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Spike-contrast: A novel time scale independent and multivariate measure of spike train synchrony

Manuel Ciba[a,*], Takuya Isomura[b], Yasuhiko Jimbo[c], Andreas Bahmer[d], Christiane Thielemann[a]

[a] BioMEMS Lab, University of Applied Sciences Aschaffenburg, 63743 Aschaffenburg, Germany
[b] Department of Human and Engineered Environmental Studies, Graduate School of Frontier Sciences, The University of Tokyo, Bunkyo-ku, Tokyo 113-8656, Japan
[c] Department of Precision Engineering, School of Engineering, University of Tokyo, Bunkyo-ku, Tokyo 113-8656, Japan
[d] University ENT-Clinic Würzburg, Theoretical and Experimental Neurophysiology, 97080 Würzburg, Germany

HIGHLIGHTS

- A novel spike train synchrony measure is proposed called *Spike-contrast*.
- It yields similar results as *SPIKE-distance* by Kreuz et al.
- It performs faster than *SPIKE-distance* for large data sets.
- It provides a single synchrony value but also a synchrony curve (synchrony as function of bin size).

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ABSTRACT

Background: Synchrony within neuronal networks is thought to be a fundamental feature of neuronal networks. In order to quantify synchrony between spike trains, various synchrony measures were developed. Most of them are time scale dependent and thus require the setting of an appropriate time scale. Recently, alternative methods have been developed, such as the time scale independent *SPIKE-distance* by Kreuz et al.
New method: In this study, a novel time-scale independent spike train synchrony measure called *Spike-contrast* is proposed. The algorithm is based on the temporal "contrast" (activity vs. non-activity in certain temporal bins) and not only provides a single synchrony value, but also a synchrony curve as a function of the bin size.
Results: For most test data sets synchrony values obtained with *Spike-contrast* are highly correlated with those of the *SPIKE-distance* (Spearman correlation value of 0.99). Correlation was lower for data containing multiple time scales (Spearman correlation value of 0.89). When analyzing large sets of data, *Spike-contrast* performed faster.
Comparison of existing method: Spike-contrast is compared to the *SPIKE-distance* algorithm. The test data consisted of artificial spike trains with various levels of synchrony, including Poisson spike trains and bursts, spike trains from simulated neuronal Izhikevich networks, and bursts made of smaller bursts (sub-bursts).
Conclusions: The high correlation of *Spike-contrast* with the established *SPIKE-distance* for most test data, suggests the suitability of the proposed measure. Both measures are complementary as *SPIKE-distance* provides a synchrony profile over time, whereas *Spike-contrast* provides a synchrony curve over bin size.

1. Introduction

Synchrony within neuronal networks is thought to play an important role since it is related to e.g. cognitive processes (Ward, 2003), sensory awareness (Engel et al., 2001) as well as pathological states such as epilepsy (Fisher et al., 2005; Truccolo et al., 2014), and

* Corresponding author at: BioMEMS Lab Aschaffenburg Hochschule, Würzburger Str. 45 63743, Aschaffenburg, Germany.
E-mail address: manuel.ciba@h-ab.de (M. Ciba).

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Parkinson's disease (Pare et al., 1990; Arnulfo et al., 2015). Recorded neuronal signals are often reduced to spike time series to conduct further analyses as it is assumed that information is mostly coded in the time of occurrence (Rieke, 1999). Such a sequence of spike times is called a spike train. The level of synchrony among two or more spike trains can be used to e.g. evaluate theoretical neuronal models (Jolivet et al., 2008), test stimulus response reliability of neurons (Mainen and Sejnowski, 1995), or quantify the effect of drugs in *in vitro* biosensor applications (Selinger et al., 2004; Flachs and Ciba, 2016).

In general, synchrony means "the state of two or more events occurring at the same time". Whether two events can be considered synchronous depends on how "at the same time" is specified. In neuronal networks such a time can be absolute due to latencies or synaptic delays (Jeffress et al., 1948; Bahmer and Langner, 2006), but also relative depending on the oscillatory rhythms. For instance, oscillations in the brain vary between milliseconds and slower time scales, such as the 24-h period of the circadian rhythm (Buzsaki, 2006).

In order to quantify the level of synchrony, many different methods have been developed. When applied to spike train data, most of them are time scale dependent, requiring the user to define a relevant time scale (Victor and Purpura, 1996; van Rossum, 2001; Quian Quiroga et al., 2002; Schreiber et al., 2003; Selinger et al., 2004; Chiappalone et al., 2007; Cutts and Eglen, 2014). Thereby, a risk exists of choosing suboptimal time scales, affecting the comparability or validity of results. In contrast, time scale independent measures are able to perform optimally without choosing the optimal time scale beforehand (Kreuz et al., 2007). Recently, time scale independent measures have been developed, such as *ISI-distance* (Kreuz et al., 2007, 2009), *SPIKE-distance* (Kreuz et al., 2013), and *SPIKE-synchronization* (Kreuz et al., 2015).

