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Analýza jednotkové neuronové aktivity v Parkinsonově chorobě

Analysis of single-neuron activity in Parkinson desease

Summary

This lecture focuses on analysis of single-neuron signals gathered during surgery of Parkinson disease patients using advanced statistical approaches. In the first part, we describe important pre-processing steps which must be performed for any consecutive analysis of single-neuron recordings: artifact segmentation and detection; and sorting of action potentials. We report that artifact detection algorithm based on statistical learning achieved performance of 90%. Regarding spike sorting, we perform comparative analysis of three available open-source methods concluding that waveclust approach is the most suitable for the task of spike classification. In the second part of the lecture, we talk about involvement of subthalamic region in emotional-behaviour processing. We conclude that subthalamic region participates in nonmotor circuits thus supporting complex role of subthalamic area in information processing in human cortex and basal ganglia. Our results contribute to better understanding of the affective complications seen in Parkinson patients treated with subthalamic stimulation.

Souhrn

V této přednášce se soustředíme na zpracování signálu jednotkové aktivity u pacientů trpící Parkinsonovou chorobou pomocí pokročilích statistických metod a metod digitalního zpracovaní signálu. V první části popíšeme dva základní kroky, které jsou nezbytné pro další analýzu signálu neuronové jednotkové aktivity: detekce artefaktů a klasifikace akčních potenciálů. Efektivita algoritmu pro detekci artefaktů dosáhla 90% s použitím rozhodovacích stromů. V případě akčních potenciálů byly porovnány tři dostupné algoritmy, z nichž algoritmus waveclust vykazuje nejlepší separační výsledky. V druhé části přednášky se zaměříme na non–motorické úlohy subthalamického jádra, zejména zpracování kognitivních funkcí jako jsou emoce. Ukážeme, že toto jádro ovlivňuje i emoční zpracování informace, což je jedním z prvních důkazů u člověka o non-motorické funkci subthalamického jádra a jeho afektivní úlohy při léčbě Parkinsonovy nemoci pomocí hloubkové mozkové stimulace.

Klíčová slova: neuron, artefakty, mikroelektrodový záznam, třídění akčních potenciálů, hloubková mozková stimulace, Parkinsonova porucha
Keywords: single neuron, artifacts, microelectrode recordings, spike sorting, deep brain stimulation, Parkinson's disease

Obsah

1 Introduction

One of the most used technique to explore the information coding representation in brain are extracellular recording of neurons in densely packed neural structure as hippocampus or basal ganglia. We propose the framework to better understand underlying principles of Deep Brain Stimulation (DBS) in Parkinson disease (PD) by analysing microelectrode recordings (MER) of single neurons.

About 6.3 million people worldwide suffer from a common neurodegenerative chronic disorder affecting mostly elderly people.

Parkinson disease is a motor system disorder, which is the result of the loss of dopamine-producing brain cells. The main symptoms are tremor (trembling of arms, hands, legs); bradykinesia (a movement slowness); rigidity (arm, leg stiffness) and postural instability. PD is accompanied by secondary symptoms as depression or another emotional changes, difficulty speaking, sleep problems, urinary problems, etc [Farris and Giroux, 2011].

The origin of symptoms is impaired function of the basal ganglia; an anatomical region at the base of the forebrain, responsible mainly for control of voluntary movements. The basal ganglia play an important role in other processes including control of eye movements, procedural learning and cognitive and emotional processes.

PD is currently not curable, but different approaches to medications schemes significantly improve patients' life quality. Just to mention the main medical treatment, levodopa combined with carbidopa is used due to the fact that levodopa is exploited by cells in brain to compensate low dopamine levels.

DBS is nowadays used in variety of neurological treatment programmes. It is a surgical procedure applied to treat the symptoms of Parkinson's disease, such as rigidity, bradykinesia and tremor. This treatment is currently only used for patients whose symptoms can no longer be sustained with medications [Abosch et al., 2013]. During DBS procedure, MER is used by surgeon as an additional tool to improve the accuracy of placement of the surgical probe.

