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A novel tri-component scheme for classifying neuronal discharge patterns

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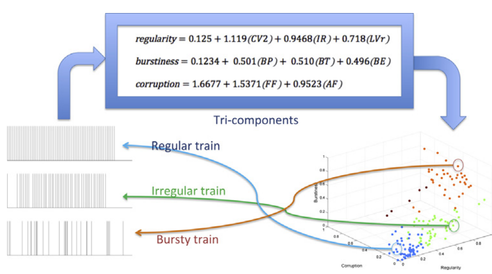
HIGHLIGHTS

- Spike pattern discrimination metrics were tested on simulated spike trains.
- Effective metrics were identified and new burst metrics were developed.
- Metrics were grouped/weighted into proxies: regularity, burstiness, and corruption.
- The tri-component classifier was validated on representative neuronal spike trains.
- We introduce a new, accurate multi-faceted classifier of neuronal spike patterns.

GRAPHICAL ABSTRACT



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ABSTRACT

Background: Neuronal discharge patterns can be described by three principle patterns, namely, regular, irregular, and bursty.
New method: Available discrimination metrics, including global ISI metrics (e.g., coefficient of variation (CV), asymmetric index), local variables (CV2, CV for a sequence of two ISIs; IR, difference of log of two adjacent ISIs; LVr, local variation with refractory period), Fano factor (FF) and Allan factor (AF), and three new burst metrics, 'burst percentage' (BP), 'burst tendency' (BT) and 'burst entropy' (BE), were extensively tested on representative simulated spike trains. Upon verifying that individual metrics could not by themselves reliably classify the diverse simulation patterns, a novel tri-component classification algorithm was developed. Inadequate metrics were rejected and the remaining selected metrics were grouped and weighted using multiple metric optimization to form three proxy metrics: 'regularity' (combining local variables), 'burstiness' (combining BP, BT and BE), and 'corruption' (combining FF and AF).
Results: The accuracy of the proxy metrics was verified on a large set of neuronal spike trains extracellularly recorded from multiple regions of the brain in unsedated normal and dystonic rats. Cross-validation of the tri-component classifier against meticulous subjective classification of these data demonstrated an agreement of 95.9%, with a high discriminatory power of 2.6.
Comparison with existing methods: The tri-component classifier was demonstrated to well outperform individual metrics on all aspects of pattern and corruption discrimination.

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Conclusions: The tri-component classifier provides a novel, reliable algorithm to differentiate highly diverse neuronal discharge patterns and discriminate natural or erroneous corruption in the signal.

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1. Introduction

Formerly, the pattern of neuronal spike trains was commonly thought to be a largely stochastic process with information chiefly coded by the discharge rates. However, increasingly, researchers are recognizing that information is conveyed to a major extent by the temporal patterns of occurrence of discharges. As such, reliable objective metrics to characterize neuronal discharge patterns are essential to understand the intricate signaling between different nuclei. Such metrics must be able to effectively delineate three main features in the spike train: Poissonian irregularity, burstiness, and non-stationarity. The first two features are required to classify the spike pattern, while the third is needed to define the variability and extent of noise in the signal. Presently, no published analysis programs allow satisfactory categorization of the greatly varying neuronal discharge patterns encountered throughout the brain.

Limitations posed by subjective neuronal classification schemes (Kaneoke and Vitek, 1996) have led to the development of objective metrics. Since spike trains can be modeled as a Poisson process and defined by their inter-spike interval (ISI) distribution (Mitra and Bokil, 2007), several metrics have been introduced based on objective characterization of the ISI distribution. Coefficient of variation of ISI (CV) (Feng and Brown, 1999 Christodoulou and Bugmann, 2001) is commonly used to describe the variability in discharge activity over the spike train, though does not differentiate the various ISI patterns. Other metrics, including asymmetric index (AI), skewness (Sk) (Doane and Seward, 2011) and kurtosis (kr), define the shape of ISI histogram. Global measures, such as CV and AI, are however limited by being sensitive to the discharge rate (Holt et al., 1996; Shinomoto et al., 2009) and do not adequately account for non-stationary signals and corruptions in the spike train. To overcome these limitations, local variables were developed, which compare adjacent ISIs, and as such, are relatively insensitive to rate variations. The local ISI metrics include CV2, the coefficient of variation for a sequence of two ISIs (Holt et al., 1996; Taube, 2010); IR, the difference of the log of two adjacent ISIs (Davies et al., 2006); LV, local variation of ISIs (Shinomoto et al., 2003); and LVr, a local variation parameter with refractory period information (Shinomoto et al., 2009).

