Preprints of the 19th World Congress
The International Federation of Automatic Control
Cape Town, South Africa. August 24-29, 2014

Automatic warning of epileptic seizures by SVM: the long road ahead to success

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Abstract: Predicting epileptic seizures would change the life of millions of people. This work presents the results of a large study involving 216 patients with long-term scalp (sEEG) and intracranial (iEEG) records. A high-dimensional features space is built using time series data of 6 channels and 22 features per channel Patient-specific predictors based on SVM are developed and evaluated in relation to sensitivity and false-prediction rate. A substantial number of seizures has been correctly predicted and a comparative study is made with relation to the choice of electrodes, localization lateralization and pre-ictal time duration. For a set of patients the results may be considered of clinical relevance compared to an analytic random predictor.

Keywords: seizure prediction, epilepsy, SVM, biomedical engineering, bio-signal processing.

1. INTRODUCTION

Epilepsy is the second most frequent brain disorder (after stroke) and about 1% of the population in any country will have epileptic seizures sometime in their lives (Duncan et al. 2006). About one third of these are irresponsive to drugs and surgery is not possible (refractory epilepsy). Millions of people must live daily with the agonizing possibility to have a seizure, anytime and anywhere. Their lives are strongly constrained by this possibility, professionally, socially, and emotionally. The aim to build a transportable device that receives the signals captured by the Electroencephalogram (EEG), process them and raises an alarm, if a seizure is predicted, is being pursued since almost 40 years, but progresses are yet very short. For an extensive review see (Mormann et al. 2007). In fact the lack of appropriate datasets, coupled with the lack of good predicting algorithms has prevented this aim. In this work a contribution is given through personalized algorithms, based on Support Vector Machines (SVM) that are developed and applied to a collection of 216 datasets of the European Database on Epilepsy, an outcome of the FP 7 EPILEPSIAE project (Klatt et al. 2012). The study has been developed as illustrated in Figure 1.

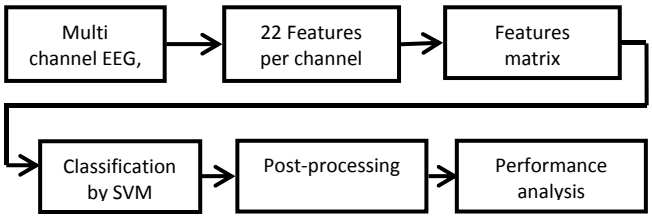


Figure 1. Stages of the study for each patient.

Section 2 presents briefly the used features and the high dimensional features space. SVM classifiers are built in section 3. Section 4 presents the post-processing and performance analysis. Finally results and conclusions are the subject of section 5.

2. THE HIGH DIMENSIONAL FEATURES SPACE

2.1 The features per EEG channel

A channel in EEG is an electrical differential signal captured by an electrode fixed on the scalp (surface EEG or sEEG) or inside the brain (intracranial EEG or iEEG). This raw signal is notch-filtered for 50 Hz and then several features (properties) in time, in frequency and statistic are extracted. Each feature is computed for a moving time window of 5 seconds, from the original signal sampled at 250 to 2500 Hz depending on the patient and on the used technology. Table 1 contains these features. They are compatible with real-time computation made possible by current multi-core technology.

Table 1. Features per EEG channel.

Feature	
AR model error	
Energy	
Decorrelation time	
Hjorth	
Relative power in several bands considered relevant by neurologists	Delta (0.1-4Hz)
	Theta (4-8Hz)
	Alpha (8-15Hz)
	Beta (15-30Hz)
	Gamma band (30Hz-Nyquist frequency)
Spectral edge	Power
	Frequency
Statistics moments	1st Mean
	2nd Variance
	3rd Skewness
	4th Kurtosis
Energy of wavelet coefficients	Six levels

For a detailed description of these features see Teixeira et al. (2011).

