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Neuronal cell spike sorting using signal features extracted by PARAFAC*

T. Just, T. Kautz, M. Weis, A. Williamson, and P. Husar, *Senior Member IEEE*

***Abstract*—In this contribution we present first investigations for the signal processing on Micro Electrode Arrays (MEAs) used to observe the growth of biological neural networks. Neural cells produce ion currents, which can be measured extracellularly as differences in electric potentials. In order to measure these potentials (spikes), neuronal stem cells are cultivated on the surface of MEAs. These stem cells are allowed to build interconnections over a period of up to 30 days. If a cell or a group of cells produces currents spontaneously or evoked by a stimulus, a spike signal can be measured by the electrodes of the MEA. However, it remains difficult to identify which cells are signal sources and which cells are simply responding to a stimulus, with the additional complication of identifying the path of the signal itself. An initial solution to some of these difficulties is the use of spike sorting. In general, a spike sorting algorithm can assign spikes to different clusters, from which we can identify the different possible sources in the neural network. Subsequently, causality analysis (i.e. analysis of signal path) can be performed using the clusters. In this paper we present a novel and efficient method for separating neuronal spikes using individual waveform features. Thereby, we use the PARAFAC algorithm for the extraction of the features in order to exploit the multi-dimensional structure of the MEA data.**

I. Introduction

Neuronal cells are the basis for human brain function. These highly specialized cells and cell structures build connections between each other resulting in the formation of a neuronal network able to transmit 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 then forwarded to its axon and dendrites.

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

If a neuron is spiking randomly or induced by a stimulus, a current is evoked. By means of charge transfer a potential difference between intra- and extra-cellular spaces is generated, and this potential difference can be measured using the MEA. Essentially, spikes are measured at every electrode of the MEA. In order to analyze which neuronal cell at which electrode could be 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 want to compare two methods for calculating the signal features. With this features a spike sorting and clustering will be performed. The already published method is using Principal Component Analysis to calculate the features, which are used to sort all spikes [1]. The second method for extracting features is PARAFAC. The performance of both clustering methods is investigated in chapter III.

II. Methods

The basis for analyzing communication channels of neuronal networks is the allocation of detected spikes to the spiking neuron. Evoked by cells with different sizes and forms, different time series properties of the spikes are detectable. In order to achieve a unique assignment between the type of neuron and its corresponding spike waveform, it is important to identify specific relevant characteristics to discriminate between the spikes. These characteristics are described with the help of features, which then form a space in which the spikes can be clustered. Fig. 1 shows the block diagram of the necessary data analysis steps for the spike clustering. The input signal $x(t)$ represents simulated neuronal activity with known spike time and a pre-clustered type for every spike. A time-frequency decomposition is computed yielding multi-dimensional (time, frequency, and spike realization) output information for all extracted spikes. The Parallel Factor Decomposition (PARAFAC) determines the components which will be used for clustering as the last step. The result is an ensemble of clustered spikes.

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T. Just is with Ilmenau University of Technology, Institute of Biomedical Engineering and Informatics, Biosignal processing group, Ilmenau, POP 100565, 98684 Ilmenau, Germany (corresponding author, phone: +49-36377-692860; fax: +49-3677-691311; e-mail: thomas.just@tu-ilmenau.de).

T. Kautz[1], M. Weis[2] and P. Husar[3] are with Ilmenau University of Technology, Institute of Biomedical Engineering and Informatics, Biosignal processing group, Ilmenau, POP 100565, 98684 Ilmenau, Germany, [1]thomas.kautz@tu-ilmenau.de, [2]martin.weis@tu-ilmenau.de, [3]peter.husar@tu-ilmenau.de

A. Willamson is with Ilmenau University of Technology, Institut für Chemie und Biotechnik, Nano-biosystem Technology, adam.willamson@tu-ilmenau.de

