Spike Detection and Sorting using PARAFAC2 Method

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Abstract— **In this contribution we introduce the Parallel Factor 2 (PARAFAC2) analysis as a novel method for the simultaneous detection and classification of neural action potentials. In order to measure these action potentials (spike signals), stem cell derived neuronal cells are cultivated on the surface of a Micro Electrode Array (MEA). Here, the neuronal cells produce ion currents, which can be measured as extracellular electric potentials. Whenever a cell or a group of cells produces ion currents, either spontaneously or evoked by a stimulus, a spike signal can be measured by the electrodes of the MEA. Stimulated cells produce spikes and groups of spikes (bursts) which propagate in space over the MEA. In the recorded data, different source types (e.g., cells which respond directly to external stimuli and cells which are triggered by other neural cells) are characterized by different spike shapes. The proposed PARAFAC2 method is able to separate these spike shapes (sources) in time, frequency and space (channels) enabling an improved performance in noisy scenarios. Furthermore, PARAFAC2 allows for a causality analysis on the measured spike signals (i.e. the identification of different signal paths). Thereby, the PARAFAC2 decomposition is able to exploit the multi-dimensional structure of the MEA data.**

I. Introduction

Neuronal cells are the basic functional unit of the human brain. They are highly specialized cells and able to build intercellular connections forming neuronal networks. They communicate by the transmission of various types of signals. The communication between two or more neuronal cells is performed by neuronal excitation messengers or neurotransmitters (e.g. neuropeptides, endorphins). The receiving cell converts the messenger-based excitation into an ion signal which is forwarded to its dendrites and axon.

When attempting to understand complex neuronal networks, the use of MEAs provides a fast, nonintrusive, extracellular recording method capable of simultaneously measuring the activity over a certain area covering the network. In the evaluation of these recordings, the identification of spontaneous and stimulated activity is necessary. Active cells produce spikes and group of spikes which can be analyzed by e.g., statistical methods.

Given a neuron is spiking randomly or induced by a stimulus, a current is evoked. By means of ion transfer across the cell membrane a potential difference between the intra- and extra-cellular spaces is generated. This potential difference can be measured using the MEA. Essentially, spikes are measured at every electrode of the MEA. In order to identify which neuronal cell at which electrode is the source of a specific spike, it is necessary to classify all detected spike waveforms. This information allows for a time based sorting of the spikes in order to obtain knowledge about the type of neuron and its location.

In this contribution we use PARAFAC2 to detect spikes of noisy signals and to sort the spikes. Meaning the spike detection and spike sorting is performed within one step. The method performs successfully using simulated as well as real measured data.

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II. Methods

The starting point to analyze communication channels between active, living cells is to identify and separate different kinds of spiking neurons. Different time series characteristics are detectable caused through different forms and sizes of the cells. In case an intercellular connection is established the information from an initiating cell is conducted to the next connected cell or cells. The activation or action potential can be measured along a path on a MEA. Polarization, depolarization, and refractory period of the neural cell [1] causes a specific delay across the channels. The action potential is moving across the electrodes of the MEA. Multiple kinds of connections exist between cells on a MEA. It is likely having two or more connection paths within one cell structure. The PARAFAC2 method is able to separate these paths. The influence of the noise to the correct detection of the potentials is also analyzed.

PARAFAC2 is a multi-dimensional signal decomposition, the input dimensions are time, frequency and channel. The first preprocessing step was the calculation of the Reduced Interference Distribution (RID), a special kind of the Wigner Ville Distribution (WVD) [2] with a corresponding kernel to minimize interferences between auto terms. The advantage of this time frequency distribution is the high time and high frequency resolution. The RID is calculated for each channel with a moving signal source. Through PARAFAC2 decomposition it is possible to determine signatures which change in only one dimension. The variable signature of a moving source is the time. Another important parameter of PARAFAC2 is the order which determines the number of different sources.

