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Seizure Prediction Methods: A Review of the Current Predicting Techniques

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ABSTRACT

Epilepsy is a common neurological disorder affecting more than 1.5 percent worldwide. Twenty percent of epilepsies are drug resistant. Therefore, early detection of prediction of epileptic seizures is of prime significance to decrease the burdens of the disease. There is strong evidence indicating seizures develop minutes to hours before clinical onset. This change is based on quantitative studies of long term electroencephalographic monitoring (EEG) from patients administered for epilepsy surgery. The possibility of early prediction of seizure has drawn the research interest of diverse fields in medical, engineering, and patent publications. Techniques used to predict seizures include frequency-based methods, statistical analysis of EEG signals, non-linear dynamics (chaos), and intelligent expert systems. Developing efficient methods to predict seizures can lead to designing novel diagnostic and therapeutic techniques for the early diagnosis of seizure attack or preventing the attacks through appropriate modulations of brain activities. The present study reviews the most important and recent methods for seizure prediction. In line with introduction of different efficient seizure predicting approaches, great research interest has been focused on developing new modalities that incorporate these approaches to predict early onset of seizures minutes to hours before they initiate. These modalities will enable experts to develop new interventional treatments such as appropriate responsive electric stimulation applied immediately after the prediction to prevent the seizures or modulating stimulation in controlling the seizure attacks. In the near future, seizures can be predicted in time and prevented before clinical and physical indications.

Key words: Seizure prediction, frequency based prediction, epilepsy, non-linear seizure prediction.

INTRODUCTION

Epilepsy is a neurological disorder characterized by recurrent seizures. Epileptic recurrent seizures are manifestations of epilepsy affecting more than 1.5 percent of worldwide population. After the stroke, epilepsy is the most dangerous dynamical disorder. About one third of epileptic patients are drug resistant[1-4]. The treatment option for these patients is respective surgery where the epileptic focus is removed from the brain. Predicting seizure significantly improves the possibilities of epilepsy therapy[5]. One of the most challenging aspects of seizure is its unpredictable nature. In this regard, for the 25% of epileptic patients whose seizures cannot be completely controlled, seizure prediction is an important aim of clinical management and treatment. From a broader view, various seizure prediction methods and the acquired knowledge have shed light on epilepsy and the basic mechanisms underlying seizure generation. Before, development of seizure prediction methods, researchers believed seizures are isolated and abrupt events, but we now know seizures are the processes that develop over time and space in epileptic networks.

Like other neurological disorders, epilepsy can be assessed by the electroencephalogram (EEG)[6]. The field of seizure prediction, in which combined medical and engineering technologies are used to decode brain signals to determined precursors of impending epileptic seizures, holds great promise to elucidate the dynamical mechanisms underlying the disorder, effective control and treatment of epilepsy through implantable devices to intervene in time to treat epilepsy (Aarabi, 2009 #98;Andrzejak, 2009 #101;Bandarabadi, 2012 #53;Castellaro, 2011 #68;Lehnertz, 2007 #112;Litt, 2002 #158;Navarro, 2011 #82;Sackellares, 2008 #105;Viglione, 1975 #153) [7].

Studies on seizure prediction through electroencephalograph (EEG) recording started in the 1960s. Since then, a large number of studies have been performed to manifest the characteristics of seizures in the preictal state and differentiate them with the ictal state. There have been various models for seizure prediction. They use appropriate features as precursors of impending seizures and try to predict the seizure onset. The approach, under which these measures are analyzed to make a relation by the seizure onset, uses different processing designs divided into linear methods such as phase synchronization, auto regressive spectral analysis or non-linear methods such as correlation dimension, Lyapunov exponent, and Kolmogrov entropy[8-28].

This paper aims to review the most current seizure prediction methods, sketch their background and principal procedure, and to compare their efficiency in predicting seizure.

The earliest approaches to seizure predictions in the 1970s and 80s were based on spectral analysis or pattern detection[29]. Following the advent of nonlinear dynamics theory in the 1980s, time series analysis has emerged as promising tool for seizure prediction. During the 1990s several quantitative EEG studies reported preictal phenomena using characterizing measures such as the largest Lyapunov exponent[30], the correlation density[31] or a dynamical similarity index[32-34].

