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Correlated transition between two activity states of neurons

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In order to understand the dynamical properties of a neural network, it is important to characterize the relation between spike trains of two neurons in the network. In this study, we show that in some neuron pairs in inferior temporal cortices of macaque monkeys, spike trains of a pair are described by a two-dimensional Poisson process whose means are modulated by a common two-state Markov process. The common two-state Markov process describes a correlated state transition between firing and nonfiring states of the constituent neurons of the pair.

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I. INTRODUCTION

In order to characterize the dynamical properties of a network composed of many neurons, it is important to determine not only the stochastic dynamics of each neuron's spike train but also the relation among the spike activities of neurons in the network. Although the simultaneous recording of spike activities of multiple neurons has progressed rapidly in recent times [1], evaluating the relation among spike activities of more than three neurons is still difficult because statistical methods for analysis of multiple spike trains are limited [2]. However, the relation between spike activities of two neurons in a network can be well characterized by a cross correlogram between spike trains of the neurons. In a previous study, we showed that a broad peak appears in a cross correlogram between spike trains of neurons in inferior temporal (IT) cortices of macaque monkeys [3]. The IT cortex is a visual area that is considered to play an essential role in the perception and recognition of an object. In this study, we formulated a stochastic model for spike trains of a neuron pair in the IT cortex on the basis of cross- and autocorrelation analysis of experimentally recorded spike trains. Using this model, we characterized the relation between the spike activities of an IT neuron pair and the spike train dynamics of the constituent neurons of the pair.

II. EXPERIMENTAL PROCEDURE AND DATA ANALYSIS

We penetrated two to four electrodes (interelectrode distance 580–2380 μm) into the IT cortices of two macaque monkeys and simultaneously recorded spike activities of neurons under anesthetized condition (a mixture of 70% N_2O and 30% O_2, and up to 2% isoflurane). Spontaneous activities of neurons for 1 s were recorded 300–1360 times (trials). The experimental protocol was approved by the Experimental Animal Committee of the RIKEN Institute. All experimental procedures were done in accordance with the guidelines of the RIKEN Institute and the National Institutes of Health.

After the recording, a single cellular spike activity was extracted by applying a template matching method to spike wave forms. Denoting the extracted spike train of a neuron i ($i=1,2$) on the kth trial as $S_i^k(t)$, we estimated average firing rate of the neuron $\hat{R}_i$ as follows:

$$\hat{R}_i = \overline{\hat{H}_i(t)}, \tag{1}$$

where the overbar indicates time average and $\hat{H}_i(t)$ is given by

$$\hat{H}_i(t) = \langle S_i^k(t) \rangle_{tri}. \tag{2}$$

In this equation, $\langle\,\rangle_{tri}$ indicates the trial average. The cross- and autocorrelograms $\hat{R}_{ij}(\tau)$ $(i,j=1,2)$ were also calculated as follows:

$$\hat{R}_{ij}(\tau) = \langle \overline{[S_i^k(t) - \hat{H}_i(t)][S_j^k(t+\tau) - \hat{H}_j(t+\tau)]} \rangle_{tri}. \tag{3}$$

The width of the time bin used in the calculation was 10 ms. The cross correlogram was estimated only for spike trains recorded from different electrodes.

The statistical significance of a peak in the cross correlogram was estimated as follows. First, we shuffled the trial order of the spike trains of one neuron and then calculated the cross correlogram $\hat{R}_{12}^{sh}(\tau)$ as follows:

$$\hat{R}_{12}^{sh}(\tau) = \langle \overline{[S_1^k(t) - \hat{H}_1(t)][S_2^{o(k)}(t+\tau) - \hat{H}_2(t+\tau)]} \rangle_{tri}, \tag{4}$$

where $o(k)$ represents the trial order after the shuffle. This correlogram is called the shuffle correlogram. We shuffled the trial order 1000 times and thereby obtained a total of 1000 shuffle correlograms. On the basis of these shuffle correlograms, we estimated 95% confidence limits of the cross correlograms. If five consecutive bins in the cross correlograms exceeded the upper limit, then we regarded the peak as significant.