In this study, a novel spike train synchrony measure called *Spike-contrast* is proposed and evaluated. The general idea of the synchrony measure is based on an intuitive visual contrast when displaying spike trains as a raster plot. Synchronized spike trains can be observed as vertical bars whose visual contrast increases with increasing synchrony. Thus, by means of *Spike-contrast*, the synchrony between spike trains is calculated. To avoid the limitations of a fixed time window for which spikes are considered synchronous, the time window length is varied (this can be regarded as "zooming"). Synchrony is calculated as a function of the time scale, producing a synchrony curve whose maximum is defined as the overall synchrony value. If more than one maximum appears, this indicates that spike train data are synchronized at different time scales.

The mathematical description of the new measure is given in the method Section 2.1. Implementation details are in method Sections 2.2 and 2.3. *Spike-contrast* is compared to the synchrony measure *SPIKE-distance* (Kreuz et al., 2013) as *SPIKE-distance* has been successfully used in different applications, e.g. discrimination of the synchrony increase mediated by bicuculline and cyclothiazide in cultured hippocampal neurons (Eisenman et al., 2015), evaluation of a bioinspired locomotion system for a quadruped robot (Espinal et al., 2016), and correlating behavioral metrics and spike trains in an inverse neurocontroller (Dura-Bernal et al., 2016). For the comparison, both synchrony measures were applied to artificial spike train data featuring different levels of synchrony (Section 2.4). The data include Poisson distributed spike trains and spike bursts, spike trains generated from simulated neuronal Izhikevich networks, and bursts that include shorter bursts (sub-bursts). Moreover, calculation speeds were compared.

2. Material and methods

2.1. *Definition of* Spike-contrast

The proposed synchrony measure *Spike-contrast* is based on the visual observation that synchronous spike trains form vertical bars when displayed as a raster plot. Fig. 1 shows three raster plots where each spike is represented as a black dot on a white background over time. If all spike trains are perfectly synchronized, the raster plot exhibits black vertical bars separated by white bars (Fig. 1 top). Here, the transition between black and white bars is referred to as "contrast". The higher the level of synchrony, the higher the gradient of the transition between black and white bars, and the higher the contrast. However, the contrast critically depends on the considered time scale. If only shorter and shorter parts of the spike trains are considered, spike trains appear less and less synchronized (Fig. 1 middle and bottom).

To eliminate the time scale dependence of the method, different time scales are considered by "zooming" into the signal. Finally, the maximum synchrony value found across the time scales is defined as the synchrony value S of the network. The zooming process is realized using various bin sizes to construct time histograms. The following steps are required (see also Fig. 2a), where N is the total number of spike trains, Δ is the bin size, and K is the total number of bins: (1) Creation of a time histogram counting the number of spikes per kth bin (Θ_k) across all spike trains. The histogram is used to calculate a first factor *Contrast*. (2) Creation of a second time histogram counting the number of spike trains showing at least one spike per kth bin (n_k). The histogram is used to calculate a second factor *ActiveST*. This factor is needed to compensate for unwanted high *Contrast* values in cases where a single spike falls into a separate bin which is surrounded by empty bins. (3) Step one and two are repeated for different bin sizes Δ (for details see Section 2.2) resulting in two curves *Contrast*(Δ) and *ActiveST*(Δ). (4) The product of *Contrast*(Δ) and *ActiveST*(Δ) yields the synchrony curve $s(\Delta)$. (5) The maximum of $s(\Delta)$ is defined as the final synchrony value S. More precisely, the synchrony measure is defined as

$$S = \max s(\Delta) \tag{1}$$

with

$$s(\Delta) = Contrast(\Delta) \cdot ActiveST(\Delta). \tag{2}$$

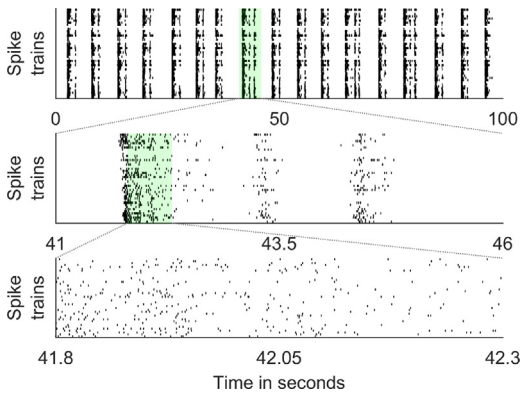

Fig. 1. Raster plots of simultaneously recorded spike trains from an *in vitro* neuronal network cultured on a microelectrode array (MEA) chip with 64 recording sites. Considering a time period of 100 s (top) spike trains appear highly synchronized. When zooming into the signal, spike trains appear less and less synchronized (middle and bottom). This leads to the problem of having to choose an appropriate time scale to measure synchrony.