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EEG Seizure Prediction: Measures and Challenges

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***Abstract*— Different types of analyses of scalp and intracranial electroencephalography (EEG) recordings using linear and nonlinear time series analysis method have been done. They showed strong evidence of detectable changes in the EEG dynamics from minutes up to several hours in advance of seizure onset. The predictive performance of univariate and bivariate measures, comprising both linear and non-linear approaches have been carried in different studies Direct comparison among different measures and methods in seizure prediction is not possible, unless they are applied to the same dataset. In this review paper, we describe different seizure prediction measures briefly and discuss the existing challenges.**

II. INTRODUCTION

Epilepsy, as one of the most common neurological disorders, affects more than approximately 1% of the world's population [1]. This disorder is characterized by episodic interruptions of cerebral electrical activities caused by abnormal spatio-temporal hypersynchronous discharges of neuronal populations referred to as seizures [2]. Nowadays 75% of epilepsy patients are controlled by antiepileptic drugs [1]. Any systems to predict in advance the occurrence of seizures can improve the therapeutic treatments. On the other hand, these systems improve the quality of epilepsy life by helping them to adjust their preventive behavior [3].

Electroencephalography (EEG), as one of the most efficient tools in the diagnosis of epilepsy, provides information about spatio-temporal patterns of brain electrical activity. Diagnostic evaluations of EEG recordings of patients are necessary to study the spatio-temporal dynamics of the EEG signal for better understanding the process leading to the seizure generation. This can provide deep insights into possible mechanisms for seizure control.

Two different scenarios have been proposed for the interictal-to-ictal transition [4], a sudden and abrupt transition as happened for generalized epilepsy, or a gradual change between interictal and ictal periods. Based on the second scenario, in which the ictal state would be preceded by detectable dynamical changes in the EEG, many studies have found that seizures follow a dynamical transition that evolves over minutes to hours [5]-[12]. In this paper, we will briefly review different measures that haven been used for seizure prediction.

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III. METHODS

This section contains a brief overview of measures commonly used to characterize EEG time series. In this review, we are interested in the practical aspects of the available seizure prediction methods and put less weight on the theoretical concepts behind the algorithms.

A. Univariate Measures

EEG analysis using univariate measures involves characterizing the state of EEG time series related to only a single recording site. Time series of EEG contain activities with different amplitudes and frequencies. Linear univariate measures are used to characterize the EEG based on the amplitude and phase (/frequency) information.

When one needs to characterize the state and dynamics of dynamical systems, then, nonlinear univariate measures, derived from nonlinear dynamics called 'chaos theory', have to be used. To this end, it is necessary first to define two key terms: "state" and "dynamics". The state describes the system at a given moment in time. The system state is described by a point in an m-dimensional space called the state (/phase) space where m is the embedding dimension. The system dynamics is the rules that describe how the system state evolves over time [11].

1) Linear measures

Linear methods, such as energy, and the spectral power require the staionarity of the time series. In this section, we review the most prominent linear tools used for seizure prediction.

a) *Statistical moments:* Statistical moments provide information on the amplitude distribution of a time series. The first (mean) and second (variance) statistical moments provide information on the location and variability of the amplitude distribution of the time series. The third (skewness) and fourth (kurtosis) moments also provide information on the shape of the distribution [12]. The ability of these measures to distinguish between the interictal period and the pre-seizure period in the IEEG data have been compared [13]. Using variance and kurtosis, a preictal period was found with significant changes (a decrease for variance and an increase for kurtosis) in comparison with the interictal period. Other attempts to extract seizure precursors from the EEG were carried out for seizure prediction using spectral analysis [14]-[15].

b) *Power spectral parameters:* The EEG signal has usually been described in terms of main frequency bands, δ (less than 4 Hz), θ (4-8 Hz), α (8-12 Hz), β (13-30 Hz), and γ (greater than 30 Hz). Relative power in any frequency band is defined as the area under the curve of the power spectrum within the bandwidth under consideration divided by total power for all bands. Mormann et al. [13] have shown that for the preictal period in comparison with the interictal period, there is a relative decrease of power in the delta band that is accompanied by a relative increase in the remaining bands.

c) *Accumulated energy:* The accumulated energy is computed for any moving observation window by averaging all successive values of energies calculated in that window. This can be considered as the running average of the energy [16]. Using this measure, promising results for seizure prediction have been reported [17]. However, the results could not be reproduced [18]-[19].