III. EXPERIMENTAL RESULTS

We recorded spike activities of neurons from 48 sites in total. The number of single neurons we could extract from a signal recorded at one site was at most 2. We could not

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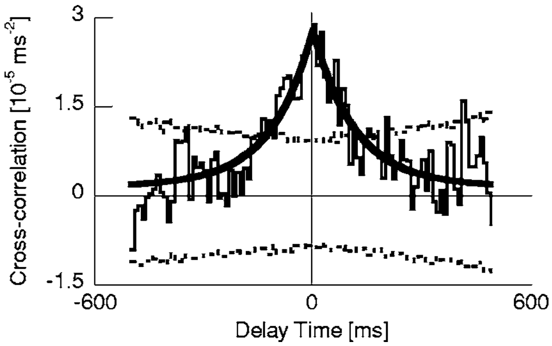

FIG. 1. Cross correlogram of spike trains of an IT neuron pair. Thin solid line for cross correlogram; broken lines for confidence limits of 95%; thick solid line for fitting curve. The fitting function was $y=ae^{-b|\tau|}+c$. $a=2.6\times10^{-5}$ ms^{-2}, $b=8.9\times10^{-3}$ ms^{-1}, $c=1.6\times10^{-6}$ ms^{-2}.

reliably extract spike activities of single neurons from the signals recorded at several sites. As a result, we obtained spike activities of 46 single neurons in total. From these 46 neurons, we obtained 57 neuron pairs. The number of neuron pairs is smaller than that of all possible combinations of the 46 neurons. This is because we did not record spike activities of all 46 neurons simultaneously.

In 17 of the 57 neuron pairs (30%), a significant peak is observed in the cross correlograms. Figure 1 shows an example of a cross correlogram in which a significant peak appears. For this neuron pair, the width of the peak is hundreds of milliseconds. It is probable that this peak resulted from correlation between temporal modulations with a time constant of hundreds of milliseconds involved in the spike trains of the constituent neurons of the pair. This is because there exist components with time constants of hundreds of milliseconds in the autocorrelograms of the constituent neurons [Fig. 2(a)]. Moreover, the components in the autocorrelograms coincide well with the peak in the cross correlogram [Fig. 2(b)]. This result suggests that the temporal modulations involved in the spike trains of the two neurons are perfectly correlated.

To further characterize the temporal modulations in the spike trains, we applied least-squares fitting to the cross correlogram. Then we found that the peak in the cross correlogram is well fitted with an exponential function (Fig. 1). From this result, we can see that the components with a time constant of hundreds of milliseconds in the autocorrelograms are also fitted with the exponential function because these components coincide well with the peak in the cross correlogram (Fig. 2).

There are two well-known stochastic processes whose autocorrelations are an exponential function. One is a two-state Markov process and the other is an Ornstein-Uhlenbeck (OU) process. To examine which process is more appropriate for describing the temporal modulations in spike trains, we formulated stochastic models of spike trains that have temporal modulations described by either the two-state Markov process or the OU process. After the formulation of the models, we estimated all the parameters of each model from experimental data and then we determined which model is more appropriate.

