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Epileptic Seizure Prediction Using Variational Mixture of Gaussians

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***Abstract*— We propose a novel patient-specific method for predicting epileptic seizures by analysis of positive zero-crossing intervals in scalp electroencephalogram (EEG). In real-time analysis, the histogram of these intervals for the current EEG epoch is computed, and the values which correspond to the bins discriminating between interictal and preictal references are selected as an observation. Then, the set of observations from the last 5 min is compared with two reference sets of data points (interictal and preictal) using a variational Gaussian mixture model (GMM) of the data, and a combined index is computed. Comparing this index with a patient-specific threshold, an alarm sequence is produced for each channel. Finally, a seizure prediction alarm is generated according to channel-based information. The proposed method was evaluated using $\sim$40.3 h of scalp EEG recordings from 6 patients with total of 28 partial seizures. A high sensitivity of 95% was achieved with a false prediction rate of 0.134/h and an average prediction time of 22.8 min for the test dataset.**

I. Introduction

Epilepsy affects almost 1% of the world's population and is associated with recurrent, unprovoked epileptic seizures resulting from a sudden disturbance of brain function, characterized by abnormal firing of cortical neurons recruiting neighboring cells into a critical mass. Medication and surgery fail to satisfactorily control seizures in $\sim$25% of affected patients [1]. A reliable seizure prediction system based on electroencephalogram (EEG) would enable clinicians to control seizures by administering therapeutic agents as early as possible and improve the quality of life and safety for patients with epilepsy. Due to the susceptibility of surface EEG to different types of artifacts and noise, most seizure prediction studies have been based on intracranial recordings [2]–[5]. However, to develop seizure forewarning techniques more clinically applicable, methods based on scalp EEG have also been the subject of research [6], [7].

Iasemidis *et al.* [4] proposed an adaptive algorithm to predict seizures based on the convergence of the short-term maximum Lyapunov exponents of the critical electrodes in the preseizure phase. Estimating the optimal settings using a training set, they reported a sensitivity of 82.6%, a false prediction rate of 0.17/hr, and an average prediction time of 100.3 min for a test set of intracranial recordings. In another study [2], a decrease in similarity between the current EEG dynamics and an interictal reference was reported during the preseizure period for depth recordings. This method was later tested on surface EEG as well, revealing $\sim$96% sensitivity and an average prediction time of 7 min (unspecified false prediction rate) [6]. Recently, an algorithm based on autoregressive modeling of EEG [5] was proposed for predicting epileptic seizures.

In this paper, we propose a seizure prediction algorithm based on scalp EEG zero-crossing interval analysis, employing variational mixture of Gaussians to compare EEG patterns with interictal and preictal references. We then compare this method to our previously developed zero-crossing based approach [8]. Sections II and III are devoted to methodology and results, and the paper is concluded by Section IV with some directions for future work.

II. Methods

The evolution of partial (focal) epileptic seizures can be explained based on a long-term gradual preseizure change (or a cascade of changes) in the brain dynamics. Indeed, there exists a preictal state defined as the transition from the interictal state to the ictal, which is supported by some clinical evidence [1]. In this section, the details of our proposed patient-specific seizure prediction method, which is based on recognizing preictal changes, are described.

A. EEG Zero-Crossings

In this study, instead of conventional time-delay embedding [9], EEG dynamics are analyzed based on the time intervals between successive positive zero-crossings (i.e., passing from negative to positive values) as a specific form of interspike intervals [10], [11], which are more meaningful in neurophysiological studies compared to amplitude information [12]. One advantage of the zero-crossing approach is its robustness against amplitude noise [2]. Accordingly, since surface EEG contains different types of noise and artifacts, this approach removes the noise components to some extent. Moreover, in this approach, dynamical information can be extracted using a significantly lower amount of data.

