Method for Feature Extraction from Electrophysiological Recordings of Epileptic Activity

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Abstract—Electrical activity of neuronal cells is thought to support brain function, being modified in disease compared to health conditions. The tools for analyzing such data are diverse and need to be tuned for each particular application. We propose a wide and diverse perspective characterization of induced epileptic activity in zebrafish field recordings. We have found that features regarding amplitude, width, inter-event-intervals and autocorrelation profiles can be automatically extracted and used as markers to differentiate between different genetic or pharmacologic conditions. The present study aims at developing a toolbox that aids the understanding of the underlying mechanisms of epileptiform discharges.

Keywords— electrophysiology, epilepsy, signal processing, ictal, neural;

1. INTRODUCTION

The human body still hides a great amount of unanswered questions. Technology attacks these questions by developing tools that can extract information, process, analyze it and pour it into the shape that the human expert can interpret.

Biologic electrical activity has been harvested as a source of information about the processes involved within the organism [4]. More specifically, brain electrical activity has been highly informative about mechanisms of cognition, attention, memory, as well as neurological disease mechanisms like Epilepsy or Parkinson's disease. There are many tools and protocols for the acquisition of electrical signals in the brain [12], but the processing and analysis of this data is highly tuned to the purpose of study and to the need of the researcher.

In our study, we have developed a software processing and analysis unit for brain electrical activity during epileptic activity. The purpose of the unit is to describe the recorded signal from diverse perspective and in a relevant manner, so as to give the researcher all the qualitative and quantitative information needed for epileptic activity characterization.

2. BACKGROUND

2.1. Electrophysiologic signals in the brain

Neural electrical signals are caused by charged ion flux through channels in a semipermeable membrane, as defined by the Goldman equation:

$$V = 58 \cdot 10^{-3} log \frac{P_K [K]_{out} + P_{Na} [Na]_{out} + P_{Cl} [Cl]_{in}}{P_K [K]_{in} + P_{Na} [Na]_{in} + P_{Cl} [Cl]_{out}}$$

Where V is the resting potential across cell membrane, P_K is the permeability of potassium ions through the cellular membrane, $[K]_{out}$ is the potassium concentration outside the cell, $[K]_{in}$ is the potassium concentration inside the cell, and so on for Sodium (Na) and chlorine (Cl) ions. These channels are gated by various factors: voltage, neurotransmitters or pharmaceutics. Therefore, biological activity of a neuron or a group of neurons can be described via its resulting electrical activity.

Field potentials are recorded from the extracellular medium of the brain and are believed to contain a combination of electric signals originating in surrounding cells in a small volume of nervous tissue [6]. The voltages measured from the extracellular media are in the range of tens or millivolts, and have a bandwidth of a few hundreds of hertz [2].

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Several concepts are particular to electrophysiological field potentials:

Baseline activity is defined as the activity occurring without any stimulus being applied, to which the analysis is referenced to.

Events are snippets of the signal in which the baseline is disrupted. The definition of an event is customized to mechanism of interest.

Refractoriness is the decrease in event occurrence probability following another event. This is due to the biological nature of the signal, having a finite amount of resources to elicit an event [10].

Oscillations are rhythmic, repetitive activities, either in the form of continuous signal or discreet periodic event occurrences [3]. Several oscillatory frequencies are visible in neural field potentials, ranging from delta (1.5 - 4 Hz) up to gamma (30 - 80 Hz) [8].

Bursts are activity patterns defined by rapid successions of events followed by quiescent periods [5].

2.2. Epileptic activity

Epilepsy is a disorder of brain function characterized by abnormal electrical activity in the brain: synchronous, excessive discharge in large groups of neurons [9]. It is estimated that about 65 million people worldwide suffer from epilepsy [13], and about 10% of them do not respond to pharmacologic or surgical treatments [11]. Understanding and characterizing neural electrical activity in conditions of epilepsy is an important step for the development of novel treatment or management strategies.

Epileptic activity in field recordings appears as a series of discharges, called ictal and inter-ictal events, with amplitude and frequency varying with seizure stage [9]. Ictal events are large amplitude (> 4 mV) prolonged (>3s) negative deflections and are accompanied by a period of post-ictal depression, when electrical activity is temporarily suppressed. Inter-ictal events are faster (< 3s) and smaller in amplitude [1].

