted to place the tissue so that the hippocampus covered the array, with parts of adjacent cortex also included. During recording, cultures were perfused at 1 ml/min with culture medium that was saturated with 95% O_2/5% CO_2. Recording sessions lasted 2–7 h.

2.2. Data analysis

2.2.1. Spike sorting

Sorting was done offline as previously described [15]. Briefly, signals that crossed a threshold of 3 SDs were marked, and the waveforms found on the marked electrode and its six adjacent neighbors were projected into five dimensional principal component space. A mixture of Gaussians model was fit to the distribution of features based on maximum likelihood. Only the neurons that had well separated clusters in principal components space and had no refractory period violations were used in further analysis.

Furthermore, we fitted Gaussian models for the Electrophysiological Image to detect the physical positions of neurons. This estimation is possible because of the high density positioning of electrodes (~60 μm).

2.2.2. Reconstruction of causal interaction

In this section, we explain about the technique to reconstruct causal interaction or connectivity among neurons estimated by spike sorting technique. To estimate the connectivity, we need to define some quantity which measures the intensity of each connection.

Garofalo et al. compared the performance to estimate structural connectivity of neurons among Mutual Information (MI), Joint-Entropy (JE), Transfer Entropy (TE) methods, and Cross-Correlation (CC) [7]. Among them, TE showed the best detectability of causal interaction relating to the structural network [7]. Garofalo et al. evaluated the estimated connectivity structure in a mathematical model mainly. However, in their experimental system, the distance between electrodes was wide (~200μm), so the estimation of positions of cells was impossible in principle because the distance between neurons having local interaction is around several tens of microns [9]. Therefore, in their research, the comparison between the experimental results and results of mathematical modeling in the level of "cells" is an intrinsically difficult problem. In our system, the distance between electrodes is small (60 μm), allowing us to estimate the position of cells by calculating which electrode is closer to the position of the neuron (refer to method of spike sorting). Therefore, with this data it is possible to visualize the network of interactions among neurons.

Recently, our group also evaluated the performance of the estimation of structural connectivity among Izhikevich neuron models [4]. The result also confirmed the priority of TE consistently.

Equation (1) expresses the definition of TE [11].

$$TE_{J\to I} = \sum_{i,j} p\left(i_{t+1}, i_t^{(k)}, j_t^{(l)}\right) \log \frac{p\left(i_{t+1} \middle| i_t^{(k)}, j_t^{(l)}\right)}{p\left(i_{t+1} \middle| i_t^{(k)}\right)} \quad \cdots \quad (1)$$

Here, i_t or j_t indicates the state of neuron i or j at time *t*. If a neuron i fired, the value is 1, and otherwise the value is 0. The shorthand notion like $i_t^{(k)}$ means $\left(i_n, \cdots, i_{n-k+1}\right)$. Briefly speaking, this equation measures the deviation from Markov property $p\left(i_{t+1} \middle| i_t^{(k)}, j_t^{(l)}\right) = p\left(i_{t+1} \middle| i_t^{(k)}\right)$. In other words, this equation measures the incorrectness of an assumption that the status of neuron *j* at time *t* has no influence on the transition of status of neuron *i* from time *t* to time *t+1*.

Between connected pair of neurons *i* and *j*, the causal dependency should be stronger than pairs of separated neurons. TE can be used to reconstruct the neuronal network by using this causal relation of neuronal spikes in short time range (< 7 ms).

2.2.3. Community detection analysis

The next step is the main part of the analysis: community detection. In this research, we show two different community detection techniques. The two techniques define communities by a global definition, or a local definition.

In the global definition, we prepare an optimization function. It is called "modularity". The representative technique is the Girvan-Newman method [8]. The modularity of them is shown in the following equation:

$$Q = \frac{1}{4m} \sum_{ij} \left[A_{ij} - \frac{k_i k_j}{2m} \right] \delta\left(c_i, c_j\right) \quad \cdots \quad (2)$$

In this equation, k_i and k_j are the degrees of the vertices and $m = 1/2 \sum_i k_i$ is the total number of edges in the network.