2.2 The appropriate number of channels and its selection

For a transportable device to be comfortable, a small number of channels should be considered, but sufficient to capture the space distribution of the signals in each instant. Six electrodes were considered as an acceptable compromise, after discussion with medical doctors and patients (Schulze-Bonhage et al. 2010). The datasets in the European Database on Epilepsy (Klatt et al. 2012) contain 31 sEEG channels or a high number of iEEG channels. The six considered channels have been selected among those by three criteria:

(i) Space coverture criteria, to have a general view of the patient scalp. According to the international 10-20 standard position system these were F7, FZ, F8, T5, PZ, and T6 covering the central, frontal and temporal areas.

(ii) Epileptic focal region and propagation criteria: three were chosen as close as possible to the region were seizure starts and three far away from the initiation point. This is intended to capture the propagation of the tournament brain waves as seizure progresses in time and space.

(iii) Random selection of six among all available electrodes. The selection is made in the beginning of the study and remains fixed until the end.

The 22 features extracted from each one of the six channels are then concatenated into a vector of 132 elements that encodes information from each feature and from the spatial relations between channels.

3. THE CLASSIFICATION PROBLEM BY SVM

3.1 Four brain states (four classes)

The recorded datasets of each patient have been divided into four classes:

(i) Inter-ictal: the normal one, corresponding to more than 90% of the recording time.

(ii) Pre-ictal: just before the seizure starts. There is no clinical definition of it but Mormann et al. (2007) concluded that electrophysiological changes might develop minutes to hours before the seizure. Taking into account the aim of the present work, several values have been considered: 10, 20, 30, and 40 minutes before the seizure which has been identified by trained epileptologist in the EEG time-series.

(iii) The ictal: duration of a seizure, varying from seizure to seizure, in orders of minutes. The end of the seizure is identified also by epileptologist.

(iv) Pos-ictal: after the seizure some time is needed until the brain reverts again to the normal state, and this interval is considered 10 minutes. Since most of the time is inter-ictal, a previous stage of balancing the four classes in the training set has been performed such that the inter-ictal dataset has as many points (randomly selected) as all the other three classes together.

3.2 Classifying by Support Vector Machines

Given the three (or two for the case of iEEG) choices of electrodes subsets and the four different pre-ictal periods considered, the total number of datasets created for each patient is 12 for sEEG and 8 for iEEG. For each one the training subset includes three or two seizures and the testing set contains the remaining seizures.

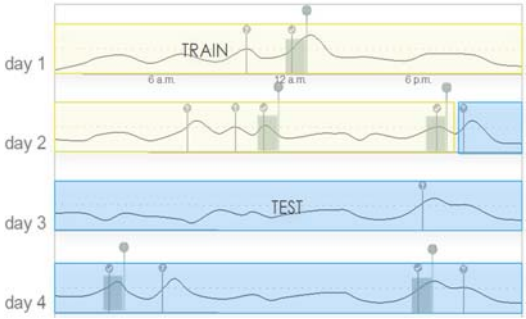
Support Vector Machines (SVM) are considered one of the most effective machine learning tools for classification (Meyer, Leisch, and Hornik 2003), due to their good generalization capability, and few number of parameters to tune. Readers can find a good review of them in (Vapnik 1999; Burges 1998). They date back to the seventies when Vapnik and Chervonenkis (1974) developed the structural minimization concept. Their advantage is the capability to treat problems which are strongly nonlinearly separable. Basically they transform the original space to a higher order space where the transformed data is linearly separable. In this higher space a frontier between the two classes is defined, and its width is optimized through a parameter C. A high value of C causes a thin frontier, while a low C produces a large "no one's land" region. One of the drawbacks of SVM is that the values of C must be found basically by trial and error. The array $[2^1, 2^2. 2^7, 2^{10}, 2^{13}, 2^{16}]$ for C values was used in this study, the best C* was chosen and then the final C was found investigating the best results for the array of neighborhood values $C \in C^*.[2^{-1.5}, 2^{-0.5}, 2^{0.5}, 2^{1.5}]$. We used the libSVM library (Chang and Lin, 2001) implemented in a MATLAB environment.

One of the difficulties of machine learning classifiers is to guarantee that after the classifier is trained it has a good generalization capability for unseen (new) data. To tackle this problem the dataset of each patient is divided into two subsets: the training set and the testing set, the latter built from unseen data.

