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Seizure prediction in intracranial EEG: A patient-specific rule-based approach

Ardalan Aarabi, *Member, IEEE,* and Bin He, *Fellow, IEEE*

***Abstract*—In this study, we report our development of a patient-specific rule-based seizure prediction system. Five univariate and one bivariate nonlinear measures were extracted from non-overlapping 10-second segments of intracranial EEG (iEEG) data recorded using both depth electrodes in the brain and subdural electrodes over the cortical surface. Nonlinear features representing the specific characteristic properties of EEG signal were then integrated spatio-temporally in a way to predict to predict seizure with high sensitivity. The present system was tested on 58 hours of iEEG data containing ten seizures recorded in two patients with medically intractable focal epilepsy. Within a prediction horizon of 30 and 60 minutes, our method showed an average sensitivity of 90% and 96.5% with an average false prediction rate of 0.06/h and 0.055/h, respectively. The present results suggest that such a rule-based system can become potentially a useful approach for predicting seizures prior to onset.**

***Index Terms*—Focal epilepsy, intracranial EEG, nonlinear dynamics, seizure prediction.**

I. Introduction

EPILEPSY is characterized by spontaneous, recurrent, and intermittent paroxysmal electrical neuronal discharges in the brain that are manifested as seizures [1]. Predicting seizures would significantly improve considerably the quality of life of epileptic patients.

To date, a great variety of linear and nonlinear techniques has been developed to identify preictal states and consequently to predict epileptic seizures [2]-[11].

In the present study, a patient-specific method is developed based on integrated univariate and bivariate measures and tested to predict partial seizures using intracranial EEG (iEEG) data. The aim of the method is to improve the performance of the seizure prediction by combining the predictability power of different measures. To achieve this goal, the information exploited by using univariate and bivariate measures from intracranial channels is spatio-temporally integrated by patient-specific rules established using a template seizure for each patient.

A. Aarabi is with the Department of Biomedical Engineering, University of Minnesota, Minneapolis, MN 55455 USA (e-mail: aaarabi@umn.edu).

B. He is with the Department of Biomedical Engineering, University of Minnesota, Minneapolis, MN 55455 USA (e-mail: binhe@umn.edu).

II. Methods

A. Seizure prediction system

The present seizure prediction system comprises three stages: *preprocessing, feature extraction, and rule-based decision making* (Fig. 1).

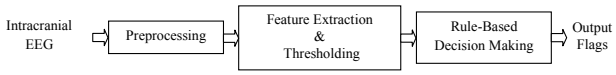

Fig. 1. Schematic diagram of the present seizure prediction system

1. Preprocessing

In this stage, the iEEG data recorded with a sampling frequency of 256 Hz were first filtered using a band-pass filter with a 0.5-100 Hz pass-band and a 50 Hz notch filter. Then, the iEEG data were divided into non-overlapping 10-second segments.

2. Feature Extraction

We extracted from each segment of the iEEG data a set of features including: Correlation Dimension (CD), Correlation Entropy (CEN), Noise Level (NL), Lempel-Ziv Complexity (LZC), Largest Lyapunov Exponent (LLE), and Nonlinear Interdependence (NI). To implement the nonlinear measures, τ (time lag) and m (embedding dimension) were estimated using the method described in [12] and [13]. The CD is considered as a measure of the dimensionality of the process being investigated. The CEN is also a dynamic measure, which represents the rate at which information needs to be created as the dynamical system evolves in time. We used the method proposed by Yu *et al.* [14] to estimate the CD and CEN, as well as the NL. As a measure of the level of randomness of patterns in the EEG time series, the LZC was extracted from iEEG segments using the algorithm described by Aboy *et al.* [15]. The LLE measures the divergence of state space trajectories, which were initially close to each other and determine the predictability of the system. We used the algorithm proposed by Rosenstein et al. [16], which is a reliable method for small data sets and robust in the presence of noise. Finally, we used the asymmetric NI introduced by Arnhold *et al.* [17] to compute the synchronization level between all possible combinations of electrode pairs.