A. PARAFAC2 method

For the analysis of 3-dimensional data R. A. Harshman introduced the Parallel Factor 2 (PARAFAC2) decomposition model in [3]. Thereby, the 3-way data is represented by a set of matrices $\boldsymbol{X}_k$ of size $N_{\mathrm{F}} \times N_{\mathrm{T}}$,

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where N_F is the number of frequency bins and N_T is the number of time samples. The channel index *k* varies in the range of $1,\ldots,N_C$ with N_C denoting the total number of channels provided by the MEA. Please notice, that the matrices $\boldsymbol{X}_k$ are generated by performing a Time-Frequency-Analysis (TFA) on every channel of the MEA recordings. The subsequent PARAFAC2 analysis decomposes the resulting set of matrices according to [3]

$$\boldsymbol{X}_k = \boldsymbol{A} \cdot \boldsymbol{D}_k \cdot \boldsymbol{T}_k^{\mathrm{T}} \tag{1}$$

where $\boldsymbol{A} = \left[\boldsymbol{a}_1,\ldots,\boldsymbol{a}_R\right] \in \mathbb{R}^{N_T \times R}$ and $\boldsymbol{T}_k = \left[\boldsymbol{t}_{k,1},\ldots,\boldsymbol{t}_{k,R}\right] \in \mathbb{R}^{N_T \times R}$ are the matrices of frequency signatures and time signatures, respectively. Here, *R* is the number of components extracted by the PARAFAC2 decomposition. Furthermore, the diagonal matrices $\boldsymbol{D}_k \in \mathbb{R}^{R \times R}$ are constructed from the rows of the matrix of channel signatures $\boldsymbol{C} = \left[\boldsymbol{c}_1,\ldots,\boldsymbol{c}_R\right] \in \mathbb{R}^{N_C \times R}$. As a result, every PARAFAC2 component is characterized by a constant frequency signature $\boldsymbol{a}_r$, a channel signature $\boldsymbol{c}_r$ and multiple time signatures $\boldsymbol{t}_{k,r}$ with $r = 1,\ldots,R$. In contrast to other 3-dimensional decomposition models, such as the Parallel Factor (PARAFAC) model [4], PARAFAC2 according to (1) supports an additional variation of the time signatures $\boldsymbol{t}_{k,r}$ over the different channels. This property is crucial for the analysis of spike shapes which may appear temporally shifted in the different channels measured at the MEA [5]. In order to obtain a unique decomposition model according to (1), the PARAFAC2 decomposition includes the Harshman constraint [5]

$$\boldsymbol{T}_k^{\mathrm{T}} \cdot \boldsymbol{T}_k = \boldsymbol{H} \tag{2}$$

which forces the sample covariance matrix $\boldsymbol{H}$ of the time signatures $\boldsymbol{t}_{k,r}$ to be independent of the channel index *k*. For the computation of the PARAFAC2 decomposition according to (1) and (2) we use the alternating least-squares based direct fitting algorithm presented in [6].

B. Simulated signals

The simulated signal is created using data of two different spike waveforms with a length of 4 ms each and a whole time series of 100 ms. These waveforms are extracted from random spiking data of earlier studies [7]. The used waveforms are the mean of the two most representative time series. Both spikes are shifted in time (2 ms) over the channels in opposite directions to fulfill the condition of the Harshman constraint (cf. eq. (2)). The whole data set consists of 47 channels. Figure 1 shows the two types of spikes (top) and how they are shifted across the channels (bottom).

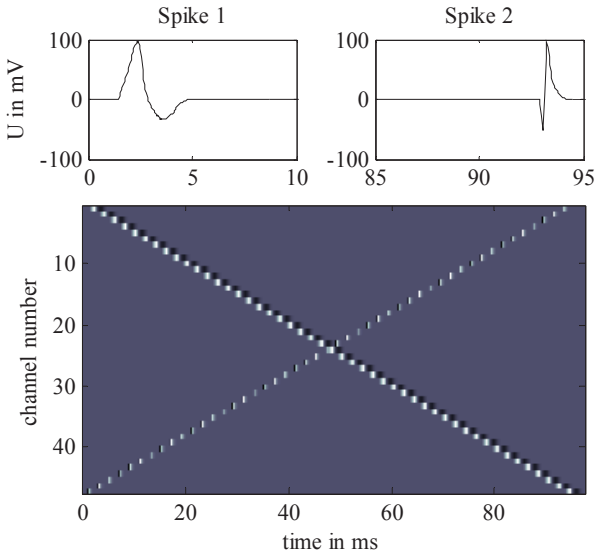

Figure 1. Simulated data set, 47 channels, and 2 different spike waveforms; shifted beyond the channels in opposite directions

To evaluate the robustness of PARAFAC2 white noise is added. The chosen signal to noise ratio is -15 and 30 dB (Figure 2). The added noise is independent between the channels.