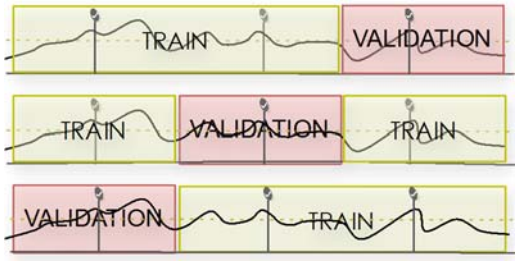
In order to improve the generalization capability, cross validation is used. In cross validation, the training set is further divided into several folds, and one fold is reserved for validation of the classifier trained in the other folds. This allows to prevent the "overfitting" of the SVM, which leads frequently to bad results in the testing set. Fig. 2 shows the general approach for training and testing used in this work. A three-fold cross validation was used (according to the number of seizures in the training set)

However by their nature SVMs are binary classifiers (two classes) and to classify four classes a combination of SVMs is needed. Several strategies may be used (Hsu and Lin 2002). The *one-against-one* technique, considered by (Hsu and Lin 2002) the most suitable, has been used. The technique constructs *k(k-1)/2* SVMs, where *k* is the number of classes (4 in this study). Each SVM is trained on data from only two classes. The final decision is made according to the

voting approach *max wins*, in which the label predicted for an input vector is the one that is voted the most among all classifiers.



(a)



(b)

Figure 2. The training and testing procedures. (a) training and testing sets for a representative patient. (b) the three-fold procedures for training: part of the training set is used for validation.

4. POST-PROCESSING AND PERFORMANCE ANALYSIS

4.1 Regularization of the output

The SVM output is a series of digits labelling the class to which the SVM affects the input vector: 1 for inter-ictal, 2 for pre-ictal, 3 for ictal, and 4 for post-ictal. The SVM classification is a point by point one, but what is needed is the identification of a potential pre-ictal state, so the label 2 is the most important label. Because of classification errors and noise in data, a pure long series of 2 is rarely obtained, but series of labels where the frequency of 2 is high (even if not consecutive) may be considered indicative of a pre-ictal state. So for each dataset a sliding time window equal to the used pre-ictal duration is constantly analysed, and if more than half of the output values in a given window is labeled pre-ictal then an alarm is raised (Teixeira et al. 2011). If a seizure appears (they are annotated in the datasets) within the next preictal time after an alarm, then we have a true positive (TP); if not we have a false positive (FP). If a pre-ictal state is not identified but a seizure finally appears, we have a false negative (FN), and a true negative (TN) occurs if there is no seizure.

4.2 Performance evaluation

Sensitivity (SS) and false predictions rate per hour (FPR) are used for performance analysis, and are defined as follows,

$$SS = \frac{TP}{TP + FN} = \frac{\text{seizures correctly predicted}}{\text{total number of seizures}} \qquad (1)$$

$$FPRh^{-1} = \frac{FP}{\text{interictal duration - (FP} \times \text{SOP)}} \qquad (2)$$

where SOP (Seizure Occurrence Period) is the considered value of the pre-ictal period.

5. RESULTS AND DISCUSSION

The data of 216 patients in the European Database on Epilepsy (Klatt et al. 2012) issued from the EPILEPSIAE project (www.epilepsiae.eu) was used, including sEEG (185 patients) and iEEG (31 patients). This database contains high quality data, and long-term EEG recordings, developed by a joining effort from three epilepsy centers (Coimbra, Paris and Freiburg), with a common annotation in a structured (Oracle) organization. Certified epileptologists from the three centers annotated the onset times, artifacts and epileptiform activity. Sampling rates varied from 256Hz to 2500Hz, depending on the used data acquisition equipment. This study of SVM was made in the University of Coimbra.

5.1 Patients with scalp sEEG

For the sEEG recordings, 932 seizures were considered. Among them 386 (41.42%) were correctly predicted and the average FPR was 0.21 h^{-1}.

For 33 (among 185) patients the best predictors reach sensitivity equal or greater than 50% and false prediction rates less than or equal to 0.25 h^{-1}.