Analyzing EEG epochs (here, 30-second segments with 50% overlap), let T_ℓ be the time of the ℓth positive zero-crossing in a particular epoch after detrending (i.e. removing the mean value and any linear trends) where $\ell = 1, 2, \ldots, L$; then, we can represent this epoch with a set of zero-crossing intervals as $\mathfrak{I} = \{I_\ell | \, I_\ell = T_{\ell+1} - T_\ell\}$. The histogram of $\mathfrak{I}$ in each epoch is then used to characterize EEG dynamics. Constructing this histogram, we adopt a varying-bin-width scheme, in which the histogram bins are selected such that

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the spectral content of EEG is reflected in the constructed histogram. Choosing the frequency band from 1 to 30 Hz (in agreement with the frequency range reported in literature for seizure onset [13]), it is split into nonoverlaping frequency subbands of 1 Hz. Let $[f_l, f_{l+1}]$ present the lth subband; then, the lth bin of the histogram is defined as $[1/f_{l+1}, 1/f_l]$. Since the sampling frequency F_s is finite (here, 256 Hz), this approach may result in some bins which are always empty. This can be tackled using a merging approach recently proposed by our group [8].

Constructing the histogram of $\mathfrak{I}$ for each EEG epoch, we represent that epoch with a d-dimensional vector $\Phi = [\varphi_1, \varphi_2, \ldots, \varphi_d]^T$, where $\varphi_i = n_i/(L-1)$, $i = 1, 2, \ldots, d$, and n_i is the number of positive zero-crossing intervals falling in the ith bin of the histogram. Choosing the minimum acceptable bin width of $\sim$12 ms (i.e., 3 sample points) in the merging process, a histogram with 13 bins is obtained for each epoch.

B. Discriminative Histogram Bins

Constructing the vector Φ, the histogram bins discriminating between the interictal and preictal states are selected based on the distribution of φ_i in the interictal and preictal reference intervals, defined for each patient specifically.

Considering a particular seizure in the training dataset, the five-minute EEG segment ending at the onset of the seizure is selected as the preictal reference and a fifteen-minute interval far from the seizure (at least 60 min before the onset) is chosen as the interictal reference. Computing φ_i for all epochs of each reference, we obtain two sets of data points for the ith histogram bin. Let $\widetilde{\Phi}^i_{int}$ and $\widetilde{\Phi}^i_{pre}$ be the resulting datasets for the interictal and preictal references, respectively. Then, we employ the Kolmogorov-Smirnov test [14] to compare the distributions of the values in the two datasets, where the null hypothesis is that $\widetilde{\Phi}^i_{int}$ and $\widetilde{\Phi}^i_{pre}$ are from the same continuous distribution. The histogram bins rejecting the null hypothesis are chosen as the discriminative bins and used in prediction of epileptic seizures. The significance level of 5% is used to reject the null hypothesis. In the case of multiple training seizures, the bins rejecting the null hypothesis for all seizures are selected.

C. Variational Mixture of Gaussians

To monitor the EEG patterns and generate alarms for upcoming seizures, we have developed a method based on Gaussian mixture models (GMMs) [15]. Given an observation $\mathbf{x}$, the mixture of Gaussian densities can be written as a weighted sum of Gaussians

$$p(\mathbf{x}|\boldsymbol{\theta}) = \sum_{m=1}^{M} \pi_m \mathcal{N}(\mathbf{x}|\boldsymbol{\mu}_m, \boldsymbol{\Sigma}_m), \tag{1}$$

where $\boldsymbol{\theta} = \{\boldsymbol{\mu}_m, \boldsymbol{\Sigma}_m, \pi_m\}$ represents model parameters, and M is the number of Gaussians (model components). $\boldsymbol{\mu}_m$ and $\boldsymbol{\Sigma}_m$ are the mean and covariance matrix of the mth Gaussian density, respectively, and parameters $\{\pi_m\}$ are mixing coefficients satisfying $0 \leq \pi_m \leq 1$ along with $\sum_m \pi_m = 1$. We may introduce an M-dimensional latent variable $\mathbf{z}$ corresponding to the observed data point $\mathbf{x}$, where $z_m \in \{0, 1\}$ and $\sum_m z_m = 1$. Then, we can rewrite the mixture distribution in terms of marginalization over the latent variable