3. DATA ACQUISITION

The electrophysiological data used in this study was acquired from the zebrafish brain, a well-known animal model of epilepsy [1].

3.1. Experimental design

Each dataset consists of one continuous recording, starting with a baseline duration of 55 minutes. Then, an epileptogenic drug was applied (PTZ). The stimulus response was recorded for 110 minutes, and was divided into two sections of 55 minutes (resp1 and resp2), due to variability in the characteristics of the activity (See Fig. 1).

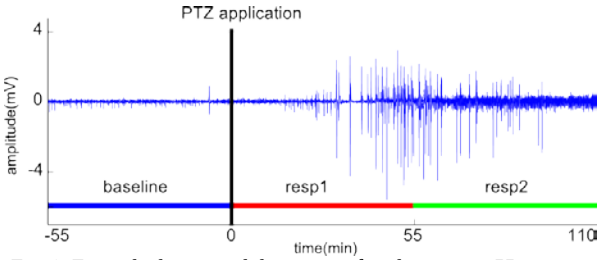


Fig. 1. Example dataset and ilustration of trial structure: 55 minutes baseline recording (blue bar) folowed by PTZ application (black marker). The response to stimulus is divided into two segments of 55 minutes each: resp1 and resp.

3.2. Equipment and method

Data used in this study was acquired via a sharp glass electrode of 2 μm diameter placed in the brain of 5-6 days old zebrafish. The signal was preamplified (CV 2003BU, Mollecular Devices) and was sent to a high precision amplifier (Axopatch 700B, Mollecular Devices) and converted to digital data via an AD converter (Digidata 1550, Mollecular Devices) and sent to a software computer interface (pClamp 10, Mollecular Devices).

3.3. Output signal parameters

The output data was sampled at 10 kHz with a 16 bit resolution and was exported into MATLAB (Mathworks) for data processing and analysis.

4. SIGNAL PROCESSING

As mentioned before, useful electrophysiological data lays within a 500 Hz bandwidth. The ictal and interictal events in field recordings are in the range of 0.005 to 0.2 Hz. Therefore, a subsampling and filtering stage was applied in order to remove high frequency noise and to reduce processing time.

4.1. Subsampling

Antialiasing filter: 125 Hz Butterworth, 5^{th} order
Subsampling: 250 Hz

4.2. Filtering

DC subtraction: Averaging filter
Low pass filter: 0.5 Hz Butterworth, 5^{th} order
High pass filter: 0.05 Hz Butterworth, 1^{st} order (High pass subtraction)

5. FEATURE EXTRACTION

In order to characterize epileptic activity, we have chosen to look both at the discrete event timing (histograms, amplitude and inter-event interval statistics) and at the continuous signal characteristics (scaled and continuous signal autocorrelations). Therefore, peaks representing ictal and inter-ictal events were extracted and a series of features were analyzed, both on all events and on different the different defined conditions.

5.1. Event extraction

Event extraction was done via local minima detection. No maxima was considered as a peak as negative peaks were of interest. The local minima that were within 15 s of the trigger were considered artifacts from drug delivery and were discarded from further analysis. The origin of each peak was computed as the maximum of a window of variable length before the peak. The length of the window depended on the absolute value of the signal at the peak time stamp:

$$L_{window} = round\left(abs\left(V_{peak}\right)\right) \cdot scale$$

Where L_{window} = window length, V_{peak} = peak value and $scale$ = 50 (determined empirically).

The amplitude of the peaks was computed as the difference between the origin value and the value of the signal at the peak timestamp. Peaks that had a negative amplitude (the detected origin was higher in amplitude then their peak) were discarded. An amplitude constrain was applied in order to eliminate noise and therefore select only valid events. For this, the amplitude distributions for the baseline period were plotted and the peaks that were located above the 0.95 quantile were selected as valid events. The determination of the value of the quantile was done empirically.

