Title:

Investigating the time course of single-trial activity of neurons that show gradual increase or decrease in histograms

Authors:

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Abstract:

The activities of some neurons in the moneky anterior cingulate cortex gradually increase or decrease with time at a nearly constant rate, as demonstrated in histograms (ex. PSTHs) (Isomura et al., 2002). We devised an analysis method to investigate the time course of neuronal activity during a single-trial. Results of application of this method to Isomura et al.'s data indicate that the neurons are bimodal, residing in the high- or low-firing state; the timing of transition from one to the other uniformly fluctuates across trials. We also put forward a computational model that provides such a single-trial neuronal activity.

Summary:

At each stage of goal-directed behaviours, a decision must be made on an action or an event in the future from information on actions or events in the past. Decision-making can therefore be viewed as a process to convert retrospective information into prospective information.

Electrophysiological recording studies have revealed neuronal activities that reflect retrospective information (most typically, working memory) or prospective information in decision processes. Retrospective activity is generally characterized by the firing rate that is sustained at a lifted level during the delay. Prospective activity, in contrast, often shows the firing rate that gradually increases with time at a nearly constant rate. It is considered that the linear growth of prospective activity will serve to integrate 'evidence', which might be represented by retrospective activity, with a constant weight. A decision might be made when prospective activity accumulates the evidence up to a certain criteria.

It should be reminded that, in usual electrophysiological experiment, the gradual increase in the neuronal activity emerges as the average of the time course of the firing rate across a number of trials (as typically demonstrated in peri-stimulus time histograms, PSTHs). For a temporal profile of the firing rate in

each trial, several possibilities can still be considered.

One might simply consider that the firing rates of individual cells gradually increase in each trial. This can be caused by intrinsic properties of individual cells (Durstewitz, 2003) or by reverberatory excitation of a recurrent network (Wang, 2002). In both cases, the average of a single-cell activity across trials shows gradual increase (**Fig. 1a**). In the former, evidence is accumulated separately at single cells. In the latter, interaction between cells by recurrent excitation is essential for the gradual increase in the fining rate of each cell. In this sense, evidence is accumulated totally at a whole network.

We examined another possibility, which was somewhat medium between the above two extremes. Imagine that individual cells cast their votes to the evidence. The timing of the vote by each cell is random, but not completely independent from those by others; cells that have already voted facilitate the votes of cells that have not yet voted (in this poll, the independence of individual voters is not strictly held). The evidence can therefore be accumulated as the collected number of cells that have already voted to the evidence.

To make the description below compact, we introduce the following symbols: f, the firing rate of a single cell; $< f >$, the average of f across the cells; $\bar{f}$, the average of f across a number of trials. It is the time course of $\bar{f}$ that is demonstrated in PSTHs. Since $< f >$ and $\bar{f}$ represent ensemble average and temporal average, respectively, they will show essentially the same course.

Consider that each cell manifests the vote to the evidence by lifting f. Therefore, f of each cell changes discontinuously. Nevertheless, the timing of this discontinuous change fluctuates across the cells, $< f >$ and hence $\bar{f}$ show gradual increase (**Fig. 1b**), as is consistent with the experimental observations.

We will show that linear accumulation of evidence through voting by cells can emerge from the stochastic dynamics of a recurrent network of bistable excitatory neurons. We consider a network of N excitatory neurons with all-to-all connections. Each neuron receives random excitation and inhibition that mimic continuous synaptic bombardment from neuron pools surrounding this network. We also introduce bistable properties into the membrane potential. The membrane-potential bistability means that, for a given input, a neuron is in either of the two stable states ('on' and 'off' states); during the 'on' state, the membrane potential is depolarised and hence f is relatively large; during the 'off' state, the membrane potential is near the resting level and f is small. Several biophysical mechanisms for the membrane potential bistability have been proposed. To be specific, we have modelled it by an afterdepolarization (ADP). The

ADP is induced by spike discharges and will facilitate further discharges of spikes. The ADP and spike discharges therefore form a positive-feedback loop, the onset of which results in regenerative spike discharges ('on' state).

The time course of $\bar{f}$ given by our model was investigated by computer simulation. In this simulation, all the neurons in the network were set in the 'off' state at an initial time and the parameter values were adjusted so that 'off-to-on' transition (see later) is dominant compared to 'on-to-off' transition. We found that, if the balance between background excitation and inhibition was properly chosen, $\bar{f}$ gradually increased at a nearly constant rate (**Fig. 2a**).

Mechanisms for the emergence of the linear growth of $\bar{f}$ can roughly be explained as follows. Because of the noise due to background excitation and inhibition, the membrane potential V randomly fluctuates around a certain equilibrium level, say V_{eq}. In our simulation, the parameter values are chosen so that V_{eq} is below the firing threshold V_θ. If the noise were absent, a neuron would never fire. In the presence of the noise, however, it discharges a spike when V hits V_θ by some chance. Once a neuron sufficiently discharges by the aid of the noise, then the ADP becomes fully active and hence the neuron, initially set on the 'off' state, settles in the 'on' state.

