Estimation of Concerted Activities Based on Subsequence Distribution Discrepancy Calculation

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***Abstract*—In the present study, a new measurement of subsequence distribution discrepancy (MSDD) was applied to analyze the concerted activity pattern of a group of spike trains. The changes of concerted pattern in a neuronal population affected by the activity of GABA inhibitory pathway were estimated using this method. Comparison between MSDD and classical cross-correlation analysis showed that the parameter B_k in MSDD can be considered as an index showing the degree of coincidence between the activity of the *k*-th neuron and that of the rest neurons in the group. These results suggest that the new algorithm MSDD can be applied to investigate the concerted activities of neuronal population efficiently. With the help of this method, physiological conditions determined by the spatio-temporal pattern of the neuronal activities can be compared.**

Keywords-multi-unit recording; population activity; multiple spike train analysis; GABA inhibition

I. INTRODUCTION

The brain accomplishes its jobs by generating coordinated patterns of electrical signals in population of neurons. Concerted activity pattern among a group of neurons is an indicative aspect to show how the neurons work together to encode stimuli's features [1, 2]. For better understanding the characteristics of concerted activity, several methods have been proposed [3-7]. However, some of them could only analyze correlation between pair-wise spike trains [3-5], other algorithms used for multiple spike train analysis were restricted to the selection of parameters [6, 7].

To estimate the concerted pattern among multiple spike trains using a single index, our group adopted a new method for multi-dimensional data analysis, which is based on the measurement of subsequence distribution discrepancy (MSDD) [8]. MSDD applies information theory to the algorithm, so it mainly depends on the original structure of spike sequences and lies little on subjective factors.

In our previous experiment [9], it was found that correlated activities between retinal ganglion cells of transient subtype caused by shared input could be enhanced when GABAergic pathway was activated. Such pair-wise correlations may be related to concerted activities among a larger group of neurons [6, 10]. In the present study, MSDD was applied to analyze the changes of concerted patterns affected by the activation of GABAergic pathway. It was found that when exogenous GABA was applied, most neurons' firing rates were decreased. At the mean time, the concerted pattern among the neuronal population is also changed. This is consistent with the phenomenon from cross-correlation analysis. These results suggest that this new method of MSDD can be applied to investigate the spatio-temporal pattern of population activity in different physiological status and reveal certain physiological significance efficiently.

II. MATERIALS AND METHODS

A. Electrophysiology Recording

Retinas from newly-hatched chicks (3-15 days post hatching) were investigated in the present study. Detailed extracellular-recording procedure can be found in one of our previous report [9]. Spikes from ganglion cells were recorded by MEA electrodes (8×8, MEA60, MCS GmbH, Germany) using a commercial multiplexed data acquisition system with a sampling rate of 20 kHz. In the pharmacological studies, 500 μM GABA (Sigma, St. Louis, MO, USA) was added to the Ringer's solution as desired.

Spatially uniform white light was generated from a video monitor (796 FD II, MAG) and was focused to form a 0.75 × 0.75 mm^2 image on the isolated retina via a lens system. Stimulus consisting of full-field white light (12.18 nW/cm^2) with duration of 1 s and dark interval of 9 s was given repeatedly for 50 times [9].

B. Multiple Spike Train Analysis

The measurement of subsequence distribution discrepancy, termed "information discrepancy" [11, 12], was applied to deal with a group of spike train sequences and analyze the spatio-temporal pattern of concerted activities among the neurons in the present study. Detailed method can be found in one of our previous reports [8].

Briefly, the spike trains were symbolized into "0" and "1" according to the "all-or-none" spiking events, where "1" represents that there is one spike in the time bin of interest and "0" represents that there is no spike in the time bin. Then the constructive information of a sequence can be transformed into a set of subsequence distributions, which was defined by Fang et al. [11].