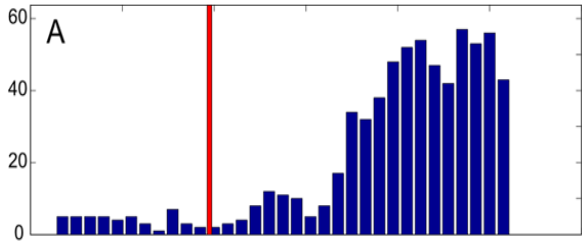
By visual inspection, several distinct types of events are identified. In order to separate them programmatically, an amplitude threshold was applied. separating events into high and low amplitude events. The threshold of this separation was dependent on the maximum amplitude in the dataset:

$$Th_{value} = max\left(amplitude\left(All_{peaks}\right)\right) \cdot Th_{scale}$$

Where Th_{value} = amplitude threshold value, $Th_{scale} = 0.2$ (determined empirically).

5.2. Peristimulus time histogram

The peristimulus time histogram (PSTH) was computed by counting the events that occur in a particular time bin. The PSTH was computed taking into consideration all the events (Fig. 2 A), but also on each of the two event subsets: low amplitude (Fig. 2. B) and high amplitude (Fig. 2 C).The time bin size for this analysis is 300s.



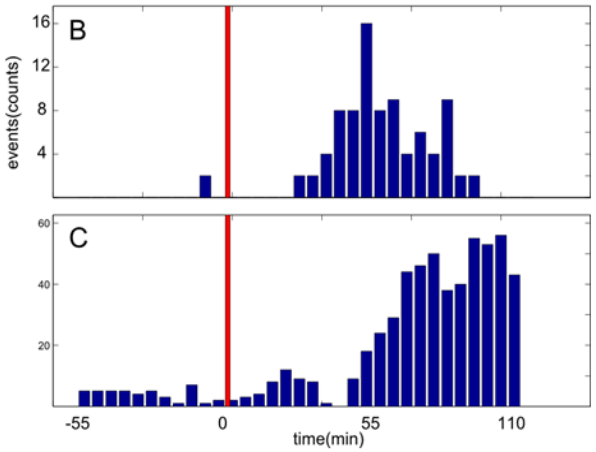


Fig. 2. Peristimulus time histogram of epileptic event. Red bar represents PTZ application. A – all events; B – high amplitude events; C – low amplitude events.

5.3. Amplitude Distributions

The amplitude distribution of the detected events was computed (see Fig. 3. A): the number of events that fall into a given amplitude range (amplitude bin). The size of the amplitude bin is 50 µV.

In order to see the amplitude variation in time, the average amplitude within each time bin was computed (see Fig. 3. B). The time bin size for this analysis is 300s.

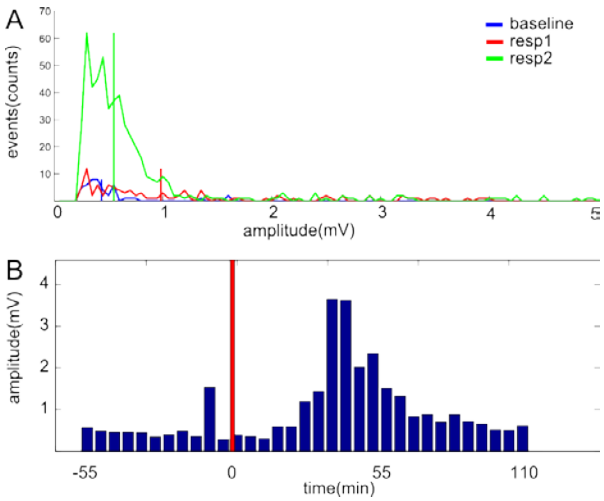
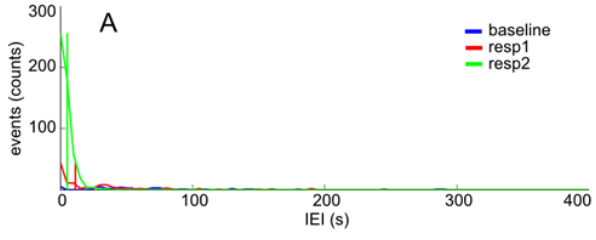


Figure 3. Amplitude analysis: A - Amplitude distribution during the three trial segments: baseline (green), resp1 (red) and resp2 (blue); vertical bars represent the median of each condition. B – Average amplitude versus time;

