Epileptic seizures prediction based on the combination of EEG and ECG for the application in a wearable device

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Abstract—Epilepsy is a neurological disorder characterized by recurrent and sudden seizures. Recently, researchers found that patients often present physiological abnormalities that precede an epileptic seizure onset. Importantly, these modifications can vary a lot among patients. While the conventional methodology for characterizing epilepsy is electroencephalogram (EEG), some evidences show that electrocardiogram (ECG) can be also useful to assess modifications associated to seizures. In this paper, a preliminary study about the integration of EEG and ECG for a patient-specific seizure prediction is presented. Synchronization patterns from the EEG and time and frequency features, as well as recurrence quantification analysis measures from the inter-beat (RR) series, were extracted. A support vector machine (SVM) classifier was then applied to classify preictal and interictal phases combining features extracted from the two signals. Results showed that, using the proposed combined approach, it is possible to predict the epileptic seizure onset with a total average sensitivity of 93.3%, specificity of 80.6% and a prediction time of about 20 min. This approach could be implemented in portable and wearable devices for a real-life patient-specific seizure prediction.

Keywords—epilepsy; electroencephalogram; electrocardiogram; recurrence quantification analysis; support vector machine; synchronization.

I. INTRODUCTION

Epilepsy is a neurological disorder [1], characterized by “epileptic seizures”, with a significant social and sanitary impact, both due to its quite high incidence and chronicity. Indeed, it is estimated that the lifetime prevalence of epilepsy is around 7.60 per 1,000 persons, whereas its incidence rate appears to be of 61.44 per 100,000 person-years [2]. The most widely applied treatment in epilepsy is the pharmacological one and, to a lesser extent, surgery. However, antiepileptic drugs have limitations [3] and are effective in about 2/3 of the patients, whereas the remainder 1/3 of patients is affected by drug-resistance, while surgery is not always possible. Thus, it is extremely clinically relevant to investigate the possibility of predicting the occurrence of epileptic seizures in advance (i.e., detecting a pre-ictal or pre-seizure state), in order to take actions to neutralize an incoming seizure or limit the injuries of a seizure occurrence (e.g., by warning alarms, through the application of short-acting drugs or electrical stimulation).

Commonly, epilepsy is diagnosed by means of electroencephalogram (EEG), which is able to detect changes in neuronal activity occurring during an epileptic seizure. Such changes normally occur within the crisis, but in some instances, they precede the seizure by a few seconds [4]. In particular, several works in the literature investigated the relationship between ictal, and preictal, states and synchronization patterns in EEG, showing that the dynamics of epilepsy can be highlighted through the study of synchronization phenomena [5,6].

Aside those evidences related to the neural activity, modifications were observed in the activation of the Autonomic Nervous System (ANS). The rationale for this association is linked to the fact that modifications of the global state of the organism, also induced by modulations of the ANS activity, often bring to variations of the neuronal microenvironment, in turn producing a change of the activation state of several neuronal populations [7]. Some studies have used both time- and frequency-domain features of the Heart Rate Variability (HRV) and observed the possibility of predicting seizures several minutes in advance [8,9]. Our group has previously developed...
algorithms for seizure prediction using scalp EEG or electrocardiogram (ECG) data, following a patient-specific approach [10-12]. In addition, previous studies have shown the capacity of improving seizure detection through the combination of EEG and ECG features [13,14]. In addition, few preliminary studies have been performed showing the possibility of using both the two signals for seizure prediction [15,16]. However, these studies did not combine features extracted from the two signals in a classification approach for a better prediction. Thus, we tested a Support Vector Machine (SVM) classification approach by combining features extracted from both scalp EEG and ECG.

Notably, seizure prediction studies can be broadly divided in two types: analysis-oriented, and prediction-oriented. In analysis-oriented studies, the focus is on analyzing the statistical properties of pre-seizure states, while prediction-oriented ones are focused on developing predictive algorithms [17]. The present study can be considered as an analysis-oriented study with regard to choosing features, which are associated with good discrimination of the pre-seizure state. Once the classifier is trained to recognize pre-seizure state, it can be applied to predict future pre-seizure events. In this sense, the classification strategy used in this study can be considered a prediction approach.

Importantly, the selection of non-invasive techniques would allow an easy real-time use of the proposed method also in portable and wearable devices, possibly able to notify patients and/or caregivers, or to take automatic actions to reduce the injuries, the severity of seizures, or to prevent them entirely.

II. METHOD

The proposed approach consists in an initial step of EEG and ECG signals preprocessing followed by feature extraction and selection. Then, a classification method, based on SVM, is implemented with the aim of accurately classifying pre-ictal and interictal segments in a patient-specific way. The block-diagram of the proposed approach is represented in Fig 1.

