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Detecting joint pausiness in parallel spike trains

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HIGHLIGHTS

- A new method that measures synchronous pausing in pairs of spike trains is proposed.
- Joint pausing is prominent in the superposition of spike trains.
- A new graphic illustrates joint pausing of two spike trains using temporal shift.
- A stochastic model assesses significance of joint pausing.
- The test investigates whether joint pausing was caused by synchronous spiking.

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ABSTRACT

Background: Transient periods with reduced neuronal discharge – called ‘pauses’ – have recently gained increasing attention. In dopamine neurons, pauses are considered important teaching signals, encoding negative reward prediction errors. Particularly simultaneous pauses are likely to have increased impact on information processing.

Comparison with existing methods: Available methods for detecting joint pausing analyze temporal overlap of pauses across spike trains. Such techniques are threshold dependent and can fail to identify joint pauses that are easily detectable by eye, particularly in spike trains with different firing rates.

New method: We introduce a new statistic called pausiness that measures the degree of synchronous pausing in spike train pairs and avoids threshold-dependent identification of specific pauses. A new graphic termed the cross-pauseogram compares the joint pausiness of two spike trains with its time shifted analogue, such that a (pausiness) peak indicates joint pausing. When assessing significance of pausiness peaks, we use a stochastic model with synchronous spikes to disentangle joint pausiness arising from synchronous spikes from additional ‘joint excess pausiness’ (JEP). Parameter estimates are obtained from auto- and cross-correlograms, and statistical significance is assessed by comparison to simulated cross-pauseograms.

Results: Our new method was applied to dopamine neuron pairs recorded in the ventral tegmental area of awake behaving mice. Significant JEP was detected in about 20% of the pairs.

Conclusion: Given the neurophysiological importance of pauses and the fact that neurons integrate multiple inputs, our findings suggest that the analysis of JEP can reveal interesting aspects in the activity of simultaneously recorded neurons.

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1. Introduction

The detection and analysis of periods with very low firing rate – so-called ‘pauses’ – has gained increasing interest in the study of neuronal firing activity. Transient pauses of firing are well-described signals for negative reward prediction errors of dopamine (DA) midbrain neurons and occur in awake behaving animals, when an expected reward is unexpectedly omitted (Schultz, 2015). Transient pauses from tonic firing cause a detectable decrease of DA release – e.g., monitored by in vivo DA voltammetry – in the striatal target areas of DA midbrain neurons and drive learning from negative feedback (Hart et al., 2014). While former studies associated the occurrence of pauses with learning, a recent optogenetic study has demonstrated the causal role of DA pausing for extinction learning (Steinberg et al., 2013).

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Particularly, pauses that are synchronized across neurons have been considered related to information processing (Shimazaki et al., 2015). Recent biophysical computer modeling demonstrated that synchronized pauses in spiking activity of multiple DA neurons can reduce information transmission in DA type 2 receptors (Dreyer et al., 2010). Similarly, studies of simple spikes of Purkinje cell (PC) pairs indicated that precise coordination of simple spikes across PCs may be solely associated with synchronous pausing (Shin and De Schutter, 2006; Wise et al., 2010). Therefore, the detection and statistical analysis of potentially synchronous pausing may be an important tool for the analysis of neuronal information processing.

The statistical analysis of pauses usually relies on detection algorithms. Roughly speaking, these algorithms segment a spike train into intervals and assign a pause measure to every interval. Then, every interval whose pause measure exceeds a preselected threshold is defined as a pause. For example, every inter spike interval (ISI) can be marked as a pause if the ISI is longer than a fixed threshold (DeLong, 1971; Shin and De Schutter, 2006; Elias et al., 2007) or longer than a spike train dependent threshold, such as a functional of a quantile of the ISI distribution (Elias et al., 2007; Wise et al., 2010). Technically more involved pause detection methods such as the Poisson Surprise (PS, Elias et al., 2007) and the Robust Gaussian Surprise (RGS, Ko et al., 2012) use pause measures that are based on probabilistic arguments similar to the PS algorithm for burst detection proposed by Legendy and Salcman (1985).

In order to detect and analyze synchronous pauses, one usually relies on the overlap of pauses identified in the individual spike trains (Shin and De Schutter, 2006; Wise et al., 2010). Interestingly, however, these methods may sometimes fail to identify synchronous pausing, as shown in an example in Fig. 1A: the leftmost large ISI is not marked as a pause in the second spike train due to the low firing rate of the spike train. Similarly, almost no pauses are detected in the second spike train and thus, no overlapping pauses can be observed. This phenomenon is independent of the algorithm used for pause detection. However, the human eye can easily detect periods in which both neurons are silent.