5.4. Event Width Distributions



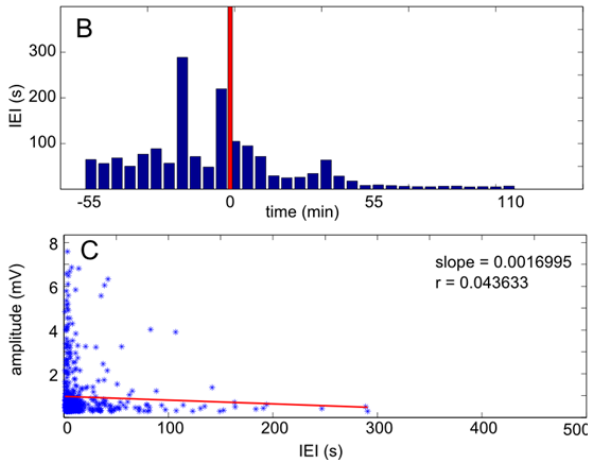


Fig. 4. Event width analysis: A – Event width distribution during the three trial segments: baseline (green), resp1 (red) and resp2 (blue); vertical bars represent the median of each condition. B – Average width versus time; C – event amplitude versus respective width. A linear fit (red line) has been applied and the slope and residual norm was computed.

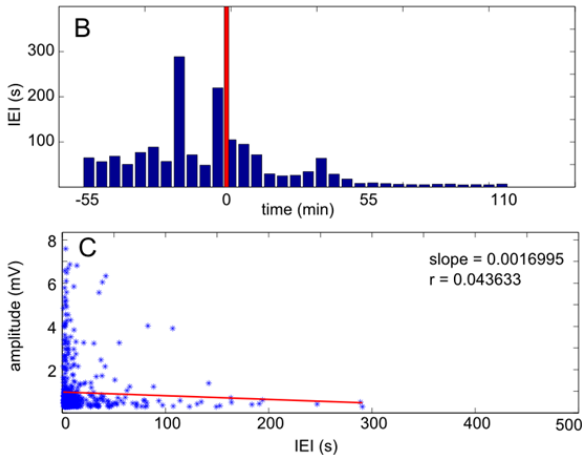


Figure 5. Inter-Event-Interval (IEI) analysis: A – IEI distribution during the three trial segments: baseline (blue), resp1 (red) and resp2 (green); vertical bars represent the median of each condition. B – Average IEI versus time; C – event amplitude versus respective IEI. A linear fit (red line) has been applied and the slope and residual norm was computed.

The width of each event was computed. Due to the asymmetry of the spike, the full width half maximum of each event was not a relevant measure. The full width 3/4 maximum was computed instead.

The width distribution of the detected events was computed: the number of events that fall into a given event width range (see Fig. 4. A). The size of the width bin is 0.15 s.

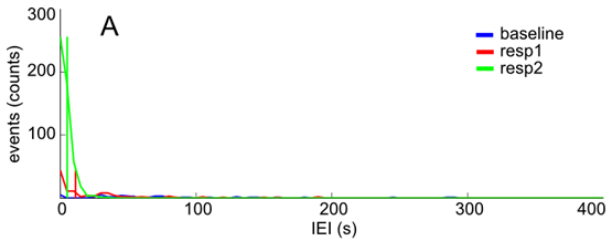
The average event width within each time bin was computed (see Fig. 4. B). The time bin size for this analysis is 300s.

For each event, amplitude was plotted against its width. A linear fit was computed for each dataset (see Fig. 4. C). The slope and the normalized residual norm was computed: the lower the r value, the better the fit.

$$r = \frac{norm\,(residuals\,)}{Nr_{events}}$$

5.5. Inter Event Interval Distributions

The inter-event-interval is defined as the time between two consecutive events. When taken as an average, it gives measure of event rate within the respective time bin. When taken as an individual characteristic of each event, it gives a measure of refractoriness that the event induces in the behavior of the network.



The inter-event-interval distribution of was computed: the number of events that fall into a given inter-event-interval range (IEI bin – see Fig. 5. A). The corresponding IEI for each event was computed as the period of time from the respective event to the following one. The size of the IEI bin is 5 s. The average IEI within each time bin was computed see (Fig. 5 B). The time bin size for this analysis is 300s.

For each event, its amplitude was plotted against its respective IEI Fig. 5. C). This analysis should reveal whether IEI and amplitude for a given event are correlated.

