Seizure lateralization in scalp EEG using Hjorth parameters

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Abstract

Objective: This paper describes and assesses a new semi-automatic method for temporal lobe seizures lateralization using raw scalp EEG signals.
Methods: We used the first two Hjorth parameters to estimate quadratic mean and dominant frequency of signals. Their mean values were computed on each side of the brain and segmented taking into account the seizure onset time identified by the electroencephalographist, to keep only the initial part of the seizure, before a possible spreading to the contralateral side. The means of segmented variables were used to characterise the seizure by a point in a (frequency, amplitude) plane. Six criteria were proposed for the partitioning of this plane for lateralization.
Results: The procedure was applied to 45 patients (85 seizures). The two best criteria yielded, for the first one, a correct lateralization for 96% of seizures and, for the other, a lateralization rate of 87% without incorrect lateralization.
Conclusions: The method produced satisfactory results, easy to interpret. The setting of procedure parameters was simple and the approach was robust to artifacts. It could constitute a help for neurophysiologists during visual inspection.
Significance: The difference of quadratic mean and dominant frequency on each side of the brain allows lateralizing the seizure onset.

1. Introduction

The presurgical evaluation of medically refractory focal epilepsy is a multi step process involving multi modal approach (Lopes da Silva, 2008) to lateralize and localize the epileptogenic zone. The first phase is said “non invasive” because it does not involve intra-cranial electrodes placement. It combines:

- the gathering of the clinical history of the epilepsy,
- the analysis of inter-ictal events recorded with electroencephalography (EEG) and magnetoencephalography (MEG), completed by the methods of source localization (Baumgartner, 2004; Gotman et al., 2006; Grova et al., 2006; Pillai and Sperling, 2006; Knowlton, 2006; Shibasaki et al., 2007; Plummer et al., 2008),
- the analysis of neuropsychological deficits and determination of the hemispheric dominance for language,
- the analysis of ictal semiology (Loddenkemper and Kotagal, 2005; So, 2006; Bonelli et al., 2007; Jan and Girvin, 2008),
- the analysis of the ictal discharges on EEG and electro-clinical correlations,
- the analysis of cranial magnetic resonance imaging (MRI) looking for potentially epileptogenic brain lesions (Hallam et al., 2006; Uijl et al., 2008; Zaknun et al., 2008),
- brain hemodynamic and metabolic analysis using single photon emission computed tomography - SPECT (Wichert-Ana et al., 2005; Knowlton, 2006; Mountz, 2007; Van Paesschen et al., 2007; Goffin et al., 2008; Zaknun et al., 2008) and positron emission tomography - PET (Wichert-Ana et al., 2005; Knowlton, 2006; Mountz, 2007; Van Paesschen et al., 2007; Goffin et al., 2008),
- and finally the integration of all these multimodal data in a multidisciplinary process of anatomo-electro-clinical correlations.

At the end of this first phase, when all the data converge towards a single focal epileptogenic zone in a functionally accessible region (typically the medial anterior temporal structures) the surgery procedure can be proposed to the patient.

When several hypotheses emerge from this first phase, intra-cranial recordings are required if a surgical procedure is still considered (Pondal-Sordo et al., 2007). In this second phase, intra-cranial recordings enable a more accurate delineation of the epileptogenic zone but at the price of a partial sampling of brain electrical activity (Maillard et al., 2009). It is therefore very important to realize that the success of this second phase primarily relies on the quality of the first non-invasive phase. In this non-invasive phase, the combinations of methods are various and depend on the considered centre. Nevertheless, scalp EEG obtained during video-EEG monitoring continues to play a pivotal role to lateralize and localize the seizure onset zone (Ray et al., 2007).

For all that, the literature dedicated to scalp EEG focuses predominantly on localization (Michel, 2004; Lopes da Silva, 2008), the ultimate goal, and less on lateralization. This lateralization task is mainly performed by visual inspection of interictal EEG (Kilpatrick et al., 2003; Grova et al., 2006; Pillai and Sperling, 2006; Uijl et al., 2008) and ictal EEG (Serles et al., 2000; Foldvary et al., 2001; Kilpatrick et al., 2003; Buechler et al., 2008; Dericioglu and Saygi, 2008; Uijl et al., 2008) and few studies report on the use of an automatic lateralization system (Caparos et al., 2006). This limited interest concerning such a system could be explained by the presence of artifacts (eye blinking, muscular artifact, movement, chewing …) that complicates the development of an automatic system; moreover, lateralization is only an intermediate step. Nevertheless, following the example of seizure detection (Saab and Gotman, 2005; Haas et al., 2007; Hopfengärtner et al., 2007; Lesser and Webber, 2008; Ocak, 2009), an automatic lateralization system could constitute a valuable help for neurologists. Indeed, in temporal lobe seizure analysis, some variability of seizure pattern can induce a false lateralization and such a system gives supplementary information, non-user-dependent, in a more quantified way. Furthermore, a quantification algorithm could extract features that can be invisible to visual inspection and be used for pre-interpretation of long duration EEG. Finally, a lateralization method could be used to reinforce clinical reasoning, namely by confirming the validity of the usually chosen lateralization criteria.

One of the first quantitative methods for lateralization with ictal EEG uses frequency information. Proposed by Murro et al. (1993), it is based on the right-left difference in averaged relative frequency band power: the best results are obtained with the pairs of electrodes T4-T6/T3-T5 and the frequency band 4-10.5 Hz. In another paper, Blanke et al. (2000), via an FFT-Approximation, computed the frequency with maximal Global Field Power (GFP) and then the epoch showing the highest GFP allows localizing the epileptic activity with a linear inverse solution algorithm. More recently, Temuçin et al. (2005) defined an Epileptic Abnormality Index (EAI) constructed from frequency band power and power asymmetry (left and right) parameters and used for EEG background activity analysis with 17 electrode recordings performed during wakefulness with eyes closed. This EAI allows lateralizing epileptic abnormalities but EEG parts containing excessive artifacts are visually rejected before analysis. Van Putten et al. (2005) defined a Brain Symmetry Index (BSI), originally designed to assist visual interpretation of EEG during carotid endarterectomy, to detect temporal lobe seizures and consequently useful for lateralization. This BSI is the absolute value of the relative interhemispheric difference in spectral density, estimated from the mean of eight left-right symmetric bipolar

EEG channels; they also define phase synchronisation related symmetry measures. Van Putten proposed an improved version of the BSI in 2007.

Another method for lateralization is the use of correlation. Jing et al. (2002) computed correlation dimensions on interictal EEG (without artifacts) recorded on six electrodes. Lateralization is determined according to the nonlinearity and complexity of signals for each pair of electrode sites (i.e. F7 and F8, T3 and T4, T5 and T6). Caparos et al. (2006) were interested in correlation between rhythmic waves (theta band of the EEG) often observed at seizure onset. They compared the mean value of nonlinear correlation coefficients on each side of the brain to lateralize. Eight pairs of electrodes (Fp2-F8, Fp2-FT10, F8-T4, FT10-P10, T4-T6, P10-O2, T6-O2 and Cz-Pz) and all the corresponding contralateral electrodes were used.

