Journal of Neuroscience Methods 261 (2016) 97–109

Contents lists available at ScienceDirect

Journal of Neuroscience Methods

journal homepage: www.elsevier.com/locate/jneumeth

Computational Neuroscience

A real-time spike classification method based on dynamic time warping for extracellular enteric neural recording with large waveform variability

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HIGHLIGHTS

- An online spike classification method based on dynamic time warping for extracellular enteric neural recording with large waveform variability.
- Automatic classification for pixel-array operations without user intervention.
- Improved classification accuracy and computational cost over conventional cross-correlation based template-matching method and PCA + k-means clustering.
- Demonstrated on mouse enteric neural recordings in response to mechanical and chemical stimuli.

ARTICLE INFO

Article history:
Received 11 August 2015
Received in revised form 5 November 2015
Accepted 12 December 2015
Available online 21 December 2015

Keywords:
Dynamic time warping
Enteric nervous system
FET sensors
Extracellular action potentials

ABSTRACT

Background: Computationally efficient spike recognition methods are required for real-time analysis of extracellular neural recordings. The enteric nervous system (ENS) is important to human health but less well-understood with few appropriate spike recognition algorithms due to large waveform variability.
New method: Here we present a method based on dynamic time warping (DTW) with high tolerance to variability in time and magnitude. Adaptive temporal gridding for "fastDTW" in similarity calculation significantly reduces the computational cost. The automated threshold selection allows for real-time classification for extracellular recordings.
Results: Our method is first evaluated on synthesized data at different noise levels, improving both classification accuracy and computational complexity over the conventional cross-correlation based template-matching method (CCTM) and PCA + k-means clustering without time warping. Our method is then applied to analyze the mouse enteric neural recording with mechanical and chemical stimuli. Successful classification of biphasic and monophasic spikes is achieved even when the spike variability is larger than millisecond in width and millivolt in magnitude.
Comparison with existing method(s): In comparison with conventional template matching and clustering methods, the fastDTW method is computationally efficient with high tolerance to waveform variability.
Conclusions: We have developed an adaptive fastDTW algorithm for real-time spike classification of ENS recording with large waveform variability against colony motility, ambient changes and cellular heterogeneity.

1. Introduction

Enteric nervous system (ENS) is composed of 200–600 million neurons found in the gastrointestinal tract and plays a vital role in upholding gut functions of motility, epithelial secretion, and intestinal barrier (Savidge et al., 2007; Furness, 2014). Disruption of ENS can cause Crohns disease (Lakhan and Kirchgessner, 2010), diabetes (Yarandi and Srinivasan, 2014), irritable bowel disease (IBD) (Straub et al., 2006), and ulcerative colitis (Bassotti et al., 2014). Different from those in the central nervous system (CNS), which is situated in the largely stationary brain, neural signals in the ENS are coupled to gut motility and peristalsis, interacting with gastrointestinal endocrine cells (Szurszewski et al., 2002) and intestinal longitudinal muscles (Thuneberg and Peters, 2001; Huizinga and

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http://dx.doi.org/10.1016/j.jneumeth.2015.12.006
0165-0270/

Chen, 2014). These movements not only alter neural activities, but also cause electrode drift during recordings. Activities of the ENS are also influenced by the immune system via cytokines and mast cell tryptase (De Giorgio et al., 2004; Lomax et al., 2006). Furthermore, the ENS consists of various types of enteric neurons embedded in dense mesh-like 2-D ganglia, called myenteric and submucosal plexuses, and hence an extracellular electrode will pick up signals from an ensemble of heterogeneous neurons with different action potential waveforms. These factors render ENS recordings large waveform variability, which is compounded by the lack of knowledge of the ENS. A spike classification method with high nonstationary tolerance is needed to reliably interpreting the ENS extracellular action potential (EAP) recording.

The recent decade has seen enormous progress in spike recognition and classification methods for CNS. Such methods typically include three steps: (1) detection of candidate spikes, (2) waveform feature extraction, and (3) clustering of spikes. Different combinations of feature extraction, e.g. principle component analysis (PCA) (Adamos et al., 2008), wavelet transform (Quiroga et al., 2004) and first and second derivative extrema (FSDE) (Paraskevopoulou et al., 2014), and clustering, e.g. k-means (Chan et al., 2008), superparamagnetic (Quiroga et al., 2004) and hierarchical adaptive means (HAM) (Paraskevopoulou et al., 2014), have been proposed for better accuracy. Overlapping spikes can be handled by either iteration and subtraction (Lewicki, 1994; Zhang et al., 2004; Prentice et al., 2011; Pillow et al., 2013; Ekanadham et al., 2014) or independent component analysis (Takahashi et al., 2003; Takahashi and Sakurai, 2005; Jäckel et al., 2012). Most of these methods are off-line, requiring the collection of all spikes before running the analysis, unsuitable for real-time closed-loop applications. Additionally, these methods require off-chip processing due to the high computational cost, limited by the stringent power density on chip for safe neural implants (Kim and McNames, 2007).

