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Quantification of pairwise neuronal interactions: Going beyond the significance lines

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HIGHLIGHTS

- The performance of five tests for detecting significant interactions is compared.
- A novel method for directly assessing the strength of neuronal interactions is introduced.
- The method provides broad coverage of diverse interactions.
- The method allows detecting time-dependent alterations in neuronal interactions.
- Reconstruction of the interaction parameters of a simulated network is demonstrated.

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ABSTRACT

Background: Normal brain function depends on intact interactions between multiple neuronal ensembles. Interactions within and between local networks comprising multiple neuronal types may occur on a range of time scales thus affecting the estimation of interaction strength. A common technique to investigate functional interactions within neuronal ensembles is pairwise cross-correlation analysis. However, conventional cross-correlation methods address the question of whether an observed peak in the cross-correlation is statistically significant relative to the null hypothesis which assumes a lack of correlation. Ultimately, these methods were not designed to evaluate the strength of the observed interactions.
New method: We devised four complementary measures – Triplets, Bin crossing, Bin height and Entropy – for assessing the strength of neuronal interactions; each is sensitive to different features of the cross-correlogram peak such as height, width and smoothness.
Results: First, a comparison of five prevalent methods for evaluating whether an observed peak in neuronal cross-correlogram is significant allowed their ranking from the most conservative to the more sensitive for purposes of selecting the appropriate method based on the data structure and preferred strategy. Second, the performance of the four measures we derived improved with interaction strength and the number of spikes in the cross-correlogram. The four measures also enabled the reconstruction of interaction parameters of simulated networks including the detection of time-dependent alterations.
Conclusions: We suggest that the combination of several measures of peak characteristics helps rectify the individual shortcomings of specific measures and can yield a broad coverage of interaction strengths and widths.

1. Introduction

Normal brain function depends on intact interactions between multiple neuronal ensembles (Gawne and Richmond, 1993; Zohary et al., 1994; Vaadia et al., 1995). Over the years, methods designed to analyze interactions between simultaneously recorded spike trains have been put forward (Perkel et al., 1967; Abeles, 1982; Aertsen et al., 1989; Nelken and Vaadia, 1990; Gawne and Richmond, 1993; Prut and Perlmutter, 2003). Nevertheless, the most popular method remains the investigation of the cross-correlogram (CC) function, which has been extensively used to detect interactions between simultaneously recorded neuronal spike trains (Perkel et al., 1967; Moore et al., 1970; Brody, 1999; Brown et al., 2004). Several significance tests have been developed to evaluate whether the observed peak (or trough) in the CC is significantly stronger (or weaker) than expected by independent neuronal firing. These tests for significant interactions are based on different statistical models of the neuronal data structure (for instance, a Poisson (Abeles, 1982) versus a normal (Sears and Stagg, 1976; Graham and Duffin, 1981; Katz et al., 2002) variable distribution). Parameter selection can at times

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seem arbitrary, such as setting confidence limits (CL) at the 95% (2 standard deviations (SD) from the mean) or the 99.9% (5 SD from the mean) as well as approaches implemented to deal with the multiple comparisons problem (Miller and SpringerLink (Online service), 1981). Surprisingly, method quality has never been compared thus making it difficult to opt for one method over another based on a given data structure. One of the reasons is that these significance tests were designed to detect strong correlations, without estimating other parameters such as the correlation strength and time scale.

Correlated activity in the brain has been observed at various time scales in spike trains, local field potentials and EEG scans and ranges from a few ms in direct common synaptic input to hundreds and even thousands of ms associated with more complicated coupling mechanisms such as motivation and attention (Brody, 1998; Smith and Kohn, 2008). Measuring the correlation width may reveal more information on network interactions and the underlying processes. Time-dependent changes in correlated activity are known to be related to mechanisms of synaptic plasticity and information transfer (Markram et al., 1997; Zhang et al., 1998). These changes may occur independently as a result of variation either in the number of correlated cells or in the correlation strength. Understanding which of these changes takes place during cognitive processes is an important step toward describing the mechanisms underlying neuronal interactions. Thus far, methods for accurate evaluation of different types of interactions still lag behind technical advances that enable the monitoring of many neurons simultaneously (Nicolelis et al., 1997; Kralik et al., 2001).