Most of the previous approaches require selection of epochs to eliminate excessive artifacts and their rate of correct lateralization is approximately equal to 80-90%. In this context, our initial motivation was to develop a method that does not imply a pre-selection of data and which would gives better results than previously reported. In routine clinical setting, spatial distribution of the ictal discharge is visually assessed: the pattern of electrodes where the ictal rhythmic activity has the greatest amplitude is used to localize and lateralize the partial seizure (with a proposed ratio of 2/1 compared to the activity seen over other regions; Foldvary et al., 2001). Consequently, our first idea was to elaborate an approach based on this criterion to quantify its efficiency. The evolution of the dominant frequency of the signals is also an element that is visually analysed; therefore, we were interested in elaborating an algorithm that combines the two pieces of information, amplitude and frequency, to improve the lateralization. Our goal, in the choice of these two parameters, was to use variables with a physical meaning and an easy-to-do interpretation for neurologists.

This research addresses the lateralization of temporal lobe epilepsy, with raw scalp EEG data, assuming that seizure detection was performed previously via another method. This was done using the dynamical evolution of amplitude and frequency of signals during the beginning of the seizure. In short, the method described in this paper was composed of the following steps:

- After a pre-processing (band-pass filtering and artifacts clipping), the temporal evolution of the quadratic mean and of the dominant frequency of each EEG signal were computed using the Hjorth parameters (Hjorth, 1970, 1973) called activity and mobility. The means of these variables were calculated for the two sides of the brain, generating four signals: an average quadratic mean and an average dominant frequency for each hemisphere. The filtered differences (right side - left side) of these means constituted two signals close to zero. The sign of these signals indicates, for one signal, the amplitude predominance of a hemisphere and, for the second signal, if the average dominant frequency is higher for one side of the brain compared to the other one. These trends were used later for lateralization.
- The two preceding signals were segmented to isolate the beginning of the seizure, before a possible spreading to the contralateral side. Next, the mean of each segmented signal was computed and the two obtained values were used as coordinates of a point in a (frequency, amplitude) plane.
- Finally, the analysis of the position of the “right-sided” points versus the “left-sided” points allowed defining six geometric criteria for seizure lateralization.

2. Materials and methods

2.1 Patients and EEG data

We enrolled 45 patients who underwent long-term video-scalp EEG for pre-surgical evaluation of medically intractable temporal lobe epilepsy (male: 21; female: 24; mean age: 34). The lateralization as well as the localization of the seizure onset zone was based on the method of anatomo-electro-clinical correlations (Maillard et al., 2004 & 2009). For example, ictal signs such as motor automatisms, dystonic posturing, ictal verbal automatisms and post-ictal verbal deficit have a strong lateralizing value (Gabr et al., 1989; Dupont et al., 1999). For EEG, seizures were lateralized according to the side of the ictal discharge which typically appears as a rhythmic 4-9 c/s discharge projecting to the temporal and basal temporal electrodes, sometimes preceded by a focal or regional flattening (Risinger et al., 1989). These data were combined together and correlated to neuroimaging data such as ictal SPECT and inter-ictal PET which have also a good lateralizing value (Knowlton et al., 2006). For each patient, the whole electro-clinical and neuroimaging data were reviewed to consensually determine the lateralization and localization of each analyzed seizure. Among the 27 operated patients, 22 were classified as Engel outcome class I, 3 as class II and 2 as class III; recurrences of seizures in class III patients always occurred on the operated side. Seizures of the 18 non-operated patients were lateralized according to the same method and with the same confidence as seizures of the operated patients.

A Micromed system (sampling frequency equal to 512 Hz down-sampled to f_S equal to 256 Hz) recorded 24 EEG channels according to the 10/20 system in longitudinal differential montage. A database containing 85 records of seizure was built: for 38 patients, two seizures were available, for six patients only one seizure was available and for one patient, three seizures were available. The temporal lobe seizures were of different kinds: uni or bilateral; mesial, lateral or mesio-lateral (Maillard et al., 2004). Several patients had very rapidly spreading seizures. Thirty-three seizures were right sided and 52 left sided. Each record

contained 22 channel pairs (Fp2-F4, F4-C4, C4-P4, P4-O2, Fp2-F8, F8-T4, T4-T6, T6-O2, Fp2-FT10, FT10-P10, P10-O2 and the contralateral pairs) with 500 s duration in a normalised way: 350 s before the seizure onset (determined by clinicians) and 150 s after. Notice that the records were not selected and contained all kinds of usual artifacts.

2.2 Lateralization criteria: a first approach

According to robustness considerations involved by the absence of record selection, we looked for simple lateralization criteria. As indicated previously, we chose to use amplitude and frequency information because, firstly, the evolution of these variables during a seizure was easy to interpret for neurologists and, secondly, our secondary purpose was to assess the lateralization value of these routine neurophysiologic parameters.

Focal ictal patterns are of different types but many ictal discharges begin with low amplitude rhythmical activity that increases in amplitude and decreases in frequency. Alternatively, the ictal pattern may evolve from a slower to a faster frequency discharge (Fisch, 1999). In the same way, the increasing of the average energy of the signals and the presence of a dominant peak in the frequency domain was pointed out by Sanei and Chambers (2007) who indicated, however, that the frequency of this peak decays with time during the onset of seizure. Murro et al. (1993) proposed also the evaluation of amplitude for visual EEG analysis: the interpreters used a greater than 50% amplitude asymmetry of rhythmic theta/alpha activity within the first 30 sec following seizure onset to determine the side of the seizure onset.

Based on the above, we assumed that, during the seizure, the mean value of the quadratic means of the EEG signals was higher on the side of the epileptogenic zone than on the other side. However, this hypothesis was not always correct because seizures beginning with lateralized activities may evolve to bitemporal, generalized or independent contralateral activities. Consequently, only the first significant change in the difference (right side - left side) of the mean values of quadratic means was considered. For instance, if we have, at the beginning of a seizure, an increasing of the difference, followed by a decreasing and, later, a zero-crossing and a negative value, we just took into account the positive part of the difference, before the zero-crossing. Thus, we used the following proposition as an *a priori* basis for a lateralization criterion:

- if (the first significant change in the difference (right side - left side) of mean values of quadratic means of EEG signals is positive),
  then (the seizure onset is right-sided located),
  else (the seizure onset is left-sided located).

Concerning the frequency, we assumed that, during the seizure, the mean value of the dominant frequencies of the EEG signals decreased most of the time more significantly at the side of the epileptogenic zone than at the other side; it was unfortunately not always true. Hence, the use of the frequency information alone did not allow lateralization. For this reason, we used frequency information as a combined criterion only, to decrease the rate of false lateralization associated with the use of the amplitude criterion alone.