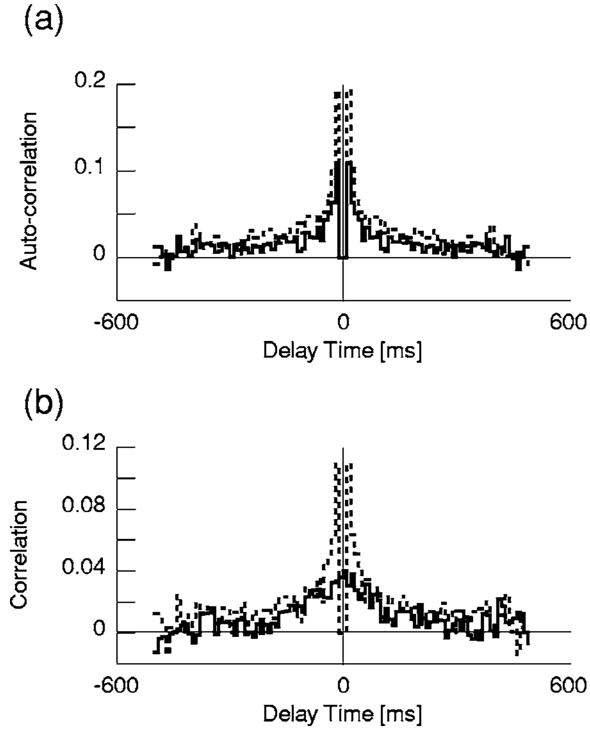

FIG. 2. Autocorrelograms of the neurons (a) and a comparison between the auto- and cross correlograms (b). In (a), solid line for autocorrelogram of one neuron; broken line for that of the other neuron. Each correlogram was normalized by the square of the average firing rate of each neuron. For display, the values at 0 time delay were set to 0. In (b), solid line for the cross correlogram shown in Fig. 1; broken line for the autocorrelogram represented by the solid line in (a). The cross correlogram was normalized by the product of the average firing rates of the neurons.

IV. TWO-DIMENSIONAL POINT PROCESS MODULATED BY A TWO-STATE MARKOV PROCESS

A. Formulation

We first formulated a stochastic model of spike trains of an IT neuron pair that are modulated by a two-state Markov process. In the model, the spike train of each neuron $S_i(t)$ $(i=1,2)$ is denoted by

$$S_i(t) = s_i(t)X(t), \tag{5}$$

where $X(t)$ represents the two-state Markov process common to the two neurons of the pair. In Eq. (5), $s_i(t)$ represents a point process whose average and autocorrelation are given by

$$\langle s_i(t)\rangle = \nu_i, \tag{6}$$

$$\langle [s_i(t)-\nu_i][s_i(t+\tau)-\nu_i]\rangle = f_i(\tau), \tag{7}$$

where $\langle\,\rangle$ represents the sample average, and $f_i(\tau)$ corresponds to a narrower peak that appears in the autocorrelogram at around the 0 time delay of each neuron [Fig. 2(a)] and does not coincide with a peak in the cross correlogram [Fig. 2(b)]. The function $f_i(\tau)$ rapidly approaches 0 as τ increases. We assume that the process $s_i(t)$ is ergodic. In addition, we assume that $s_1(t)$ and $s_2(t)$ are statistically independent, and $X(t)$ and $s_i(t)$ $(i=1,2)$ are also statistically independent. The state space of $X(t)$ is $X(t)=\{0,1\}$; we call the states $X(t)=1$ and $X(t)=0$ the up and down states, respectively. The transition rate from the down to the up state is denoted by λ, while that from the up to the down state is denoted by μ.

For this model, the average firing rate of each neuron R_i is given by

$$R_i = \nu_i \frac{\lambda}{\lambda + \mu}. \tag{8}$$

The auto- $R_{ii}(\tau)$ $(i=1,2)$ and the cross correlation $R_{12}(\tau)$ functions are given by

$$R_{ii}(\tau) \approx \nu_i^2 \frac{\lambda\mu}{(\lambda+\mu)^2} e^{-(\lambda+\mu)|\tau|} (\tau_s < \tau), \tag{9}$$

$$R_{12}(\tau) = \nu_1 \nu_2 \frac{\lambda\mu}{(\lambda+\mu)^2} e^{-(\lambda+\mu)|\tau|}, \tag{10}$$

where τ_s indicates the time constant of the function $f_i(\tau)$. From Eqs. (9) and (10), we can see that after the normalization employed in Fig. 1, the auto- and cross correlations coincide, except at around the zero time delay. Thus, this model is consistent with the result that the auto- and cross correlograms of the pair coincide well except at around the zero time delay (Fig. 2).

