LONG-TERM ANALYSIS AND DESCRIPTION OF INTERICTAL EPILEPTIFORM ACTIVITY IN INTRACRANIAL EEG RECORDINGS

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Abstract: Part of the presurgical evaluation for performing epilepsy surgery, is the invasive electroencephalogram (EEG) monitoring, which is defined as the long-term recording of the electrical brain activity using intracranial electrodes. Typically, only the ictal episodes in the intracranial recordings are used for analysis, although the interictal episodes might also contain relevant and useful information. In this paper we present a method that can be useful to analyze and summarize long-term intracranial recordings. The method consists of four steps: (i) removal of evoked potential stimulation artefacts; (ii) detection of phenomena that deviate from the background EEG activity, which we assume to have a Gaussian distribution; (iii) clustering and modeling of the detected waveforms using Ward's hierarchical clustering algorithm and a Gaussian mixture model; (iv) visualization of the results. To evaluate the performance and usefulness of the method, we compared the number of detections of the method per 5 min. with the number of epileptiform discharges labeled by an expert per 5 min. Using the method, we could reproduce the general trend of the interictal spiking as it was observed by the expert (correlation coefficient of 0.96).

Introduction

Epilepsy is a neurological disorder characterized by abnormal electrical discharges in the brain. The clinical manifestation of epilepsy is the epileptic seizure. In most cases, the seizures can be controlled by anti epileptic drugs. However, for some patients with partial epilepsy, one has to resort to surgery in order to make the patient seizure free. These patients are submitted for a presurgical evaluation in order to identify the onset zone of the seizures (i.e., the epileptogenic zone). Part of this presurgical evaluation is the invasive EEG (electroencephalogram) monitoring, which is defined as the long-term recording (during several days or weeks) of the electrical brain activity using intracranial or depth electrodes [1].

Typically, only the ictal episodes in the intracranial EEG recordings are used for analysis, because one is primarily interested in the onset zone of the seizure, although the interictal episodes might also contain relevant and useful information. For instance, during the interictal episodes, epileptiform discharges can be observed, but the exact relationship between the occurrence of these discharges and the occurrence of the seizures is still unknown. However, a visual analysis of the whole EEG recording is too tedious and time consuming, so the need for an automatic analysis algorithm is evident.

In the past, much research has already been devoted to the detection of epileptiform activity, mostly in scalp EEG recordings. These detection methods usually rely on the description of some spike-like waveform [2], and require the setting of a number of threshold values. However, given that no real consensus exists on the definition of the epileptiform activity in intracranial EEG recordings, and the fact that the choice of the threshold values is rather arbitrary and subjective, these methods are not readily applicable to long-term intracranial EEG recordings. Other methods aim at understanding the relation between different electrode sites and search for activation patterns [3], rather than search for trends in the interictal epileptiform activity over time.

In this paper we present a method that can be useful to analyze and summarize long-term intracranial EEG recordings. Possibly the method might be used to reveal some trend(s) in the interictal epileptiform activity over time and answer some medical questions regarding the relationship between ictal and interictal activity.

Materials

For the development and a first evaluation of the method, we used one long-term intracranial EEG recording of one patient with refractory epilepsy. This recording was part of a study in which a protocol was designed, based on the analysis of intracranial evoked potentials (EP), to perform long-term monitoring of neuronal excitability in the human hippocampus [4].

The EEG was recorded during two weeks, using four standard depth electrodes (placed in the left and right hippocampus and amygdala) which each contained four electrode contact points. The EEG was recorded with a sampling frequency of 200 Hz, and 0.1-30 Hz band-pass filtered.

The aforementioned study also assessed the short- and long-term variation in hippocampal excitability and its relation to interictal and ictal events. To that end, the EEG recording was analyzed by an expert who visually labeled, for 15 hours of the recording, the interictal epileptiform activity. This labeling was used to evaluate the performance of the proposed method.