2.3 Overview of the method

To evaluate the relevance of our proposition of lateralization criterion and to see how to associate amplitude and frequency information, we needed, firstly, to compute the difference (right side - left side) of average values of quadratic means and the difference (right side - left side) of average values of dominant frequencies of EEG. Secondly, we computed the boundaries of the first significant change in the difference of average values of quadratic means and we extracted the corresponding two segments of the differences of mean values for quadratic means and dominant frequencies. Then, we computed the mean of each segment. Thus, each seizure was represented by a point in a (frequency, amplitude) plane in Cartesian coordinates or, in an equivalent way, polar coordinates. Thirdly, we analysed the position on this plane of the right-sided-seizure and left-sided-seizure points for the whole database to evaluate the performance of our first proposition of criterion and to develop other criteria. The steps of this approach are summarized Fig. 1; they are detailed as follows.

2.4 Pre-processing

Before computing the quadratic mean and the dominant frequency of EEG signals using the Hjorth descriptors, a pre-processing of each signal was required to maximize useful information and minimize the effect of artifacts. Particularly, the used descriptors need zero mean and smoothed signals due to derivative computing. Fig. 2 summarizes the three steps of this pre-processing. Firstly, a finite impulse response band-pass filter of order 200 was used. According to Blanke et al. (2000) who indicated that the ictal dominant frequencies ranged from 3 to 8.5 Hz, we adjusted the cut-off frequencies of band-pass filter to 2-20 Hz. This filter minimized the effect of muscular activity and slow waves. Secondly, because of high amplitude and long duration artifacts (movement, electrode problem…), the band-pass filter was not sufficient to assure a

zero mean base line. Therefore, a median filter (windows length of one second with 256 samples) allowed obtaining the base line that was subtracted to the output of the band-pass filter. The third step of the pre-processing was the clipping of noise and artifacts of high amplitude and short duration. A median filter (windows length of one second) was applied to the absolute value of the signal and the smoothed output of this filter was multiplied by a constant value (th_C = 4). The obtained positive signal and its sign opposite negative signal determined thresholds envelop; the signal values that were outside this envelop were clipped.

More sophisticated methods for noise and artifacts removal (Krishnaveni et al., 2006; Fitzgibbon et al., 2007; Romo-Vazquez et al., 2007) are also possible. However, preliminary studies using blind source separation for artifacts elimination and wavelets for denoising did not improve the lateralization.

2.5 Hjorth parameters computation

To compute the quadratic mean and the dominant frequency of EEG signals on each side of the brain, we used the first two Hjorth descriptors (Hjorth, 1970, 1973), namely activity and mobility, but another possible way was to use the multichannel descriptors Σ and ϕ proposed by Wackermann (1999, 2007). The Hjorth parameters were originally developed for various online EEG analyses, for example in sleep staging. In fact, to estimate the amplitude and the main frequency of a signal, many tools, particularly of spectral analysis, were also possible (FFT, wavelets…). We have chosen these descriptors because of their low calculation cost.

Let us consider the spectral moment of order zero and two

$$m_0 = \int_{-\pi}^{\pi} S(\omega) d\omega = \frac{1}{T} \int_{t-T}^{t} f^2(t) dt \qquad (1)$$

$$m_2 = \int_{-\pi}^{\pi} \omega^2 S(\omega) d\omega = \frac{1}{T} \int_{t-T}^{t} \left(\frac{df}{dt} \right)^2 dt \qquad (2)$$

where $S(\omega)$ is the power density spectrum and $f(t)$ the EEG signal within an epoch of duration T. The first two Hjorth parameters are given by

$$Activity : h_0 = m_0 \qquad (3)$$

$$Mobility : h_1 = \sqrt{\frac{m_2}{m_0}} \qquad (4)$$

h_0 represents the square of the quadratic mean and h_1 reflects the dominant frequency. The discrete forms of these quantities, $h_0(k)$ and $h_1(k)$ at sampled time k, were computed within a sliding window of one second length using the open source software library BioSig.

Notice that Hjorth has also used the fourth-order spectral moment m_4 to define a measure of the bandwidth of the signal, called complexity

$$Complexity : h_2 = \sqrt{\frac{m_4}{m_2} - \frac{m_2}{m_0}} \qquad (5)$$

We tried to apply the same approach, as developed for the first two Hjorth parameters, to this third parameter, assuming that the mean value of the bandwidth was smaller at the side of the seizure onset zone than at the other side, but the results were not significant. A possible explanation was that, at seizure onset, the bandwidth of the EEG signal could be smaller for the pairs of electrodes near from the epileptogenic zone but not for all the electrodes of the considered side of the brain. Then, the difference between the mean of complexity signals from the right side and the left side of the brain seemed no to be a relevant measure of lateralization. Nevertheless, the use of complexity could probably be interesting for localization.

2.6 Right-left differences computation

For each EEG signal, output of the pre-processing step, we calculated the two Hjorth parameters. Let $h_{0,i,r}(k)$ and $h_{1,i,r}(k)$ the activity and the mobility of the i-th signal i = 1,2, …p of the right side (where p = 11 is the number of electrodes pairs) and $h_{0,i,l}(k)$ and $h_{1,i,l}(k)$ the activity and the mobility of the i-th signal of the left side. The difference right-left of mean values of quadratic means was defined as follows

$$damp(k) = \frac{\sum_{i=1}^{p} \left(\sqrt{h_{0,i,r}(k)} - \sqrt{h_{0,i,l}(k)} \right)}{p} \quad (6)$$

and the difference right-left of mean values of dominant frequencies as

$$dfreq(k) = \frac{f_s}{2\pi} \frac{\sum_{i=1}^{p} \left(h_{1,i,r}(k) - h_{1,i,l}(k) \right)}{p} \quad (7)$$

The obtained signals were noisy (Fig. 3) and needed appropriate filtering. Because the difference of mean values of quadratic means *damp(k)* was used in the following stage for the segmentation of signals, the filtering of this signal would not modify its shape. Consequently, for the difference of mean values of quadratic means *damp(k)*, we used a median filter with a large window (10 s length) to obtain a smoothed signal not distorted by peaks (Fig. 3).

The difference of mean values of dominant frequencies *dfreq(k)* was not used for segmentation and we were only interested in the global trend of this signal, for visual analysis. Therefore, we computed a sliding mean of the signal with a rectangular window of 50 s length. We had chosen this basic filtering because it had a lower calculation cost than the median filter and the result was enough for our purpose (Fig. 3).

2.7 Signal segmentation

As indicated in part 2.2, only the first significant change in the difference right-left of mean values of quadratic means was considered during the ictal time interval, the idea being to just characterize the activity of the seizure focus without taking into account a possible development to the contralateral hemisphere. Thus, we tried to detect the first significant increasing (or decreasing) of *fdamp(k)* from zero to extract the corresponding segments of *fdamp(k)* and *fdfreq(k)* for the next processing.