A. Data

The database consisted of 6 patients (2 females; 4 males; age 20.4±9.3 years) admitted at the Unit of Neurology and Neurophysiology, Department of Neurological and Neurosensorial Sciences, University of Siena, Italy. The patients were long-term monitored with a Video-EEG with a sampling frequency of 512 Hz, with electrodes arranged on the basis of the international 10-20 system. Simultaneously, ECG was acquired using three electrodes: two on the thorax and the third (reference) on the scalp, with a sampling frequency of 512 Hz. The registration length differed among subjects and ranged from 6 to 19 hours. The onset of the seizure was identified as the earliest seizure-related change in behavior (as observed on the video recording) or EEG (a modification in the EEG typical pattern associated with an epileptic seizure as recognized by two expert epileptologists). The seizure classification was performed according to the criteria of the International League Against Epilepsy (ILAE) [18]. Table I provides a detailed overview of the dataset.

The study was approved by the Ethical Committee of the University of Siena and performed in accordance with the Declaration of Helsinki. All the patients signed a written informed consent.

B. EEG signal preprocessing

A number of manipulations have been performed on each EEG signal (for a detailed description, see [10]). EEG signals were first filtered on pre-specified frequency bands and then differentiated (i.e., the absolute value of the time-derivative of the signal is computed [19]).

![Figure 1: Block diagram of the proposed approach.](image-url)
The filtering process allows the selection of the band of frequencies of interest, possibly removing undesired artifacts. As shown in [19, 20], differentiating makes the basic noise nearly flat and sharpens the regions where the signal exhibits its peaks, which are most likely to be the regions where seizures occur. Then, EEG signals are segmented into consecutive time-windows, possibly overlapping, of N points each, on which synchronization measures are computed, as detailed in sub-Section D. In our experimental results, we employed time windows of 6 s with an overlap of 1 s.

C. ECG signal preprocessing and RR reconstruction

ECG signals were first preprocessed, then, the RR was reconstructed and corrected. For a detailed description of these steps, see [11]. Briefly, pre-processing steps allowed to correct for impulsive artefacts, powerline interference (50 Hz) and baseline wandering and to improve signal-to-noise ratio. After these steps, the signal was interpolated to 1024 kHz (multiple of the sampling frequency) with Fourier transform method to get a precise time location and the QRS complexes were detected to reconstruct the inter-beat (RR) series. Finally, an algorithm was applied for the recognition and correction of non-sinusoidal beats to obtain a RR series that only contains variations due to the extension of PLI.

In WPLI, each phase difference is weighted according to the frequencies of interest, possibly removing undesired artifacts. Then, EEG signals are segmented into consecutive time-windows, possibly overlapping, of N points each, on which synchronization measures are computed, as detailed in sub-Section D. In our experimental results, we employed time windows of 6 s with an overlap of 1 s.

D. EEG features extraction

Given a patient dataset with n EEG channels, 2n features were extracted from the EEG signals. The features were computed by employing recently introduced phase-synchronization measures, namely, Phase Lag Index (PLI) and Weighted Phase Lag Index (WPLI). PLI has been introduced in [21], for the assessment of functional connectivity in the brain, and WPLI has been introduced in [22], as an extension of PLI.

Given two time series, \( x_h(t) \) and \( x_k(t) \) (e.g., related to two EEG channels) and a time window \( \Delta t \) containing N time instants, PLI and WPLI were defined as follows:

\[
PLI_{h,k,\Delta t} = \frac{1}{N} \sum_{p=1}^{N} \text{sign} (\phi_h(p) - \phi_k(p))
\]

(1)

\[
WPLI_{h,k,\Delta t} = \frac{1}{N} \sum_{p=1}^{N} \sin (\phi_h(p) - \phi_k(p))
\]

(2)

where \( \phi_h(p) \) and \( \phi_k(p) \) being the phases at time instant \( p \) of signals \( x_h(t) \) and \( x_k(t) \), respectively, which are determined by the Hilbert transformation. PLI is based on the idea of discarding the phase differences that center around 0 (mod \( \pi \)) and quantify the asymmetry of the distribution of phase differences around zero. In WPLI, each phase difference is weighted according to the magnitude of the lag. As a consequence, phase differences around zero only marginally contribute to the calculation of the WPLI. Both PLI and WPLI take values in \([0,1]\), where 0 indicates that no phase locking occurs and 1 is a perfect phase locking.