B. Parameter estimation

We estimated all the parameters of the model $\{\nu_1, \nu_2, \lambda, \mu\}$ from the experimental data. For the neuron pair used in Figs. 1 and 2, average firing rates of the constituent neurons were estimated from the experimental data using Eq. (1). The estimated average firing rates were 5.560×10^{-3} and 6.087×10^{-3} ms^{-1}. These rates correspond to Eq. (8). Thus, we obtained the following equations:

$$\nu_1 \frac{\lambda}{\lambda+\mu} = 5.560 \times 10^{-3} \text{ ms}^{-1}, \tag{11}$$

$$\nu_2 \frac{\lambda}{\lambda+\mu} = 6.087 \times 10^{-3} \text{ ms}^{-1}. \tag{12}$$

Furthermore, by comparing the result of the least-squares fitting of the cross correlogram (Fig. 1) and Eq. (10), we obtained the equations

$$\lambda + \mu = 8.9 \times 10^{-3} \text{ ms}^{-1}, \tag{13}$$

$$\nu_1 \nu_2 \frac{\lambda\mu}{(\lambda+\mu)^2} = 2.6 \times 10^{-5} \text{ ms}^{-2}. \tag{14}$$

By solving Eqs. (11)–(14), we obtained $\nu_1 = 9.9 \times 10^{-3}$ ms^{-1}, $\nu_2 = 1.1 \times 10^{-2}$ ms^{-1}, $\lambda = 5.0 \times 10^{-3}$ ms^{-1}, and $\mu = 3.9 \times 10^{-3}$ ms^{-1}. From these values, we estimated average durations of the up state T_{up} and the down state T_{down} as follows:

$$T_{up} = \frac{1}{\mu} = 2.6 \times 10^2 \text{ ms}, \tag{15}$$

$$T_{down} = \frac{1}{\lambda} = 2.0 \times 10^2 \text{ ms}. \tag{16}$$

In six of the 17 neuron pairs (35%) that have a significant peak in the cross correlograms, we could fit the cross correlograms with exponential functions and estimate the model parameters. The average durations of the up and down states over the six pairs were $4.9 \pm 1.4 \times 10^2$ and $3.2 \pm 1.8 \times 10^2$ ms, respectively.

C. Evaluation of the model

In order to examine whether our model well describes the experimentally observed spike trains of IT neuron pairs, we estimated the spike count distribution of two neurons from experimentally observed spike trains. We then statistically compared this distribution with that derived from our model using the parameters estimated from the experimental data.

For this purpose, we specified the point process $s_i(t)$ as follows. The time constant of a narrow peak in the autocorrelogram is smaller than that of the two-state Markov process $X(t)$. Thus, as long as we focus analysis on the two-state Markov process, the time constant of the narrow peak can be neglected, i.e., we can approximate the function $f_i(\tau)$ with a Dirac δ function. In addition, the inequality $\nu_i \ll 1$ holds. On the basis of these considerations, we approximated the point process $s_i(t)$ with a Poisson process.

Under this approximation, the spike count distribution of the two neurons during the interval $[0,t]$ is given by the following equation:

$$\begin{aligned} P\{N_1(t)=n, N_2(t)=m\} &= P_{nm} \\ &= E\left[\frac{\left(\nu_1 \int_0^t X(u)du\right)^n}{n!} \exp\left(-\nu_1 \int_0^t X(u)du\right) \right. \\ &\quad \left. \times \frac{\left(\nu_2 \int_0^t X(u)du\right)^m}{m!} \exp\left(-\nu_2 \int_0^t X(u)du\right) \right], \end{aligned} \tag{17}$$

where $P\{\cdots\}$ represents the spike count distribution, $N_i(t)$ the spike count of neuron i during the interval $[0,t]$, and $E[\cdots]$ the expectation value. The distribution given by Eq. (17) was calculated from 100 000 sets of two spike trains generated on the basis of the model using the parameters estimated from the experimental data. The calculated distribution was compared with that estimated from experimentally observed spike trains. In the comparison, we calculated a statistic χ^2 given by

$$\chi^2 = \sum_{i=0}^{k} \sum_{j=0}^{l} \frac{(\hat{f}_{ij} - nP_{ij})^2}{nP_{ij}}. \tag{18}$$

In this equation, $\hat{f}_{ij}$ denotes the experimentally observed frequency at spike counts i and j, n the number of trials, and k and l are the maximum spike counts of the two neurons, respectively.