A special case of the spike classification method for CNS that can be done in real-time is the template matching (TM) method, which uses the waveform in time domain directly in contrast to the extracted feature. TM compares each candidate spike to the template library and makes assignment by the largest similarity. The template library must be formulated in advance by feature extraction and clustering either from the initialization phase of the same experiment (Navajas et al., 2014) or from earlier experiments. The key step in TM is the similarity calculation, for which Euclidean distance (Rutishauser et al., 2006; Karkare et al., 2013) and cross correlation (Kim and McNames, 2007) are most widely used. Both similarity calculations can be implemented in neural implant with real-time, low-power on-chip processing to render a reduced data transmission rate (Lopez et al., 2012; Rizk et al., 2009; Wattanapanitch and Sarpeshkar, 2011).

While many of these spike classification methods are used in CNS, they cannot be used as effectively in ENS. Minimal waveform variability in phase, duration and magnitude was often assumed, which is invalid due to electrode drift and non-stationary waveforms (Bar-Hillel et al., 2006). Electrode drift is caused by the neuron movement relative to the recording electrode, as well as the change in the electrolytic property of the biological environment (Quiroga, 2009). Non-stationary waveforms refer to the change of the spike shape over time (Wolf et al., 2009). In CNS, such variability problems have been investigated previously by modeling the source neurons as a mixture of Gaussians. Bayesian clustering (Bar-Hillel et al., 2006) was employed to calculate the candidate clusters in short-time frames, and the transition probabilities among each cluster mixture determine the cluster choice as the maximum-a-posteriori solution. Simplification based on Kalman filtering (Calabrese and Paninski, 2011) can be utilized to enhance efficiency. Bayesian optimal TM (Franke et al., 2015) was also suggested for online applications. However, the main focus of these methods was on the variability of the spike magnitude caused by the movement of the cluster centers, but not on the time course, which proves critical for ENS EAP recordings due to large colony motility (Thuneberg and Peters, 2001) in the complex environment.

Here we propose dynamic time warping (DTW) as a similarity measure with high tolerance to the spike variability in both magnitude and time. DTW has proven to be very effective in speech recognition under source and ambient variations (Zhang et al., 2014) and ECG profile characterization (Huang and Kinsner, 2002), which are similar to the ENS EAP analysis at hand. We established a fastDTW method with automatic thresholding for ENS recordings with large spike variability for real-time applications. During the similarity calculation, we have also implemented adaptive temporal gridding (Salvador and Chan, 2004) with linear complexity. The performance of fastDTW is first evaluated on synthesized ENS EAP data at various noise levels, showing remarkable enhancement in accuracy and computational complexity in comparison to cross-correlation based TM (CCTM) and PCA + k-means clustering without time warping. To demonstrate the manner and degree how our fastDTW method can impact neural recording, experimental EAP of the mouse enteric neurons under different stimuli are analyzed, where our fastDTW method was able to successfully classify biphasic and monophasic spikes when the waveform variability is more than millisecond in width and millivolt in magnitude. In addition to more precise spike counting than the TM method, fastDTW also directly provides specific waveform parameters with associated changes in time for further statistical processing and behavior recognition.

2. Methodology

We will first introduce dynamic time warping (DTW) as a similarity measure with high tolerance to the spike variability. Automatic thresholding and fastDTW are then added to enhance real-time performance. We use synthesized ENS EAP recordings for accuracy benchmark. We will then describe the experimental setup for EAP recordings of mouse enteric neurons by different stimuli and inhibition with an emphasis on how variability can be captured in the presence of high noise level.

2.1. DTW in similarity calculation

We will show how DTW can be effectively and efficiently employed for similarity calculation in the neural spike classification algorithm when large variability is expected.

Let X denotes the time series of the spike template with length n, and Y denotes the time series of the candidate spike segment with length m (X and Y are normalized in magnitude before similarity calculation):

$$X = x_1, x_2, \ldots, x_i, \ldots x_n \tag{1}$$

$$Y = y_1, y_2, \ldots, y_j, \ldots y_m \tag{2}$$

where i, j are time indexes of the series X and Y, respectively.

The similarity matrix $[a]_{nm}$ is constructed where each element is the normalized Euclidean distance between a pair of points in series X and Y:

$$a_{ij} = d(x_i, y_j) = \frac{|x_i - y_j|}{m + n} \tag{3}$$

A warp path P is defined on the similarity matrix $[a]_{nm}$

$$P = p_1, p_2, \ldots, p_k, \ldots, p_l \tag{4}$$

where l is the length of the warp path and the kth element of the warp path is

$$p_k = (i, j) \tag{5}$$