Given a channel \( h \), for each time window \( \Delta t \), two values are computed as follows:

\[
PLI_{h,\Delta t} = \sum_{k \neq h} PLI_{h,k,\Delta t}
\]

(3)

\[
WPLI_{h,\Delta t} = \sum_{k \neq h} WPLI_{h,k,\Delta t}
\]

(4)

As consequence, for each channel \( h \), two time series are generated by Formulas (3) and (4), computed over all the time windows \( \Delta t \). The features are then obtained by applying a moving average procedure to the time series generated so far (see [11] for details).

E. ECG features extraction

Twenty features were extracted from the RR series (180 s windows, 60 s of overlap). As time-domain features, we computed mean of RR intervals (MeanNN - s), root mean square of successive differences (RMSSD - s) standard deviation of RR intervals (SDNN - s), number of pairs of adjacent RRI whose difference is more than 50 ms (NN50), value of NN50 divided by the total number of N-N (R-R) intervals (PNN50), variance (s), standard deviation of projection of each of the Poincaré plot points on the line perpendicular to the line of identity (SD1 - s), standard deviation of the projection of each of the Poincaré plot points on the line of identity (SD2 - s), the Cardiac Vagal Index (SD1/SD2), the Cardiac Vagal Index (log10(SD1 x SD2)), the Coefficient of Sample Entropy (CoSEn), designed for short RR intervals, and the Katz Fractal Dimension. As frequency-domain features, we calculated the normalized power of the low frequency band (0.04 Hz - 0.15 Hz) (LFn, n.u.), the normalized power of the high frequency band (0.15 Hz - 0.40 Hz) (HFn, n.u.) and the ratio LF/HF. In addition, Recurrence Quantification Analysis (RQA) features were computed (Recurrence Rate (%): quantifies the percentage of recurrent points, Determinism (%): the ratio of recurrence points on the diagonal structures to all recurrence points, Laminarity: the length of the longest diagonal line segment in the RP, excluding the main diagonal line, Entropy: the Shannon entropy of the frequency distribution of the diagonal line lengths, LMAX: the length of the longest diagonal line segment in the RP, excluding the main diagonal line and the Trapping Time: the average length of vertical line structures) [23].

F. EEG and ECG features combination

Given the different dynamics of EEG and ECG signals (i.e. the dynamic of the ANS is slower than that of the brain), features from the EEG were obtained using time windows of 6 s with an overlap of 1 s, while features from ECG were extracted in windows of 180 s with 60 s of overlap. Thus, features from the EEG were successively averaged on 180 s windows in order to get both EEG and ECG features in 180 s windows. A combined database, including EEG and ECG features, was built.

G. Segmentation of features vectors

Each vector of features was then segmented as:

- pre-ictal - from x minutes prior to the seizure onset to the onset;
Different prediction horizons (PHs), i.e. the value of \( x \), were tested: 5, 15 and 30 min. Since Patient 4 had not enough signal registration before the seizures’ onset, for this patient only a PH of 5 min was tested.

### H. Features selection and classification

Stepwise regression analysis was applied for feature selection to the database including both the EEG and ECG features. Notably, this step was patient-specific, i.e. different features were selected for each patient, as it was previously done in literature [17]. This allows to consider the huge variability in seizures that exists among the different patients. Specifically, stepwise regression analysis was applied on the whole database of EEG and ECG features of each patient (including both interictal and ictal segments) and then the selected features were used to build each individual predictive model via a SVM. The subset of selected features was found to vary among the different patients [see 11]. A binary SVM classification with kernel function (optimized for each patient) was then applied to classify RR segments as either preictal or interictal. Cost-sensitive SVMs (CSVMs) was used since the datasets were unbalanced (i.e. the number of interictal segments was much greater than the number of preictal ones) as in [17]. A double-cross validation was adopted to predict a seizure block (preictal + interictal) based on the others. Data were partitioned into two subsets: training set and test set. The training set was further separated into learning set (80%) and validation set (20%). A leave-one-out approach was applied with 5-fold cross validation: in a patient with \( N \) seizures, we used one seizure block for testing set and the other (\( N - 1 \)) blocks for training set. The average performance was then computed.

### I. Performance evaluation

The results were assessed in terms of sensitivity, specificity and the percentage of false prediction rate per hour (FP/h, %). The FP/h was calculated as the number of windows identified as pre-seizures segment outside the preictal period divided by the duration of the interictal period. This is an important measure indicating how many false alarms are provided. Sensitivity was set to 100% if at least one pre-seizure window was correctly classified. The prediction time was also calculated as the time interval from the first element of the feature vector correctly classified as “pre-seizure” and the seizure onset.