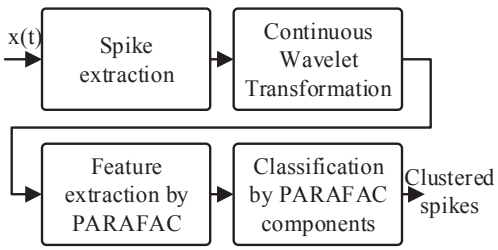

Figure 1: Block diagram of spike sorting using PARAFAC

A. Time frequency decomposition using Continuous Wavelet Transformation

The Parallel Factor Decomposition (PARAFAC) allows for the analysis of multi-dimensional data. Time domain and frequency domain information can be considered simultaneously. For the analysis of the non-stationary spike signals, the Continuous Wavelet Transformation (CWT) was applied to calculate the time-frequency domain. The CWT based on the Morlet Wavelet can be interpreted as a Short Time Fourier Transformation with a variable length of the analysis window [2]. The Wavelet coefficients C of a function $f(t)$ can be calculated using

$$C(f(t),\psi(t)s,\tau) = \int_{-\infty}^{\infty} f(t)\psi_{s,\tau}^{*}(t)dt \quad , \qquad (1)$$

where $\psi_{s,\tau}^{*}(t)$ is the wavelet function which is scaled by the factor s and shifted by the time lag τ. The scaling and shifting of the wavelet function is achieved by

$$\psi_{s,\tau}(t) = \frac{1}{\sqrt{s}}\psi\left(\frac{t-\tau}{s}\right), \quad s \in \mathbb{R} \neq 0, \tau \in \mathbb{R} \qquad (2)$$

where s and τ can be chosen freely in relation to the sampling rate. Fig. 2 shows an example of two different spikes types in time domain (Fig. 2a) and their corresponding time-frequency representations calculated by the CWT using the Morlet Wavelet (Fig. 2b). The resulting tensor has 3 dimensions corresponding to time, frequency, and realization.

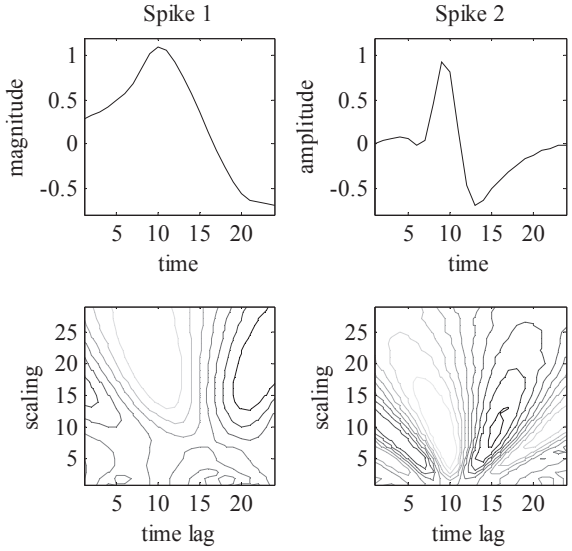

Figure 2: Example spike analysis: a) time series of two different spikes; b) CWT contour plot, Morlet-Wavelet

B. The 3-way Parallel Factor (PARAFAC) Decomposition

The PARAFAC decomposition, also known under the terms Canonical Polyiadic Decomposition or CANDECOMP, represents a multi-dimensional data analysis tool, which was developed by Harshman [3] as well as Carroll and Chang [4] in 1970. In the case of a three-dimensional data tensor $\boldsymbol{X}$ of size $\mathrm{I}_1 \times \mathrm{I}_2 \times \mathrm{I}_3$ the PARAFAC decomposition is represented by

$$\boldsymbol{X} = \sum_{\mathrm{r}=1}^{\mathrm{R}} \boldsymbol{Y}_{\mathrm{r}} = \sum_{\mathrm{r}=1}^{\mathrm{R}} \mathbf{a}_{\mathrm{r}} \circ \mathbf{b}_{\mathrm{r}} \circ \mathbf{c}_{\mathrm{r}} \quad , \qquad (3)$$

where the vectors $\mathbf{a}_{\mathrm{r}} \in \mathbb{R}^{\mathrm{I}_1}$, $\mathbf{b}_{\mathrm{r}} \in \mathbb{R}^{\mathrm{I}_2}$, and $\mathbf{c}_{\mathrm{r}} \in \mathbb{R}^{\mathrm{I}_3}$ are termed the 1-mode, 2-mode, and 3-mode loading vectors, respectively. The three-dimensional PARAFAC components $\boldsymbol{Y}_{\mathrm{r}} \in \mathbb{R}^{\mathrm{I}_1 \times \mathrm{I}_2 \times \mathrm{I}_3}$ are of tensor rank-one, i.e., they are given by the outer product of the three corresponding loading vectors $\mathbf{a}_{\mathrm{r}}$, $\mathbf{b}_{\mathrm{r}}$, and $\mathbf{c}_{\mathrm{r}}$. Furthermore, R represents the tensor rank of $\boldsymbol{X}$, which is the minimum number of PARAFAC components $\boldsymbol{Y}_{\mathrm{r}}$ such that equation (3) is fulfilled.