d) *Hjorth parameters*: Hjorth [20] defined three time-domain parameters, activity, mobility and complexity, also called normalized slope descriptors. The activity is the variance of the signal which gives a measure of mean power. The mobility is the ratio of the root mean square (RMS) of the slopes of the signal to the RMS of the amplitude. This parameter may be considered as an estimate of the mean frequency. The complexity gives a measure of the RMS of the rate of slope changes with reference to an ideal possible curve. This parameter gives an estimate of the bandwidth of the signal. Mormann et al. [13] found a preictal period with a significant increase in the Hjorth mobility and complexity with respect to the interictal period.

e) *Decorrelation time:* Autocorrelation is the correlation between values of the signal at different points in time. It is computed as a function of the two times or of the time difference. It is usually used to detect “whiteness” in data. The first zero-crossing of this function is defined as the decorrelation time [12], [21]. Mormann et al. [13] could distinguish a preictal period from the interictal period by observing a decrease in the decorrelation time.

f) *Linear modeling*: In linear modeling of a time series, one assumes that each value of the series depends only on a weighted sum of the previous values of the same series plus "noise". The main assumption in linear modeling is the stationarity of the signal. So, for non-stationary signals like EEG, one needs to segment it into stationary parts. Using autoregressive modeling, preictal changes have been reported before seizure onset [14],[22].

2) Nonlinear measures

The nature of the mechanism leading to epileptic process is still not well understood. The linear assumption about EEG signals may not be true. Therefore, one may need nonlinear analysis. In this section, we present a review on the promising nonlinear measures for seizure prediction.

a) *Correlation dimension:* The correlation dimension and the following two measures are centered on the concept of the correlation integral, which can be computed from the state space representation of EEG time series. The correlation integral is defined as the probability that any two randomly chosen points on the state space lie within a given distance of each other [23].

The correlation dimension gives a measure of the dimensionality of the state space. This measure is used to distinguish random signals from deterministic time series [24]. The ability of the correlation dimension for seizure prediction has been proved in [25]. Lehnertz and Elger [25] demonstrated that significant drops in correlation dimension occurred prior to seizures. However, Harrison et al. [26] suggest strongly that the correlation dimension has no predictive power for epileptic seizures.

b) *Correlation density:* The correlation density is calculated by computing the correlation integral for a fixed radius and using a combination of time delay and spatial embedding of EEG time series [12]. Martinerie et al. [27] demonstrated that in most cases, seizure onset could be anticipated well in advance. However, the ability of this measure for seizure prediction was questioned by McSharry et al. [28].

c) *Kolmogorov entropy:* The Kolmogorov entropy is a dynamic measure representing the rate at which information needs to be created as the dynamical system evolves over time [29]. It gives a measure of the level of uncertainty about the future state of the system [12]. The feasibility of using trends in Kolmogorov entropy to anticipate seizures in pediatric patients with intractable epilepsy has been demonstrated in [30]. It has been concluded that the Kolmogorov entropy is as effective as the correlation dimension in anticipating seizures.

d) *Marginal predictability:* The marginal predictability is defined as the ratio of the correlation integral computed for different embedding dimensions. Different marginal predictability have been proposed [31]-[32] and applied for seizure prediction [33]. Li et al. [33] found that the difference between the marginal predictabilities computed for the remote and adjacent electrodes decreases several tens of minutes prior to seizure onset, compared to its value in the interictal periods.

e) *Dynamical similarity index:* Dynamical similarity index is composed of the phase space reconstruction of the EEG time series using time intervals between two positive zero-crossings and the measurement of dynamical similarity between a reference window and test windows using the cross-correlation integral. Le Van Quyen et al. [34] showed that the method can track in real time spatio-temporal changes in brain dynamics several minutes prior to seizure. However, other studies [35]-[36] questioned the reliability of the optimistic results reported for the dynamical similarity index in [34].

f) *Largest Lyapunov exponent:* The Lyapunov exponents quantify the exponential divergence of initially close state-space trajectories and determine the predictability of a dynamical system. The largest Lyapunov exponent gives a measure for detecting the presence of chaos in a dynamical system [37]. Iasemedis et al. [38] used the largest Lyapunov exponent for characterizing intracranial EEG recordings and noted premonitory events several minutes prior to the onset of seizures in several recordings [39]. However Lai et al. [40] raised doubts about the ability of the Lyapunov exponent for seizure prediction.

