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Research Paper

Advanced correlation grid: Analysis and visualisation of functional connectivity among multiple spike trains

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HIGHLIGHTS

- A new method to define functional connectivity of multiple spike trains is proposed.
- The method combines the cross-correlation function with statistical techniques.
- The method automatically distinguishes between direct and common source connectivity.
- An accurate diagram of connections is visualised.

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ABSTRACT

Background: This study analyses multiple spike trains (MST) data, defines its functional connectivity and subsequently visualises an accurate diagram of connections. This is a challenging problem. For example, it is difficult to distinguish the common input and the direct functional connection of two spike trains.
New method: The new method presented in this paper is based on the traditional pairwise cross-correlation function (CCF) and a new combination of statistical techniques. First, the CCF is used to create the Advanced Correlation Grid (ACG) correlation where both the significant peak of the CCF and the corresponding time delay are used for detailed analysis of connectivity. Second, these two features of functional connectivity are used to classify connections. Finally, the visualization technique is used to represent the topology of functional connections.
Results: Examples are presented in the paper to demonstrate the new Advanced Correlation Grid method and to show how it enables discrimination between (i) influence from one spike train to another through an intermediate spike train and (ii) influence from one common spike train to another pair of analysed spike trains.
Comparison with existing methods: The ACG method enables scientists to automatically distinguish between direct connections from spurious connections such as common source connection and indirect connection whereas existing methods require in-depth analysis to identify such connections.
Conclusions: The ACG is a new and effective method for studying functional connectivity of multiple spike trains. This method can identify accurately all the direct connections and can distinguish common source and indirect connections automatically.

1. Introduction

The brain receives, processes, and transmits information regarding a particular stimulus through stereotyped electrical discharges called action potentials, or spikes. The signals which come from the stimulus, are transformed into sequences of spikes, at an early stage of processing within the central nervous system. Spike trains are the starting point for most of the processing performed by the brain (Kandel, 2000; Dayan and Abbott, 2001). Characterizing the relationship between the stimulus and the spike trains is an important issue in Neuroscience as it underpins how the brain works in response to the stimulus. Many studies have been performed into this relationship between stimulus and spike trains (Espinosa and Gerstein, 1988; Gerstein and Kirkland, 2001; Gochin et al., 1990, 1991; Eggermont, 1991; Lindsey et al., 1992; Vaadia et al., 1995; Wilson and McNaughton, 1994; Skaggs and McNaughton, 1996; Li et al., 1999; Shannon et al., 2000; Louie and Wilson, 2001; Pillow et al., 2008).

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In addition to the relationship between stimulus and spike trains, it is also important to understand the functional connectivity between spike trains in response to a particular stimulus. This is another challenging problem within Neuroscience which could benefit from statistical methods to analyse multiple spike trains (Brown et al., 2004; Haslinger et al., 2013). In order to study the functional connectivity of the spike trains, it is essential to assess the spiking activity of multiple single neurons recorded simultaneously.

In Neuroscience, the Cross-Correlation Function (CCF) is a widely used measure of functional connectivity between spike trains (Perkel et al., 1967). The CCF has been applied to many neural systems in order to make powerful inferences about functional connectivity. Fundamentally, it is a statistical technique used to test the independence of two spike trains using the theory of stochastic point processes. This technique is also applied to assess oscillation, propagation delay, effective connection strength, synchronization, and the spatiotemporal structure of a network (Konig et al., 1995; Brown et al., 2004; Pillow et al., 2008; Nicolic et al., 2012).

In order to make inferences from the CCF, Brillinger (1976) introduced a normalization technique for the CCF using a confidence interval. Thus, peaks exceeding the confidence interval of the CCF are considered to be significant. A peak in a CCF indicates that there is a high probability that a spike in one spike train is caused by a spike in another spike train with some time delay involved. The significant peak in the CCF indicates that the null hypothesis on independence of two spike trains is not supported by the data and should be rejected. Consequently, there is an influence from one spike train to another. However, the interpretation of this influence, in terms of functional connectivity, is challenging. This is due to the fact that this influence can be considered to be (i) a direct connection between two spike trains, (ii) the result of some common source to both spike trains or (iii) an indirect connection, defined as a connection via some intermediate neuron.

There are several methods in the literature for the analysis of multiple spike trains (for example, Pillow et al., 2008; Stevenson, 2008; Grün and Rotter, 2010; Kriener et al., 2009; Masud and Borisyuk, 2011; Reimer et al., 2012; Jovanović and Rotter, 2016). One such method is the correlation grid (Stuart et al., 2005). The correlation grid is a visualization technique used to analyse the synchronous firings of simultaneously recorded multiple spike trains. The fundamental idea of this technique is to arrange spike trains into clusters that are functionally connected and display them in a symmetrical grid. A measure of distance, based on normalized CCF of two spike trains is used to perform the cluster analysis.