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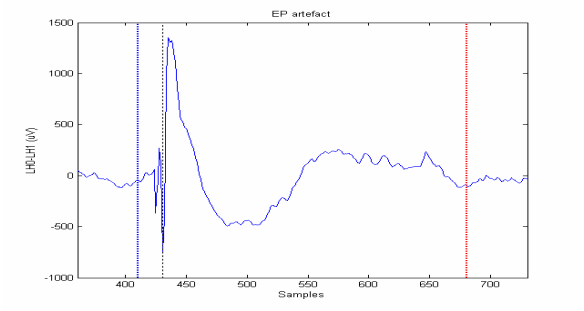

Figure 1: An example of one EP stimulation artefact. The position of the artefact is marked with a black line (at sample 431). The beginning and ending of the artefact (100 ms before and 1250 after the artefact position) are marked with, respectively, a blue and red line.

Method

The method performs the analysis on one channel of the intracranial EEG recording (LH0-LH1, LH = left hippocampus), which we denote by $x[n]$. The method consists of four steps.

I. Removal of EP stimulation artefacts Because of the evoked potential stimulation, every (approximately) 10 sec. (2000 samples) the intracranial EEG recording is disturbed by an electrical stimulation artefact. Since the presence of these artefacts severely hampers the detection of the epileptiform discharges, in the first step of the method this artefact is removed. To make this step fully automatic, we first search for the starting point of the first EP artefact by looking at the maximum of the following cost function, which aligns a comb function (with three combs) with the positions of the first three EP artefacts:

$$\tau = \arg\max_{\tau} \sum_{n=1}^{3T} x[n] f_c[n-\tau], \quad \tau = 1 \ldots T \qquad (1)$$

$$f_c^1[n] = \begin{cases} -1 & 1 \le n \le D/4 \\ 1 & D/4+1 \le n \le D \\ 0 & D+1 \le n \le T \end{cases} \qquad (2)$$

with $D = 40$ samples, $T = 2000$ samples and $f_c^1[n]$ the first of the three combs of the comb function. This comb function was chosen because of the particular waveform of the EP stimulation artefact (see Figure 1). We define the position of an artefact by the minimum of the artefact. Once the position of the first artefact is found (i.e., after the initialization step), the positions of the other artefacts are found one by one, by searching for the minimum of the EEG in a neighborhood of 3 samples around the time instance 10 sec. after the previously found position. By realigning every step on the minimum of the artefact, we compensate for the fact that the stimulation does not occur every time precisely 10 sec. after the previous one (also, the time between two consecutive stimulations changes slightly over time). Furthermore, during some periods of the registration no EEG was available. Every time this occurs, the pointer to the current artefact position was automatically reinitialized.

For every artefact, the EEG in a window of 1350 ms around the artefact position (100 ms before and 1250 ms after the artefact position) was discarded.

II. Detection In the detection step we search for phenomena that deviate from the background EEG activity. We assume that the background activity has a Gaussian distribution, and calculate a robust estimate of its parameters based on the 25th and 75th percentiles of the data:

$$\mu = p_{50}, \qquad (3)$$

$$\sigma = (p_{75} - p_{25})/(2*0.675), \qquad (4)$$

since $$\int_{\mu-0.675\sigma}^{\mu+0.675\sigma} (\sigma\sqrt{2\pi})^{-1} \exp\left(-\frac{(x-\mu)^2}{2\sigma^2}\right) = 0.500 \qquad (5)$$

Both parameters are estimated adaptively using a moving window and are used to mark EEG samples that deviate from the background activity as follows. First μ and σ are initialized using the first 4 min. of the EEG and equation (3) and (4). Next, in a moving window (length 0.5 sec., non-overlapping), EEG samples for which $x[n] < \mu - \gamma * \sigma$ holds are marked (i.e., a detection of the negative peaks in the EEG signal that deviate from the background activity), with γ set to 3 or 5 (see below). If no time instances are marked, and if there are no samples for which $x[n] > \mu + \gamma * \sigma$ obtains (i.e., we can assume that the current window only contains background EEG), the EEG samples from the current window are added to a background EEG buffer of 2 min., or, once the buffer is full, the oldest 0.5 sec. of EEG data that were placed in the buffer, are replaced by the samples from the current window. As soon as the buffer is full, for each position of the moving window, μ and σ are estimated using the current data in the background EEG buffer.

