Use of ‘relative-phase’ analysis to assess correlation between neuronal spike trains

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Abstract. We propose a new method of studying the correlation between neuronal spike trains. This technique is based on the analysis of relative phase between two point processes. Relative phase here is defined as the relative timing difference between two spike trains normalized by the associated interspike interval of one cell. This phase measurement is intended to reveal the relative timing relationship between spike trains at different firing rates. We apply this method to a numerical example and an example from two cerebellar neuronal spike trains of a behaving rat. The results are compared with classical cross-correlation analysis. We show that the technique can avoid some of the limitations of cross-correlation methods, reveal certain statistical dependencies that cannot be shown by cross correlation, and provide information as to the direction of influence between two spike trains.

1 Introduction

A widely used technique to study the interactions among multiple neuronal spike trains is the cross-correlation method or (shuffle-corrected) cross-correlogram (Perkel et al. 1967). However, there are limitations to the use of this method (Rosenberg et al. 1989). For example, cross correlations of two independent pacemakers of the same mean rate may still show periodic peaks at that frequency and may lead to false identification of dependence (Perkel et al. 1967). Recent work has also demonstrated that cross correlation may not be able to discriminate between spike timing synchrony, rate covariations, or stimulus-response latency covariations (Brody 1999).

Frequency-domain approaches to the study of neuronal interactions have also been developed, including cross spectrum, coherence, and other techniques that traditionally were applied to continuous time series (Rosenberg et al. 1989). One hazard of using these approaches is that a direct Fourier transform of a point process may generate multiple harmonics of a true frequency component. If, for instance, the variability of the frequency is high enough, harmonics may overlap and lead to ambiguous phase information.

Here we present an alternative method of studying correlations between neuronal spike trains using relative phase measurement. This technique does not involve the Fourier transforms of discrete point events. It is related to a method applied to the blow-fly motor system (Wyman 1965). We give the mathematical definition of relative phase and prove that the relative phases between two independent spike trains are evenly distributed, providing a criterion for detection of interdependence. We also discuss properties of the relative phase definition and directional information contained in the relative-phase distributions between two spike trains. A simple numerical example, as well as data from simultaneously recorded cerebellar neurons, is presented to demonstrate the unique ability of this method to detect relationships between spike trains that are not revealed by the cross-correlation technique.

2 Testing dependency between spike trains using relative phase

Suppose we have two stationary spike trains as shown in Fig. 1. “Stationary” here means that their interspike intervals (ISIs) are drawn from the same probability density functions (PDFs, we denote as $f_A(\tau)$ and $f_B(\tau)$), which arise from physically realizable processes and do not change over time. Their mean ISIs ($\mu_A$ and $\mu_B$) also exist and are finite. A more explicit definition of stationarity can be found in Cox and Lewis (1966). We also use $F_A(\tau)$ and $F_B(\tau)$ to describe their ISI cumulative distribution (i.e., $F_A(\tau) = \int_0^\tau f_A(t)dt = \text{prob}(T \leq \tau)$). Perkel et al. (1967) showed that the definition of cross correlation between two point processes is directly related to the statistics of waiting (or recurrence) times. Forward or backward waiting times of order $i$ $W_i$ and
$W^{-i}$ are defined as the time from a spike in train A to the $i$–th subsequent spike in train B counting forward, or to the $i$–th previous spike counting backward (see Fig. 1). Let us assume the interspike interval associated with the spike in A is $I_A$. We can define a normalized relative-phase measure $\phi_i$ as the waiting time $W_i$ normalized by the ISI after the spike in train A:

$$\phi_i = W_i/I_A .$$  

(1)

