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Unsupervised neural spike sorting for high-density microelectrode arrays with convolutive independent component analysis

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HIGHLIGHTS

- We propose an unsupervised spike sorting algorithm that accounts for spike overlaps and performed comparable to a supervised algorithm.
- Spike sorting performance was assessed with ground-truth data on 4365 electrodes – generated from experimentally derived templates.
- We show how ICA based spike sorting has to be extended in order to retrieve a larger number of accurately sorted neural spike trains.
- Our new algorithm constitutes a fast solution for spike sorting data from thousands of electrodes.

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ABSTRACT

Background: Unsupervised identification of action potentials in multi-channel extracellular recordings, in particular from high-density microelectrode arrays with thousands of sensors, is an unresolved problem. While independent component analysis (ICA) achieves rapid unsupervised sorting, it ignores the convolutive structure of extracellular data, thus limiting the unmixing to a subset of neurons.
New method: Here we present a spike sorting algorithm based on convolutive ICA (cICA) to retrieve a larger number of accurately sorted neurons than with instantaneous ICA while accounting for signal overlaps. Spike sorting was applied to datasets with varying signal-to-noise ratios (SNR: 3–12) and 27% spike overlaps, sampled at either 11.5 or 23 kHz on 4365 electrodes.
Results: We demonstrate how the instantaneity assumption in ICA-based algorithms has to be relaxed in order to improve the spike sorting performance for high-density microelectrode array recordings. Reformulating the convolutive mixture as an instantaneous mixture by modeling several delayed samples jointly is necessary to increase signal-to-noise ratio. Our results emphasize that different cICA algorithms are not equivalent.
Comparison with existing methods: Spike sorting performance was assessed with ground-truth data generated from experimentally derived templates. The presented spike sorter was able to extract ≈90% of the true spike trains with an error rate below 2%. It was superior to two alternative (c)ICA methods (≈80% accurately sorted neurons) and comparable to a supervised sorting.
Conclusion: Our new algorithm represents a fast solution to overcome the current bottleneck in spike sorting of large datasets generated by simultaneous recording with thousands of electrodes.

1. Introduction

Action potentials are the most important building blocks for information processing in neural networks. State-of-the-art microelectrode arrays (MEAs) map the activity of up to several hundreds of neurons with varying spatial and temporal resolution (Buzsáki, 2004; Litke et al., 2004; Blanche et al., 2005; Imfeld et al., 2008; Frey et al., 2009; Lambacher et al., 2011; Marre et al., 2012; Zeck et al., 2011). The assignment of extracellular voltages caused by action potentials to the corresponding cells – i.e., spike sorting – is an important analysis step for many neuroscientific questions as well as neuroprosthetic applications. However, the development of new data analysis methods lags behind current hardware

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technologies (Einevoll et al., 2011). Widely-used spike sorting methods are based on clustering extracellular signals by similarity (Quiroga, 2007; Lewicki, 1998), and recent work extended this idea to large and dense array data (Kadir et al., 2014; Rossant et al., 2013; Lambacher et al., 2011). However, clustering approaches suffer fundamentally from the problem that extracellular voltages overlap in space and time and thus near-synchronous activity cannot be resolved (Pillow et al., 2013).

Methods for multiple electrodes which address the overlap of extracellular signals (Segev et al., 2004; Marre et al., 2012) have been developed, considering realtime capabilities (Franke, 2011) and probabilistic modeling (Prentice et al., 2011; Pillow et al., 2013; Ekanadham et al., 2014; Franke et al., 2015, 2015). These methods account for overlaps by fitting combinations of pre-defined extracellular waveforms (templates), and thus require a preceding clustering stage for template identification. To account for the superposition of spikes, manual intervention is needed to accept, reject and/or refine templates, which does not scale well for recordings with thousands of channels.