Localization and lateralization

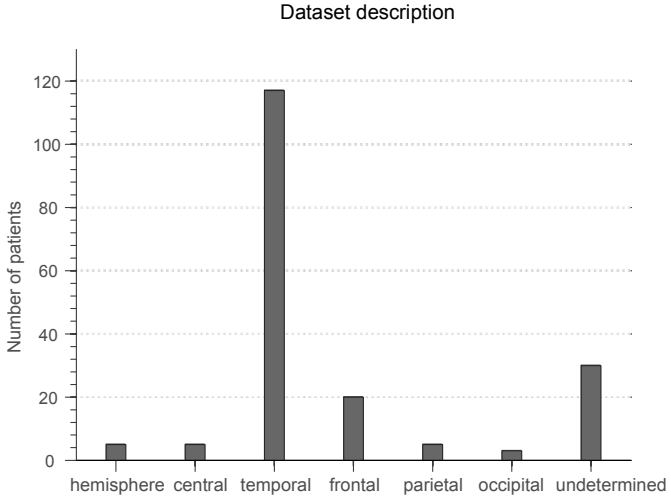


Figure 3. Distribution of epileptic focus localization among the 7 regions of the brain. Most are in the temporal lobe.

Analysing the performance per brain region, the results shown in Fig. 4 are obtained. Seven regions are considered: complete hemisphere, central, temporal, frontal, parietal, occcipital, and underetermined (insuficient information). Fig. 3 shows the distribution of patients among these seven regions. The best results are obtained for frontal and parietal regions.

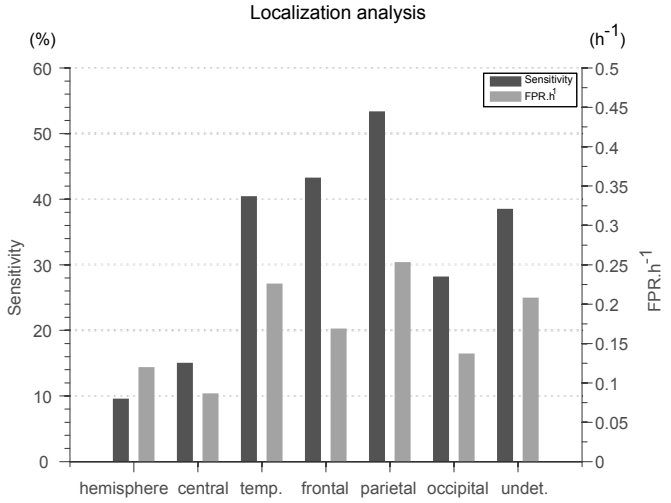


Fig 4 Sensitivity and FPR.h^{-1} grouped according to the type of epilepsy. The best sensitivity is obtained for patients suffering from parietal lobe epilepsy and the lower FPR.h^{-1} are presented when the focal origin lies in the central region.

Fig. 5 presents the results concerning lateralization (left, right, bilateral, and undetermined). The bilateral configuration presents the highest SS but simultaneously a high FPR. Right and left present similar SS; however the right presents a lower FPR.

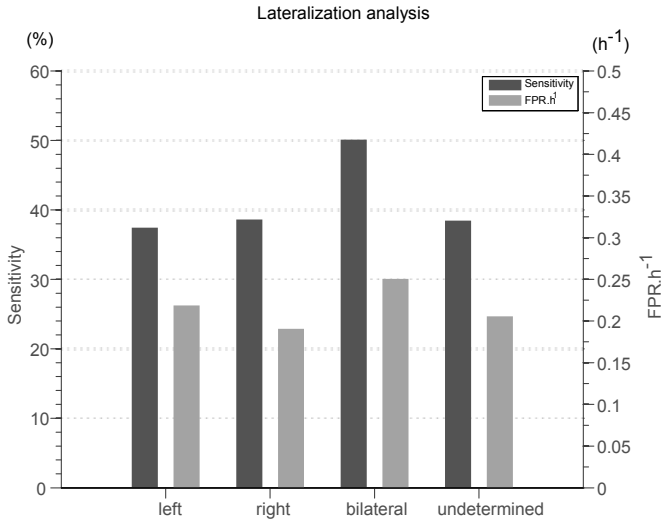


Fig.5. Performance measures grouped according to the lateralization.