In short, a significant change was detected if the absolute value of *fdamp(k)* was greater than a threshold th_1. We assumed that this change was located within a window of 50 s after the seizure onset t_0. The estimation of the boundaries of the corresponding segment was carried out as follows:

- By default, the beginning of segment corresponded to the seizure onset but, sometimes, the increasing of the absolute value of *fdamp(k)* occurred several seconds after the seizure onset and then, before this time of increasing, the value of *fdamp(k)* was close to zero with possible oscillations and zero-crossings. This oscillatory part of small amplitude was not useful for lateralization and had to be removed from the segment. In this case, the beginning of the segment corresponded to the last zero crossing, just before the detection of a significant change, for which *fdamp(k)* was smaller than a threshold th_2 (lower than th_1) on the part between the seizure onset and the zero crossing.
- The end of segment corresponded to the first zero crossing after the detection of a significant change or to the end of the seizure window (50 s) if there was no zero crossing.

Some patterns illustrating the segmentation process for an increasing of *fdamp(k)* are presented Fig. 4 and real boundaries are indicated Fig. 3.

More precisely, the segmentation was carried out in two steps, the estimation of the end of the first significant change and the estimation of its beginning (Fig. 5):

- Firstly, we detected a zero crossing of the *fdamp(k)* signal going backward from sampled time (t_0+ *50 s*) to sampled time t_0 where t_0 was the estimation of the seizure onset. Next, we compared the maximum of the absolute value of *fdamp(k)* within the window from t_0 to t_Z, where t_Z was the time of zero crossing, to a threshold th_1 = 1. If $\max\left(\left| fdamp(k) \right| \right)_{t_0}^{t_Z} > th_1$, then t_Z was assumed to be the end of a significant change. This procedure was repeated until t_0 was reached and the first (in time) t_Z instant was assumed the end of the first significant change and was designated t_{end}. If no zero crossing occurred or if $\max\left(\left| fdamp(k) \right| \right)_{t_0}^{t_Z} < th_1$, t_{end} was assumed to be (t_0+ *50 s*).
- Secondly, we detected a zero crossing of the *fdamp(k)* signal going forward from time t_0 to time t_{end}. Then we compared max ($\left| fdamp(k) \right|$) to another threshold th_2 = 0.5 within a window from t_0 to t_Z

where t_Z was the time of zero crossing. If $\max\left(\left|fdamp(k)\right|\right)_{t_o}^{t_Z} < th_2$, t_Z was assumed to be the beginning of a significant change. This procedure was repeated until t_{end} was reached and the last (in time) t_Z instant was the beginning of the first significant change and was called t_{beg}. If no zero crossing occurred or if $\max\left(\left|fdamp(k)\right|\right)_{t_o}^{t_Z} > th_2$, t_{beg} was assumed to be t_o.

2.8 Seizure characterization

Seizure characterization was the first step towards classification (lateralization). Our aim, in this paper, was exploratory and retrospective: we tried to find if the proposed Hjorth parameters and the previous segmentation approach can be used to separate between left and right originated seizures.

After segmentation, each EEG recording was described by two curves: the filtered difference of mean values of quadratic means, *fdamp(k)* and the filtered difference of mean values of dominant frequencies, *fdfreq(k)*, *k* being the time index between t_{beg} and t_{end}. Consider a plane where *fdfreq* represent the abscissa and *fdamp* the ordinate, the variation of *fdamp(k)* against *fdfreq(k)* generates a curve in this plane (Fig. 6).

As can be seen on Fig. 6, the domains of the left-side and right-side seizure curves were quite different: they were almost included in the lower-right quadrant and in the upper-left quadrant respectively. To verify this hypothesis in a synthetic way, we computed the mean values of *fdamp* and *fdfreq* for each seizure, obtaining therefore points in the (*fdfreq*, *fdamp*) plane (52 for the left-side and 33 for the right-side seizures):

$$fdamp_{\mu} = \left(\overline{fdamp(k)}\right)_{t_{beg}}^{t_{end}} \quad (8)$$

$$fdfreq_{\mu} = \left(\overline{fdfreq(k)}\right)_{t_{beg}}^{t_{end}} \quad (9)$$

This new synthetic representation (Fig. 7a) was the basis for our first proposal for lateralization criteria. At this point, every seizure was characterized by two parameters and thus could be represented as a point in a plane. Lateralizing seizures implied finding a frontier in this plane separating between left and right. For anatomical and physiological reasons (brain symmetry), this frontier should be symmetric reported to the origin: ($fdfreq_{\mu}$, $fdamp_{\mu}$) = (0, 0).

Several questions were arising: were these parameters ($fdfreq_{\mu}$ and $fdamp_{\mu}$) discriminant? Both of them, or was only one sufficient to separate between the two classes (left – right seizures)? In other words, the frontier would be one of the axes or some (odd) function in the plane? Was this function linear (i.e. was the frontier a line passing through the origin) or non-linear?

Both parametric *t*-tests and non-parametric Wilcoxon tests (as we were not sure about the gaussianity of the variables) were performed for the two parameters and the results confirmed the visual analysis of Fig. 7a: according to both $fdfreq_{\mu}$ and $fdamp_{\mu}$, the left and right seizures are different with a highly significant *p*-value (≈ 0). We also investigated their redundancy by computing the correlation coefficient. The obtained value was ≈ -0.4, indicating a low level of redundancy. Orthogonalizing the data by principal component analysis has not reduced the number of the necessary features for lateralization. This rapid analysis showed that probably both features were required for the classification. The simplest frontier was then a line passing through the origin and our exploratory approach leaded to similar results as a linear discriminant analysis.

On the other hand, if the frontier between left and right seizures was linear and contained the origin, it was uniquely determined by its angle, so it seemed logical to transform the data to obtain this angle explicitly. Indeed, the “tilted” repartition of the points suggested another representation and, consequently, another lateralization approach. Consider the polar coordinates of the 85 points: the angle θ with the horizontal axis (counterclockwise) and the magnitude ρ (distance from the origin):

$$\theta = \arctan\left(\frac{fdamp_{\mu}}{fdfreq_{\mu}}\right) \quad (10)$$

$$\rho = \sqrt{\left(fdamp_{\mu}^2 + fdfreq_{\mu}^2\right)} \quad (11)$$

The seizure points can then be figured using θ as abscise and ρ as ordinate (Fig. 7b), and some new lateralization criteria were determined using this polar representation. These two new features were analysed using the same procedure as previously: *t*-test and Wilcoxon test showed that, in the polar plane, the angle coordinate θ leads to the most significant difference between the two types of seizures, but no significant difference can be made according to the magnitude ρ (*p*-value $\approx$ 0.7). The two polar characteristics are almost orthogonal (very low redundancy), with a correlation coefficient of 0.08, which meant that lateralization would be easier in the polar plane, and probably quite good performances should be attained by using only the angle coordinate θ.

Different lateralization criteria, based on the two alternative representations (Cartesian and polar) were proposed and evaluated in the next sections.