$$p(\mathbf{x}|\boldsymbol{\theta}) = \sum_{\mathbf{z}} p(\mathbf{x}|\mathbf{z}, \{\boldsymbol{\mu}_m, \boldsymbol{\Sigma}_m\}) p(\mathbf{z}|\{\pi_m\}) \tag{2}$$

where $p(\mathbf{x}|\mathbf{z}, \{\boldsymbol{\mu}_m, \boldsymbol{\Sigma}_m\}) = \prod_m \mathcal{N}(\mathbf{x}|\boldsymbol{\mu}_m, \boldsymbol{\Sigma}_m)^{z_m}$ and $p(\mathbf{z}|\{\pi_m\}) = \prod_m (\pi_m)^{z_m}$. Considering the latent variable, the parameters of the GMM can be estimated using maximum likelihood framework. However, the traditional maximum likelihood GMM suffers from over-fitting and singularities [15]. Therefore, in this study, we adopt the variational GMM in which the posterior distributions over model parameters are approximated (instead of point estimation of their values) through a fully Bayesian framework. Let $\mathbf{X}$ and $\mathbf{Z}$ be the sets of observations and the corresponding latent variables respectively. Then, defining prior distributions over all parameters, the variational posterior distribution $q(\mathbf{Z}, \boldsymbol{\theta})$ which approximates the true posterior $p(\mathbf{Z}, \boldsymbol{\theta}|\mathbf{X})$ is computed by maximizing the functional $\mathcal{L}(q)$ as the lower bound of the log marginal likelihood $\ln p(\mathbf{X})$ (also known as the model evidence) [15]

$$\mathcal{L}(q) = \sum_{\mathbf{z}} \int q(\mathbf{Z}, \boldsymbol{\theta}) \ln \frac{p(\mathbf{X}, \mathbf{Z}, \boldsymbol{\theta})}{q(\mathbf{Z}, \boldsymbol{\theta})} \, d\boldsymbol{\theta} \tag{3}$$

where the approximating distribution is restricted to the factorized form $q(\mathbf{Z}, \boldsymbol{\theta}) = q(\mathbf{Z})q(\boldsymbol{\theta})$. Then, the variational posterior distribution over each parameter is computed iteratively through the variational equivalent of the expectation-maximization algorithm [15].

Once the discriminative histogram bins are determined, we are able to monitor the EEG patterns and generate alarms predicting upcoming seizures based on variational GMM of data. Let D be the number of selected bins (i.e., bins rejecting the null hypothesis) and $\{i^*_l\}$ indicate the corresponding set, where $l = 1, 2, \ldots, D$. Each EEG epoch can be then represented by $\mathbf{x} = [\varphi_{i^*_1}, \varphi_{i^*_2}, \ldots, \varphi_{i^*_D}]^T$.

After computing $\mathbf{x}_k$ for the kth EEG epoch (current epoch in real-time processing), the current observation set is defined as $\mathbf{X}_k = \{\mathbf{x}_{k-N_k+1}, \ldots, \mathbf{x}_{k-1}, \mathbf{x}_k\}$, where N_k is the total number of epochs in the last 5 min of the EEG (including the current epoch). This set of observations is then compared with the interictal ($\mathbf{X}_{int}$) and preictal ($\mathbf{X}_{pre}$) reference sets. $\mathbf{X}_{pre}$ is simply the set of $\mathbf{x}$ computed for all epochs of the preictal reference. Selecting $\mathbf{X}_{int}$, we choose a more local interictal reference (closer to the current epoch) instead of the interictal reference defined in Section II-B in order to avoid false alarms resulting from high variability of the interictal patterns over time. This 5-min interictal reference is updated every hour in the case of long recordings. For discontinuous recordings, the first 5-min of each recording is considered as the reference. We define the size of $\mathbf{X}_{int}$ and $\mathbf{X}_{pre}$ as N_{int} and N_{pre} respectively.

