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An Entropy-Based Approach to Predict Seizures in Temporal Lobe Epilepsy Using Scalp EEG

Ali Shahidi Zandi*, *Student Member, IEEE,* Guy A. Dumont*, *Fellow, IEEE,* Manouchehr Javidan†, and Reza Tafreshi‡, *Member, IEEE*

Abstract— **We describe a novel algorithm for the prediction of epileptic seizures using scalp EEG. The method is based on the analysis of the positive zero-crossing interval series of the EEG signal and its first and second derivatives as a measure of brain dynamics. In a moving-window analysis, we estimated the probability density of these intervals and computed the differential entropy. The resultant entropy time series were then inspected using the cumulative sum (CUSUM) procedure to detect decreases as precursors of upcoming seizures. In the next step, the alarm sequences resulting from analysis of the EEG waveform and its derivatives were combined. Finally, a seizure prediction index was generated based on the spatio-temporal processing of the combined CUSUM alarms. We evaluated our algorithm using a dataset of ∼21.5 hours of multichannel scalp EEG recordings from four patients with temporal lobe epilepsy, resulting in 87.5% sensitivity, a false prediction rate of 0.28/hr, and an average prediction time of 25 min.**

I. Introduction

Epilepsy is a common chronic neurological disorder, affecting almost 60 million people around the world [1], and is associated with recurrent, unprovoked seizures. Epileptic seizures result from a sudden disturbance of brain function which is characterized by abnormal discharges of cortical neurons recruiting neighboring cells into a critical mass.

Medication and surgery fail to completely control seizures in about 25% of patients [1]. As a result, several studies have addressed forewarning algorithms for epileptic seizures using the electroencephalogram (EEG) [2], [3]. Not only would a reliable seizure prediction procedure enable clinicians to control seizures by administering the therapeutic agents as early as possible, it would also improve the quality of life and safety for patients with epilepsy.

Since the surface EEG is often being affected by different types of artifacts and noise, most epileptic seizure prediction algorithms have been derived from analysis of intracranial recordings [4]–[7]. However, extending the seizure anticipation techniques to the scalp EEG has been the objective of research [8], [9] to make them more clinically applicable. Iasemidis *et al.* [7] proposed an adaptive seizure prediction algorithm, based on the convergence of the short-term maximum Lyapunov exponents of the critical electrodes in the preseizure phase. Applying this method to a dataset of intracranial recordings, more than 80% of the seizures were predicted with an average prediction time of 71.7 min. and a false prediction rate of 0.16/hr. Analyzing the depth EEG recordings using the correlation dimension as a measure of complexity, Lehnertz *et al.* [4] found that the complexity dropped prior to the seizure onset and remained significantly below a specific threshold. In another study [5], a similarity measure was developed for intracranial recordings to compare the current dynamics with a reference constructed from a long-term interictal period. The study showed that the similarity measure decreased during the preseizure period gradually and reached its minimum value at the ictal phase. This method was also later applied to the scalp EEG [8]. The phase synchronization between different recording sites was also studied to anticipate the seizure onset [6], [10]. These studies reported significant changes in synchronization between EEG channels during the preictal period in most cases. This enabled prediction of the seizures several minutes before the onset.

In this paper, we propose an approach to predict epileptic seizures by analyzing the entropy level corresponding to the positive zero-crossing intervals in the surface EEG and its derivatives. In Section II, the details of our method are described. Section III is devoted to present the results of this approach. The scalp EEG recordings from four patients with temporal lobe epilepsy (TLE) were used to evaluate the method. Finally, the paper is concluded by Section IV with some directions for future work.

II. Methods

One scenario which is usually considered to describe the evolution of partial epileptic seizures maintains that there are long-term gradual dynamic changes leading to the ictal state. Indeed, it emphasizes the existence of a preictal state which can be considered as a transition from the interictal to the ictal state and is supported by some clinical findings [3]. In the following paragraphs, details of our method to predict epileptic seizures based on preictal changes are described.

A. EEG Underlying Dynamics

We propose a real-time, patient-specific prediction algorithm based on a moving-window analysis of scalp EEG recordings. In this approach, instead of the conventional time-delay embedding approach [11], the dynamics of EEG signals are analyzed based on the time intervals between the successive positive zero-crossings (passing from negative to positive values) [12], [13]. One of the advantages of this

*Department of Electrical & Computer Engineering at The University of British Columbia (UBC), Vancouver, BC, V6T 1Z4, Canada
†MD, FRCPC, Division of Neurology, Department of Medicine at The University of British Columbia (UBC); Director, Neurophysiology Lab. at Vancouver General Hospital (VGH), Vancouver, BC, V5Z 1M9, Canada
‡Department of Mechanical Engineering at Texas A&M University at Qatar, Doha, P.O. Box 23874, Qatar