We aim at understanding underlying principles of DBS mechanisms, mainly how affect non-motor functions of basal ganglia nucleus. This goal compromises the whole chain of single-unit neuron processing. In this lecture, we will point out the whole process of MER analysis: from segmentation and detection of artifacts, spike sorting of action potentials and assessing number of neurons, to identification of visual and emotion neurons, especially in STN region.

2 Preprocessing of single–neuron recordings

2.1 Artifacts detection

Artifacts' occurrence in a MER signal may have dramatic consequences on data quality of subsequent signal processing, such as spike detection and sorting. MER signals compromise a large amount of external noise, caused by numerous sources as patient speech or movement, power electricity inference or vibrations of the stereotactic frame - see Figure 1. These noise sources lead to corrupting subsequent data analysis [Stacey et al., 2013]. We proposed an model framework based on multiple time domain and spectral features to segment and detect artifacts. The models are based on decision trees, support-vector-machines and boosting techniques. The models were evaluated on a database consisting of patients data from four DBS centers. The classification results of artifacts detection reveals, that the best performing classifiers is bagging tool with 75 learners and the decision tree. The achieved classification accuracy was close to 90 % on the cross-validation set and achieved accuracy higher than 86 % [Bakstein et al., 2015]. En example of artifact detection can bee seen in Figure 2.

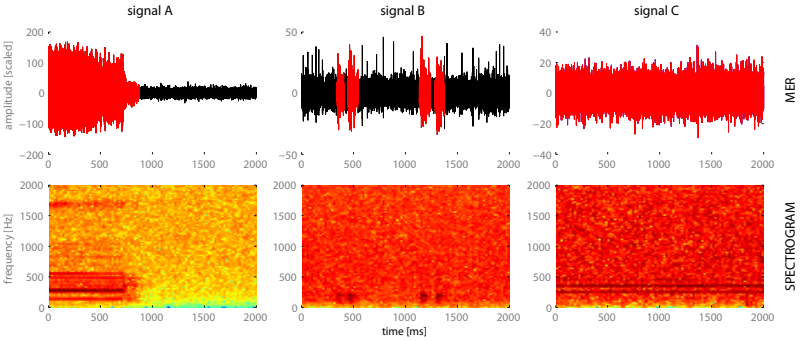


Figure 1: Two second samples of the most commonly inspected artifacts: raw MER signal with artifact regions in red (top row) and corresponding spectrogram (bottom row). Signal A) shows intermittent electromagnetic interference, signal B) mechanical artifact and signal C) uninterrupted electromagnetic interference at 235 and 350 Hz. [Bakstein, 2017]

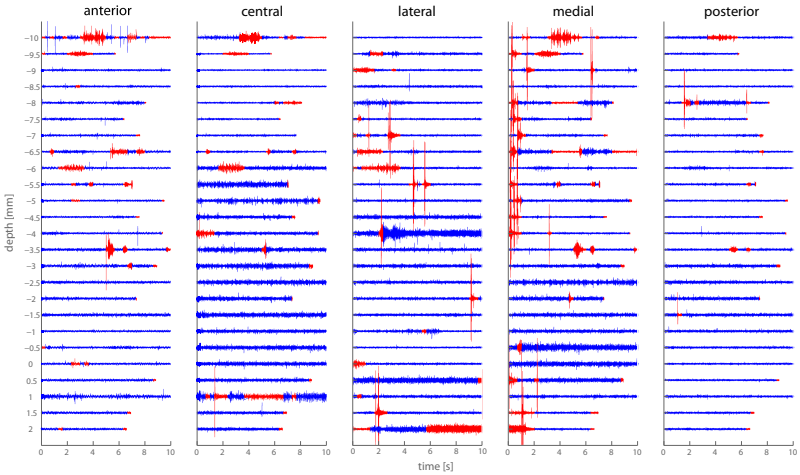


Figure 2: Example of artifact detection on MER recordings with five parallel electrode trajectories. [Bakstein, 2017]

2.2 Spike detection

One of the essential steps in the preprocessing chain of many cognitive studies in neurophysiology is a detection of action potentials. Accurate separation of the activity of single neurons can be cumbersome to achieve due to the large amount of the background noise and presence of several neurons superimposed in a single electrode. Thus, spike detection enables to separately measure the activity of the individual neurons.