The list of marked time instances is then post-processed as follows: (i) Consecutive time instances are replaced by the time instance that corresponds to the local minima in the EEG; (ii) In this new list of time instances, time instances that are closer then 400 ms of each other are replaced by the first time instance.

At this step in the algorithm, one can decide to include extra restrictions on the detected time instances (and the corresponding waveforms in the EEG) in order to increase the selectivity of the detection step with regard to the interictal epileptiform activity we are interested in. However, since we don't have any (a priori) knowledge on the epileptiform waveform(s), we decided to run the algorithm twice. In the *first run*, we set γ to 5, without any additional restrictions on the detected time instances or waveforms, and observed the obtained waveforms after clustering (see next step). Based on the judgment of the expert, we could easily identify the epileptiform discharges, and add the following (extra) criteria to increase the selectivity: (iii) the minimum of the waveform should precede the maximum, and their time difference should not be greater then 90 ms; (iv) the amplitude of the maximum should be at least half the amplitude of the minimum.

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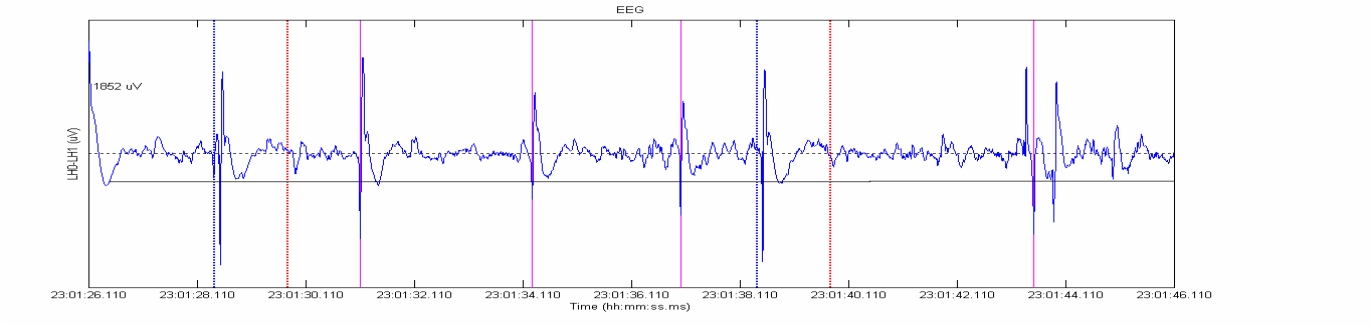

Figure 2: EEG fragment of 20 sec. Beginning and ending of the EP stimulation artefacts (around time instances 23:01:29 and 23:01:39) are marked with, respectively, a blue and red line. Detections are marked with a purple line. The adaptive amplitude threshold is shown in black.

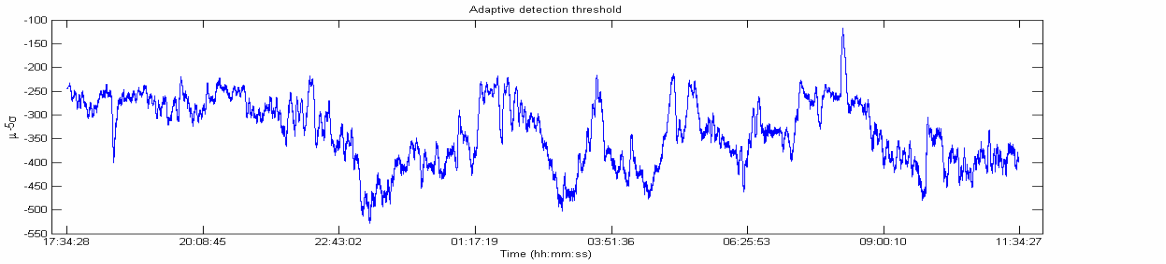

Figure 3: The evolution over time of the adaptive detection threshold $\mu - 5*\sigma$, shown for the last 18 hours of the EEG recording.

In the *second run*, we used these two additional criteria to increase the selectivity, and set γ to 3 to increase the sensitivity.