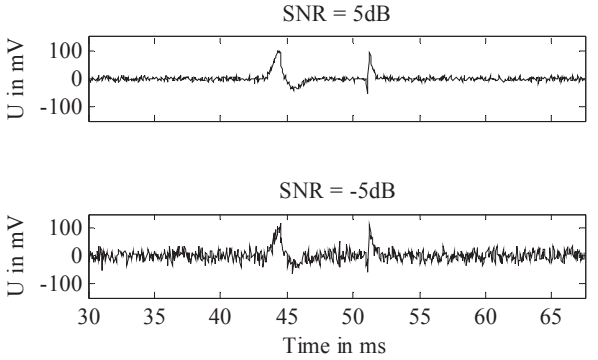

Figure 2. Two channels of the simulated data set, white noise added (-5 dB and 5 dB)

C. Random spiking data

To evaluate PARAFAC2 using real signals we use a multichannel random spiking dataset of stem cells derived neuronal activity. For the analysis a time window of 200 ms is applied. For preprocessing all 60 channels are transformed into the time frequency domain utilizing the RID.

III. Results

A. Simulated signals with two sources

PARAFAC2 is able to decompose the signal of all channels in time, frequency, and channel signature successfully. The order is determined by the given number of spikes of the simulated signal. Figure 3 shows the two components of the time-frequency-signature. The two different spikes can be clearly distinguished (Figure 3 and Figure 4, white). The input signal has a SNR of -5 dB.

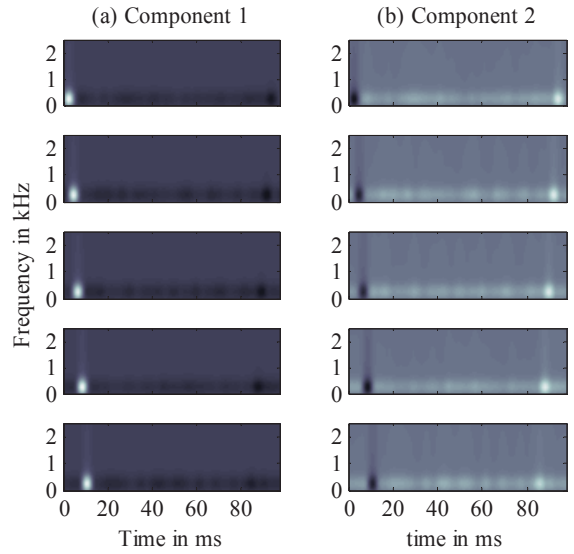

Figure 3. Time-frequency signature of the first 5 of 47 channels is displayed at a SNR of -5 dB. Red color implicates the position of the spike, (a) spike class 1, (b) spike class 2.

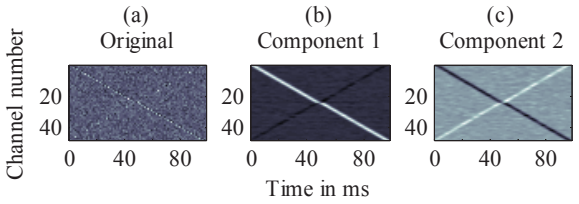

Figure 4. (a) allocation of the spikes of both classes and -5 dB SNR; (b) PARAFAC2 decomposition of class 1; (c) PARAFAC2 decomposition of class 2.

B. *Spike detection rate*

The simulated signal with two sources (spikes) is also generated using noise. The robustness of PARAFAC2 spike detection and sorting is evaluated at various signal to noise ratios (SNR). Figure 5 shows the rate in percent of correct detected spikes. Up to an SNR of -5 dB 100 % of the spikes are detected and sorted correctly. Between -10 and -5 dB approx. 75 % of all spikes could be detected correctly independent of their class.

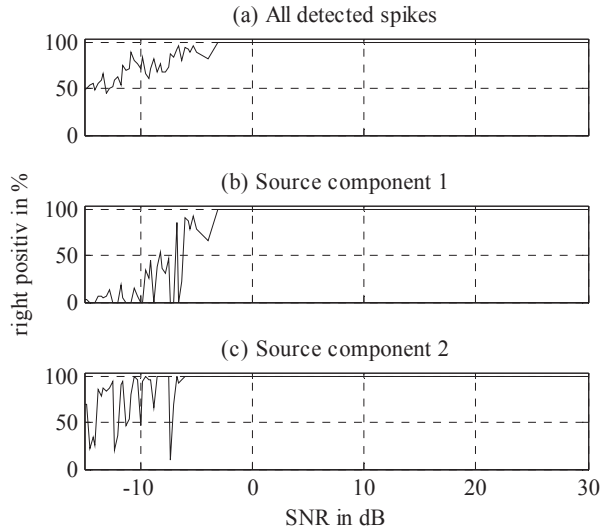

Figure 5. Correct detected and classified spikes in relation to the SNR

B. *Random spiking activity*

To analyze real spiking data PARAFAC2, data containing two classes of spikes are analyzed. Figure 6 illustrates one channel of a 60 channel dataset. There are three spikes of component one and one spike of component two. PARAFAC2 does not distinguish between spikes of different polarization caused by their same frequency signature.