In this paper we compare the performance of some of the most commonly used methods for detecting significant neuronal correlations, so as to facilitate appropriate method selection with respect to the recorded data. In addition, we introduce a novel technique aimed at measuring the strength of neuronal interactions rather than determining their significance. This technique utilizes four simple measures of the correlation strength each sensitive to different features of the CC peak such as smoothness and width. We found that: (1) the new technique enables the detection of time-dependent alterations in neuronal interactions; and (2) the combination of several measures can overcome the individual weaknesses of one specific measure. We demonstrate this complementarity by reconstruction of simulated network interaction parameters using the proposed technique. The implications of this technique as well as possible applications are discussed. For simplicity, we focus here on excitatory couplings; however all the calculations can be used for inhibitory couplings by making minor adjustments.

2. Materials and methods

2.1. Simulated coupled pairs

We numerically simulated binary spike trains of T seconds ($T = 300$ s unless stated otherwise) with a resolution of $\Delta t = 1$ ms, and the refractory period, t_{ref}, was set to 1 ms. Correlated spike trains were produced in the following way: the first spike train was constructed randomly by defining the probability of spike generation at time t as:

$$P_{spike}(t) = \frac{r(t)}{(1/\Delta t)(1 - r(t) \cdot t_{ref})}$$

where $r(t)$ is the desired firing rate that may be time dependent. After every generated spike, $t_{ref}/\Delta t$ bins were set to zero to adjust for the refractory period. This procedure generates pseudo-random spike trains that imitate a Poisson point process with a refractory period (Abeles, 1982; Dayan and Abbott, 2001). The second spike train was generated with a correlation to the first spike train and was determined by three parameters: the coupling strength p which is the fraction of spikes to be correlated (from 0 to 0.9), the mean of the coupling delay, which was set to 10 ms, and the correlation time scale (i.e. the standard deviation of the coupling delay) σ, that varied from 2.5 ms to 100 ms. First, p of the spikes in the first train were chosen randomly. Each was assigned with a coupling delay drawn from the normal distribution $N(10\,\text{ms}, \sigma)$ and was placed in the second spike train at the time of its occurrence in the first train plus the corresponding coupling delay. The remaining spikes to be added to the second spike train (according to the desired rate) were generated randomly as described above and the refractory period was also adjusted by setting $t_{ref}/\Delta t$ bins after every spike to zero. The mean of the coupling delay does not play an important role in the specific correlation measurements addressed in this work since the distance of the peak in the CC from zero has no impact on the significance or strength of the coupling. However, σ, the standard deviation of the coupling delay, plays a crucial role determining the width of the CC.

In order to further validate our results we have also generated artificial spike trains using different statistics which do not follow a Poisson process but a Cox process (Brette, 2009). Cross-correlograms generated with these spike trains were similar to those obtained with Poisson process and had similar statistical properties as expected when sufficiently large spike counts are used.

2.2. Definition of the significance tests

To compare the efficacy and reliability of different significance tests we selected five of the commonly-used tests described below.

Test 1: The CC values are scaled to firing rates, and then smoothed with a 10 ms Gaussian window. The resulting values of the outer parts are assumed to follow a Poisson-point process and CLs, calculated separately for each bin, are chosen at the 0.5 and 99.5 percentile of the corresponding Poisson distribution function (Fig. 1a, pink lines). The CC is considered significant if a straight line placed between the CLs crosses them; i.e. if the maximum lower CL within the inner bins is higher than the minimum upper CL within the outer parts (Abeles, 1982; Frostig et al., 2008; Ma and Lowe, 2010).

Test 2: The CC values are converted to firing rates, and the resulting values of the outer parts are assumed to follow a Poisson-point process. CLs are chosen at the 0.5 and 99.5 percentile of the corresponding Poisson distribution function (Fig. 1a, orange line). The CC is considered significant if one inner bin crosses the CLs (Perkel et al., 1967; Ma and Lowe, 2010).

In the following three tests, the CC values of the outer parts are assumed to follow a normal distribution with mean (M) and standard deviation (SD).

Test 3: The CLs are chosen at the 1st and 99th percentile of the corresponding normal distribution function, divided by the number of bins, in order to take into account multiple comparisons (Fig. 1a, purple line). The CC is considered significant if one inner bin crosses the CL (Bar-Gad et al., 2003; Rivlin-Etzion et al., 2006).

Test 4: The CLs are chosen at the 5th and 95th percentile of the corresponding normal distribution function. Neuronal pairs are considered significantly correlated if 3 consecutive bins of the inner part values cross the CLs (Nevet et al., 2007; Oliveira-Maia et al., 2012).

In this case, the number of triplets can be evaluated by the following equation:

$$\#\text{triplets in CC} = \frac{\alpha(\alpha n - 2)(\alpha n - 4)}{8(n - 1)}$$

Here, α is the confidence level determined by the number of SD from the mean and n is the number of bins in the CC. For example,