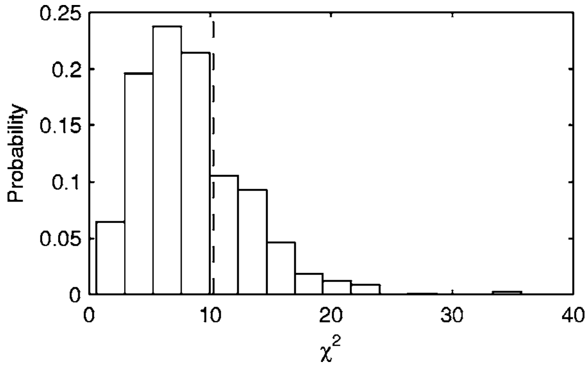

FIG. 3. Probability distribution of χ^2. The dashed line indicates $\chi^2=10.3$.

For a statistical test of χ^2, we require its sample distribution. In order to estimate this distribution, we first generated sets of two spike trains on the basis of our model using the parameters estimated from the experimental data. The spike generation was repeated as many times (trials) as the experiment. The generated spike trains were regarded as experimental data and the spike count distribution that corresponds to the experimentally observed distribution was estimated from the generated spike trains. Subsequently, the parameters of the model were estimated from the generated spike trains in the same manner as in the preceding subsection. On the basis of the model using the estimated parameters, we generated 100 000 sets of two spike trains and calculated the spike count distribution that corresponds to the model distribution. Finally, we calculated χ^2 from the calculated spike count distributions. We repeated this procedure 1000 times. As a result, we obtained 1000 samples of χ^2. On the basis of these samples, we estimated the sample distribution of χ^2 (Fig. 3).

Figure 4 shows the experimentally observed spike count distribution of two neurons whose cross correlogram is shown in Fig. 1 and the distribution based on the model using the parameters estimated from the experimental data. As shown in Fig. 4, the two distributions are very similar. In fact, χ^2 was 10.3, providing $P(\chi^2>10.3)=0.27$ (Fig. 3). Thus, we cannot reject the null hypothesis that the experimentally observed spike count distribution is a sample distribution derived from the model. We obtained the same results for all the six pairs. These results suggest that spike trains of 35% of the IT neuron pairs that have significant correlation are well described by a two-dimensional Poisson process whose means are modulated by a two-state Markov process.

V. TWO-DIMENSIONAL POISSON PROCESS MODULATED BY AN ORNSTEIN-UHLENBECK PROCESS

A. Formulation

Next, we examined whether spike trains of an IT neuron pair can be described by a two-dimensional Poisson process whose means are modulated by an OU process. When the change of firing rates of two neurons is described by an OU