A thresholding procedure was applied to the feature values extracted from the iEEG segments. For each separate patient, we first selected a seizure-free interictal period far from any seizures (see EEG data section). Then, for any given feature and channel, the feature values of the whole iEEG data were thresholded using the mean and standard deviation calculated over the feature values extracted from the iEEG segments within the reference window.

3. *Rule-based Decision Making*

The rule-based decision making stage includes the spatial combiner to integrate the spatial information exploited from the multichannel iEEG data, and the feature integrators to combine the information embedded in features in a way that optimizes the proportion of seizures predicted (Fig. 2).

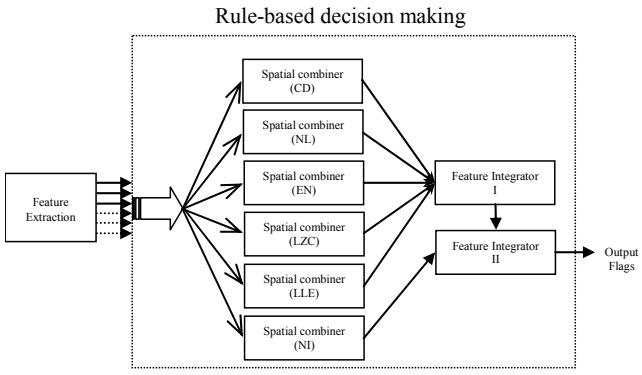

Fig. 2. Schematic diagram of the rule-based decision making stage

For each patient, the first seizure was selected as a template. Then, feature values in the 50-min preictal period were compared to those separately obtained within the reference window for each feature and channel. If the median of the thresholded feature values in the preictal period was greater (or lower) than the value computed in the reference window, a label G (or L) was assigned to that feature and channel. For the same patient, this procedure was repeated for all features and channels. It should be mentioned that for each of the features, the labels for the epileptic and remote channels were collected in a vector termed Spatial Feature Pattern Vector (SFPV). This vector was considered as the spatio-temporal profile of the feature characterizing the preictal state of the patient. Therefore, for each patient there were six SFPVs for the univariate and bivariate features used in this study.

Based on the SFPVs, the spatial combiner included the criteria for spatially combining the information embedded in features values extracted from the iEEG of different channels. The spatial combiner worked on a single feature-multichannel basis. The spatial combiner was applied to each feature separately to identify multichannel seizure precursors (Fig. 2).

For a given feature and segment, if N ($\geq N_{ch}$) channels (out of 6 for the univariate measures and out of 15 for the bivariate measure) exhibited behaviors like those expected in the SFPV of the feature, then that segment was temporarily considered as a seizure precursor and a flag *I* was raised for the segment. The flag *I* was given a value by averaging the channels' absolute feature values, which showed the behavior predicted in the SFPV of the feature. The location and value of all flag *I*s at this step were saved and fed into the feature integrators. There were six spatial combiners acting on the five univariate features and the bivariate feature (Fig. 2).

Feature Integrator I & II

Feature integrator I integrated decisions made for any segment in the previous step using the bivariate measures to locate seizure precursors. To this end, for any segment, if M ($\geq N_F$) flag *I*s (out of 5) whose values were higher than a significance threshold T_{c1} were raised, then a flag *II* was raised for the segment. Following this, a value was assigned to the flag *II* by averaging the values of the flag *I*s contributing to the decision made for that segment. The flag *II*s represented a higher probability of correct seizure prediction for the segment. All the flag *II*s from the feature integrator I output were fed into the feature integrator II for a higher level decision. For any segment, if a flag II whose value exceeded a significance threshold T_{c2} was raised, and if simultaneously a flag *I* was raised using the bivariate measure (Fig. 2), then a flag *III* representing a definite seizure precursor was raised for that segment.

In the postprocessing step, any definite flag *III* not followed by at least three other consecutive flag *III*s was rejected as false short predictions representing precursors whose lengths did not exceed 40 seconds. All of the remaining flag *III*s were considered as true predictions.