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In the present study, the neuronal firing activities were symbolized into sequences of two symbols "0" and "1" ($m = 2$) with time bin width of 2 ms ($L = 2$). All the sequences were separated into 6-letter overlapping subsequences ($l = 6$), with moving step being one time bin. The subsequence distributions can thus uniquely represent all the structure information of each sequence:

$$\begin{aligned} U_1^l &:= (p_{11}^l, p_{21}^l, \ldots, p_{m(l)1}^l)^T \\ U_2^l &:= (p_{12}^l, p_{22}^l, \ldots, p_{m(l)2}^l)^T \\ &\vdots \\ U_s^l &:= (p_{1s}^l, p_{2s}^l, \ldots, p_{m(l)s}^l)^T \end{aligned}, \qquad (1)$$

where $m(l)$ is the number of all the possible combination of subsequences in the symbol set ($m(l) = 2^6$, when $m = 2$ and $l = 6$), p_{ik}^l is the probability of the i-th subsequence in the k-th sequence ($\sum_{i=1}^{m(l)} p_{ik}^l = 1, k = 1,2,\ldots,s$).

The discrepancy measurement can then be defined as:

$$B_k(U_1^l, U_2^l, \ldots, U_s^l) = \sum_{i=1}^{m(l)} p_{ik}^l \log \frac{p_{ik}^l}{\sum_{k=1}^{s} p_{ik}^l / s}, \qquad (2)$$

where the measurement B_k represents a measurement of discrepancy between the subsequence distribution of the k-th sequence (U_k^l) and the subsequence distribution calculated for all s sequences of the whole group $(U_1^l, U_2^l, \cdots, U_s^l)$. It implies that if two spike trains are completely synchronized, they will have exactly equal values for B_k; at the same time, a large B_k value is related to profound difference between the temporal structure of the k-th sequence and the rest of the group.

C. Cross-correlation Analysis

In order to testify the validity of MSDD, the cross-correlation function between pair-wise retinal ganglion cells was analyzed as follows [13]:

$$c_{xy}(m) = \begin{cases} \sum_{n=0}^{N-|m|-1} x_n y_{n+m} \Big/ R & m \geq 0 \\ c_{yx}(-m) & m < 0 \end{cases}, \quad R = \sqrt{\sum_{i=1}^{N} x_i^2 \sum_{i=1}^{N} y_i^2}, \qquad (3)$$

where x_n denotes the value of sequence x at moment n; y_{n+m} is the value of sequence y at moment $n + m$; $c_{xy}(m)$, by definition, represents the correlation between sequences x and y with a time lag of m, which reflects the effect of signal x exerts on signal y with a time delay m; R is the normalizing factor.

III. Results

In the present study, ganglion cells of transient subtype, which responded to light-ON and/or -OFF transients of white light flash were investigated.

Fig. 1 illustrates the geometric position of 13 transient subtype ganglion cells recorded from one retina using multi-electrode array (MEA). Example recordings of these neurons' light responses are shown in Fig. 2. During control experiment, every neuron fired spikes at a comparatively high rate. But there are a few "odd" neurons that fired action potentials in weak synchrony with their neighboring neurons. Neuron #17 is one of such "odd" cell that it fired frequently, but its activity was less synchronized with its neighboring neurons, as indicated by a large B_k value in Fig. 3 (solid line). This is confirmed by cross-correlation between this neuron and one of its neighboring neuron (#23) in Fig. 4a (this is the general situation, other data are not shown). At the same time, other neurons with small B_k values have strong synchronized firing activities with each other, an example is given in Fig. 4b (#23 *vs* #24).

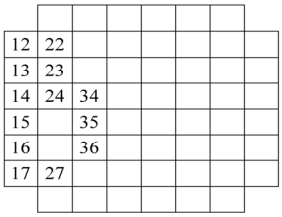
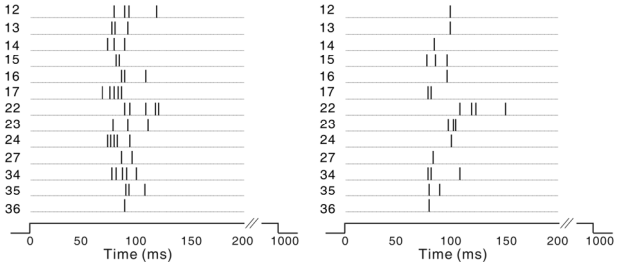


Figure 1. Geometric position of 13 neurons recorded from one example retina during normal control and with GABA application.



(a) Normal (b) GABA

Figure 2. Raster plot of the neurons indicated in Fig. 1. Responses are selected from one trial, lasting 200 ms after the light-ON time. (a) The responses of the neurons during normal control. (b) The responses of the neurons during GABA application.