If the recurrent connections were absent, 'from-off-to-on' transitions of individual neurons would occur independently, giving exponentially decelerating growth of $< f >$. Since the probability for 'from-off-to-on' transition per unit time is inversely related to the difference between V_θ and V_{eq}, recurrent input will increase this probability by shifting V_{eq} towards V_θ. Therefore, as the number of neurons in the 'on' state grows, the amplitude of recurrent input increases, accelerating further transitions of neurons that have been still in the 'off' state. It is therefore possible that the deceleration and the acceleration will balance to give linear growth of $< f >$. Hence $\bar{f}$ also show gradual increase at a nearly constant rate.

Our model predicts that change in f in each trial is essentially discontinuous (**Fig. 1b**). To examine this prediction, we introduce an analysis method to discriminate whether given spike trains follow discontinuous (**Fig. 1b**) or gradual (**Fig. 1a**) change. Let the i-th time step in the j-th trial be labelled by (i, j). If the time step (i, j) is within the inter spike interval of the length L, then define the frequency of this time step by $\phi(i, j) = 1/L$. For the i-th time step, we can consider a distribution of the firing frequencies across all the trials, say $p(f; i)$. It is useful to represent it by a contour

diagram with a grey scale. A distribution of frequencies across all the trials and time steps, say $P(f)$, is given by integrating $p(f;i)$ with respect to i.

If f changes discontinuously in each trial (**Fig. 1b**), the contour diagram will exhibit two separated bright regions. As i increases (i.e., as time advances), one gradually vanishes and the other gradually emerges. Consistent with this, $P(f)$ will have double peaks. We confirmed that spike trains given by our model did produce such profiles (**Fig. 2b, left and right**).

In contrast, if f gradually in each trial (**Fig. 1a**), the contour diagram will display a diagonal bright region and, therefore, $P(f)$ will have a single peak. To demonstrate these, we considered a variable Poisson process with the rate that gradually increased with time, taking as a simple model for neuronal activity that follows gradual change in f in each trial (**Fig. 2c**). We confirmed that the variable Poisson process actually produced a diagonal bright region in the contour diagram and $P(f)$ with a single peak (**Fig. 2d, left and right**).

To examine which type of profiles (Fig. 1a or Fig. 1b) real spike trains obey, the above analysis method was applied to experimental data obtained by Isomura et al. (2003). They electrophysiologically recorded from the cingulate cortex of the monkey performing delayed conditional Go/No-go discrimination tasks. They found a population of neurons showing delay period activity that was specific to Go or No-go responses that would be executed after the end of the delay (i.e. activity reflecting prospective information). Substantial part of them showed gradual increase in f over the delay. An example is shown in **Figs. 3a**. For this cell, one can see two separated bright regions in the contour diagram (**Fig. 3b, left**) and double peaks for $P(f)$ (**Fig. 3b, right**). It can therefore be concluded that, at least in the monkey cingulate cortex, the gradual increase in $\bar{f}$ follows discontinuous change in f in each trial (**Fig. 1b**), which is consistent with the prediction from our model.

Isomura et al. also found delay period activity that showed gradual decrease in $\bar{f}$. Actually, gradual decrease in $\bar{f}$ at a nearly constant rate is also often observed in animal brains during decision tasks. Although it is not certain whether such activity also involved in accumulation of evidence, similar mechanisms may underlie both gradual decrease and increase in $\bar{f}$. Indeed, our model produce can produce gradual decrease in $\bar{f}$ at a nearly constant rate also (data not shown).

Application of our analysis method to the gradually decreasing activity observed by Isomura et al. clearly shows two separated bright regions in the contour diagram and double peaks for $P(f)$ (data not shown). This indicates that the gradual decrease in $\bar{f}$ also follows discontinuous change in f in each trial.