B. EEG data

The iEEG data of two patients with medically intractable focal epilepsy were analyzed in this study to test the performance of the developed method. The data were selected from the Freiburg Seizure Prediction EEG (FSPEEG) database [18] with authorization, having been recorded by a Neurofile NT digital video-EEG system (IT-Med, Usingen, Germany) with a 256 Hz sampling rate. In the database, the first two patients who met the following criteria were selected for analysis: 1) having maximum number of seizures; and 2) having seizures of frontal or temporal lobe origin. To record iEEG data, grid-, strip-, and depth-electrodes were used. For each patient, six contacts had been selected by visual inspection of iEEG data by an experienced epileptologist: three near the epileptic focus, and three in remote locations. No hyperventilation or photostimulation had been used to provoke seizures.

In total, 58 h of iEEG data containing 10 seizures with at least 50 min pre-ictal data were analyzed. The onset and offset times of seizures had also been determined by the

epileptologist. Table I summarizes the details of the iEEG data used in this study.

TABLE I
CHARACTERISTICS OF THE INTRACRANIAL EEG DATA AND THE PATIENTS

Patient	Seizure type	HC/NC	Origin	Electrodes	No. of seizures	interictal EEG duration (h)
1	SP,CP	NC	Frontal	g,s	5	24
2	SP,CP,GTC	HC	Temporal	d,g,s	5	24

SP = simple partial, CP = complex partial, GTC = generalized tonic-clonic
g: grid, s: strip, d: depth, HC: Hippocampal, NC: Neocortical

For each patient, a reference window (4 h) was selected as a steady state baseline from the seizure-free interictal data to optimize the system. To construct the reference window, four one-hour interictal data segments were selected randomly from the whole 24-hour interictal data and concatenated. The remaining interictal data were used for evaluating the system performance.

C. Data Processing

The iEEG data of the patients were first band-pass filtered and segmented. Then, all aforementioned features were extracted from iEEG segments and thresholded using the method described in the feature extraction section. Finally, the resultant features were integrated by the rule-based decision making stage. All produced flag *III*s were used for the evaluation of the system's performance.

D. System Optimization and Evaluation

The performance of the seizure prediction system was assessed using seizure-free interictal EEG data, which were completely independent from those used for optimizing the system parameters, in terms of sensitivity, specificity, false prediction rate, minimum prediction time, and portion of time under false predictions as a function of prediction horizon (in this study, 30 or 60 min) [10]. The optimal values of the thresholds, N_{ch}, N_F, T_{c1} and T_{c2}, were determined using a trial-and-error method, in which each patient's thresholds were changed one by one and the sensitivity and false prediction rate were computed using the flag *III*s produced by the system for the reference window and the preictal data of the template seizure. This procedure was repeated in a way to obtain maximum sensitivity and specificity. The optimal parameters found at this step were used to assess the system's performance.

To evaluate the dependence of the system's performance on reference window, a procedure was run 10 times for each patient and at each run a reference window was randomly selected with the method explained in the EEG data section and the system performance was evaluated on the reference window. Then, for each patient, the overall system performance was computed by averaging the system performance obtained using the ten different reference windows.

III. RESULTS

In the two patients used for evaluation, the results showed an average sensitivity of 90% and 96.5% with an average false prediction rate of 0.06/h and 0.055/h, within respective prediction horizons of 30 and 60 min.

A. Overall System Performance

The performance of the system as a function of the prediction horizon for each patient is listed in Table II. For each patient, the total, average system performance was computed by averaging the system performance obtained using the ten reference windows randomly selected for each patient.