III. Clustering and modeling of detected waveforms After the detection step, we search for recurrent patterns in the detected phenomena. We model the detected waveforms using a Gaussian mixture model (GMM) with full covariance matrices. The GMM parameters were estimated using the expectation-maximization (EM) algorithm, initialized with the results of Ward's hierarchical clustering algorithm [5,6,7].

The clustering proceeds as follows. For every detected time instance, we obtain a one dimensional signal by observing the EEG in a window of length 225 ms around the marked time instance (i.e., 45 samples, starting 19 samples before the detected time instance, so that all signals are aligned on the negative peak at sample 20). Each signal was normalized through division by the Euclidean norm, and these signals were stacked into a pattern matrix. To reduce the dimensionality of the feature space, a singular value decomposition (SVD) was performed, and we retained as many components as necessary to explain at least 95% of the signal's energy. A proximity matrix was constructed using the Euclidean distances between every signal and this proximity matrix was input into Ward's (minimum variance) hierarchical clustering algorithm. As a result we obtain a dendrogram that gives a visual representation of the hierarchy of the obtained clusters. To decide on the number of clusters (i.e., to decide on the specific level at which to cut the dendrogram), we used the stopping rule as found in [8], with k set to 8. This setting resulted in a plausible estimate of the number of clusters. Based on this clustering, we calculated for each cluster the maximum likelihood (ML) estimate of the mean and (full) covariance matrix, and used these to initialize the EM algorithm. The number of clusters was small enough so that each cluster contained sufficient signals to estimate the parameters of the GMM. Next, all waveforms were classified into classes using the Bayesian classification rule (i.e., according to the highest a posterior probabilities computed from the constructed GMM).

IV. Visualization of the results We plotted the number of detections per 5 min. to display the general trend of the epileptiform discharges as a summary of the interictal epileptiform activity in the EEG recording. We also plotted all detected waveforms per cluster/class so that the expert can decide which clusters/classes contain epileptiform signals.

Results

Figure 2 shows the results, on a fragment of 20 sec. of the recording, of the *first run* of the method. The EP stimulation artefacts and detection time instances are marked, together with the adaptive amplitude threshold. Figure 3 depicts the variation of the threshold over the last 18 hours of the recording.

Figures 4, 5 and 6 show the output of the *first run* of the method. In the detection step we obtained 2521 waveforms. Using the stopping rule with k set to 8, the number of clusters was 6 (in Figure 6, the clusters are plotted from left to right and from top to bottom, according to the order of the clusters in the dendrogram as shown in Figure 4). Clusters 3, 6 and 5 were

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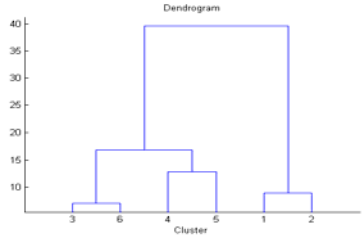

Figure 4: Dendrogram of the hierarchical clustering for the *first run* of the algorithm (γ = 5, no additional restrictions on the detected time instances/waveforms).

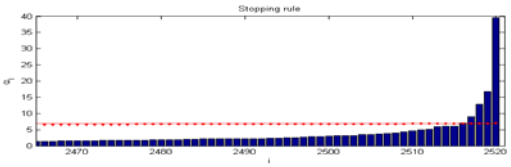

Figure 5: Application of the stopping rule. The figure shows the distance between the clusters α_i aggregated at step i in the hierarchical clustering algorithm for the *first run* of the algorithm. The red dots show the predicted increase, the red line shows the threshold that indicates a significant increase of α_i.

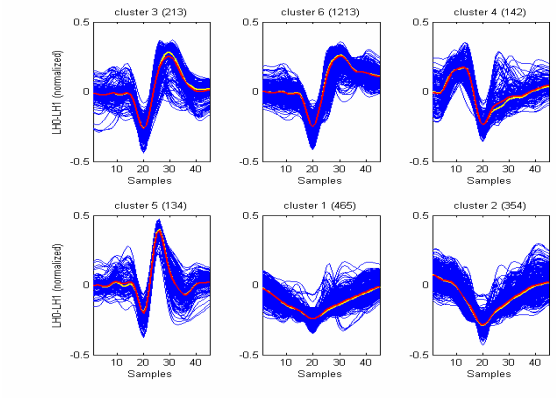

Figure 6: Results of Ward's hierarchical clustering algorithm for the *first run* of the algorithm: plot of all detected waveforms (in blue; the number of signals is shown in brackets), the mean (in red) and median (in yellow) per cluster.