In contrast to matrix-based signal decomposition techniques, such as the Singular Value Decomposition (SVD) or Independent Component Analysis (ICA), the PARAFAC decomposition (3) is essentially unique under less restrictive conditions [5]. Thus, the PARAFAC model can be applied to multi-way data without imposing any artificial constraints as, e.g., orthogonality (as required by the SVD) or statistical independence (as required by the ICA). The superior uniqueness properties of the PARAFAC decomposition are also the main reason for its successful application as a Blind Source Separation (BSS) technique in the field of neuroscience [6]. However, over the last years PARAFAC has also been successfully applied in a variety of other fields involving multi-dimensional data, such as chemometrics, image processing, and data mining.

The computational methods for the identification of the PARAFAC model (3) can be divided into the class of iterative algorithms and the class of semi-algebraic algorithms. We use an iterative PARAFAC algorithm based on alternating least squares iterations including enhanced line search, as published within the n-way toolbox for MATALAB [7].

C. Hierarchical clustering

After using PARAFAC to extract the features that describe the spikes in a compact way, it is necessary to define quantitative limits in the feature space, which can be used to assign every single spike to clusters of similar spikes. Each of these clusters ideally represents only spikes generated by a single type of neuron. There are many possible methods for the automatic clustering of the data. Tests with simulated and measured spike data proved hierarchical clustering using Ward´s method [8] to be adequate for our application. In hierarchical clustering similar objects are successively joined to clusters starting from single elements in the data set. According to Ward's Method the distance measure d to express the similarity between two clusters r and s with centers $\overrightarrow{z_r}$ and $\overrightarrow{z_s}$, containing n_r and n_s elements, respectively, is defined as according to

$$d(r,s) = \frac{n_r \cdot n_s}{n_r + n_s} \cdot \|\overrightarrow{z_r} - \overrightarrow{z_s}\|_F \,. \quad (4)$$

Thereby, the cluster variances are minimized iteratively. For this clustering algorithm to yield expedient results, it is necessary to define the total number of clusters k beforehand. This can be achieved by determining cluster validity for different values of k and then choosing the best solution. To evaluate cluster validity we propose a combined measure based on Caliński-Harabasz [9] and Krzanowski-Lai [10] indices such that k is the minimum of the number of clusters found to be optimal according to each of the indices, thus avoiding over-segmentation of the data.

III. Results

According to [11], the transmembrane potentials of neuronal cells may be resolved into potential changes due to cell activity and resting potential. The latter may be classified into three different types. The pacemaker potential is the intrinsic activity of the cell. The second type is caused by the transducer potential across the membrane, which can be inhibitory or exhibitory. As a consequence of the transmembrane potential further response can be evoked. A nerve or action potential will be produced, which proceeds unattenuated along the fiber or axon. However, the gel or liquid in the intercellular space modifies the potentials, which is why more than three spike clusters can exist [11].

In this case it is necessary to find and to cluster all spikes from the measured signal. In addition the number of clusters should be determined by the algorithm. The algorithm separates the detected spikes into three clusters (Fig. 3). The percentage of correct cluster assignment is 99.2 %.

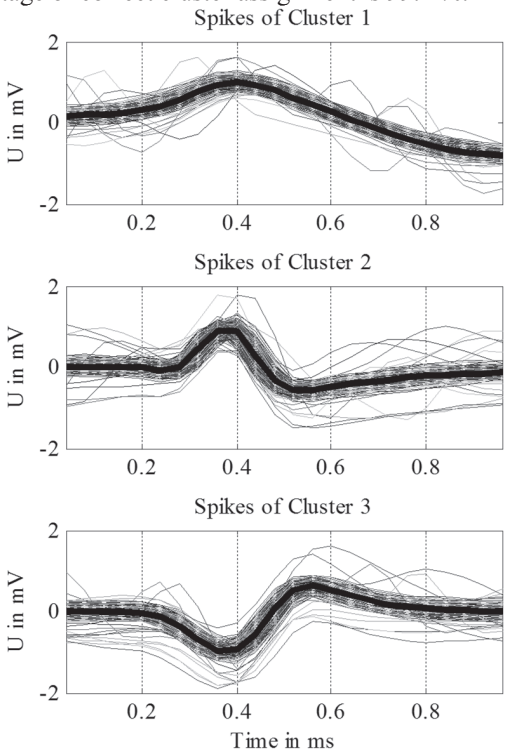

Figure 3: Generated clusters and all related spikes.