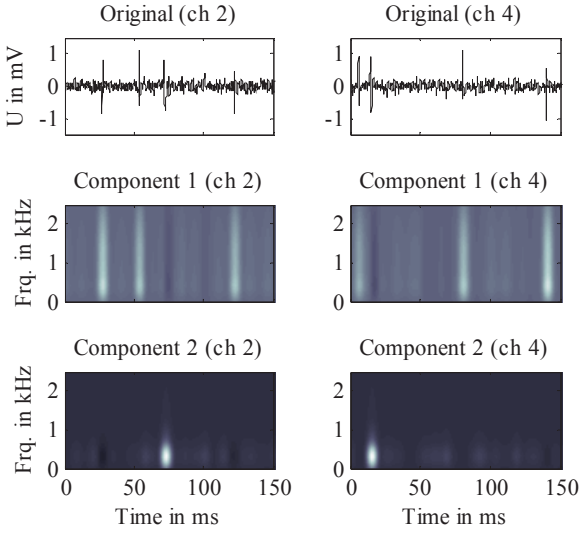

Figure 6. Spike sorting and detection of a real time series with spiking neurons of channel 2 (left) and channel 4 (right). In the original signal (top) two types of spikes (class 1: middle; class 2 bottom) were found. They are detected and separated.

IV. Discussion

Two different spike waveforms in opposite directions are successfully separated by PARAFAC2. To successfully apply PARAFAC2 several signal characteristics have to be met: spike classes differ in the time-frequency domain, and the shift is not equal between them across the channels. The Harshman constraint restricts the correlation matrix of the factor matrices $\boldsymbol{T}_k^{\mathrm{T}} \cdot \boldsymbol{T}_k$ (time signatures $\boldsymbol{T}$ of channel k) to be invariant over all channels.

Between a SNR of -10 dB and -5 dB more than 75 % of all spikes are successfully detected. In this range PARAFAC2 is not able to distinguish between the spikes. Since they have a high similarity caused by the noise. At this noise level the Harshman constraint is not fulfilled. Due to low differences in signatures between the channels.

PARAFAC2 detected and sorted the spikes of a multichannel MEA recording of self-spiking cells. One channel and its four nearest neighbors was selected to calculate the time and frequency signature. The different spike forms were exactly separated over all channels and a causality analysis by using template matching can be performed. Figure 7 shows the time frequency signature plot of five neighboring channels. Component 1 describes all spike with high frequency parts, component 2 describes spike with low frequency parts. In component 2 a moving of the signal is visible.

PARAFAC2 has only separated spikes which are varying in time and not in frequency over the channels.

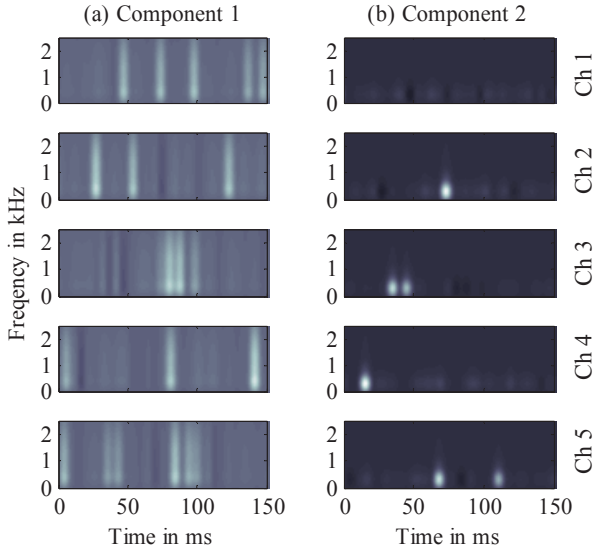

Figure 7. Spike sorting and detection of a real time series separated into two components. Component 1 (a) from channel 1 to 5 with high frequency spikes, Component 2 (b) from channel 1 to 5 with low frequency spikes.

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The project homepage can be found under: http://www.3dneuron.eu.

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