One main idea in the present paper is that, while these periods cannot be detected in overlapping individual pauses, these periods can be very pronounced in the superposition of the spike trains (Fig. 1B). One could therefore consider measuring joint pausing using the overall proportion of identified pauses in the superposition of spike trains. However, one should note that this ‘pause proportion’ is highly dependent on the threshold chosen for the detection of specific pauses. Therefore, we propose to avoid the choice of a threshold (cmp. also similar methods in Kreuz et al. (2007) used for the measurement of synchrony). Instead, we measure the degree of joint ‘pausiness’ by integrating the pause proportion over all values of the threshold. Note that in this setting, intervals with higher pause measures automatically have a stronger impact on the pausiness statistic. This pausiness statistic can in principle be based on any set of intervals and pause measures derived from any pause detection algorithm. Here we focus on a simple approach that assigns to every ISI a pause measure. This approach can be easily implemented and avoids complex algorithmic procedures and parameter choices.

The remainder of the article is organized as follows. In Section 2 we describe the pausiness approach (Section 2.1) and compare its capability of discriminating between spike trains with and without synchronous pauses to a similarity measure proposed by Lyttle and Fellous (2011), called LF, which can be adjusted to be sensitive to bursts and/or pauses (Sections 2.2 and 2.3). We then introduce a graphical representation, the so-called cross-pauseogram, which compares the pausiness of the superposition of two spike trains with the pausiness of the superposition of the same spike trains shifted in time relative to each other (Section 2.4). A peak in the cross-pauseogram indicates joint pausing. In order to test the statistical significance of such peaks in Section 3, we first observe that such peaks can also originate from synchronous firing activity. In order to disentangle joint pausing that is associated with synchronous firing from additional *joint excess pausiness* (JEP), we use a null model of Gamma processes with added synchronous spikes and compare the observed joint pausiness to the degree of joint pausiness expected by chance in this null model. In Section 4 we apply the test to simultaneously recorded pharmacologically identified DA neurons from freely moving mice.

2. Pausiness: a threshold free approach for the analysis of joint pausing

2.1. Pausiness

Here we propose to measure the degree of joint pausing in a pair of spike trains by applying a new statistic called pausiness to the superposition of the spike trains. Formally, let $x=(x_0, \ldots, x_n)$ denote the superposition of spike trains of recording length T. A pause measure π_j is then assigned to every ISI $I_j := x_j - x_{j-1}$, $j=1, \ldots, n$. One typical analysis would then be to choose a threshold ϑ, to label only intervals with $\pi_j \geq \vartheta$ as pauses, and then to sum across all such pause lengths, yielding the pause proportion

$$\mathcal{P}_x(\vartheta) := \frac{1}{T_n}\sum_{j=1}^{n} I_j \mathbf{1}_{\{\pi_j \geq \vartheta\}},$$

where $T_n := x_n - x_0$. Because the pause proportion is highly dependent on the choice of the threshold ϑ, we propose to avoid choosing ϑ by integrating the pause proportion over all possible values of $\vartheta \geq 0$. This results in our so-called pausiness value for the superposition of spike trains (Definition 2.1).

Definition 2.1. Let $x=(x_0, \ldots, x_n)$ denote a spike train, and let π_j denote the pause measure of ISI I_j, $j=1, \ldots, n$. The pausiness π_x of the spike train x is then given by

$$\begin{aligned}\pi_x := & \int_0^\infty \frac{1}{T_n}\sum_{j=1}^{n} I_j \mathbf{1}_{\{\pi_j \geq \vartheta\}}\, d\vartheta = \frac{1}{T_n}\sum_{j=1}^{n} I_j \int_0^\infty \mathbf{1}_{\{\pi_j \geq \vartheta\}}\, d\vartheta \\ = & \frac{1}{T_n}\sum_{j=1}^{n} I_j \pi_j .\end{aligned}$$

Note that this automatically assigns a weight to each ISI I_j proportional to its pause measure π_j, such that intervals with higher pause measures have a stronger impact on the pausiness statistic. The normalization by T_n allows comparability of spike trains with different recording lengths.

In order to derive the pause measures π_j required for the pausiness statistic, various pause measures can be plausible candidates. In principle, one could also use intervals consisting of more than one ISI as derived in pause detection algorithms by Elias et al. (2007) and Ko et al. (2012). Here we focus on individual ISIs and apply two pause measures.

First, in analogy to the PS pause detection, we use

$$\pi_j^{(\mathrm{PS})} := \lambda I_j - \log(1+\lambda I_j),\; j=1, \ldots, n, \tag{1}$$

where λ is the average firing rate of the spike train. This measure is related to the PS pause detection algorithm because under the assumption of a stationary Poisson process (which is not necessary here), $\pi_j^{(\mathrm{PS})}$ would equal the negative logarithm of the probability (i.e., the surprise) of finding at most one spike in an interval of length

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