2.9 Seizure lateralization

2.9.1. Cartesian coordinates lateralization criteria

The first lateralization criterion C_1 was based on the difference (right side - left side) of mean values of quadratic means of EEG signals (see part 2.2). The sign of the $fdamp_\mu$ (eq. 7) revealed the side of the seizure onset:

- If ($fdamp_\mu > 0$) then (the seizure onset is right-sided located), else (the seizure onset is left-sided located). (C_1)

On Fig. 7a, the frontier between left and right seizures defined by C_1 criterion is the horizontal axis and several points are in the wrong half-plane. To avoid misclassifications (and thus increase the specificity of our lateralization criterion), we proposed an indeterminate zone corresponding to small amplitude differences between left and right (small $fdamp_\mu$). A second more specific lateralization criterion C_2 was:

- If ($fdamp_\mu > th_a$) then (the seizure onset is right-sided located),
- if ($fdamp_\mu < - th_a$) then (the seizure onset is left-sided located), (C_2)
- if ($- th_a < fdamp_\mu < th_a$) then (the seizure onset location is undetermined).

The chosen threshold was set to eliminate misclassification, th_a = 2.5 μV. The shaded zones on Fig. 7 show the indeterminacy zone both in Cartesian (a) and polar coordinates (b).

The analysis of the repartition of the points on Fig. 7a indicated a trend suggesting that the frequency difference was also important. Thus, all points in the upper-left quadrant corresponded to right-sided seizures, while all points from the lower-right quadrant corresponded to left-sided seizures. Moreover, in the remaining indeterminate quadrants, the ambiguous points had low $fdamp_\mu$ and low $fdfreq_\mu$. Therefore, a more restrained indeterminacy zone was defined: uncertain lateralization corresponds to seizures situated in quadrants 1 and 3 and having an absolute value of the mean $fdamp_\mu$ smaller than th_a = 2.5 μV. Then, the third proposed (bivariate) lateralization criterion C_3 was:

- if ($fdamp_\mu > 0$) then
  - if ($fdfreq_\mu < 0$) or ($fdamp_\mu > th_a$), then (the seizure onset is right-sided located), else (the seizure onset location is undetermined); (C_3)
- if ($fdamp_\mu < 0$) then
  - if ($fdfreq_\mu > 0$) or ($fdamp_\mu < -th_a$), then (the seizure onset is left-sided located), else (the seizure onset location is undetermined).

2.9.2. Polar coordinates lateralization criteria

In Cartesian coordinates, instead of considering the horizontal axis as the separation line between right and left seizures, a new line having a constant angle ϕ with the horizontal axis was employed (Fig. 7a). The points situated above the separating line were classified as right-side seizures, the points below the line being left-side seizures. In polar coordinates, this new frontier corresponds to two vertical lines: $\theta = \phi$ and θ = -180° + ϕ (Fig. 7b). For this polar representation, the points situated outside the subspace defined by the separating lines ($\phi < \theta <$ 180° and -180° + $\phi < \theta <$ ϕ) were classified as right-side seizures, the points situated inside the subspace defined by the lines (-180° + $\phi < \theta < \phi$) being left-side seizures.

Several angles ϕ (slopes) for the separation line were tested and we have chosen the one giving the highest rate of good lateralization. The best performances were obtained for ϕ = 60° in the first quadrant (Fig. 8) corresponding also to an angle of (-180° + ϕ) = -120° in the third quadrant (Fig. 7b).

To summarize, the fourth (highly sensitive) criterion C_4 was expressed, in polar coordinates, as:

- if ($\theta \in$ [-180° + ϕ, ϕ]) then (the seizure onset is left-sided located), else (the seizure onset is right-sided located). (C_4)

with ϕ = 60°.

Finally, a fifth more specific criterion C_5 was derived in polar coordinates assuming that points having small magnitude ρ and angle θ close to ϕ were considered as indeterminate:

- if ($\rho > th_\rho$) then
  - if ($\theta \in$ [-180° + ϕ, ϕ]) then (the seizure onset is left-sided located),
  - else (the seizure onset is right-sided located);
- if ($\rho < th_\rho$) then (C_5)
  - if ($\theta \in$ [-180° + ϕ + th_θ, ϕ - th_θ]) then (the seizure onset is left-sided located),
  - if ($\theta \in$ [-180°, -180° + ϕ - th_θ] $\cup$ [ϕ + th_θ, 180°]) then (the seizure onset is right-sided located),
  - else (the seizure onset location is undetermined).

The indeterminacy zone is shaded in Fig. 9, both in Cartesian (a) and polar coordinates (b). The thresholds were fixed as for C_2 to obtain a maximum specificity (no misclassification): th_θ = 27° (3π/20) and th_ρ = 2.5. One can notice that, as the magnitude ρ is not very discriminant, a composite equivalent criterion C_6 might be obtained by using the threshold th_θ for the angle θ and the threshold th_a for the amplitude difference $fdamp_\mu$:

- if ($|fdamp_\mu| > th_a$) then
  - if ($\theta \in$ [-180° + ϕ, ϕ]) then (the seizure onset is left-sided located),
  - else (the seizure onset is right-sided located);
- if ($|fdamp_\mu| < th_a$) then (C_6)
  - if ($\theta \in$ [-180° + ϕ + th_θ, ϕ - th_θ]) then (the seizure onset is left-sided located),
  - if ($\theta \in$ [-180°, -180° + ϕ - th_θ] $\cup$ [ϕ + th_θ, 180°]) then (the seizure onset is right-sided located),
  - else (the seizure onset location is undetermined).

The indeterminacy zone is inside the two triangles in Fig. 9a. The results, as can be deduced from this figure, were identical for C_5 and C_6 criteria.

3. Results

The whole procedure was applied to the database (n = 85). The segmentation step gave t_{end} = (t_O + 50 s) for 60 records (70%), here there was no contralateral spreading within a 50 s window after the seizure onset. For the other 30% corresponding to a change of side, the mean time of change was equal to t_O + 26 s. In the same manner, t_{beg} = t_O for 56 records: the first significant change began at seizure onset for 66% and later for 33%. Here, the mean value of the beginning was t_{beg} = (t_O + 7 s).

Concerning the lateralization performances (Table 1), the main criteria were based on the amplitude difference $fdamp_\mu$ (C_1) or on the angle θ (C_4), the others (bivariate) criteria being derived to avoid misclassification and thus to increase the specificity: in fact, the second characteristic ($fdfreq_\mu$, respectively ρ) was only used to define the indeterminacy zone. In addition, to appreciate the effect of a variation in the determination of the onset time, we applied the criteria on the records with a positive and negative shift in time of five seconds from t_O. The results showed that the efficiency of the procedure was slightly worse but not significantly.

Physical characteristics $fdamp_\mu$ and $fdfreq_\mu$ (Cartesian coordinates) allowed to obtain quite good lateralization performances (C_1 and C_3 especially). The C_3 criterion needed only one empirically determined threshold (th_a, on the amplitude difference). Using polar coordinates criteria improved lateralization performances, both in monovariate case (C_4) and in bivariate case (C_5). Two parameters were needed in this last case: the slope ϕ of the separating line (Fig. 7a and 9a) and the range of uncertainty for the θ angle (th_θ). Still, the slope at ϕ = 60° had the same function as the horizontal axis in the Cartesian coordinate system and it was not highly critical: all angles between approximately 55° and 70° leaded to almost similar performances (Fig. 8). The threshold th_θ was empirically chosen in the same way as th_a, that is to include in the indeterminacy zone the ambiguous cases from the database. A prospective study is in progress to validate the value of thresholds but actually, the control dataset is a little bit small to conclude definitively.