Pre-ictal times SOP

The analysis of the average values of SS and FPR, according to the SOP duration, lead to the results of Fig. 6.

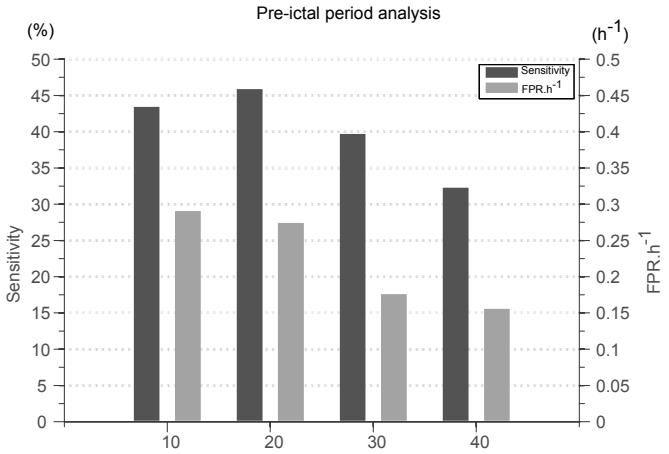


Fig. 6 Average performance by SOP duration. Shorter SOP present higher SS but also higher FPR.

Electrode selection

Fig. 7 summarizes the influence of the electrode selection, presenting the average SS and FPR by selection (considering the best model for each patient).

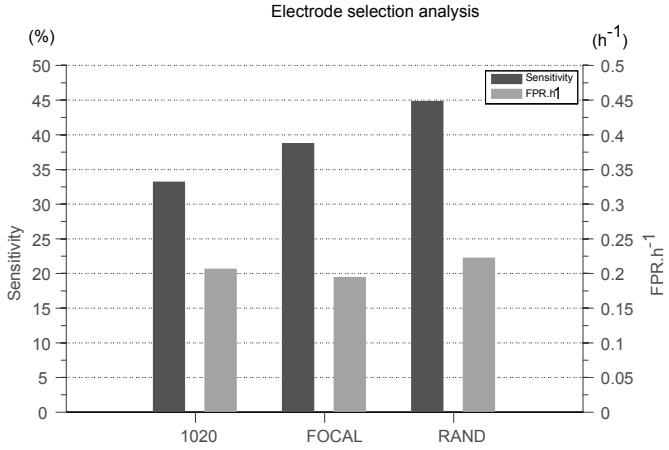


Fig. 7. Average performance by electrode selection.

5.2 Patients with intracranial iEEG

For this intracranial case there is no 10-20 electrode positioning scheme, and so the electrode choices are only random and focal. Keeping the same 4 values of SOP, 8 data sets are available for SVM predictors were trained for each patient in a similar way as for sEEG case.

The testing sets involve 274 seizures from which 28 (28.5%) were correctly predicted with an average FPR of 0.23h^{-1}.

Localization and lateralization

Approximately 42% of the patients in this group presented focal temporal seizures (see Fig. 8).

Figure 9 summarizes the average SS and FPR for the best models grouped by focal region.

Concerning the lateralization, Fig. 10 summarizes the results.