The correlation grid has been successfully used for the study of functional connectivity. However, the correlation grid cannot automatically distinguish between direct and spurious (both indirect and common source) connections. The aim of this paper is to present a statistical method called the 'Advanced Correlation Grid (ACG)' to analyse the functional connectivity of a large number of spike trains (15–1000 spike trains) using the CCF. The main advantage of the ACG method is that ACG makes it possible to define an accurate diagram of functional connections. More specifically, the ACG method can reliably differentiate direct connections from spurious (indirect and common source) connections using an automatic algorithm.

Section 2 of this paper describes the CCF in detail. Then Section 3 reviews the original correlation grid. Following this, Section 4 describes functional connectivity and Section 5 describes the ACG in detail. Sections 6 and 7 present case studies to report the operational of the ACG in detail. The case studies use data generated by ELIF (Enhanced Leaky Integrate and Fire) model (Borisyuk, 2002). The first case study consists of a small set of fifteen spike trains. In this set, all the connections have medium strength of influence with one exception, a single connection with very strong influence. The second case study consist of a large set of fifty spike trains in which all the connection strengths are of medium influence. The effectiveness of the ACG method is presented in Section 8. In order to study the accuracy of the method different scenarios of spike train data set such as same strength of influence, low noise and high noise are considered. In this section, the result of the functional connectivity obtained by the AVG method is compared to an existing called the Cox method. Section 9 presents the application of ACG to the experimental data recorded from the visual cortex of the cat. Conclusions of the work are presented in Section 10. Finally, Appendix A presents the description, dynamics and the parameter values for the ELIF generator.

2. Cross correlation function

The CCF algorithm (Masud et al., 2011) is applied to a pair of spike trains A and B where it is assumed that these spike trains are stationary. One spike train is arbitrarily assigned to be the target spike train and the other becomes the reference spike train. A correlation window is defined as $(2 * u + 1)$ bins of short time intervals h, where both h and u are values selected by the investigator. For each spike, on the reference spike train, the correlation window is positioned such that its center is directly aligned with the current spike. Thus, there are u bins to the left and right of the current spike; the correlation window is effectively centred over that spike. Refer to Fig. 1, where h = 1 ms and u = 2 for the purpose of presenting the algorithm only. For each spike on the reference spike train (B), the counting function $n_{AB}(\nu)$ counts and accumulates the number of times that spikes on the target train (A) coincide with the current reference spike. Thus, the counting function $n_{AB}(\nu)$ is calculated over the recording time T.

In order to test the independence of two spike trains, Brillinger (1976) proposed the estimate $\hat{\rho}_{AB}(\nu) = \sqrt{\hat{p}_{AB}(\nu)/\hat{p}_A\hat{p}_B}$, where $\hat{p}_{AB}(\nu) = n_{AB}(\nu)/2hT$, $\hat{p}_A = n_A/T$ and $\hat{p}_B = n_B/T$. This normalises the counting function $n_{AB}(\nu)$ accordingly. Here, n_A *and* n_B denote the number of spikes in the spike trains A and B, respectively.

For a large sample size the random variables $\hat{\rho}_{AB}(\nu)$ are independent and their distribution is the normal with mean $m = \sqrt{\hat{p}_{AB}(\nu)/\hat{p}_A\hat{p}_B}$ and standard deviation $s = 1/(2\sqrt{2hT\hat{p}_A\hat{p}_B})$. Thus, when spike trains A and B are independent, the mean of $\hat{\rho}_{AB}(\nu)$ is equal to one, since $\hat{p}_{AB}(\nu) = \hat{p}_A\hat{p}_B$.

The null hypothesis H_0 states that the two spike trains are independent. An alternative hypothesis H_1 is that there is dependence, at least for some time shift (bin), between spike trains. To test this hypothesis, the CCF values for all bins are considered. If these values are sufficiently small (inside the confidence interval) then the data does not contradict the H_0 hypothesis. The method used to calculate the confidence interval for testing this hypothesis was defined by Brillinger (1979). The boundaries of the confidence interval at the significance level α are plotted by two horizontal lines at levels $1 \pm Q_{cr}^{\alpha}/(2\sqrt{2hT\hat{p}_A\hat{p}_B})$, where Q_{cr}^{α} is the critical value of the normal distribution corresponding to the significance level α. If H_0 is correct then all values of the CCF should fall inside the confidence interval and the estimated value of the CCF $\left(\hat{\rho}_{AB}(\nu)\right)$ must be zero. If some value of the CCF exceeds the upper boundary of the confidence interval, then the null hypothesis H_0 must be rejected. Thus, it is concluded that the two spike trains are not independent. The peak is defined by the values of the normalized CCFs which lie outside the confidence interval (Fig. 2). Each of these peaks is characterised by the corresponding bin which defines the position of the peak. The bin is selected in order to maximise deviation from the upper boundary of the significance interval. This peak is referred to as the significant peak. Note that if there is more than one significant peak in the cross-correlation function, then the highest significant peak is considered to be the main peak.