Considering the criterion with the higher rate of incorrect lateralization (C_1), the eight corresponding seizures belonged to eight patients classified as follows: three were operated, four had bitemporal epilepsy and one was waiting for an intra-cranial analysis. Then the rate of correct lateralization was equal to 94% (45/48) for operated patients, equal to 71% (10/14) for non-operated patients with bitemporal epilepsy and

equal to 96% (22/23) for other non-operated patients. For the other criterion with incorrect lateralization (C_4), two of the three incorrect lateralization were related to bitemporal epilepsy. That means that our approach seemed less efficient for epileptogenic zone lateralization in case of bitemporal epilepsy. A possible explanation was that the considered seizures became too quickly bilateral to be correctly lateralized.

To improve the results, an alternative clinically reasonable approach was to use intra-patient redundancy. Indeed, in our database we counted 39 patients having more than one epileptic seizure recording (38 patients with two EEG and one with three EEG = 79 recordings). This redundancy modified the classification by constructing a lateralization score: each right-sided detected seizure had a score of 1, each left-sided detected seizure had a score of -1 and undetermined seizures counted 0. For each of the five criteria C_1 to C_5, we computed their redundant scores C_{1r} to C_{5r} for the 39 patients (Table 2) using the following lateralization rule:

- if the score $C_{ir} \geq 1$, the patient has a right temporal focus,
- if the score $C_{ir} \leq -1$, the patient has a left-temporal focus,
- if the score $C_{ir} = 0$, the patient has an undetermined focus or a bifocal epilepsy.

with $i = 1, 2, \ldots 5$. For the five criteria, only one patient was incorrectly lateralized (with C_{1r}). This patient had a bi-temporofrontal epilepsy. Moreover, for the two most powerful criteria (Cartesian C_{3r} and polar C_{5r}) both indicated one undetermined / bifocal patient and the concerned patient was the same. In a way, one can conclude that the accuracy of both criteria C_{3r} and C_{5r} was 100% except the fact that we have regrouped undetermined and bifocal lateralization although analyse of intermediate results helped make some difference. Indeed, considering for instance two seizures of a patient, for bifocal epilepsy the score C_{ir} could be –1+1 = 0 and for an undetermined focus it could be 0+0 = 0. The final result was the same but not its meaning. Anyway, in case of doubtful result (undetermined / bifocal lateralization), the limits of our semi-automatic approach were reached and it seemed more sensible to let the neurophysiologist analyse all the available information. In this context, the inspection of the temporal evolution of the mean of quadratic means and of the mean of dominant frequencies of the EEG signals of the whole brain, computed in the same way as presented in section two, could be helpful to discriminate between bifocal and undetermined lateralization.

4. Discussion and conclusions

To lateralize seizure onset, neurophysiologists analyse simultaneously several characteristics of EEG signals and their evolution in time and distribution: amplitude, main frequency, correlations, specific ictal patterns …. This paper indicates that two of these characteristics, namely amplitude (in fact, quadratic mean) and dominant frequency, could be also used in a quantitative approach for lateralization of ictal focus, assuming that the seizure onset was determined before by an automatic system or by visual inspection. To estimate quadratic mean and main frequency we used the first two Hjorth parameters, activity and mobility. The computation of these parameters, within a sliding window, was easily made and allowed to obtain, with simple transformation, values with physical units (μV and Hz). After a suitable segmentation, the filtered differences right-left of mean values of quadratic means and dominant frequencies, *fdamp(k)* and *fdfreq(k)*, were a basis to determine the coordinates of a point in a (frequency, amplitude) plane, characterizing the analyzed seizure. This segmentation step was induced by the spreading of the seizure on the contralateral side that concerned 30% of the analysed records. Therefore, only the first part of signals, before spreading, was taken into account.

Compared to results of lateralization using ictal EEG previously reported in the introduction part, our method gave satisfactory results. With the first binary criterion based on amplitude (C_1), we obtained 87.2% of correct seizure lateralization ($n = 85$) versus 81.6% ($n = 87$) with the use of non-linear correlation (Caparos et al., 2006). Applied to 29 patients, the study of Murro et al. (1993) gives a rate of correct lateralization equal to 79%, using a threshold probability of 0.75 for classification, and equal to 90% with a threshold probability of 0.5. Another multi-centre study by Zaknun et al. (2008) indicates 86.3% of correct lateralization with 74 patients. Finally, this result confirmed, in a quantified way, the clinical approach taking into account the amplitude of the ictal discharges.

A transformation of the initial binary criterion into a ternary one by the introduction of an undetermined zone between right-sided and left-sided parts of the Cartesian plane allowed suppressing incorrect lateralization with a rate of correct lateralization equal to 83.5% (C_3 criterion). Another possible improvement was to associate the dominant frequency information to the amplitude information. The use of a separation line with an adapted slope between right and left domains was a way to integrate this frequency information into a balanced criterion. Thus, it led to a binary criterion (C_4) with a rate of correct lateralization equal to 96.5%. Then, with the introduction of an undermined zone, we had a ternary criterion (C_5) without false lateralisation and with 87.1% of correct lateralization. Lastly, we noticed that, in a case of several seizure

records for the same patient, the use of this redundancy improved the results: we obtained 97.4% of correct lateralization (C_3 and C_5 criteria) without incorrect lateralization.

The analysis of the incorrect lateralization has shown that bitemporal epilepsy was more difficult to classify. This was a limitation of the method, probably related to a faster contralateral spreading of the seizure: a correct lateralization needed a suitable chronology of the seizure and the segmentation step did not resolve this problem.

One of the advantages of the proposed method was that no selection of the raw data was made thus saving time. Indeed, some lateralization approaches need exclusion of epochs with electrode "pop", cable movement (Murro et al., 1993) or excessive artifacts (Jing et al., 2002; Temuçin et al., 2005). We used a pre-processing method to limit the bandwidth and artifacts effects. This method could have been regarded as oversimplified; nevertheless, its substitution by a more sophisticated approach of artifacts elimination and denoising has not improved the lateralization. Consequently, the proposed approach was considered robust to artifacts. In the same way, the method was also robust to small uncertainty in the determination of the seizure onset time. Another positive point was that the whole procedure was easy to tune because there were few parameters to adjust and all of these parameters had a physical meaning. The involved parameters were the length of sliding windows, the level of the thresholds used for segmentation (th_1 and th_2) and seizure classification (th_a, th_ρ and th_θ) and the slope ϕ. The length of sliding windows modified the smoothed aspect of signals. The segmentation thresholds allowed defining what a significant change was. The slope modified the position of the separating line and the classification thresholds defined the shape of the undetermined zone.