A. Standard deviation

With the standard deviation of the loading vectors, the compactness of the detected clusters can be measured. The number of components which had to be determined (Fig. 4) was defined before. The PCA components three to five show a high standard deviation compared to components one and two. In contrast to this, the standard deviation of PARAFAC is smaller than 0.4 in all components and significant smaller than the standard deviation of PCA. Therefore, the PARAFAC features lead to a more compact assignment of the different clusters than the PCA features. As a result, the clustering can be performed much more robust. So, the PARAFAC features are more compact than the PCA features and clustering can be performed much better.

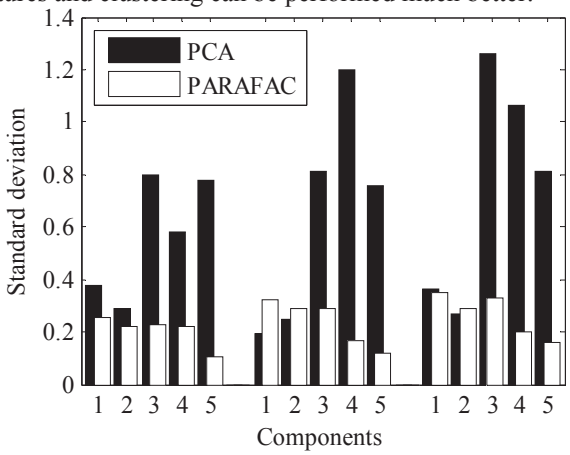

Figure 4: Standard deviation of the five components of cluster 1, 2 and 3.

B. Silhouette plot

The value of silhouette plot is a measure of how well the clustered component is similar to components in its own cluster. These values range between -1 and +1. If one spike is clustered correctly, a value between 0 and 1 is assigned. If it is possibly wrong clustered, the algorithm assigns a value between 0 and -1 [12]. A perfect clustering of all spikes produces a rectangular silhouette. Fig. 5a shows a good approximation of a rectangle. In contrast to this, Fig. 5b shows that a lot of points in the feature space generated by the PCA components show a longer distance to the cluster than the corresponding points based on the PARAFAC features.

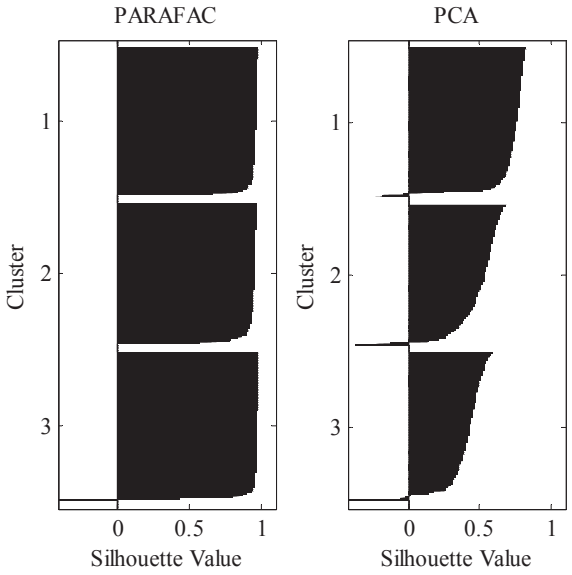

Figure 5: Silhouette plot of the similarity of one point to its cluster; left: clustered PARAFAC components of the three clusters; right: clustered PCA components of the three clusters.

IV. Conclusion

We calculated a time-frequency decomposition of all spikes and utilized the PARAFAC decomposition to determine the signal features. In a direct comparison with PCA based methods, the PARAFAC based method leads to a more compact representation of the different spike clusters in the feature space. Only a few components are on the decision limit of the cluster. This shows the good rectangular approximation in the silhouette plot and a small value of the standard deviation. Therefore, it is robust against disturbances and wrong assignments can be avoided. All spikes were clustered with a certainty of more than 99 %.

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

[1] University of Tampere

[2] Tampere University of Technology

[3] Biomeditech

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