The spike detection task can be described as a clustering problem due to a lower-dimensional representation of the spikes and neglecting the times at which the spikes occurred. Therefore, most of the known unsupervised learning approaches have been applied to spike detection: hierarchical [Fee et al., 1996], k-means [Sarna et al., 1988], super paramagnetic clustering [Quiroga et al., 2004], as well as mixtures of Gaussians and mixtures of t-distributions [Shoham et al., 2003]. An example of spike sorting is depicted in Figure 3.

We described a comparative analysis of the three most cited spike-sorting approaches with a publicly available source-code: WaveClus [Quiroga et al., 2004], OSort [Rutishauser et al., 2006] and KlustaKwik [Harris et al., 2000].

We evaluated the clustering algorithms using 112 artificial signals

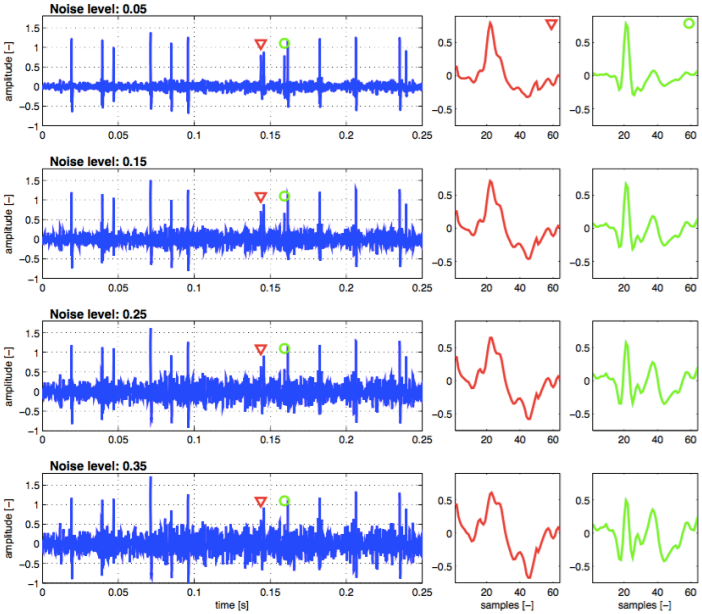
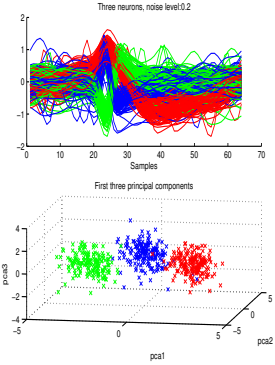


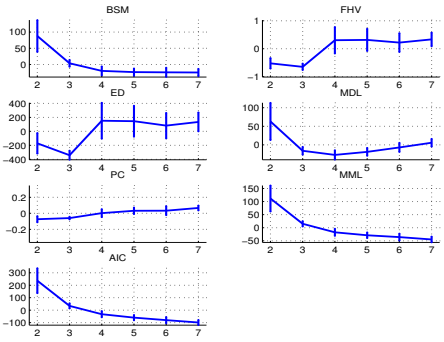
Figure 3: Example of spike detection with different noise levels ranging from 0.05 to 0.35. The spikes marked in the signal by a triangle and a circle each belonged to a different neuron and are shown in greater detail on the right side - in the case of a higher noise level at 0.25 and 0.35, a new noisy spike could be misleadingly detected. [Wild et al., 2012]

(publicly available online [1]) with 2–9 different neurons and varying noise levels between 0.00 and 0.60. We applied an optimisation tool based on adjusted mutual information to search for parameter settings for a given artificial signal and algorithm. The three clustering algorithms performed significantly better ($p < 0.01$) with optimised parameters than with the default ones. WaveClus was the most accurate spike detection algorithm, obtaining the best performance score in 60 % of all signals. From point of real-time detection, OSort worked at almost five times the speed of the other algorithms. In terms of accuracy, OSort performed significantly less well ($p < 0.01$) than WaveClus for signals with a larger noise level in the range $0.15 - 0.30$. Finally, the third clustering approach KlustaKwik performed similarly to WaveClus for