### III. RESULTS

In Table II, the classification results on the test seizures by the trained-SVM are reported for each PH. The average performance, calculated as the mean of the performances obtained for each seizure, is displayed for each patient. The average performance for all patients is also reported. To better represent the performance of the algorithm, the average performance in terms of sensitivity and specificity of the SVM classifier for the three different tested PHs is represented in Fig. 2. It can be observed that the PH of 30 min was the one that provided the best performance.

### IV. DISCUSSION

In this study, we proposed a method to predict seizures based on the combination of EEG and ECG features and a machine learning approach. To the best of our knowledge, although other studies have applied such a combination for seizure detection [13,14], this is the first attempt to combine EEG and ECG features for seizure prediction. Indeed, previous pilot studies considering the two above-mentioned signals for prediction did not combine the information provided by such signals. Specifically, in [15] the authors just observed that EEG and R-R interval dropped down simultaneously before seizure onset, while in [16] the classification was applied to the two signals.
separately. Thus, our study showed, for the first time, the good performance that can be obtained in the challenging task of seizure prediction combining the two signals.

The results obtained by the present study show that the combination of the synchronization measurements calculated on the EEG and the features characterizing HRV, including RQA measures, seems to provide good performances in seizure prediction. Three different PHs were tested in order to find the optimal time frame allowing an efficient prediction, i.e. with a good sensibility and specificity. We observed that, with a PH of 30 min, the performances are quite good, especially concerning the sensitivity, with an average sensitivity of 93.3%. It can be observed that the proposed approach seems to be more efficient in those patients featuring repeatable and stereotypical seizures, i.e. patients with IAS type of seizures.

The inclusion of the predictive information contained in the features extracted from the synchronization measurements calculated on the EEG allows to estimate a patient-specific classifier where the rate of false positives per hour drops compared to the use of the ECG alone, while the prediction time increases compared to the use of EEG alone as obtained in our previous research [10-12]. This result leads to the conclusion that the integration between ECG and EEG signals is essential for improving the performance of the epileptic seizure system. However, the value of Fp/h (10.7) is still quite high, overestimating the risk of a seizure, possibly triggering unnecessary alarms to the patient. Thus, future research should be addressed at improving the specificity of the algorithm.

Importantly, the prediction time obtained with our algorithm is large enough to suggest the patient stopping their potentially at-risk activities, and possibly preventing the seizure by administering a rapid, effective pharmacological treatment (in case of drug-sensitive epilepsy).

An important aspect of this work is the patient-specific approach. We decided to adopt this strategy given that EEG and ANS response can vary a lot among different patients according to several factors, the most important of which are the localization of the seizure, the lateralization and the use of drugs [24]. Therefore, a universal approach, defined for all patients independently from their disease’s characteristics, would fail in effectively classifying a seizure block, thus potentially affecting the positive outcome of the preventive strategy and, in some instances, of the treatment. Indeed, according to the variability in the classification performance for the different patients or seizures, we conclude that quite a large between-patient and within-patient variability exists in the autonomic response associated to seizures, thus a patient-tailored, or even seizure-specific approach, rather than a one-fits-all system and features, should be adopted and realized for individualized alarm systems.

In a larger sample, it would be possible to apply the SVM classification in different homogeneous subgroups to evaluate how the performances change according to the different characteristics of the subjects, including seizure location, lateralization and patient condition (sleep or awakening).

Given the non-invasiveness of the used signals, as well as the quite low computational cost of our developed algorithm, the proposed approach can be easily implemented in a wearable device for real-time use. In this framework, a wearable prototype based on the OPEN-BCI technologies has been developed, implementing our seizure prediction approach. The device embeds two main software modules:

- A first module for real-time collecting EEG and ECG signals and computing the features, as described in Sections II.B-II.G.
- A second module for operating a real-time binary SVM classification on the features provided by the first module.

In the second module, the SVM classifier operates on the features provided by the first module considering them as testing data, on which to operate a binary classification. The feature selection and the training of the SVM classifier are not executed by this module, but are performed off-line (before the real-time use of the device) on the historical data of the specific patient, and given as inputs to the module before the real-time use of the device.

Preliminary testing have been performed using this prototype, which showed the feasibility of using this system for monitoring interictal and ictal activity.

V. CONCLUSION

Overall, the findings of the present work highlight the occurrence of significant changes in EEG and ANS activity several minutes before the onset of epileptic seizures. As mentioned above, this relatively large time frame can allow the patient stopping their potentially risky activities, and administering them a rapid pharmacological treatment in case of drug-sensitive epilepsy.

Future research directions include the testing of our approach on larger datasets, and the real-time application of the proposed classifiers for their implementation on the wearable devices for real-life use.

REFERENCES