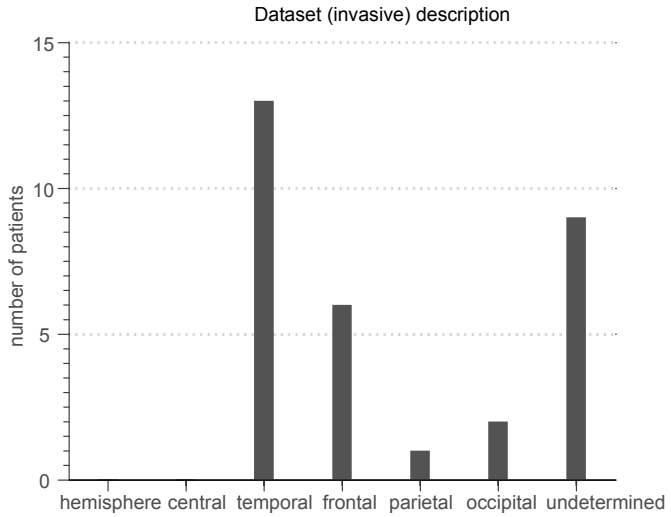


Figure 8. Region distribution of the 31 iEEG patients

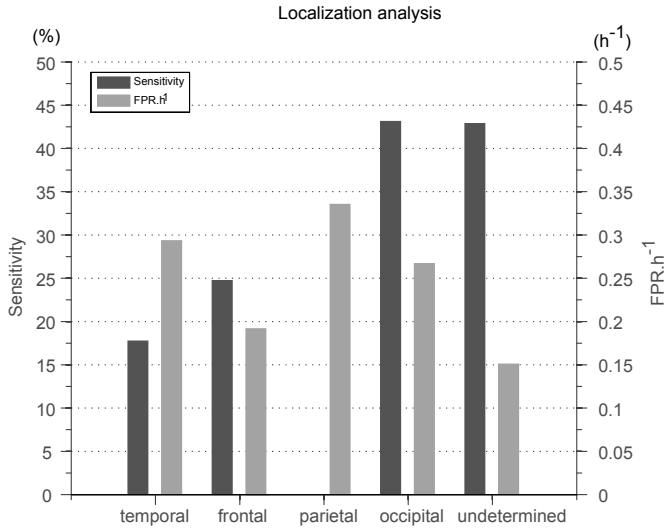


Figure 9. Results obtained grouped by the location of the epileptic focus. The temporal and parietal lobe epilepsy patients present a low sensitivity while occipital lobe epilepsy patients (two patients) present a sensitivity of approximately 50%.

SOP and Electrode selection

The preictal duration influence is shown in Fig. 11: the best results are obtained with a SOP = 30 minutes. This seems an interesting value to plan an intervention to disarm the seizure.

Concerning the selection of the electrodes, there is no significant difference between the two studied possibilities, as shown in Fig. 12.

5.3 Statistical analysis

In order to measure the statistical significance of the results with respect to the so-called "random predictor", the analytic random predictor proposed by (Schelter et al. 2006) was used.

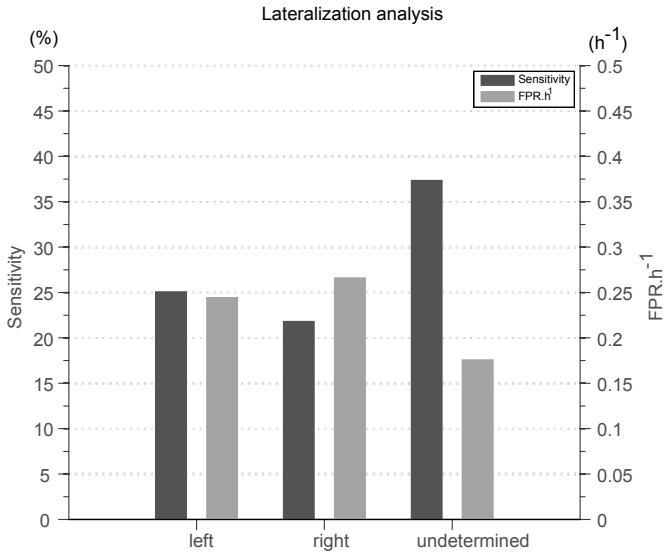


Figure 10. Results grouped according to lateralization of the epileptic focus (average values of the best predictor for each patient).

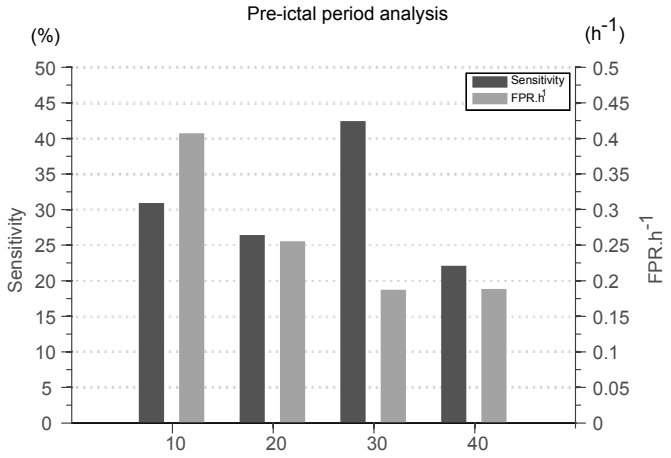


Figure 11. Average performance per SOP values (in the horizontal axis)