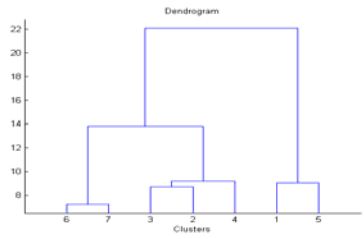

Figure 7: Dendrogram of the hierarchical clustering for the *second run* of the algorithm (γ = 3, with the additional restrictions (iii) and (iv) on the detected time instances/waveforms).

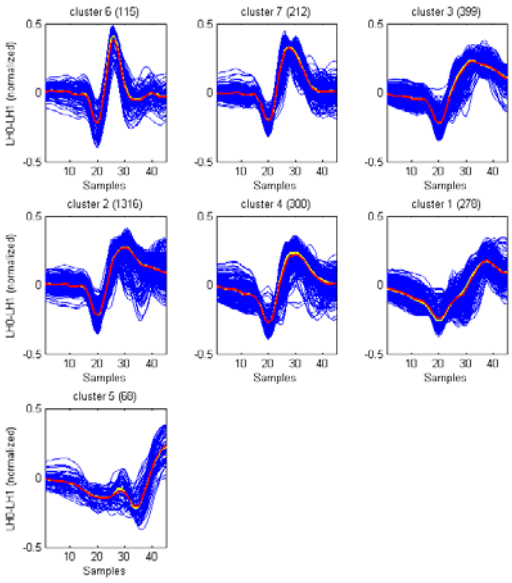

Figure 8: Results of Ward's hierarchical clustering algorithm, for the *second run* of the algorithm: plot of all detected waveforms (in blue; the number of signals is shown in brackets), the mean (in red) and median (in yellow) per cluster.

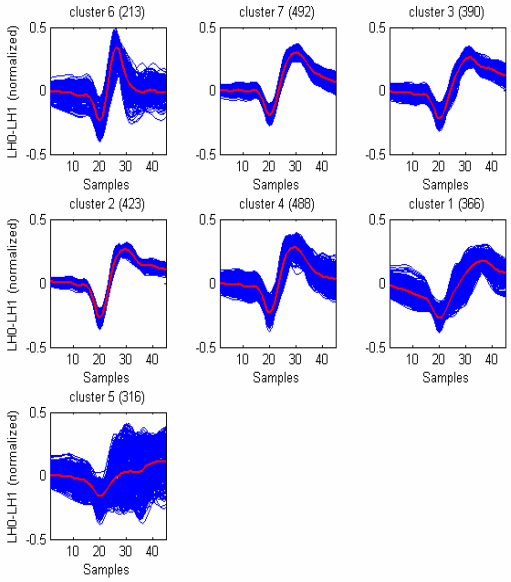

Figure 9: Classes obtained using the Bayesian classification rule with the constructed GMM, for the *second run* of the algorithm: plot of all detected waveforms (in blue; the number of signals is shown in brackets), the mean (in red) and median (in yellow) per class.