For high-density microelectrode arrays (HD-MEAs) for which the sensor density outweighs the neuron density, spike sorting could be facilitated by overdetermined blind source separation (BSS) methods (Comon and Jutten, 2010). This would allow retrieving templates while immediately accounting for overlapping activity. A prominent method is independent component analysis (ICA) (Jutten and Herault, 1991; Comon, 1994; Hyvärinen, 2013), where the data is considered to be an instantaneous mixture of independent signal sources. Benefits of applying ICA to the analysis of biomedical signals and particularly to spike sorting have been pointed out previously (Brown et al., 2001; Takahashi et al., 2003, 2003; Madany Mamlouk et al., 2005; Takahashi and Sakurai, 2005; Hermle et al., 2005; Snellings et al., 2006; Hill, 2010; Tiganj and Mboup, 2012; Jäckel et al., 2012). Spike sorting could benefit from the following ICA properties: (1) it is unsupervised, (2) achieves redundancy reduction, (3) separates artifacts based on signal statistics, and (4) increases the signal-to-noise ratio. Furthermore, (5) contributions of neurons to different sensors can be retrieved via the learned (un)mixing matrix, and (6) computationally efficient fastICA algorithms (Hyvärinen, 1999) could reduce analysis time. ICA based spike sorting algorithms (Takahashi et al., 2003, 2003; Madany Mamlouk et al., 2005; Takahashi and Sakurai, 2005; Hermle et al., 2005; Snellings et al., 2006; Hill, 2010; Tiganj and Mboup, 2012; Jäckel et al., 2012), however, restrict spike templates to have linearly dependent waveforms across different channels and neglect the temporal structure of neuronal extracellular signals. Recently, it was confirmed that extracellular recordings are not instantaneous mixtures of neuronal sources (Shiraishi et al., 2009; Jäckel et al., 2012). This result can also be understood based on the biophysics of neurons, assuming that the spike is initiated at the axon hillock and propagates back into the soma as well as down the axon (Plonsey and Barr, 2007). The necessity of developing ICA-based spike sorting algorithms that relax the instantaneous mixture assumption – i.e. that model the recordings with several instead of just one single mixing matrix, was suggested (Shiraishi et al., 2009; Tiganj and Mboup, 2012), but tested only for small datasets with low numbers of neurons and high signal-to-noise ratio (SNR) (Jäckel et al., 2011; Shiraishi et al., 2011).

Here we present a novel approach that estimates neuronal signals directly from the data using convolutive ICA (cICA) (Dyrholm, 2005; Pedersen et al., 2007). We developed a spike sorting solution that outperformed conventional ICA-based sorting by making use of both the spatial as well as the temporal redundancy of the recorded data. Thereby, both the spike trains and spike templates could be learned in an unsupervised fashion, yielding spike sorting results comparable to the performance achieved by a supervised setting that used the templates.

The paper is organized as follows. We briefly introduce general properties of cICA methods to motivate the choice of the particular approaches assessed here (Section 2.1). Specifically, we present two cICA based spike sorting algorithms (Section 2.2) that are applicable to regions-of-interest on a high-density array comprising hundreds of densely arranged sensors. The relevant convolutive structure was automatically determined from extracellular recordings from retinal ganglion cell activity (Section 2.3). In the result section, we analyze the representation of neural signals induced by convolutive vs. instantaneous ICA (Sections 3.1 and 3.2). The quantitative spike sorting performance was assessed (Section 3.3) with simulated recordings for which the true spike trains were known. The applicability of cICA-based spike sorting to experimental recordings from retinal ganglion cell populations is demonstrated in Section 3.4. The performance difference of the two cICA algorithms is discussed in a separate section. This paper shows that in the context of spike sorting, different cICA methods are not equivalent and one needs to enforce the accumulation of signal energy over time in order to outperform ICA based sorting.

2. Materials and methods

2.1. Convolutive ICA

The task of identifying the signal-generating sources and the mixing matrix given a recorded dataset X (Eq. (1)) is coined *blind source separation* (BSS) (Comon and Jutten, 2010). A particular approach is independent component analysis (ICA), where the sources are assumed to be statistically independent. Equivalently, if the mixture is of convolutive nature (Eq. (2)), we speak of *convolutive BSS* and *convolutive ICA* (cICA) respectively. We emphasize that cICA should not be confused with methods that exploit the time structure of the source signals (Hyvärinen et al., 2001, chapter 18), for solving the instantaneous mixing model (Eq. (1)) (Tong et al., 1990; Molgedey and Schuster, 1994). Structured reviews on convolutive BSS methods and their connection to ICA are provided in Hyvärinen et al. (2001) and Pedersen et al. (2007). A detailed treatment is beyond the scope of this work, but the main aspects relevant to the problem at hand are mentioned here to make this work self-contained.

2.1.1. The mathematical model

ICA assumes the data $\mathbf{x}_t$ to be a linear mixture, given by the mixing matrix A, of hidden sources $\mathbf{s}_t$:

$$\mathbf{x}_t = \mathbf{A} \cdot \mathbf{s}_t \tag{1}$$

Without knowing the mixing matrix $\mathbf{A}$ nor the underlying source activations $\mathbf{s}_t, (t \in 1, \ldots, T)$, both can be learned if the M components of $\mathbf{s}_t$ are – instantaneously (i.e. for a given time t) – statistically independent. If ICA were able to achieve a complete unmixing of the sources, one could interpret the independent component (IC) $s_{i,t}$, $(t \in 1, \ldots, T)$ as the activity of a single neuron i, whose spike times are then obtained simply by thresholding that time series (Fig. 1). This approach allows to resolve overlaps by construction as each participating neuron should exhibit a spike in its associated source.

Extracellular action potential waveforms from the same neuron may exhibit differences across neighboring electrodes, such as phase shifts, that cannot be captured by the instantaneous model (Eq. (1)). These differences can be modeled using L delayed mixing matrices:

$$\mathbf{x}_t = \sum_{\tau=0}^{L} \mathbf{A}_\tau \mathbf{s}_{t-\tau} \tag{2}$$