EEG based measures for seizure prediction

Measures, precursors or features of EEG used in seizure prediction models are referred to any variable with strong correlation with different stages of epilepsy cycle especially preictal and ictal stages. All predicting models try to find out reliable measures as precursors of impending seizures. The measures should have strong correlation with the preictal stage of epilepsy cycle. The EEG based measures for seizure prediction can be divided into univariate, bivariate, and multivariate measures. We can categorize the EEG features into three main groups of univariate, bivariate, and multivariate. One can distinguish between univariate measures, computed on each EEG channel separately, and bivariate (or multivariate) measures, which quantify some relationship, such as synchronization, between two (or more EEG channels). Mormann *et al* (2005) conducted a comprehensive review comparing most univariate and bivariate techniques[35] and showed despite of various univariate features proposed for seizure prediction[8, 36-40], none of them has succeeded in a reliable seizure prediction. They concluded the superiority of bivariate measurements for seizure prediction. In line with the studies seeking new measures as seizure precursors, the knowledge on neurological mechanisms and features of the preictal brain state has evolved. The researchers have hypothesized that brainwave synchronization patterns might differentiate interictal, preictal and ictal states[41]. Clinical observations of the synchronization of neural activity, have suggested that interictal phases correspond to moderate synchronization within the brain at large frequency bands, and in preictal stage; the beta range synchronization between the epileptic focus and other brain areas decreases. This is followed by a subsequent hyper-synchronization at the seizure onset. This pattern can be used as a measure for developing seizure prediction model.

Each group of univariate, bivariate and multivariate can be divided into two groups of linear and nonlinear measures. The most common univariate linear measures include statistical moments, spectral band power, spectral edge frequency, characteristics of the autocorrelation function, Hjorth parameters. The univariate non-linear measures include Estimate of an effective correlation dimension, largest Lyapunov exponent, local flow, algorithmic complexity, surrogate time series and surrogate correction, and loss of recurrence. The common bivariate linear measure includes maximum linear cross-correlation and finally the non-linear bivariate measures include non-linear interdependence, measures based on phase synchronization, conditional probability based index, and index based on Shannon entropy. For a general comparison between the univariate and bivariate, univariate measures are sensitive to those changes before a seizure only in relation to the period immediately preceding these changes. However, bivariate measures were found to reflect changes in dynamics on a longer time scale starting hours before a seizure. Despite various models have been proposed for seizure prediction, most of them focused on the univariate measures from individual EEG channels[38, 41, 42]. The correlation measurement between various channels has recently been noted as a potentially more efficient standard for seizure prediction. Phase synchronization between different brain regions is found to decrease before seizure onset in EEG[43].

A remarkable finding of the comparisons of previous prediction models is that both among the univariate and the bivariate approaches linear measures have higher performance than non-linear measures. Several studies showed that "phase space similarity" measure was better to other indicators in predicting an impending seizure in the localized records[44-45].

Among the previously proposed measures, correlation dimension, synchronization, especially phase synchronization, entropy, and largest Lyapunov exponent seem to have higher potential for developing more robust predicting models. The seizure predicting models based on correlation dimension, phase synchronization and entropy are discussed in more details.

Correlation Dimension

One of important non-linear method of seizure prediction is correlation dimension. In chaos theory, the correlation dimension is a measure of the dimensionality of the space occupied by a set of random points, often referred to as a kind of fractal dimension[46].

There are different ways of measuring dimension but the correlation dimension has the privilege of being straightforwardly and rapidly computed, of being less noisy when only a short signal and data points are accessible, and is often in agreement with other calculations of dimension. Pijn et al (1997) used the correlation dimension for seizure prediction and found that a seizure activity often, occurs as a low-dimensional oscillation[47]. In general, during a seizure as a non-stationary phenomenon, both phases of low and high complexity may occur. Nevertheless a low dimension may be found mainly in the zone of ictal onset and nearby structures[47]. Using correlation dimension and "point-wise dimension" Feucht et al (1999) identified "strong epileptic activity" compared with the control data[48]. In artificial neural network and non-linear predicting methods, correlation dimension is one the most important measures used for designing predictive algorithms.

Phase Synchronization

Phase synchronization is among the most important and common measures used for seizure prediction. Phase synchronization is the process by which two or more cyclic signals tend to fluctuate with a repeating sequence of relative phase angles. It is usually applied to two waveforms of the same frequency with same phase angles with each cycle. However it can be applied if there is an integer relationship of frequency, such that the cyclic signals share a repeating sequence of phase angles over consecutive cycles. These integer relationships are called Arnold tongues which follow from branch of the circle map. A few years ago, synchronization in chaotic systems have attracted much consideration in the field of nonlinear dynamics and have found applications in areas such as laser dynamics[49], solid state physics[50], electronics[51], biology[52]. As a specific type of synchronization, the concept of phase synchronization was introduced for coupled chaotic model systems by Rosenblum, *et al.,*[53] that was experimentally confirmed[54]. Recently, this concept has been applied to biological time series such as respiratory rate in humans[55] and the magneto encephalogram of Parkinsonian patients[56]. The notion of synchronization was introduced to physics by Huygens[57]. In the 17th century for two coupled frictionless harmonic oscillators. Before investigating the spatial variability of the mean phase coherence as a measure of synchronization, it is important to found that there is no straightforward, symmetric phase coherence calculated from signals measured at two different locations to a single point or region within the brain. The mean phase coherence should be projected onto one of the respective electrode contacts, onto both of them, onto their line of interconnection, or onto the middle of this line, respectively, remains a nontrivial problem to be discussed[8].