Of course, the proposed approach was not intended to replace the human inspection but rather to help neurophysiologists. The position of the point characterizing the seizure on a Cartesian or polar plane gave some interpretation indications during the first phase of a temporal lobe seizure (segmented curves *fdamp(k)* and *fdfreq(k)*). These indications could also be used in a more elaborate automatic decision-aid method: a future research direction focuses on statistical classification algorithms (linear or quadratic discriminant analysis), trained on the present dataset. An important direction of future research is to introduce an automatic detection step and/or a more elaborated segmentation procedure to detect the initial phase of a seizure. Another interesting approach would be to interpret also the temporal evolutions of *fdamp(k)* and *fdfreq(k)* during the segmented interval: if in this paper we concentrated our attention on a static point a view to validate the lateralization method, in future work we will try to analyse the seizures with a dynamical point of view. We think that such an approach may introduce a feedback in the interpretation process. Moreover, we will also assess the lateralizing value of these methods in other types of partial seizures such as frontal lobe seizures, where lateralization of the ictal discharge is even more problematic.

As a summary, the results suggest that, during a seizure, the difference of quadratic mean and dominant frequency computed on each side of the brain are useful to lateralize the seizure onset for partial epilepsy.

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Legends

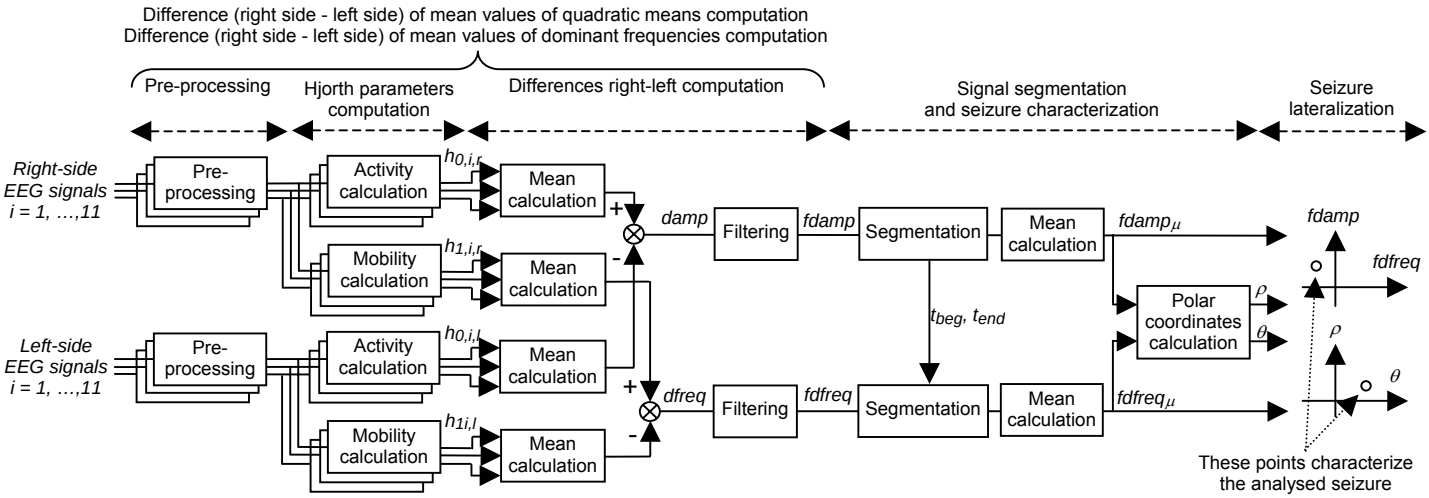

Fig. 1. The different steps of the method.
$h_{0,i,r}$: Hjorth parameter "Activity" (square of the quadratic mean) of the i-th EEG signal of the right side of the brain; $h_{0,i,l}$: same for the left side
$h_{1,i,r}$: Hjorth parameter "Mobility" (dominant frequency) of the i-th EEG signal of the right side of the brain; $h_{1,i,l}$: same for the left side
damp: difference right-left of mean values of quadratic means; *fdamp*: filtered difference right-left of mean values of quadratic means
dfreq: difference right-left of mean values of dominant frequencies; *fdfreq*: filtered difference right-left of mean values of dominant frequencies
t_{beg}: beginning of the first significant change; t_{end}: end of the first significant change
$fdamp_\mu$: mean of *fdamp* between t_{beg} and t_{end}; $fdfreq_\mu$: mean of *fdfreq* between t_{beg} and t_{end}
ρ: magnitude of the point ($fdamp_\mu$, $fdfreq_\mu$) in polar coordinates; θ: angle of the point ($fdamp_\mu$, $fdfreq_\mu$) in polar coordinates

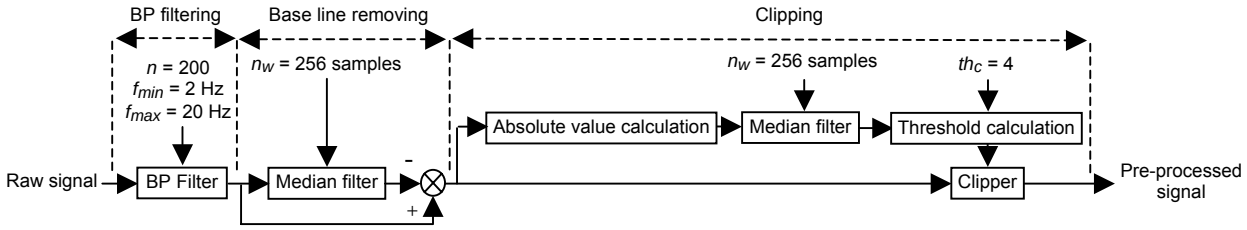

Fig. 2. The different steps of EEG signals pre-processing.

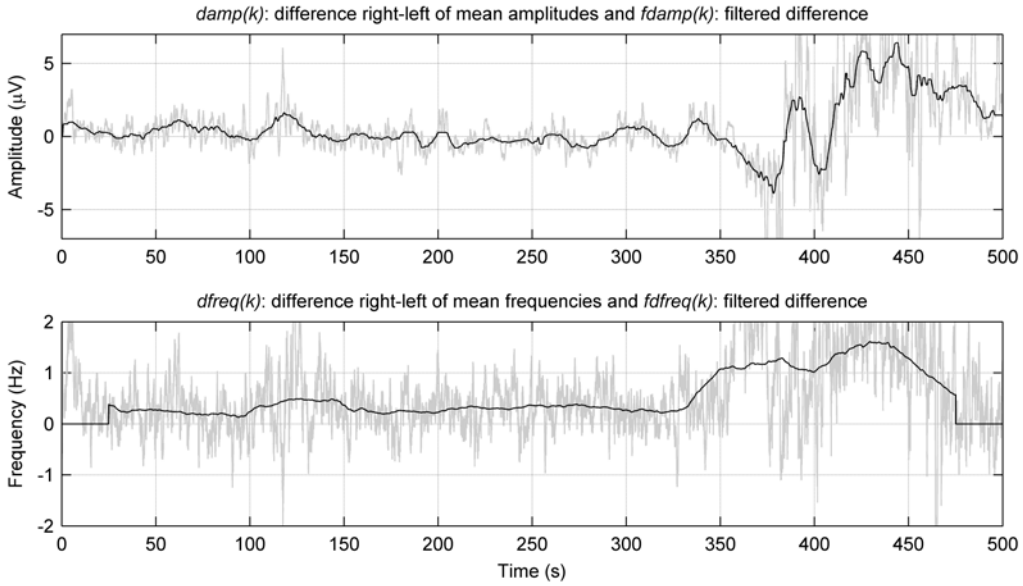

Fig. 3. Example of difference right-left of mean values of quadratic means and dominant frequencies for a left side epileptogenic zone.
The raw differences and the filtered differences are respectively represented by grey lines and black lines.
The seizure begins at t = 350 s. The segmentation step produced t_{beg} = 354 s and t_{end} = 385 s (see 2.7)