Another technique for measurement of regularity and burstiness is based on inspection of the shape and the location of peaks of the autocorrelation histogram (ACH) of spike trains (Paladini, Robinson, Morikawa, Williams, and Palmiter, 2002; Perkel, Gerstein, and Moore, 1967). Markus et al. (2011) objectified this technique by quantifying shape defining features of the ACH. However, the reliability is limited for non-oscillatory irregular trains and for non-stationary trains, including trains with varying underlying firing rates (Holt et al., 1996). Also, ACH techniques are restricted in their ability to detect the multiple features which define burstiness. Because these classification techniques are robust and reliable for oscillatory spike trains, we used them for additional support for our initial visual subjective classifications. However since ACH classification parameters would not have strengthened our classification scheme, we did not incorporate this methodology into our final objective algorithm.

Towards our present aim of defining robust metrics for characterizing diverse neuronal discharge patterns, we extensively tested available classification metrics on representative simulated spike trains and on a large data set of extracellular neuronal recordings from primary motor cortex (MC), several basal ganglia nuclei, hippocampus, and thalamus in normal and dystonic rats. To account for non-stationarity in spike trains, we also assessed Fano factor (FF) (Eden and Kramer, 2010; DeWeese et al., 2003) and Allan factor (AF) (Gaudry and Reinagel, 2007), which estimate spike count variability and provide additional measures of the burstiness of the spike train (Anteneodoa et al., 2010). Since FF and AF are sensitive to Poissonian noise and to across trial variability (Churchland et al., 2010), these metrics are able to detect local variations in pattern or rate. Two additional novel metrics, post spike suppression (PSP) (Benhamou et al., 2012) and residual metrics (Maimon and Assad, 2009) were also assessed, but were found to be not particularly useful. Because current metrics, including CV, LVr, and density histogram (Leblois et al., 2010), were found here to be inadequate for delineating burstiness, we developed a new burst discrimination metric. In our prior study (Baron et al., 2011), we established reliable burst detection parameters for the customizable interval method (Plexon Inc. Neuroexplorer MaxInterval Method), while determining that other popularized burst detection metrics, including the Poisson surprise method (Legéndy and Salcman, 1985; Kaneoke and Vitek, 1996), were unreliable. The burst discrimination metric introduced here first delineates bursts in the spike train using the interval method and then defines the burstiness of the spike train based on burst parameters ('burst percentage' (BP), 'burst tendency' (BT), and 'burst entropy' (BE)).

We establish here that individual metrics cannot reliably classify diverse neuronal discharge patterns. Therefore, we chose to develop a novel tri-component classification scheme based on weighting combinations of desirable metrics using multiple metric optimization (MMO) and feature space clustering. Furthermore, transitions from regular to irregular discharge firing and from non-bursty to bursty lack clear unique designations. Therefore, rather than defining specific threshold cut-offs, we obviated this issue by utilizing multiple metrics to initially approximate the relevant features of the spike trains and then applying multidimensional semi-supervised clustering to finalize the classifications of the spike trains. Our comprehensive tri-component classification methodology is demonstrated here to dependably classify neuronal spike trains from diverse regions of the brain in the normal and in a representative diseased state.

2. Methods

2.1. Delineation of bursts and development of novel burstiness metrics

As mentioned in the introduction, after determining from the simulations that available metrics could not adequately delineate burstiness, we chose to develop three new burstiness metrics: 'BP', 'BT', and 'BE'. These new metrics, as well as the parameters chosen to define neuronal bursts using the interval method, are detailed below.

2.1.1. Detection of bursts using the interval method

The interval method (Chen, Deng, Luo, Wang, & Zeng, 2009) (Plexon Inc. Neuroexplorer MaxInterval Method) incorporates five definable parameters to delineate individual bursts (box figure). Based on previous extensive visual inspection of spike trains in dystonic and control Gunn rats, values for each of these parameters were chosen and subsequently modified until they proved to be highly reliable in delineating individual bursts in the spike train (Baron et al., 2011). The final derived values are as follows: max. interval to start a burst = 6 ms, max. inter-spike interval in a

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