Fig. 1a

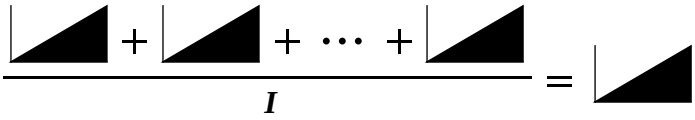


Fig. 1b

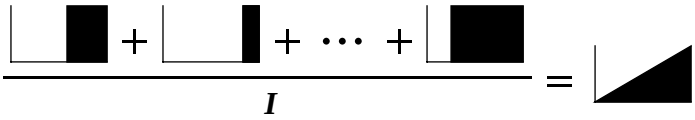


Fig. 2

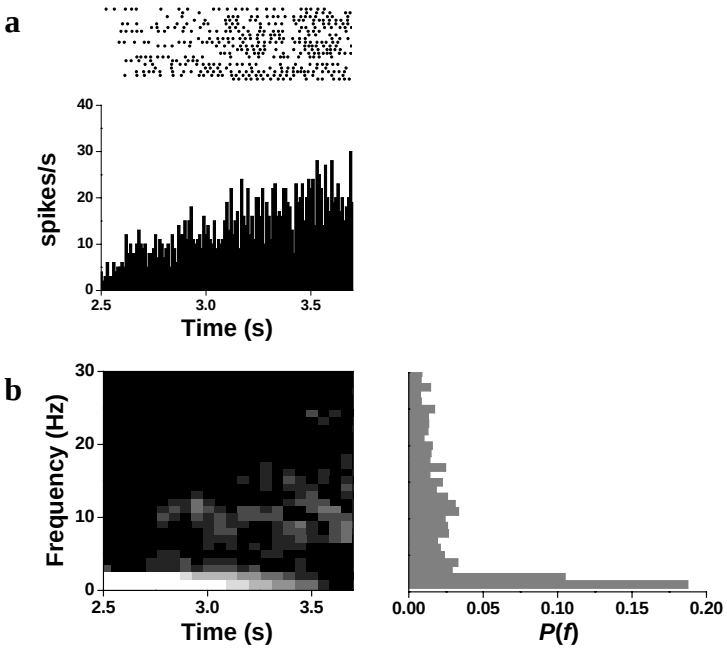
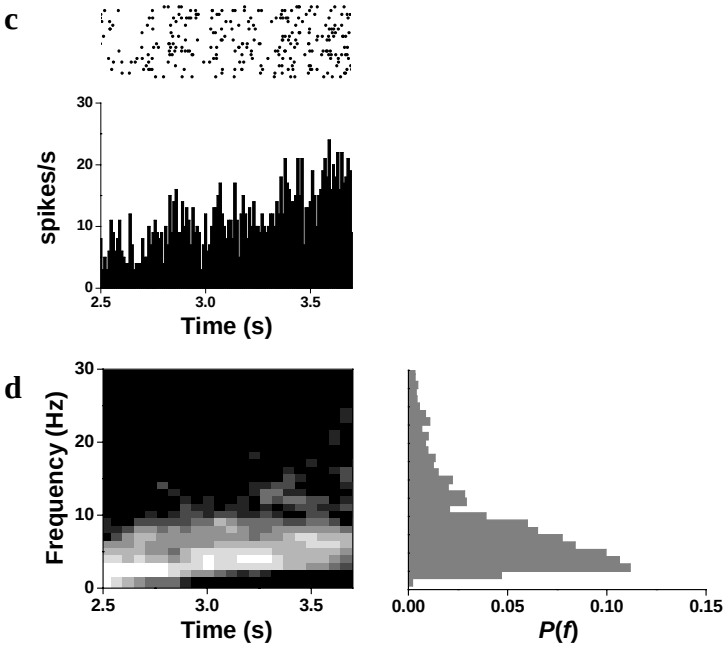


Fig. 2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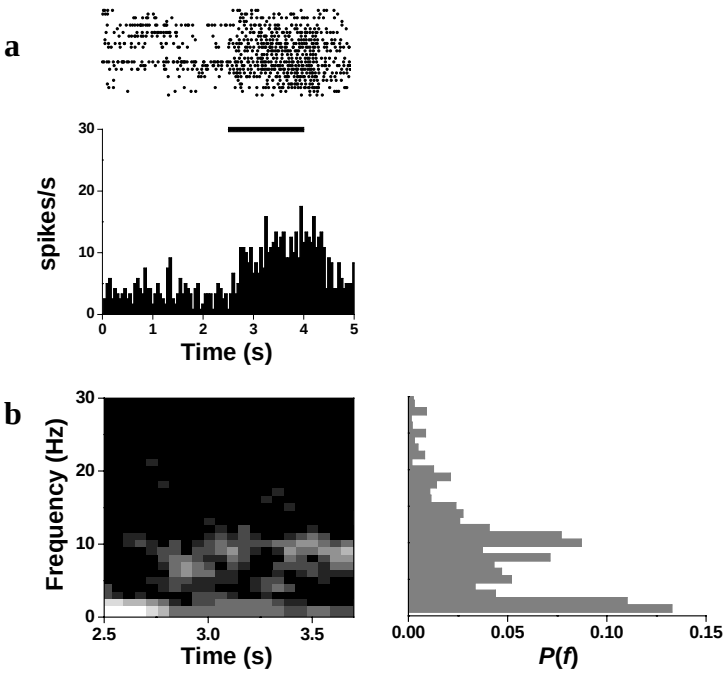
P(f)

Fig. 3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