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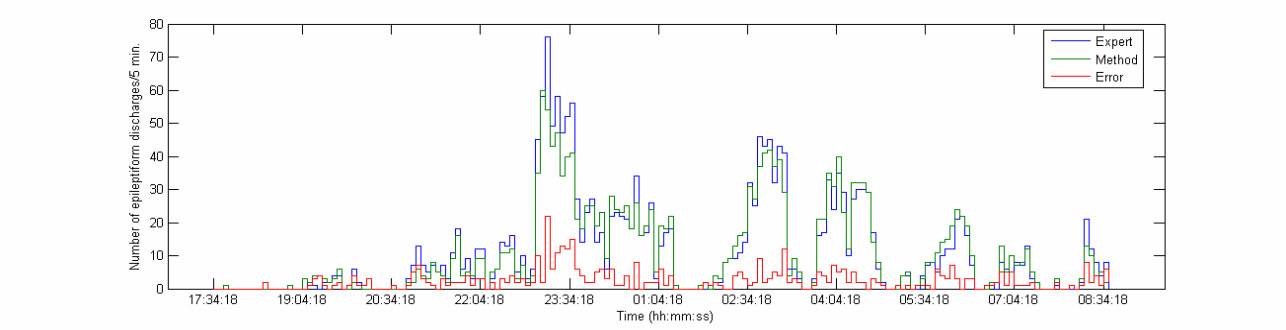

Figure 10: Number of labeled epileptiform discharges per 5 min. ('Expert', in blue), number of detections of the method per 5 min. ('Method', in green), and the difference between both ('Error', in red).

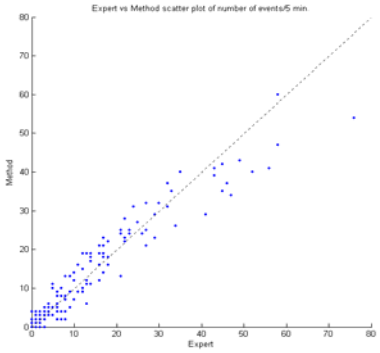

Figure 11: Scatter plot of the number of labeled epileptiform discharges per 5 min. ('Expert', x-axis) versus the number of detections of the method per 5 min ('Method', y-axis).

recognized as genuine epileptiform activity, and these waveforms led to the formulation of the two extra criteria (iii) and (iv) in the detection step.

Figures 7, 8 and 9 show the output of the *second run* of the method. In the detection step, the method marked 17197 waveforms, from which 14509 could be rejected based on the extra criteria (iii) and (iv). From Figure 9, which shows the classes obtained with the GMM, the expert identified the classes 6, 7, 3, 2 and 4 as epileptiform waveforms. Figure 10 shows the number of detected waveforms in these classes per 5 min. versus the number of labeled epileptiform discharges per 5 min. (mean number of events in the expert labeling: 11 events per 5 min.), together with the error between them. We can observe that the general trend of the epileptiform activity is recovered. To quantify the differences, we calculated the following error measures: the mean absolute difference, the correlation coefficient and the relative residual energy, and obtained, respectively, 2.37 events/5 min., 0.96 and 0.046. Note that these figures depend on the length of the time interval over which the events are summed. We choose a time interval of 5 min. because it is precise enough to see the general trend. The correspondence between the results of the method and the expert labeling can also be appreciated from Figure 11.

Discussion and conclusions

The main difficulty of a method such as the one presented here, lies in the evaluation and validation of the method. Since there is no clear consensus on the definition of epileptiform activity in the intracranial EEG, it comes of no surprise to find a poor agreement between the epileptiform labelings from different experts. Therefore, a comparison of the detection results with a visual labeling of the epileptiform discharges by an expert, is not straightforward, nor conclusive.

In fact, the method can not be seen as a replacement of a visual analysis, because at present nobody is doing such an full and elaborate visual analysis of the intracranial EEG recordings. The method should not be thought of as an epileptiform detection method as such, but rather as a method that tries to summarize the whole EEG recording in a meaningful way and that might point to some trend(s) in the long-term EEG recording.

We used the labeling of one expert to have a first indication on the performance and usefulness of the method. Using the method in two runs, and with a visual identification of the epileptiform classes in the GMM, we could reproduce the general trend of the interictal spiking as it was observed by the expert.

Future research will aim at further automating the method in order to arrive at a self-contained algorithm that can be used to automatically analyze and summarize the interictal activity in intracranial EEG recordings. In particular, other EEG recordings will be used to check whether the choices made in the current analysis (e.g., the additional detection criteria, the stopping rule, etc.) generalize. Also the constructed probabilistic model (GMM) will be further exploited to automate the detection, characterize the obtained detection results and investigate the long-term evolution of the epileptiform patterns.

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