[1] http://neuro.felk.cvut.cz/supplementary/spikesorting-comparison/



(a) Spike Trains of three neurons



(b) Model selection criterion results

Figure 4: (a): Three neurons with noise level at 0.2. Outliers were introduced by superimposition at background noise, (b): In this example only FHV and ED measures support three-clusters underlying model. Note that the number of clusters is clearly seen in PCA projection on the three biggest principal components of FHV and ED measures. [Novak et al., 2009]

signals with low noise level 0.00–0.15 [Wild et al., 2012].

2.2.1 Identifying Number of Neurons

Several methods of automatically identifying and separating the neurons using unsupervised learning were described - see section 2.2. An important part of the sorting is determining the number of constituent clusters which best describe the data. A natural choice is to consider that each neuron represented by set of action potentials is generated by simple probability distribution and that the whole data set can be described as a weighted sum of these simpler distributions.

We assume that our data are generated by finite mixture models. Indeed in case, such as with stationary action potentionals and uncorrelated noise, the clusters will be nearly spherical in which the model can be very accurate. In less ideal situations, such as correlated noise or non-stationary spike shapes, the partition can be modelled by general Gaussian mixture models.

Several selection methods have been proposed to estimate the number of components of a mixture [McLachlan and Peel, 2005]. The fol-

lowing criteria based on theory of Occam's razor has been chosen in the comparative study: Bayesian selection method (BSM), Akaikes information criteria (AIC), minimum description length (MDL), minimum message length (MML), fuzzy hyper volume (FHV), evidence density (ED) and partition coefficient (PC). In order to validate the procedure, an experimental comparative study was carried out, comparing the proposed methodology with three spike sorting algorithms - see section 2.2. The proposed methodology has an advantage of setting the minimum number of parameters and is very robust to background noise. We conclude that only fuzzy hyper volume and evidence density criteria - see Figure 4 are able to identify the correct number of neurons across different noise levels [Novak et al., 2009].

3 Visual-emotional neurons

The subthalamic nucleus, which is one of the main targets for DBS, is considered an important centre of motor function [Okun, 2012]. However, the non-motor symptoms resulting in post-operative neuropsychiatric complications has recently attracted interested [Castrioto et al., 2014]. Furthermore, additional functional aspect of the STN in emotional and motivational mechanisms has been shown both in animal and human experiments [Serranova et al., 2013].

3.1 Visual neurons

The execution of STN in eye movements (EM) scanning is not clear yet although the involvement of both the basal ganglia and STN has already been reported [Fawcett et al., 2005]. We explored the role of single-neurons in subthalamic region in control and scanning of eye movements [Sieger et al., 2013].

Nineteen patients suffering from PD, which received treatment by implanting DBS electrodes, were involved in the experiment. EM were recorded using single channel electrooculography. Next, a patient observed a series of colored pictures selected from the International Affective Picture System. Spike detection was performed by the WaveClus clustering algorithm - see section 2.2. The interrelationship between eye movements and neuronal firing rate was analyzed by cross-correlation analysis - see Figure 5. In total, 183 neurons were identified and 130 were classified in the STN. Twenty percent of the neurons were linked to eye movement-related activity. It can be concluded that a large

number of single-neurons in basal ganglia were involved in control of eye movements.