One major advantage of the variational GMM over the traditional GMM is a tradeoff between the model complexity and fitting data. This feature provides the possibility of

keeping the effective model components, while eliminating those with small expected mixing coefficients, $\mathbb{E}(\pi_m)$, which is the basis for comparison between the current epochs and references in our proposed method. Measuring the similarity between current observations and preictal reference set using the GMM, we set the number of model components (M) to 2 and define $\mathbf{X} = \{\mathbf{X}_{pre}, \mathbf{X}_k\}$. The *similarity index* for the kth epoch, termed $\hat{s}_k$, is then determined as follows. After convergence, if the number of (effective) components is one, it shows that $\mathbf{X}_{pre}$ and $\mathbf{X}_k$ are significantly similar, and therefore, $\hat{s}_k = 1$; otherwise, $\hat{s}_k = \mathcal{J}_{pre} \times (1 - \zeta_{pre})$ where $\mathcal{J}_{pre}$ and ζ_{pre} are the matching and isolation measures respectively. Measure $\mathcal{J}_{pre}$ shows how matched the two clusters resulting from GMM are with the original sets $\mathbf{X}_{pre}$ and $\mathbf{X}_k$. Suppose N'_k is the maximum number of data points from $\mathbf{X}_k$ which fall in a single cluster after GMM convergence. Also, let N'_{pre} be a similar quantity for $\mathbf{X}_{pre}$. Then, $\mathcal{J}_{pre} = \sqrt{(N'_k/N_k) \times (N'_{pre}/N_{pre})}$.

Measure ζ_{pre} reveals how isolated $\mathbf{X}_{pre}$ and $\mathbf{X}_k$ are. This measure is calculated using the labels of the l nearest neighbors of each data point $\mathbf{x} \in \mathbf{X}$ [16]. That is, $\zeta_{pre} = \frac{1}{N}\sum_{\mathbf{x}} \vartheta_l(\mathbf{x})$ where $\vartheta_l(\mathbf{x})$ is the fraction of the l nearest neighbors of $\mathbf{x}$ that have the same label as $\mathbf{x}$, and N is size of $\mathbf{X}$. In the case of multiple training seizures, the average of $\hat{s}_k$ over all preictal references is considered as the final similarity measure.

Similarly, we compare $\mathbf{X}_k$ with $\mathbf{X}_{int}$ to compute the *dissimilarity index* $\hat{d}_k$. Defining $\mathbf{X} = \{\mathbf{X}_{int}, \mathbf{X}_k\}$ and setting the number of GMM components to 2, if there exists only one effective component after convergence, $\hat{d}_k = 0$. Otherwise, we define $\hat{d}_k = \mathcal{J}_{int} \times \zeta_{int}$, where $\mathcal{J}_{int}$ and ζ_{int} are the matching and isolation measures computed using $\mathbf{X}_{int}$. By definition, both $\hat{s}_k$ and $\hat{d}_k$ are between 0 and 1.

D. Seizure Prediction Alarm

Having calculated the similarity and dissimilarity indices, a *combined index* for the kth epoch is defined as

$$\mathcal{C}_k = \text{median}\{\hat{c}_k, \hat{c}_{k-1}, \ldots, \hat{c}_{k-N_k+1}\}, \tag{4}$$

where $\hat{c}_k = (\hat{s}_k \times \hat{d}_k)^{0.5}$ and N_k is the number of epochs over the last 5 min. In the preictal interval, $\mathcal{C}_k$ increases since both $\hat{s}_k$ and $\hat{d}_k$ increase, i.e. observed data points get closer to the preictal reference and more distant from interictal. Then, we define the following *cumulative measure*, comparing the combined index with threshold η_c,