In a series of studies conducted on phase synchronization on the interictal state of the epileptic patients, the findings showed that 70% of seizures shows that a specific state of brain synchronization that can be observed several hours before the seizure. However, both increases and decreases in synchronization could be detected within the 4-15 Hz frequency band. The team hedged in their final results that this analysis "does not organize genuine seizure prediction," but "may provide useful data for prospective seizure warning"[41, 58, 59].

Entropy

Another non-linear measure used in seizure predicting method is entropy. Four entropy features namely approximate entropy, sample entropy, phase entropy 1 (*S1*), and phase entropy 2 (*S2*) are extracted from the EEG recordings. These features are usually fed to pattern recognition or classifying models to produce the measures correlated with preictal or ictal stages. Some of the common classifiers are Fuzzy Sugeno Classifier (FSC), Support Vector Machine (SVM), K-Nearest Neighbour (KNN), Probabilistic Neural Network (PNN), Decision Tree (DT), Gaussian Mixture Model (GMM), and Naive Bayes Classifier (NBC) (6) (60).

Drongelen *et al.,* (2003) used Kolmogrov entropy to anticipate seizure in pediatric patients and could predict the impending seizures 2 to 40 min before their onset[61]. Li *et al.,* (2007) evaluated the permutation entropy to predict the absence seizure[62]. They demonstrated that the permutation entropy can be used to predict the transient dynamics prior to the absence seizure through following the dynamical changes of EEG[62]. Bedeeuzzaman *et al*. (2012) proposed an automatic seizure forecasting method using wavelet entropy (WE) and mean absolute deviation (MAD)[19]

Seizure Prediction Methods

The prediction methods use intracranial or surface EEG for extracting measures. Intracranial EEG recording is invasive method but conveys more information through high amplitude of brain electrical fluctuations and higher resolutions.

All of the seizure prediction models have certain common features. Most of them have two necessary steps. First; all of them try to detect and extract EEG-based measures over time characterizing different stages of the epilepsy cycle including interictal, preictal, ictal, and postictal stages. In this regard, they use a moving window analysis in which a linear or nonlinear characterizing measure is calculated from a window of EEG data with a predefined length[21, 63]. The duration of the analysis windows usually ranges 10 to 40 s. The second step is distinguishing and classifying the measures into preictal and ictal state. The two other states are not important in seizure prediction as they represent the undergoing seizure and the prediction process aims to determine and warn an impending seizure (26 2006, 2007, 36 2006, 2007, 59, 64-66). When the employed measure is used to characterize a single channel, it is referred to as univariate. If the measure characterizes the relations between two or more EEG channels, it is a bivariate or multivariate measure, respectively. The moving window analysis yields time profiles of a characterizing measure for different channels or channel combinations. In next step, a protocol or study design should be used to evaluate these time profiles. The study design is statistical or algorithmic. A statistical design is retrospective by nature and compares the amplitude distributions of the characterizing measures obtained in the interictal with the preictal period. The temporal structure of the time profiles is typically not preserved in this type of analysis. The statistical design is useful to assess and compare the potential predictive performance of different characterizing measures under different conditions. In contrast, an algorithmic analysis produces a time-resolved output where for each point of the time profile one output is produced. The algorithm is usually prospective, that is, its output at a given time should be a function of the information available at this time. Prediction algorithms usually employ certain thresholds. When the time profile of a characterizing measure exceeds the threshold, the algorithm produces an alarm indicating an impending seizure.

Techniques used to predict seizures include frequency-based methods, statistical analysis of EEG signals, non-linear dynamics (chaos), and intelligent expert systems. The frequency- and statistical-based methods have good performance especially for univariate measures. The non-linear dynamics and intelligent expert systems have shown more promising results in efficient seizure predicting models. The applications and advantages of two methods are discussed below in more details

Nonlinear (chaos) predicting methods

The characteristic feature of brain electrical activity is its irregular behavior. This time series activity is dynamic with strong nonlinear properties. On the other hand, deterministic chaos offers effective and striking explanation for potential for apparently irregular behavior. The framework of the theory of non-linear dynamics provides new concepts and powerful algorithms to analyze such time series. However, different influencing factors impose some limitations on the use of non-linear measures to predict seizure. Nevertheless, if interpreted with care, particularly the correlation dimension or the Lyapunov-exponents provide a means to reliably characterize different states of normal and pathological brain function.