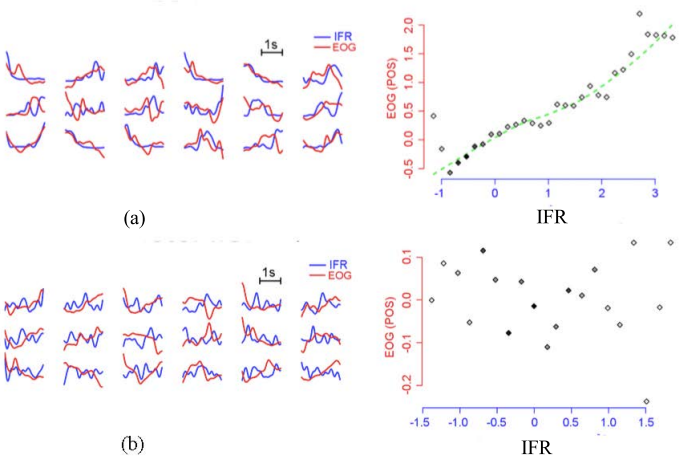


Figure 5: Neuronal activity during the scanning movement task. Example of neuron related (a) and unrelated (b) to eye movements based on correlation analysis of the instantaneous firing rate (IFR) and eye position derived from the electrooculography (EOG). [Sieger et al., 2013]

3.2 Emotional neurons

Involvement of the STN region at the single-neuron level during analysis of emotions has not been explored in human beings yet. However, single-neuron activity linked to pre-defined emotional groups (e.g., positive vs. negative) has been investigated in a few human brain anatomical structures, including the prefrontal and subcallosal cortex, amygdala and hippocampus [Wang et al., 2014].

According to [Russell, 2003], emotional state can be aligned to two psychophysiological descriptors: emotional valence (from unpleasant to pleasant) and arousal (from low to high).

We aimed to detect single-neuron firing pattern changes in the STN region in relation to emotional arousal and valence. The scoring of descriptors was performed individually based on emotionally charged and neutral pictures which were presented to PD patients during DBS surgery.

Since our main interest is focused on affective content of visual processing, the alpha oscillations (8–12 Hz) parameter was selected for further analysis due to previous experiments which used local field potential recordings [Brucke et al., 2007], [Kuhn et al., 2005]. Therefore, the power spectra bands were applied for analysis of the single-neuron signal during affective picture presentation [Huebl et al., 2011].

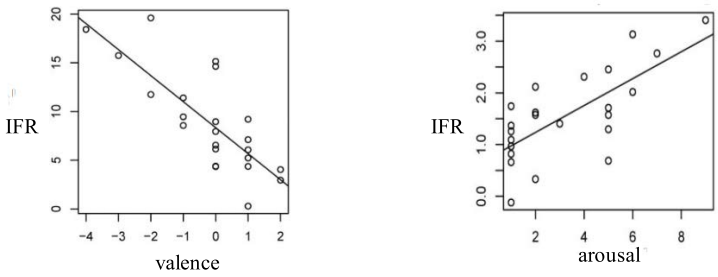


Figure 6: Relationship of the single-neuron instantaneous firing rate (IFR) alpha band activity during emotional picture presentation to individual valence and arousal ratings of the presented pictures in two neurons of the STN in patients with PD.[Jech et al., 2014]

Single-neuron activity was recorded in 13 PD patients.The patients were instructed to observe a presentation with pleasant, unpleasant, and neutral pictures displayed for 2,000 ms, preceded by a black screen with a white fixating cross presented for 3,500–5,500 ms. In total, 97 MER signals were registered in the STN area, in which of 125 neurons were detected. The activity of 35 neurons was related to eye movements, therefore these neurons were omitted from further analysis – see section 3.1. The remaining 90 neurons were analysed for tracks of perceptual and emotional behaviour.

Actions potentials were detected by WaveClus method - see section 2.2.1. Next, the individual alpha firing activity using instantaneous firing rate (IFR) from single neurons was calculated and was correlated to subjective ratings of the emotional valence and arousal of each presented picture. Finally, those neurons were mapped into the STN anatomical model [Morel, 2007] - see Figure 7. A neuron was classified as affective if the correlation between activity in the alpa band was significantly with these ratings.

As a results, the alpha band activity of 15 of 90 neurons (17%) was related to the emotional content of the presented pictures expressed in

individual valence or arousal ratings ($P < 0.05$) [Sieger et al., 2015]. However, the correlation was only significant for the late period of picture presentation epochs (500–2,000 ms after stimulus onset). The activity of other nine neurons (10%) correlated with the arousal ratings (seven neurons positively, two neurons negatively) - see Figure 6.