$$U_k = \max\left\{0, \varepsilon_k\left[1 + \frac{1}{\eta_c^2}\left(1 - \mathbb{H}(\varepsilon_k)\right)\right] + U_{k-1}\right\}, \tag{5}$$

where $\varepsilon_k = \mathcal{C}_k - \eta_c$, $0 \leq \eta_c \leq 1$, and $\mathbb{H}(\cdot)$ is the step function. It is worth noting that the proposed cumulative measure is equivalent to the standard cumulative sum [17] when $\varepsilon_k \geq 0$. However, if $\varepsilon_k < 0$, ε_k is magnified by $(1 + 1/\eta_c^2)$ and the sum decreases significantly. This reduces the number of false alarms, especially when η_c is small. Finally, the alarm sequence is generated by $\gamma_k = 1 - \exp(-\eta_s U_k)$, where $0 \leq \eta_s \leq 1$. Now, considering all EEG channels together, the γ values from all channels at the same epoch are sorted in descending order, and the first $\mathcal{P}$ values are averaged. Let $\widetilde{\gamma}_k$ be the resulting average for the kth epoch; the *seizure prediction alarm* Γ_k is then generated as

$$\Gamma_k = \begin{cases} 1, & \text{if } \widetilde{\gamma}_k \geq \eta_a \\ 0, & \text{otherwise} \end{cases} \tag{6}$$

Parameters η_c, η_s, and η_a are determined specifically for each patient during the training step.

III. Results

A. Epilepsy Data

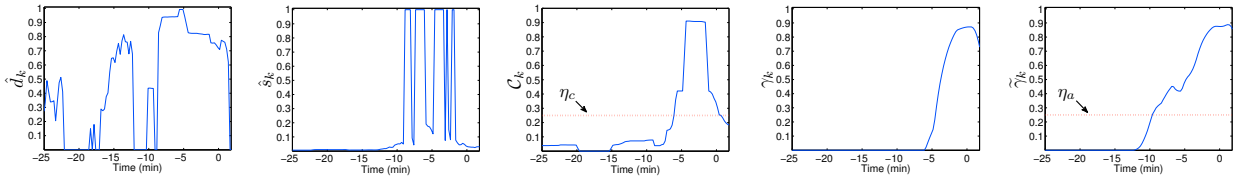
With ethics approval, a scalp EEG dataset provided by the EEG department of Vancouver General Hospital (VGH) from 6 patients with focal epilepsy (4 females and 2 males) was utilized to evaluate the performance of the proposed seizure prediction algorithm. The multichannel EEG data included ~40.3 h (6.71±2.71 h per patient) with total of 28 seizures (3 to 8 seizures per patient) and were acquired in the seizure investigation unit based on the International 10-20 system, bandpass-filtered between 0.1 and 100 Hz, and sampled at 256 Hz. In this work, we used a bipolar-montage scheme including 15 channels. To apply a moving-window analysis, each EEG recording was segmented into thirty-second epochs with fifteen-second overlap.

B. Seizure Prediction Results

Evaluating the proposed method, surface EEG recordings from each patient were divided into the training and test sets. The training set was used to extract the interictal and preictal references (Section II-B) and determine the discriminative histogram bins. Moreover, parameters η_c, η_s, and η_a were determined for each patient such that the algorithm achieved the highest performance (high sensitivity along with a low false prediction rate) for the training dataset of that patient. Overall, the test set included ~29.9 h (4.98±2.14 h per patient) with total of 20 seizures (2 to 6 seizures per patient), and the training set consisted of ~10.4 h (1.73±0.63 h per patient) and 8 seizures (up to 2 seizures per patient).