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approach is its robustness against noise [5]. Accordingly, since the surface EEG contains different types of noise and artifacts, this approach removes the noise components to some extent. Suppose T_m is the time of the mth positive zero-crossing in an EEG epoch after detrending; then, we can represent this epoch with a M-dimensional vector defined as $V = [I_1, I_2, \cdots, I_M]^T$ where $I_m = T_{m+1} - T_m$, $m = 1, 2, \cdots M$, and M is the total number of intervals. The probability density function (PDF) of I_m in each epoch is then used to characterize EEG dynamics. We employ the kernel density estimation [14] as a nonparametric approach to estimate the PDF of zero-crossing intervals. Given N data points $\{x_1, x_2, \cdots, x_N\}$ of an unknown PDF, $p(x)$, the kernel estimator with kernel K is defined as

$$\hat{p}(x) = \frac{1}{Nw} \sum_{j=1}^{N} K\left(\frac{x - x_j}{w}\right) \tag{1}$$

where w is the smoothing parameter, also called the window width. Choosing a Gaussian kernel in this work, we estimate the window width by

$$w = \sigma \left(\frac{4}{3N}\right)^{1/5} \tag{2}$$

where σ is the estimated standard deviation of data. This equation results in an optimal window width for a normal PDF [14] and a suboptimal estimation for non-Gaussian distributions.

In addition to the EEG signal, we also include the first and second derivatives of EEG in characterization of the underlying mechanisms. Empirically, we have found that preictal changes of the distribution of positive zero-crossing intervals are more pronounced in EEG derivatives than EEG in some cases. In fact, by including the first and second derivatives of EEG, we also analyze the PDF of intervals between the extrema (1st derivative) as well as saddle points (2nd derivative). To reduce the effect of noise and artifacts and improve the specificity of the method, it is first necessary to define a range of acceptable positive zero-crossing intervals (AZI) which is patient-specific. Indeed, we only consider the values lying in this range in estimation of the PDFs and recognize the rest as outliers. Here, we determine AZI based on the power spectral density of EEG waveforms during the ictal period. That is, analyzing the EEG in the seizure period, we can define a rough frequency range $[f_0, f_1]$ characterizing the ictal activities. This frequency band is then extended to $[f_0(1-\delta), f_1(1+\delta)]$, and AZI is defined as $[1/f_1(1+\delta), 1/f_0(1-\delta)]$ where $0 \le \delta \le 1$. The dominant frequency band of the ictal period does not change significantly from one seizure to another for a specific patient. Thus, for each patient, analyzing one seizure episode and choosing a specific δ, we can define the AZI range properly.

B. Entropy as a Measure of Irregularity in EEG

Epileptic seizures can be interpreted as manifestations of the brain transitions from chaos to order [15]. By monitoring the irregularity level of EEG, it would be possible to characterize these dynamic changes. In this work, the PDF of positive zero-crossing intervals for the nth epoch in the EEG signal and its first and second derivatives are estimated, respectively named $\hat{p}_n^0, \hat{p}_n^1$, and $\hat{p}_n^2$. Then, the differential entropy [16] of each PDF is calculated by

$$h(X) = -\int_{-\infty}^{\infty} p(x) \log p(x)\, dx \tag{3}$$

where $p(x)$ is the given PDF. As approaching to the seizure onset, the synchronization of neuronal activities increases which is associated with a loss/reduction of inhibitory mechanisms. As a result, we expect the entropy decreases during the preictal period and reaches the lowest value as the seizure happens. Therefore, applying a change detection procedure to the resulting entropy time series, we are able to make alarms for impending seizures.

C. Upcoming Seizure Alarm

To detect decreases in the entropy time series, we employ an one-sided cumulative sum (CUSUM) procedure [17]. As a robust statistics, CUSUM minimizes the detection delay for any fixed false alarm rate [18]. Let us define the three entropy time series as $\{h_n^0\}$ (EEG), $\{h_n^1\}$ (1st derivative), and $\{h_n^2\}$ (2nd derivative), where n represents the epoch number and h_n^i is computed by (3) from $\hat{p}_n^i$ (i = 0, 1, and 2). Then, the one-sided CUSUM test to detect a decrease in h_n^i can be performed in a recursive form [19] as

$$S_n^i = \max\left\{0, (\gamma^i - k_s^i) - h_n^i + S_{n-1}^i\right\} \tag{4}$$

where S_n^i is the CUSUM value for the nth epoch, γ^i is the goal value and k_s^i is a positive threshold. Then, defining a decision boundary g_s, an alarm sequence is generated by

$$r_n^i = \begin{cases} 1, & S_n^i \ge g_s; \\ 0, & \text{Otherwise.} \end{cases} \tag{5}$$