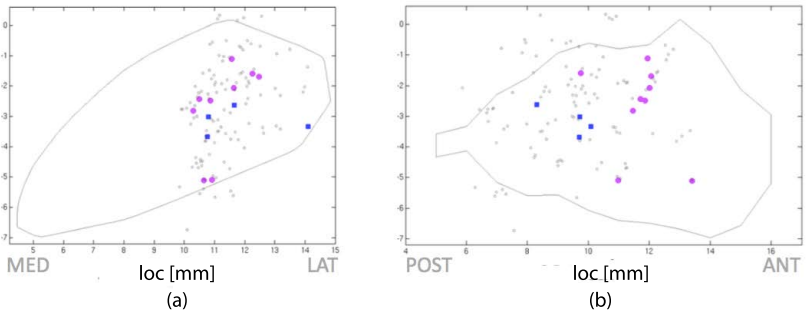


Figure 7: Locations of STN neurons related to emotional content of the presented pictures in (a) coronal and (b) sagittal views of the STN model. Valence-related neurons are depicted as blue rectangles, arousal-related neurons as cyan circles. [Jech et al., 2014]

Once, commonly accepted consensus stated that the STN area is divided into three functional zones: limbic, associative, and sensorimotor regions, residing in the anteromedial, middle, and dorsolateral portions, respectively, of the STN [Parent and Hazrati, 1995]. This statement has been challenged by several recent electrophysiologic, neuroanatomic, and neuroimaging experiments concluding incomplete separation of the subthalamic territories [Haynes and Haber, 2013]. Therefore, it is not surprising that we found the affective neurons in the sensorimotor regions, suggesting that motor and nonmotor regions overlap in the STN region - see Figure 7.

4 Conclusion

This lecture focused on analyses of single-neuron signals gathered during treatment of Parkinson disease patients using advanced statistical approaches and new methods of exploration, mainly in basal-ganglia area. In the first part of the talk, we described important pre-processing steps which must be performed for any consecutive analysis of brain

recordings: artifact segmentation and detection and action potentials detection and sorting. We reported that artifact detection algorithm based on statistical learning achieved performance of 90%. Regarding spike sorting, we performed comparative analysis of three available open-source methods concluding that waveclust approach is the most suitable for the task of spike sorting. In the second part of the lecture, we talked about involvement of subthalamic region in emotional - behaviour processing. We concluded that subthalamic region participates in non-motor circuits thus supporting complex role of subthalamic area in information processing in human basal ganglia and cortex. Our results contribute to better understanding of the affective complications seen in Parkinson patients treated with deep brain stimulation technique.

Acknowledgment

I would like to thank professors Olga Stepankova and Robert Jech, for giving me opportunity to this highly interesting research topic. I would like also to thank my research colleagues and co-authors of research journals and conference contributions Tomas Sieger, Eduard Bakstein, Jiri Wild, Pavel Vostatek and Jakub Schneider for enabling me to reach interesting outcomes from neuroscience field.

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Citations and Impact

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Research Activities

- *Journal reviews:* IEEE Tr. on Biomedical Engineering, IEEE Tr. Systems, Man and Cybernetics, Computer Methods and Programs in Biomedicine and Medical Engineering & Physics, IGI Global books.
- *Project reviews:* EU FP7, Horizont 2020 reviewer, Dutch Diabetes Research Foundation and Czech Technological Agency.

Selected Journal Publications

1. P. Kavalkova, M. Mraz, P. Trachta, J. Klouckova, A. Cinkajzlova, Z. Lacinova, D. Haluzikova,M. Benes, Z. Vlasakova, V. Burda, D. Novak, T. Petr, L. Vitek, T. Pelikanova and M. Haluzik, Endocrine effects of duodenal-jejunal exclusion in obese patients with type 2 diabetes mellitus, Journal of Endocrinology, 231(1), p.11-22, 2016

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