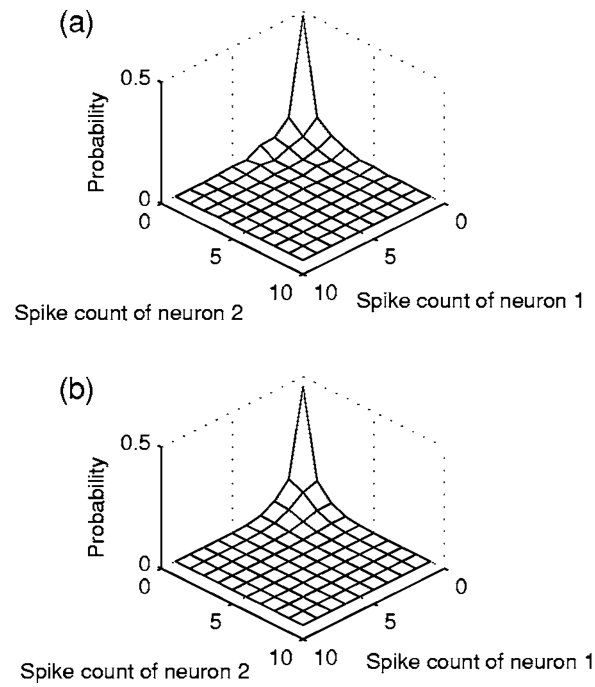

FIG. 4. Spike count distribution of two neurons. Spike counts for 100 ms were estimated. (a) Distribution estimated from the experimental data. (b) Distribution derived from the model using the estimated parameters.

process, the firing rate of each neuron, $Y_i(t)$ $(i=1,2)$, is given by

$$Y_i(t) = \sqrt{\alpha_i}\int_{-\infty}^{t} e^{-\kappa(t-s)}dB(s) + \beta_i, \tag{19}$$

$$\langle dB(t)\rangle = 0, \tag{20}$$

$$\langle dB(t)dB(t')\rangle = \delta(t-t')dt\,dt', \tag{21}$$

where α_i, β_i, and κ are constants. From Eqs. (19)–(21), the average firing rate of neuron i is given by

$$R_i = \beta_i. \tag{22}$$

Moreover, the auto- and cross correlations of the spike trains are given by

$$R_{ii}(\tau) = \frac{\alpha_i}{2\kappa}e^{-\kappa|\tau|}(\kappa \neq 0), \tag{23}$$

$$R_{12}(\tau) = \frac{\sqrt{\alpha_1\alpha_2}}{2\kappa}e^{-\kappa|\tau|}. \tag{24}$$

From these equations, we can see that this model can explain the result shown in Fig. 3 when the following equation holds:

$$\frac{\alpha_1}{\beta_1^2} = \frac{\alpha_2}{\beta_2^2}. \tag{25}$$

In addition, to explain the experimental data by this model, the fluctuation of the firing rate must be less than the average firing rate. This is because the firing rate cannot be negative. Thus, when the variance of the firing rate of each neuron is denoted by V_i, the inequality $V_i \ll R_i^2$ must hold. This inequality can be written as

$$\alpha_i \ll 2\kappa\beta_i^2, \tag{26}$$

because V_i is given by

$$V_i = \frac{\alpha_i}{2\kappa}. \tag{27}$$

B. Parameter estimation and evaluation of the model

From the experimental data, we can estimate all the parameters of the model. The average firing rates of the neurons estimated from the experimental data were 5.560×10^{-3} and 6.087×10^{-3} ms^{-1} (see Sec. IV B). Thus, from Eq. (22) we obtained the equations

$$\beta_1 = 5.560 \times 10^{-3} \text{ ms}^{-1}, \tag{28}$$

$$\beta_2 = 6.087 \times 10^{-3} \text{ ms}^{-1}. \tag{29}$$

In addition, from the result of the least-squares fitting of the cross correlogram (Fig. 1) and Eq. (24), we obtained the following equations:

$$\kappa = 8.9 \times 10^{-3} \text{ ms}^{-1}, \tag{30}$$

$$\frac{\sqrt{\alpha_1\alpha_2}}{2\kappa} = 2.6 \times 10^{-5} \text{ ms}^{-2}. \tag{31}$$

By solving Eqs. (28)–(31) and (25), we obtained $\alpha_1 = 4.2 \times 10^{-7}$ ms^{-3} and $\alpha_2 = 4.6 \times 10^{-7}$ ms^{-3}.