The goal value γ^i is determined adaptively for each epoch in this work. A moving background is defined which starts several minutes before the current epoch and lasts for some minutes (here, 15 and 10 min. respectively). Then, the median of the corresponding entropy values in the background is considered as the goal value. However, to avoid the false alarms resulting from sudden increases in the entropy followed by a decrease, e.g. the increase of entropy in the postictal period, the goal value is modified using an interictal segment as a reference. Let μ^i and σ^i be the mean and standard deviation of $\{h_n^i\}$ for the reference. Then, the computed γ^i is acceptable only if $\gamma^i \le \mu^i + \sigma^i$; otherwise, $\gamma^i = \mu^i$. After determining the goal value for the current epoch, we defined $k_s^i = \alpha\gamma^i$ ($0 \le \alpha \le 1$). The parameters α and g_s are determined specifically for each patient and are fixed for all entropy time series.

After generating the alarm sequences for the three time series, they are combined for each EEG channel as

$$r_n = \eta_0 r_n^0 + \eta_1 r_n^1 + \eta_2 r_n^2 \tag{6}$$

where $\sum_{i=1}^{3} \eta_i = 1$ and $\eta_i \ge 0$. Now, considering different EEG channels and analyzing them as described above, we are able to process combined alarm sequences from all channels

in a time window with the length of L epochs, i.e. spatio-temporal analysis. Defining a forgetting factor λ, the seizure prediction index, termed SP, is defined as a multivariate index for the nth epoch by

$$SP_n = \min\left\{1, \frac{1}{C_{min}\sum_{l=0}^{L-1} e^{-\lambda l}} \sum_{l=0}^{L-1} e^{-\lambda l} R_{n-l}\right\} \quad (7)$$

where C_{min} is the minimum number of channels which must show an entropy drop to make a prediction alarm, and R_n is defined as

$$R_n = \sum_{c=1}^{C_T} r_{n,c} \quad (8)$$

where $r_{n,c}$ is the combined alarm sequence of channel c for the nth epoch, computed by (6), and C_T is the total number of EEG channels. Finally, an alarm warning of an upcoming seizure is made as soon as SP_n surpasses a predefined threshold, termed TH_p. This threshold is defined specifically for each patient as the maximum of the SP index for the interictal reference. In this study, for all cases, we set parameters λ, C_{min}, and L to 0.01, 3, and 60 respectively.

III. Results

A. Epilepsy Data

To evaluate the performance of the proposed seizure prediction algorithm, an EEG dataset provided by the EEG department of Vancouver General Hospital (VGH) after ethics approval was utilized. This dataset included ~21.5 hours of multichannel surface EEG recorded according to the International 10-20 systems from 4 patients with TLE (5.37 ± 2.07 hr), contained 16 seizures, and was sampled at 256 Hz. We used bipolar-montage scheme in this work.

To apply a moving-window analysis, each EEG recording was segmented into thirty-second windows with twenty-second overlap.

B. Experimental Results

Analyzing EEG recordings of each patient, the AZI range was determined separately using the first epileptic seizure of that patient. Also, an interictal segment starting long time (about 60 min.) before the first seizure in the first recording was selected as a reference to set the threshold TH_p as well as to control the false alarm rate as described above.

Fig. 1 shows the typical entropy waveform for different states of the EEG signal in channel T_4-T_6 of patient 3 suffering from right TLE. While the entropy level does not change significantly during the interictal state, it drops several minutes before the seizure onset (dashed line) and reaches it minimum value in the ictal period. Consecutively, the entropy increases in postictal phase. The spatial sum of the combined alarm sequences (R), computed by (8), and the SP index are presented in Fig. 2(a) and 2(b) respectively for this case. As shown, there is a significant increase in the SP index before the seizure onset.

In the quantitative evaluation of the proposed method, we compared the SP index with the threshold TH_p. A prediction was considered to be true if a seizure happened within

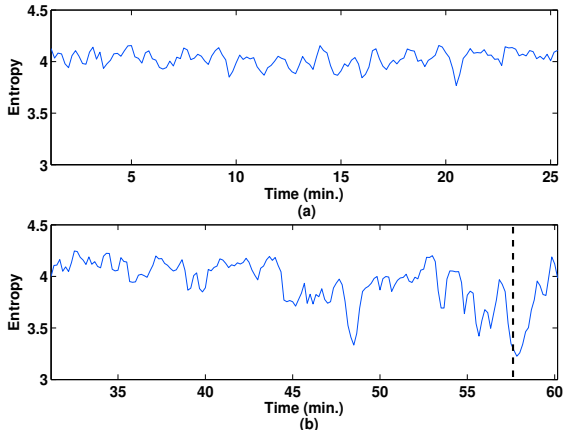

Fig. 1. The entropy waveform for positive zero-crossing intervals of the EEG signal in bipolar channel T_4-T_6 of patient 3 with right TLE; AZI = [125 334]ms. (a) Interictal period. (b) Several minutes before the seizure onset to a few minutes after. Dashed line indicates the onset.