Figs. 1(a)-1(d) present different measures calculated for channel T_5-O_1 of Patient 6 for the interval from 25 min before to ~2 min after the electrographic seizure onset. As shown, the average of similarity index increases noticeably 10 min before the onset. The dissimilarity index also gets greater in average as approaching to the seizure, although fluctuates considerably. As the result, the combined index shows a significant increase and surpasses threshold η_c (here, 0.25) during the preictal interval, and alarms are generated ($\eta_s = 0.2$). Fig. 1(e) shows $\widetilde{\gamma}_k$ for the same interval of the same patient (for $\mathcal{P} = 3$), revealing that the proposed algorithm is able to predict the upcoming seizure ~10 min earlier ($\eta_a = 0.25$).

Results of the proposed seizure prediction method, applied to EEG recordings of all patients, are summarized in Table I for both the training and test sets. To better evaluate this method, we also compared it with our previously developed algorithm which compares the distribution of discriminative



(a) (b) (c) (d) (e)

Fig. 1. Different measures calculated for an EEG interval from Patient 6 ($\eta_c = 0.25$, $\eta_s = 0.2$, and $\eta_a = 0.25$): (a)-(d) present respectively $\hat{d}_k$, $\hat{s}_k$, $\mathcal{C}_k$, and γ_k for channel T_5-O_1, and (e) shows $\widetilde{\gamma}_k$ obtained using the top 3 channel alarms ($\mathcal{P} = 3$). Time axis is scaled with respect to the electrographic seizure onset.

TABLE I

RESULTS OF THE PROPOSED VARIATIONAL GMM BASED METHOD IN COMPARISON TO THE METHOD BASED ON KL DIVERGENCE.

Method	Training Set			Test Set		
	SE	FPR	APT	SE	FPR	APT
Variational GMM	100	0.096	18.1	95	0.134	22.8
KL-Based [8]	75	0.096	15.2	80	0.167	24.6

SE: sensitivity (%); FPR: false prediction rate (/h); APT: average prediction time (min).

TABLE II

VARIATIONAL GMM BASED METHOD RESULTS PER PATIENT (TEST SET).

Patient	1	2	3	4	5	6
Type of Epilepsy	TLE	TLE	TLE	TLE	eTLE	TLE
Sensitivity (%)	66.67	100	100	100	100	100
FPR (/h)	0	0	0	0.590	0	0.203
APT (min)	24.8	25.2	28.4	8.9	23.5	20.2

TLE: temporal lobe epilepsy; eTLE: extratemporal lobe epilepsy.

bins estimated over the last 5 min of EEG with the preictal and interictal reference distributions using Kullback–Leibler (KL) divergence [8]. For both methods, the top 3 channel alarms at each epoch ($\mathcal{P} = 3$) were used to generate the final alarms (i.e., Γ_k=1). In this evaluation, a prediction alarm was considered to be true if a seizure happened within 40 min after the alarm; otherwise, it was labeled as a false alarm. The successive alarms with an interval less than 40 min were assumed as a single alarm. The prediction time was defined as the time difference between the alarm and the electrographic seizure onset. Alarms with prediction time of less than 3 min were ignored and the corresponding seizures were considered as missed seizures, since there would not be sufficient time to prevent/control seizures under this condition. As shown in Table I, the proposed method predicted ∼95% of the test seizures with a false prediction rate of 0.134/h and an average prediction time of 22.8 min. Comparison of the two methods reveals that GMM-based approach is significantly superior to the KL-based method. Table II shows the results of the proposed variational GMM-based method for test data of each patient.

IV. CONCLUSION

An epileptic seizure prediction method based on variational GMM of the zero-crossing intervals in scalp EEG was proposed. Applying the algorithm to EEG recordings from 6 patients, 19 out of 20 test seizures were predicted with an average prediction time of 22.8 min and a false prediction rate of 0.134/h, favorably comparing with previously published approaches. To better assess the performance of the proposed method, we will, in the future, apply the algorithm to a set of long-term EEG recordings from a larger number of patients and will test it against random predictors.

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