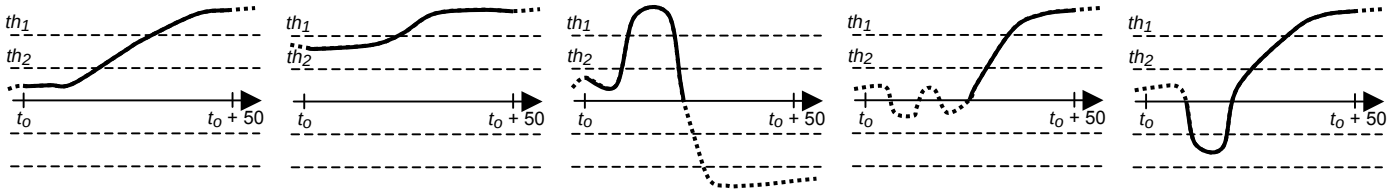

Fig. 4. Examples of possible patterns for the segmentation of the first significant change.
The dotted line corresponds to the signal *fdamp(k)* before segmentation and the solid line to the obtained segment.
t_o: seizure onset time, th_1: threshold for significant change detection, th_2: threshold for small value detection

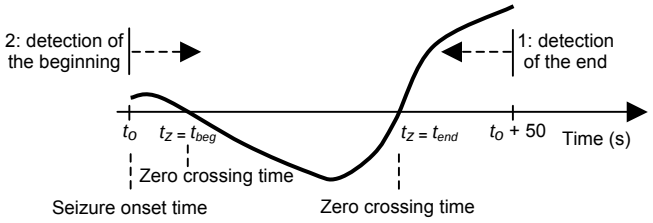

Fig. 5. Segmentation of the first significant change.

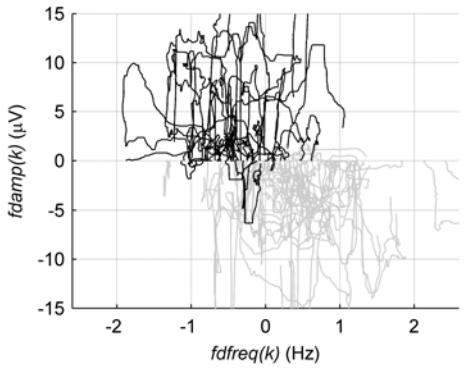

Fig. 6. Filtered difference of mean values of quadratic means *fdamp* against filtered difference of mean values of dominant frequencies *fdfreq*
The grey lines correspond to left-side seizures (*n* = 52) and the black lines to right-side seizures (*n* = 33).

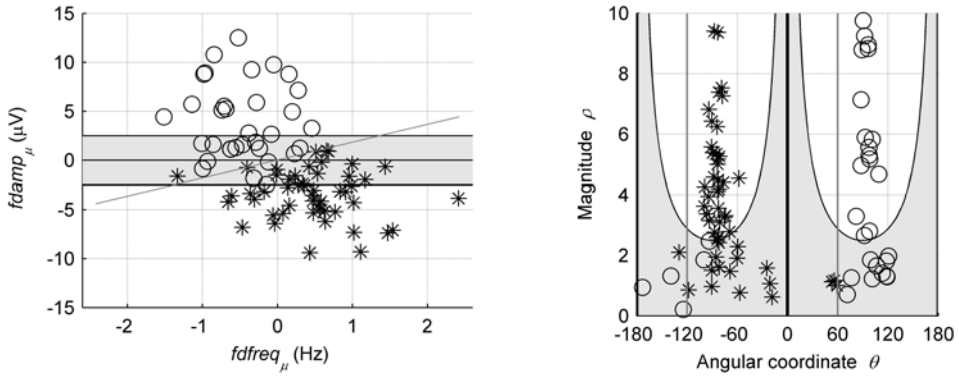

Fig. 7. Cartesian and polar representation of left-side (∗) and right-side (○) seizures.
The shaded zone corresponds to the indeterminacy zone of C_2 criterion.
The grey lines correspond to the separation lines of C_4 criterion.
The angle ϕ is taken equal to 60°.
a) Cartesian coordinates ($fdfreq_\mu$, $fdamp_\mu$)
b) Polar coordinates (θ, ρ)

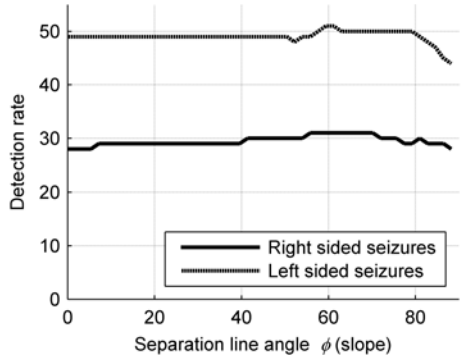

Fig. 8. Good classification rate for different slopes of the separating line.

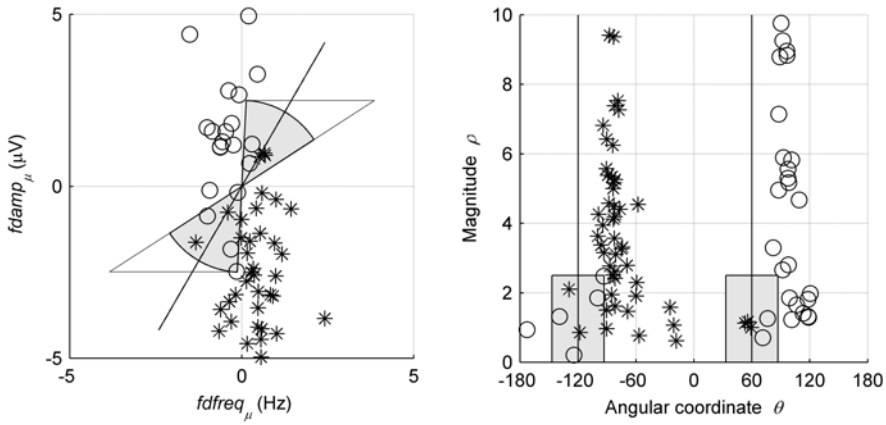

Fig. 9. Cartesian and polar representation of left-side (∗) and right-side (○) seizures with the separating line at $\phi = 60°$ and the shaded indeterminacy zone according to C_5.
The two triangles in figure a) mark the uncertainty zone for C_6 criterion.
a) Cartesian coordinates ($fdfreq_\mu$, $fdamp_\mu$)
b) Polar coordinates (θ, ρ)