45 min. after the alarm; otherwise, it was labeled as a false alarm. The prediction time was defined as the time difference between the alarm and the visual seizure onset (electrographic onset). To investigate the contribution of the brain hemisphere not including the seizure focus, i.e. the other hemisphere, in anticipation of upcoming seizures, we applied the algorithm to the EEG dataset with and without considering the channels of the other hemisphere for each patient (Fig. 3). As shown, the inclusion of the other channels increased the number of true alarms in all patients except one. This implies that dynamic changes before epileptic seizures are not confined to the side of the seizure focus.

Investigating the effect of EEG derivatives on the seizure prediction was another part of this study. We applied the algorithm to all recordings of the four patients with different values of weighting parameters (η_0, η_1, and η_2), while all EEG channels were considered ($C_T = 15$). Results are summarized in Table I and revealed that considering the first

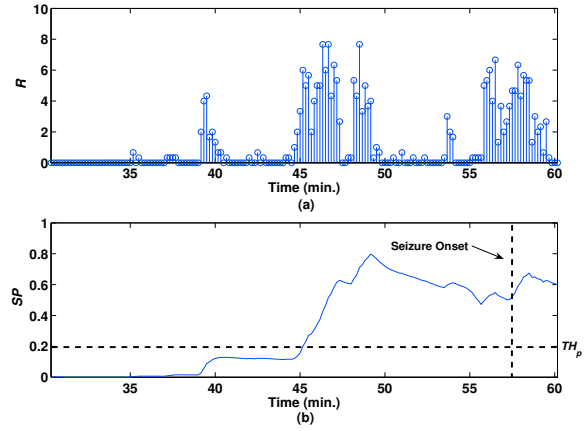

Fig. 2. (a) The spatial sum of the combined alarm sequences, R, and (b) the seizure prediction index, SP, for the case presented in Fig. 1.

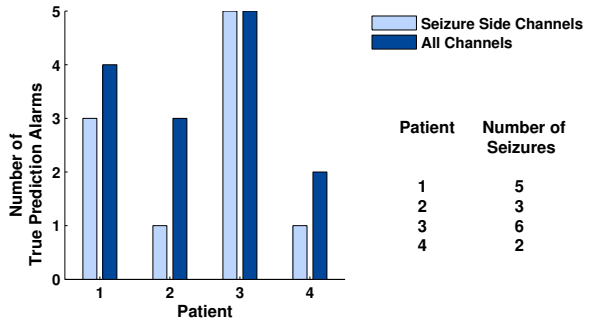

Fig. 3. Results of the proposed seizure prediction algorithm applied to all EEG channels and the channels on the side of the seizure focus in all patients.

TABLE I

RESULTS OF APPLYING THE SEIZURE PREDICTION ALGORITHM TO THE EPILEPSY DATA WITH DIFFERENT WEIGHTING PARAMETERS.

Weighting Parameters (η_0, η_1, and η_2)	Sensitivity (%)	False Prediction Rate (/hr)	Average Prediction Time (min.)
$\eta_0 = 1, \eta_1 = \eta_2 = 0$	62.5	0.09	30.5
$\eta_0 = \eta_1 = \frac{1}{2}, \eta_2 = 0$	81.25	0.28	24.8
$\eta_0 = \eta_1 = \eta_2 = \frac{1}{3}$	87.5	0.28	25

($\eta_1 \neq 0$) and second ($\eta_2 \neq 0$) derivatives of the EEG signal increased the sensitivity of the algorithm significantly, while the prediction time decreased slightly. Although specificity decreased due to EEG derivatives, the false prediction rate was acceptable by considering the fact that scalp recordings were highly corrupted by different artifacts and noise.

IV. CONCLUSION

An entropy-based approach for predicting epileptic seizures using the surface EEG was proposed in this work. Estimating PDFs of the positive zero-crossing intervals in the EEG signal and its first and second derivatives, we found significants drops in the entropy of these distributions several minutes before the seizure onsets. Applying the algorithm to scalp EEG recordings from 4 patients with TLE, 14 out of 16 seizures (87.5%) were predicted with an average prediction time of 25 min. and a false prediction rate of 0.28/hr. Results revealed that channels not belonging to the side of the seizure focus also showed dynamic changes before seizures.

In order to better evaluate the proposed method and confirm the preliminary results, we will apply the algorithm to a larger set of EEG recordings in the future. In addition, the algorithm will be tested for statistical validity using surrogate data [20]. Also, we will test the algorithm on EEG data from patients with different types of epilepsy to investigate the predictability of epileptic seizures emanating from other lobes. Finally, we intend to combine this method with our previously proposed seizure detection algorithm [21] to make it capable of self-assessing the prediction alarms and adapting the related parameters.

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