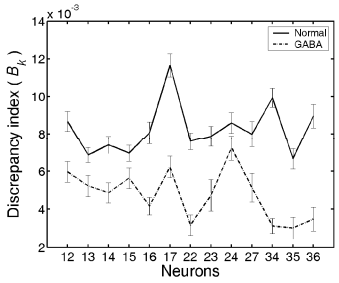


Figure 3. Averaged B_k values of the neurons during control and GABA application as indicated in Fig. 1 (50 repeats). Error bars show the standard errors.

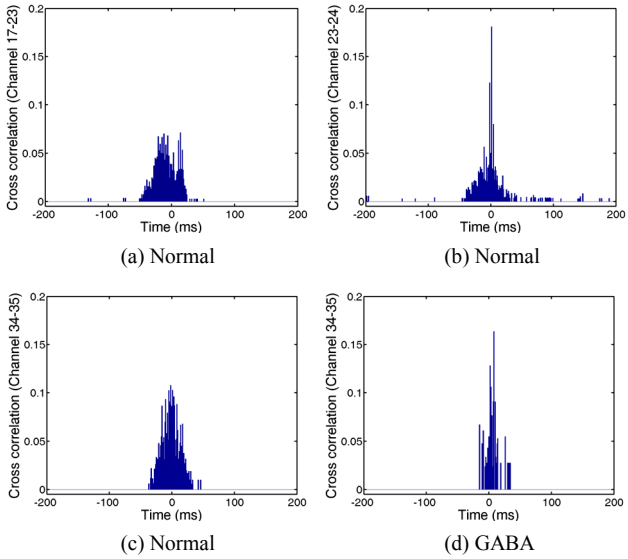


Figure 4. Cross-correlation analysis of 3 example neuron pairs. (a) Cross-correlation function of neurons #17 and #23 in normal Ringer's solution. (b) Cross-correlation function of neurons #23 and #24 in normal Ringer's solution. (c) Cross-correlation function of neurons #34 and #35 in normal Ringer's solution. (d) Cross-correlation function of the same neuron pair as shown in c during GABA application.

Another neuron that is less synchronized with other neurons during normal condition is neuron #34, this is indicated by a large B_k value in Fig. 3 (solid line) and a weak cross-correlation as shown in Fig. 4c (#34 *vs* #35). However, when GABA was applied to the retina, the cross-correlation between neuron #34 and its neighboring neurons was strengthened, which is indicated by a small B_k value in Fig. 3 (dash-dot line), this is also confirmed by cross-correlation presented in Fig. 4d as compared to Fig. 4c.

GABA is the main inhibitory transmitter in the central nervous system, the activity of which normally result in a decrease in neuronal activity. Our results reveal that the local concerted pattern of a group of neurons can also be influenced by the GABAergic pathway, and suggest that this new method MSDD can be applied to investigate the changes of concerted pattern of population activity between different physiological status. Meanwhile, the comparisons between the B_k values of MSDD and the classical cross-correlation analysis further support the notion that the B_k value can be considered as an index showing the degree of coincidence between the activity of the k-th neuron and that of the rest neurons in the group.

IV. Discussion

In the present study, a measurement of subsequence distribution discrepancy (MSDD) is adopted to investigate the concerted activities of a group of neurons at the same time. This approach not only largely reduces the amount of calculation work compared to the pair-wise methods, but also provides an objective judgment to the comparison and analysis of multiple sequences. This means that the new method can be used to assess the concerted pattern in a population efficiently.

Although MSDD is an objective and efficient method, some considerations for using this new measurement should be concerned.

First, a few parameters are required for preparing the raw spike trains and the subsequences, such as time bin width (L) and the length of subsequence (l). Our previous work [8] has discussed the details about the influence of these parameters to the results. In the present study, all the parameters chosen for calculation were suitable according to the firing rate and the length of the whole sequence.

Second, there is no absolute criterion to quantify the degree of concerted activities of a neuronal population or the similarity between relevant sequences. Just as the intensity of correlation in the cross-correlation analysis, the strength of concerted activities in MSDD described by B_k is also a relative value. The degree of concerted activities of one population should be assessed after comparing with other populations in the same condition or the same population in other conditions. The similarity of B_k values also relies on their relevant height within the group.

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