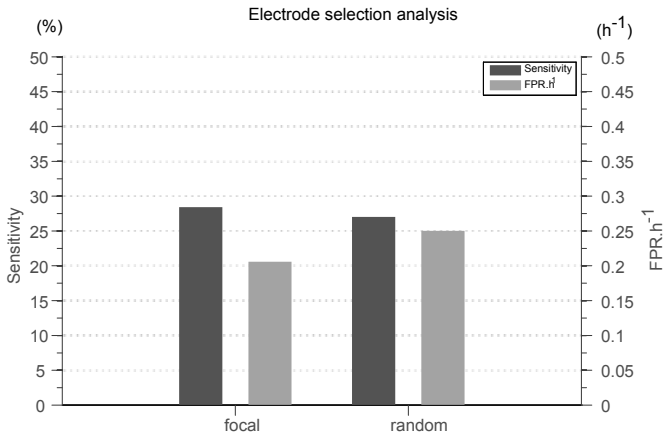


Figure 12. Influence of the selected electrode array.

Although this predictor is rather conservative in its hypothesis, as it tends to despise predictors that resulted from the choice of a high number of possibilities, as in this study,

it can give some insights into the clinical usability of the predictors. Finally it tries to answer the question: suppose that in a given instant you decide by chance if there will come a seizure or not. Does your predictor perform better than chance? The limitations of the random predictor lies in the following fact: if you decide by chance twice (in the same instant) you will have 50% of the hypothesis to decide differently, while if you have a trained predictor it will act time invariant by giving the same output for the same input independently of the times you predict and independently of the way you obtained the predictor. This is an interesting question, because there is the need to sustain the results issued from a high number of values of parameters and conditions, leading to a high number of predictors that are applied and compared. In the authors' opinion this issue is not yet tackled in a sound statistical way.

In any case the "analytic random predictor" of Schelter et al.,(2006) gave the following results:

- For the sEEG patients, the best SVM found in this study is better than the random predictor for 19 patients (10.3%). The results were considered statistically significant to a binomial distribution test at the group level (5% significance level); the p-value obtained was 0.0025.

- For iEEG patients, the results are above the random predictor for 5 patients (16.1%). The same binomial statistical significance as in sEEG was used.

Discussion

The results strengthen one conclusion: for each patient there exists a best predictor, and it is different from all of the others. There is no general clear tendency for any of the alternatives of pré-ictal phase, electrodes, localization, and lateralization. For each patient a high number of predictors must be trained, and the best must be chosen. This brings up the fundamental question: how can this be done in real time, for a transportable predictor?

In the authors' opinion any perspective for a transportable device must include a phase of customization and training: the patient must carry the device for a considerable time only for data acquisition and predictors training (without feedback and alarming) and the training requires probably the transmission of the data to a medical computer center where specialists will customize and train some predictors for the patient. The obtained predictors should then be downloaded into the transportable device to be run in real time and now with active alarming capability.

The minimum performance acceptable in clinical judgment is sensitivity greater than 50% (more than half of the seizures are well predicted) and FPR=0.15 h^{-1} (one false alarm at most every 6 hours).This is not obtained for most of our patients. More research is needed for better predictors.

Moreover there is another important question. Are the features used in this study the best ones? This is the main research point. Probably other types of features are needed, with a more discriminant capacity, improving the classification performance. The present study does not consider all the medical knowledge. Fusing physiologic knowledge with pure data-driven approaches is probably the way to get better solutions that can be accepted by the medical community and finally allowing to reach the ultimate goal: to make refractory epileptic people lives more safe, social and happy.

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Acknowledgements: This work was partially supported by Epilepsiae FP7 Grant 211713 and iCIS MAISCENTRO project CENTRO-07-0224-FEDER-002003. Mojtaba Bandarabadi would particularly like to acknowledge the Portuguese Foundation for Science and Technology (FCT- SFRH/BD/71497/2010). .