g) *Loss of recurrence:* The loss of recurrence quantifies the degree of non-stationarity in a time series [41]. The frequency distribution of time distances under stationary conditions with respect to each reference point is first computed. If the system is non-stationary, an increased deviation from this distribution is observed due to the absence of distant time indices in the neighborhood of the reference. That is considered as a loss of recurrence. The predictability of this measure for epileptic seizures has been shown in [13].

h) *Algorithmic complexity:* Algorithmic complexity is a method based on symbolic dynamics to characterize dynamical systems by a discrete space consisting of infinite sequences of abstract symbols, each of which corresponds to a state of the system. To this end, the state space is partitioned into a finite number of regions, each of which represented with some symbols. So each point in the state space gives an infinite sequence of symbols [42]. The algorithmic complexity values exhibited a preictal increase before the seizure onset with respect to the interictal period [13].

i) *Local flow:* The local flow aims at discriminating deterministic from stochastic dynamics [43]. This measure has been used to characterize epileptic EEG time series based on the hypothesis that the generation mechanism behind the epileptic process is characterized as nonlinear deterministic dynamics. Strong indications of nonlinear determinism were found in interictal EEG recordings from the epileptogenic zone, while EEG signals from other sites mainly resembled linear stochastic dynamics [44]. The ability of this measure for seizure prediction has been shown in [13].

B. Bivariate Measures

EEG time series analysis using bivariate measures involves the extraction of information reflecting interactions between different regions of the brain.

1) Linear measures

Linear bivariate measures aim in extracting linear synchronization patterns between different cortical regions.

a) *Autoregressive measure of synchrony:* The autoregressive measure of synchrony is derived from a multichannel model of the EEG. In this model, each point is described as a linear combination of the previous values from all selected channels. The "goodness of fit" (GOF) of this model to the EEG shows how best the model is fitted for channels. With a higher degree of synchrony between channels, a better GOF is obtained [45]. Using this measure, no significant preictal changes were reported unless contaminated by residual postictal changes in closely clustered seizures.

b) *Maximum linear cross-correlation:* The maximum linear cross correlation measure implies that two systems are linearly synchronized if their characteristic variables evolve identically over time [46]. A preictal loss in synchronization between EEG signals recorded simultaneously from different locations in the brain has been observed [13].

2) Nonlinear measures

Nonlinear bivariate measures give an indication of nonlinear spatiotemporal synchronization between different cortical regions.

a) *Dynamical entrainment:* The dynamical entrainment is defined as a measure indicating 'entrainment between two regions of the brain'. This measure indicates the statistical difference between the largest Lyapunov exponents over a number of consecutive time windows for two signals recorded from the brain regions using the T-index derived from a paired t-test for comparison of means. This measure has shown a good predictive power for prediction of epileptic seizures, with a relatively low false warning rate [47].

b) *Phase synchronization:* The phase synchronization measures the degree to which two signals are phase-locked during a short time period. In intracranial EEG data, this measure has shown its power to discriminate transient synchronization [48]. Analysis of long EEG recordings has shown that the epileptogenic process during the interictal state can be characterized by a pathologically increased level of synchronization as measured by the mean phase coherence [46]. In another study, a specific state of brain synchronization has been observed several hours before the actual seizure. The changes involved both increases and decreases of the synchronization levels often localized near the primary epileptogenic zone [49].

c) *Nonlinear interdependence*: For coupled systems without symmetries in a drive-response type configuration, the synchronization can develop nonlinear structure. In contrast, the nonlinear interdependence measure, an asymmetric measure, attempts to characterize statistical relationships between two time series in the state space. This measure provides additional information about the direction of interdependence [50]. Using this measure, studies have shown extremely low dependences between the epileptic generating areas before the seizure onset.

IV. Conclusion

Several studies have compared linear and nonlinear measures for seizure prediction [5]-[12]. Some of them found no clear superiority of the nonlinear measures over linear measures [46], [13]. Mormann et al. [13] provided a vast investigation to compare a number of linear/nonlinear and univariate/bivariate measures to distinguish the preictal state from the interictal state in a very statistical way. While several measures showed significance differences, bivariate measures were generally more effective.

Although promising results have been reported by different methods but none of them could obtain a robust tool being able to predict seizures for different seizures and patients. It seems a combination of different univariate and bivariate measuress in an optimal manner may result in a better approach for seizure prediction with high sensitivity and low false alarm rate. Special attention has to be paid for channel selection if one needs to provide a real time seizure prediction tool.

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