5.6. Autocorrelations

Autocorrelation analysis provides insight into temporal and spectral properties of the signal.

-Scaled Autocorrelations

-The continuous signal for each condition in the baseline and response period (resp1 and resp2) was subsampled according to the parameters below. The autocorrelation was computed, using the scaled correlation method [7] in order to visualize particular timescale features, eliminating lower frequency behavior (see Figure 6 A).

-Autocorrelation window = 10 s

-Scale segment = 1 s

-Sub sampling frequency = 10 Hz

The length of the scale segment is chosen based on the frequencies of interest. For example, a scale segment of 1 s allows the identification of the 2.5 s period events (0.4 Hz).

-Autocorrelation Histograms

The timestamps of events extracted previously were used as binary events. The resolution of the timestamps was decreased so as to achieve data subsampling.

Classical binary autocorrelations were computed with the following parameters (see Figure 6 B):

-Autocorrelation window = 10 s

-Sub sampling frequency = 10 Hz

-Scaled Autocorrelation Histograms

Scaling the autocorrelation histogram has the same effect as in the scaled autocorrelation described above: it allows analysis on particular frequency scales, removing the lower frequency, higher power fluctuations which would mask fast, low power features (see Fig. 4. C).

-Autocorrelation window = 50 s

-Scale segment = 10 s

-Sub sampling frequency = 1.5 Hz

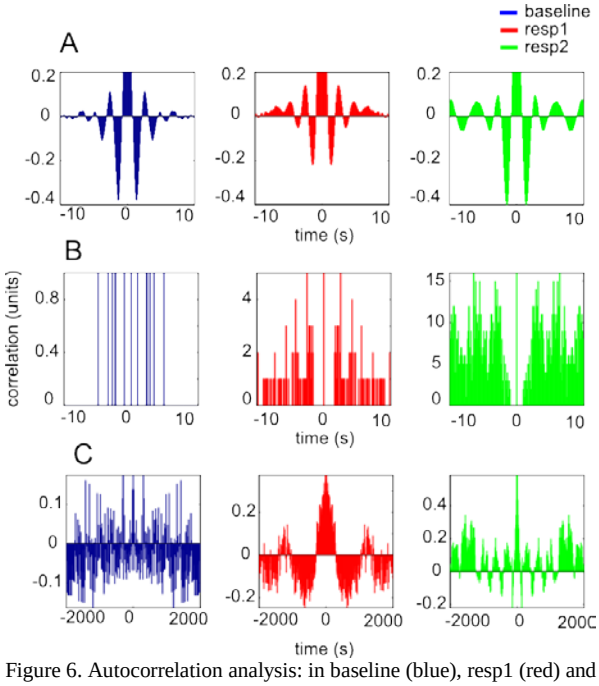


Figure 6. Autocorrelation analysis: in baseline (blue), resp1 (red) and resp2 (green); A – Scaled autocorrelation (scale segment = 1 s) on field signal; B – Autocorrelation histograms on event timestamps; C – Scaled autocorrelation histograms (scale segment = 10 s) on event timestamps;

6. DISCUSSION

The analyses presented reveals features in the epileptic activity of field recordings in the zebrafish brain: Peristimulus time histogram (Fig. 2) shows a steep increase in event count after PTZ application. In the first response period (resp1), high amplitude events are more numerous, but in the last response period, high amplitude events disappear and small amplitude ones dominate. Therefore, there is a peak in epileptic activity, around minute 45, after which the network is saturated or exhausted and cannot sustain high amplitude events.

The same effect is seen in the average amplitude plot in Figure 3: around minute 30-40, there is a peak in mean amplitude, representing the domination of high amplitude events throughout that period.

When looking at the width of the events, it also increases in the response periods with respect to baseline. A weak positive correlation between amplitude and event width is visible (Fig. 4 C).

Regarding inter-event-intervals, the correlation with amplitude is much smaller, but the effect of PTZ on the average IEI is obvious: epileptic activity is associated with smaller IEI, which decreases constantly throughout the response periods.