By using the estimated value of α_i and Eqs. (28)–(30), we can estimate the right-hand side of Eq. (26) as follows:

$$2\kappa\beta_1^2 = 5.5 \times 10^{-7} \text{ ms}^{-3}, \tag{32}$$

$$2\kappa\beta_2^2 = 6.6 \times 10^{-7} \text{ ms}^{-3}. \tag{33}$$

From these equations, we can see that the inequality (26) does not hold. We obtained the same results for the six neuron pairs. Thus, this model does not describe spike trains of an IT neuron pair.

VI. DISCUSSION

In this study, we have quantitatively shown that there exist IT neuron pairs whose spike trains are well described by a two-dimensional Poisson process whose means are modulated by a common two-state Markov process. Raster plots of the neurons of a pair confirmed qualitatively that the modulations are not described by an OU process but by a two-state Markov process (Fig. 5). The plots show that in the spike train of each neuron there are two distinct periods: the period during which the neuron fires (firing period) and the period during which the neuron does not fire (nonfiring period). The firing and nonfiring periods are likely to correspond to the up and down states, respectively. The plots also confirmed that a two-state Markov process is common to the neurons of the pair. The firing periods and the nonfiring periods of the neurons overlap well, respectively (Fig. 5).

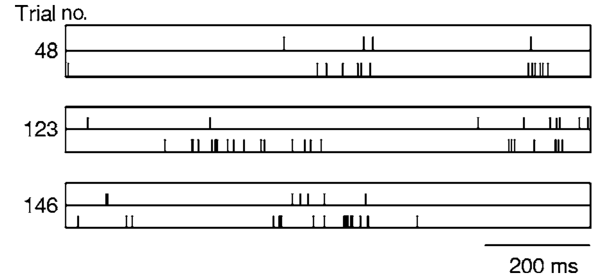

FIG. 5. Raster plots of the neurons of the pair whose cross correlogram is shown in Fig. 1. The vertical lines indicate spike timing. For each trial, spike timing of one neuron is indicated in the top row and that of the other neuron in the bottom row.

What is the physiological meaning of the states? One of the interpretations is that the two activity states correspond to two states of membrane potential of a neuron [4,5]. For example, the membrane potential of a neuron in the striatum shows two states: the neuron fires during the up state (average potential -49.02 ± 4.16 mV), while it does not fire during the down state (average potential -71.51 ± 3.81 mV) [4]. The relation between the firing and the states of the membrane potential is very similar to our model. In the striatum, the average duration of the up state is 422.57 ± 84.81 ms and that of the down state is 313.01 ± 43.20 ms [4]. These values are comparable to the average durations of the up and down states of IT neurons we estimated. In addition, a correlated state transition of membrane potentials of neurons has been observed in the striatum and other brain areas [6–8]. This is also consistent with the correlated state transition in our model.

The sources of the two activity states and the underlying mechanism to generate a correlated state transition of IT neurons remain unknown. One possible source is the nonlinearity of a single neuron. The dynamics of the membrane potential of a single neuron is described by nonlinear equations. Thus, if an appropriate ion channel exists, the membrane potential can have two stable states [9]. Another possibility is that the two activity states of a neuron emerge only at the network level. For example, an ensemble of neurons in the network composed of excitatory neurons expressing the H current [10] and inhibitory neurons show a correlated transition between two states of membrane potential [11]. In this case, the correlated state transition between two neurons in a network can reflect the state transition of the network.

VII. CONCLUSION

In this study, we have shown that in some of IT neuron pairs, spike trains of a pair are well described by a two-dimensional Poisson process whose means are modulated by a common two-state Markov process that describes a correlated state transition between firing and nonfiring states of the constituent neurons of the pair. This correlated state transition leads to a broad peak in the cross correlogram between the spike trains of the pair. A broad peak in the cross correlogram has also been observed in the primary visual cortices of macaque monkeys [12] and cats [13]. However, the type of relation between spike activities of neurons that leads to a broad peak remains unknown. Thus, we consider it meaningful to have succeeded in the quantitative characterization of a broad peak in the cross correlogram of an IT neuron pair and revealed the relation between spike activities of the pair.

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