Various studies have shown that applying non-linear time series analysis (NTSA) to EEG offers new information about the complex dynamics of underlying neuronal networks[40, 47, 67-69]. Within this physical-mathematical framework a variety of measures e.g. Lyapunov exponents, correlation dimension or Kolmogorov entropy allow characterization of different static and dynamic properties of a time series. However, well-known problems in extracting non-linear measures from short, noisy, and non-stationary data would exclude the use of these measures to characterize EEG dynamics. The problem can be mainly resolved using differential measures with respect to time and recording site. Findings of various studies showed strong evidence indicating superiority of information supplied by NTSA compared with conventional parametric or non-parametric analyses in both time and frequency domain.

One of promising methods for seizure prediction is Lyapunov exponent[69,70,65,41]. This method is a non-linear technique to predict seizure. The Lyapunov exponent, L, is a criterion of the chaocity level of a system. Studies showed a sudden fall in L at seizure onset[41]. For the electrodes far the focus, the decline was smaller. Different studies showed that the largest average L could be useful for seizure detection[41, 65]. The wavelet transform has been introduced as another approach for the seizure predicting model. A new method called "wavelet based nonlinearity index" was used to predict seizures, and the beta frequency band 10-30 Hz proved to be the best for prediction[19, 22, 25, 71].
Effective correlation dimension[7,34,66], dynamical similarity index[33, 41, 59], and an increments of accumulated energy[37] are three most promising nonlinear seizure predicting methods yielding higher reliability in predicting seizures.

Intelligent expert systems.

Intelligent systems like artificial neural networks have shown a good potential in pattern recognition and EEG measure classification that can be used in seizure prediction models[3,15,25,26,72-76]. In addition, adaptive neuro-fuzzy inference systems have been used for seizure predictions by different groups[75,76]. The artificial neural network based models usually used nonlinear EEG features such similarity index, phase synchronization, and nonlinear interdependence. Chernihovskyi et al. (2005) used a nonlinear medium consisting of model neurons and asserted that this cellular neural network could be trained to approximate the degree of synchronization for seizure prediction[67]. Rabbi *et al.* (2010) proposed a fuzzy rule-based seizure prediction based on correlation dimension changes in intracranial EEG (75). Different artificial neural networks have been used in seizure prediction models. Aarabi et al. (2014) used neural mass model to simulate the macro-scale dynamics of intracranial EEG data for seizure prediction[9]. Their model used different measures like correlation dimension for the prediction.

Future Research attitude in seizure predicting methods

The main limit of previous seizure predicting models was that their focus was mainly limited to the preictal period and did not include an evaluation of control recordings from the seizure-free interval. Therefore, the specificity of these models was not assessed. In addition, most of previous seizure prediction methods up to now rely on the posteriori knowledge that can impose bias or partiality on selecting the appropriate measures. For example choosing certain channels out of a large number of channels or using in-sample evidence of parameters used to calculate measures for the extraction of predictive information. To date rare prospective or quasi-prospective seizure prediction model have been published. A major problem with most of these predicting models is that they do not sufficiently (or not at all) evaluate the specificity of the proposed measures using interictal EEG as control. Regarding the unique characteristics and intra-individual differences of EEG, any seizure predicting model needs statistical validation to assess the statistical significance of the predictive performance for a given EEG measure[77-79]. The performance of a reliable prediction method has to be superior to a prediction in a random, periodic, or other nonspecific manner, independent of any prior information.

Furthermore, to establish efficient seizure predicting model we need further studies with continuous long-term-recordings over days obtained from different patients from different centers using distinctive pre-surgical evaluation protocols and acquisition systems. In addition, regarding the limitations of the previous studies, for evaluation of any seizure predicting method both sensitivity and false prediction rate[80] should be used. On the other hand, statistical criteria should be combined clinical considerations for a robust performance assessment of predicting method.

CONCLUSION

Review of the current seizure predicting models showed that advances in seizure prediction have promised bright future in seizure control and management. One possible scenario is using implantable devices able to warn of impending seizures in combined with appropriate interventions like electrical stimulation or focal drug infusion applied on demand to prevent seizures or at least minimize the side-effects in epileptic patients. Further studies are needed to increase the sensitivity of prediction model as well as developing best EEG based measures as precursor of impending seizures.

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