Correlation analysis revealed qualitative information about the effect of PTZ on field recordings: The scaled autocorrelation (scale segment of 1s) on the field signal exhibited oscillatory components around 0.4 Hz in all conditions. Frequency and continuity varied throughout baseline and response periods: A strong refractory peak (first negative alternation) in baseline and resp2 periods, and short duration oscillatory activity in baseline and resp1. In resp2 however, we see a slight decrease in frequency and a more durable oscillatory behavior. Autocorrelation histograms computed on the extracted events evidenced a wide refractory period (~ 2 s), followed by a secondary peak and an oscillatory modulation (~ 3 s). Scaled autocorrelation histograms (scale segment of 1000s) show strong changes in autocorrelation profile from one period to the other: In the baseline, there is no noticeable oscillatory behavior. Resp1 period shows an oscillatory modulation (1000 s). However, resp2 period exhibits a slow bursting oscillation (~3 cycles, 130 s) followed by a baseline, indicating PTZ has an effect on oscillatory activity during epileptic activity.

7. CONCLUSION

The performed analyses aim at characterizing epileptic activity from a wide perspective. The processing steps have been optimized so as to reveal a multitude of features present in the acquired signal. Ultimately, the processing unit can be used to discern between different activity types: belonging to different genetic conditions or susceptibilities to epileptic discharges, as well as response to pharmacologic factors. Having a method for quantitatively and qualitatively describing epileptic activity aids to the understanding of the underlying mechanisms of epileptiform discharges and leads to a higher chance in finding more potent drugs to alleviate symptoms.

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REFERENCES

1. Tatiana Afrikanova, Ann-Sophie K Serruys, Olivia EM Buenafe, Ralph Clinckers, Ilse Smolders, Peter AM de Witte, Alexander D Crawford, and Camila V Esguerra. Validation of the zebrafish pentylenetetrazol seizure model: locomotor versus electrographic responses to antiepileptic drugs. *PloS one*, 8(1):e54166, 2013.

2. Claude Bédard, Helmut Kröger, and Alain Destexhe. Modeling extracellular field potentials and the frequency-filtering properties of extracellular space. *Biophysical journal*, 86(3):1829–1842, 2004.
3. Gyorgy Buzsaki. *Rhythms of the Brain*. Oxford University Press, 2006.
4. Brian Francis Hoffman and Paul Frederic Cranefield. *Electrophysiology of the Heart*. McGraw-Hill, Blakiston Division, 1960.
5. Eugene M Izhikevich. Neural excitability, spiking and bursting. *International Journal of Bifurcation and Chaos*, 10(06):1171–1266, 2000.
6. Alan D Legatt, Joseph Arezzo, and Herbert G Vaughan. Averaged multiple unit activity as an estimate of phasic changes in local neuronal activity: effects of volume-conducted potentials. *Journal of neuroscience methods*, 2(2):203–217, 1980.
7. Danko Nikolic, Raul C Muresan, Weijia Feng, and Wolf Singer. Scaled correlation analysis: a better way to compute a cross-correlogram. *European Journal of Neuroscience*, 35(5):742–762, 2012.
8. Markku Penttonen and György Buzsáki. Natural logarithmic relationship between brain oscillators. *Thalamus & Related Systems*, 2(02):145–152, 2003.
9. David A Prince. Neurophysiology of epilepsy. *Annual review of neuroscience*, 1(1):395–415, 1978.
10. Dale Purves, GJ Augustine, D Fitzpatrick, WC Hall, AS LaMantia, JO McNamara, and LE White. Neuroscience. *De Boeck, Sinauer, Sunderland, Mass*, 2008.
11. Pantaleo Romanelli, Pasquale Striano, Manlio Barbarisi, Giangennaro Coppola, and David J Anschel. Non-resective surgery and radiosurgery for treatment of drug-resistant epilepsy. *Epilepsy research*, 99(3):193–201, 2012.
12. Massimo Scanziani and Michael Häusser. Electrophysiology in the age of light. *Nature*, 461(7266):930–939, 2009.
13. David J Thurman, Ettore Beghi, Charles E Begley, Anne T Berg, Jeffrey R Buchhalter, Ding Ding, Dale C Hesdorffer, W Allen Hauser, Lewis Kazis, Rosemarie Kobau, et al. Standards for epidemiologic studies and surveillance of epilepsy. *Epilepsia*, 52(s7):2–26, 2011.

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