If the community in which node i belongs, is same as the community in which node j belongs, the Delta function $\delta\left(c_i, c_j\right)$ becomes 1, and if their communities are not same, the value is 0. If changing the border between communities, this value changes. Here A_{ij} means the weight of the connection between nodes (neurons) *i* and *j*. The $k_i k_j / 2m$ means the expected value of the node i and node j. Therefore, $\left[A_{ij} - k_i k_j / 2m \right]$ indicates how much more strongly the real graph is connected than a random graph. As a result, if the term becomes larger for a pair of nodes belonging in same community, *Q* becomes larger. In other words, if *Q* becomes larger, the pair of nodes connected well with each other will join a same community. Nodes connected densely to each other should be grouped together. Therefore, by maximizing the optimization function, we can estimate the best border for the weight matrix of the connectivity. The 4m at the top of the equation is used as the normalization factor to compare different structures of connection fairly.

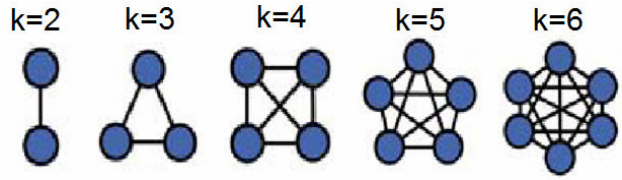

Figure 1: k-cliques

The clique means fully connected network group, when defining community structure by using k-core technique. We regard the neurons connecting each other over some threshold number k as a community.

A representative technique in local definition is the k-clique technique [12]. This technique naturally expresses an empirical knowledge that the friend of a friend is also often a friend. Community in the k-clique technique is defined in a very strict sense as a community, all of whose members are connected to each other. This group is called clique. The k-core method allows us to define a group of friends by a milder definition such that, in one community, each node connected to at least k other nodes. We used the k-core technique with (k=4) to analyze our spike data. In this technique, the main parameter is only k, the size of the number of nodes connecting each other in a same community (Figure 1).

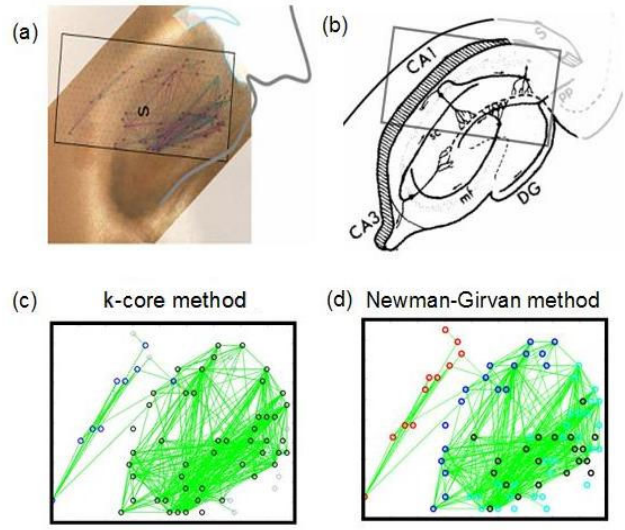

Figure 2: Example results of community detection

(a) Anatomical image of the hippocampus [10]. (b) Circuit diagram of known axon pathways in hippocampus. (c) The communities classified by the k-core technique. (d) The communities classified by the Girvan-Newman technique. In figures (c), (d), the different colors mean that their groups are different.

3. Results

3.1. Reconstruction of causal interactions

In this research, we reconstructed the directed connectivity graph by using Transfer Entropy. (Figure 2-(a,c,d)). The graph told the structure of network can detect the abstract form of hippocampus.

3.2. Community detection and anatomy

For extracting more detailed divisions, we applied two community detection techniques. The result of the k-clique method succeeded in dividing between the hippocampus and the cortex clearly (Figure 2-(c)). Furthermore, the Girvan-Newman method succeeded in separating the internal structure within the hippocampus (CA1, CA3, and DG) (Figure 2-(d)). We could observe the anatomical correspondence with the illustration shown in figure 2-(b).

3.3. Supplemental results

In the community detection analysis, we can observe the structure in one spatial scale. However, the network architecture has multi-scale structure. Supplimentaly, as the primitive analysis, we introduce the result of distribution of the degree distribution of the network architecture.

4. Discussion

In this research, we demonstrated the correspondence between the information-theoretical causal interactions among neurons reconstructed by using Transfer Entropy and neuronal structural connectivity. Particularly, we clarified that the community detection technique could visualize the dividing line between the cortex and the hippocampus as well as between CA1, 3, and DG.

We will introduce several current research topics relating to the concept of *Neuronal Avalanche* [1].

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