TABLE II
SYSTEM PERFORMANCE AS A FUNCTION OF PREDICTION HORIZON

Patient	Prediction horizon (min)	Sensitivity (%)	Specificity (%)	False prediction rate (/h)	Portion of time under false predictions (h)	Minimum prediction time (min)
1	30	80 ± 8	98.8±0.6	0.12±0.04	0.33±0.25	2.9±0.8
	60	93 ± 7		0.11±0.03		3.1±0.5
2	30	100 ± 0	100±0	0 ± 0	0 ± 0	11.4±0.1
	60	100 ± 0		0 ± 0		40.9±2
Average	**30**	**90 ± 10**	**99.4±0.6**	**0.06±0.06**	**0.165±0.21**	**7.2±4.3**
	60	**96.5 ± 5.3**		**0.055±0.055**		**22.2±18.9**

Results are expressed as mean ± absolute deviation.

As can be seen from the deviation of the performance parameters, the system is relatively insensitive to the choice of reference windows. Only slight changes were observed in the system performance obtained for patient 1. No performance changes were found in patient 2.

Relatively lower sensitivities and higher false prediction rates were observed in patient 1 with the prediction horizon of 30 min. Even using optimally-tuned thresholds, the system failed to identify one seizure using the prediction horizon of 30 min in this patient. For both patients, on average a specificity of 99.4% was observed.

B. Feature significance evaluation

To compare the predictability power of the features separately, we compared the performance of the system based on single features. For this purpose, our system was tuned up and its performance was evaluated using only one feature at a time and the first randomly selected reference window (the feature integrator was deactivated for this step). Table III compares the performance of the system using single or multiple features as a function of the prediction horizon. As shown, the contribution of single features in performance improvement is largely disparate, but the entire system based on combined features shows a better performance for both prediction horizons. As shown, among the single-feature based systems, those utilizing the CEN and LZC features obtained relatively lower sensitivities and false prediction rates with higher specificities.

TABLE III

AVERAGE PERFORMANCE PARAMETERS OF THE SINGLE-FEATURE BASED SYSTEM AND THE ENTIRE SYSTEM ACROSS PATIENTS

Prediction horizon (min)	System	Sensitivity (%)	Specificity (%)	False prediction rate (/h)	Portion of time under false predictions (h)	Minimum prediction time (min)
30	*CD-based*	87.5	98.9	0.15	0.2	23.4
	NL-based	87.5	99	0.08	0.2	8.9
	CEN-based	62.5	99.6	0.05	0.08	14.3
	LZC-based	62.5	99.7	0.03	0.06	36.5
	LLE-based	87.5	97.8	0.13	0.45	16.7
	NI-based	100	98	0.22	0.42	7.3
	Entire system	90	99.4	0.06	0.165	7.2
60	*CD-based*	100	98.9	0.1	0.2	52.5
	NL-based	100	99	0.05	0.2	27.5
	CEN-based	87	99.6	0.05	0.08	14.3
	LZC-based	75	99.7	0.03	0.06	49.1
	LLE-based	100	97.8	0.1	0.45	28.1
	NI-based	100	98	0.2	0.42	21.8
	Entire system	96.5	99.4	0.055	0.165	22.2

In summary, in the present study we have developed a rule-based seizure prediction method that includes first, extracting univariate and bivariate nonlinear dynamical features from iEEG segments, and then, spatio-temporally integrating the dynamic characteristics using the patient-specific rules established based on the dynamic behavior of the nonlinear measures in the preictal state of the template seizure. The method was tested for seizure prediction and preictal characterization in two patients with medically intractable focal epilepsy. From a clinical perspective, the system achieved promising results, including an average sensitivity of 96.5% with a false prediction rate of 0.055/h within a prediction horizon of 60 min.

In a comparative study, Maiwald *et al.* [18] compared the performance of the dynamic similarity index, the accumulated energy, and the effective CD. With a false prediction rate of less than 0.15/h and a prediction horizon of up to 30 min, these features achieved sensitivity ranges of 21-42%, 18-31% and 13-30%, respectively. With a prediction horizon of 30 min, our system achieved an average sensitivity of 90%. With a maximum false prediction rate of 0.15/h and a prediction horizon of 60 min, the sensitivity increased to 96.5%. While promising, our system has only been tested on the intracranial EEG of two patients, thus requires further evaluation using a larger group of patients.

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