For simplicity, we call this “relative phase,” or “phase.” Here index $i$ can be positive or negative integers that correspond to forward or backward waiting times, respectively. We can use $\phi$ to denote the phase variable resulting from the summation of phases at all orders. If we define all the backward waiting times as having negative values, phase $\phi$ defined in Eq. 1 can be any real number ($\phi \in -\infty, \infty$), with different ranges of values having different meaning. For example, $\phi \in [0, 1]$ represents the relative phases of train B between adjacent spikes of train A and provides relative timing information of discharge in B subsequent to each spike of train A normalized by the associated ISI. Any other value of $\phi$, e.g., $(1, 2)$, represents the influence or the correlation of a spike in A with all the spikes in B after one “cycle” defined by the ISI of A. Phase distributions at ranges other than $[0, 1]$ emphasize “delayed” or “lagged” relative timing information between two spike trains. When train A and train B are independent of each other, the following procedure will prove that $\phi$ is evenly distributed across $-\infty$ to $\infty$. This result provides the basis for setting criteria, based on probability, for the detection of significantly correlated activity.

From Perkel et al. (1967), forward and backward waiting times $W_i$ of the first order have the same PDF:

$$g_1(\tau) = g_{-1}(\tau) = [1 - F_B(\tau)]/\mu_B .$$  

(2)

McFadden (1962) proved that the summation of waiting times at all orders (forward or backward) is evenly distributed:

$$G_B(\tau) \equiv \sum_{i=1}^{\infty} g_i(\tau) + \sum_{i=-\infty}^{-1} g_i(\tau) = 1/\mu_B .$$  

(3)

This result was found applicable to both renewal and nonrenewal processes.

So for any spike in train A with an ISI equal to $x$ (probability is $f_A(x)$), the probability of relative phase $\phi$ being smaller than a specific value $\phi$ is equivalent to the cumulative probability of the waiting times of all orders ($F_{W_{\phi}}$) being smaller than $\phi$:

$$F_{\phi}(\phi \leq \phi, x) = F_{W_{\phi}}(\tau \leq \phi x) = f_A(x) \int_{-\infty}^{\phi x} G_B(\tau)d\tau .$$  

(4)

From Eq. 4 and Eq. 3 we can obtain the PDF of the relative phase as a function of $\phi$ and $x$:

$$f_{\phi}(\phi, x) = \frac{\partial F_{\phi}(\phi, x)}{\partial \phi} = xf_A(x)/\mu_B .$$  

(5)

We see that $f_{\phi}$ is related to the specific value of $x$ (ISI) but does not depend on the value of $\phi$. So for two independent spike trains the relative-phase distribution is a constant at any given ISI value. Because $x$ is proportional to the instantaneous firing rate or frequency $(1/x)$ of train A, $f_{\phi}(\phi, x)$ can be viewed as a “relative-phase spectrum” between two spike trains. Estimation of this function may reveal distinct relative timing information across different firing frequency ranges.

If we wish to look at the overall relative phase distribution across all ISI values, we can average Eq. 5 across all possible values of $x$. For two independent spike trains:

$$f_{\phi}(\phi) = \int_{0}^{\infty} f_{\phi}(\phi, x)dx$$

$$= 1/\mu_B \int_{0}^{\infty} xf_A(x)dx = \mu_A/\mu_B .$$  

(6)

Intuitively, the above result makes sense. It basically shows that, for two independent point processes A and B, events from B will be evenly distributed between any two events in process A. The probability of finding events from B in any interval in A is determined by the ratio of their averaged firing rates. Deviation from this value could indicate interdependency and correlation with a certain phase relationship.

Several important issues should be discussed for the phase measurement defined in Eq. (1). These issues, discussed in the next three sections, relate to the differences between phase and cross-correlation analysis and the practical calculation of relative-phase distribution.

### 2.1 Differences between cross-correlation and relative-phase analysis

Relative phase defined in Eq. 1 is a dimensionless scalar variable. As shown by Perkel et al. (1967), cross correlation between two point processes is related to the distribution of waiting timings at all orders. Relative phase $\phi$ here is also based on the statistics of waiting times but takes into account the immediate ISI associated with each event. It thus becomes possible to decompose and control for the relative timing informa-