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# A rule-based seizure prediction method for focal neocortical epilepsy

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HIGHLIGHTS

- Our rule-based seizure prediction algorithm provided an average sensitivity of >90% and false prediction rate of <0.15/h for a seizure occurrence period of 50 min and a seizure prediction horizon of 10 s in 11 patients with focal neocortical epilepsy.
- Nonlinear analysis of iEEG in the period prior to seizures revealed patient-specific spatio-temporal changes significantly different from those observed within baselines in the majority of the seizures.
- The preictal changes were observed in the electrodes located in the epileptogenic zone as well as in remote areas.

ABSTRACT

*Objective:* In the present study, we have developed a novel patient-specific rule-based seizure prediction system for focal neocortical epilepsy.
*Methods:* Five univariate measures including correlation dimension, correlation entropy, noise level, Lempel-Ziv complexity, and largest Lyapunov exponent as well as one bivariate measure, nonlinear interdependence, were extracted from non-overlapping 10-s segments of intracranial electroencephalogram (iEEG) data recorded using electrodes implanted deep in the brain and/or placed on the cortical surface. The spatio-temporal information was then integrated by using rules established based on patient-specific changes observed in the period prior to a seizure sample for each patient. The system was tested on 316 h of iEEG data containing 49 seizures recorded in 11 patients with medically intractable focal neocortical epilepsy.
*Results:* For seizure occurrence periods of 30 and 50 min our method showed an average sensitivity of 79.9% and 90.2% with an average false prediction rate of 0.17 and 0.11/h, respectively. In terms of sensitivity and false prediction rate, the system showed superiority to random and periodical predictors.
*Conclusions:* The nonlinear analysis of iEEG in the period prior to seizures revealed patient-specific spatio-temporal changes that were significantly different from those observed within baselines in the majority of the seizures analyzed in this study.
*Significance:* The present results suggest that the patient specific rule-based approach may become a potentially useful approach for predicting seizures prior to onset.


## 1. Introduction

As a chronic neurological disorder, epilepsy is characterized by recurrent unprovoked seizures which are paroxysmal hypersynchronous electrical discharges of cerebral neurons (Chaovalitwongse et al., 2006). With an incidence of epilepsy estimated at 30–50 individuals per 100,000 population (Browne and Holmes, 2008), there remain a significant number of epileptic patients at risk of serious injury or death (Cockerell et al., 1994). The quality of life of epileptic patients would be significantly improved if seizures could be predicted.

To date, many attempts have been made to identify precursors of epileptic seizures by investigating various characteristics of the EEG time series using linear (Gotman and Koffler, 1989; Katz et al., 1991) and nonlinear univariate measures (Iasemidis et al., 1990; Lehnertz and Elger, 1998; Martinerie and Adam, 1998; Le Van Quyen et al., 2001; van Drongelen et al., 2003; Drury et al., 2003). Among these measures, those taken from the theory of chaotic dynamics, including the correlation dimension (Lehnertz and Elger, 1998), correlation density (Martinerie and Adam, 1998), largest Lyapunov exponent (Iasemidis et al., 1990), dynamic similarity index (Le Van Quyen et al., 2001), entropy (van Drongelen et al., 2003) and predictability (Drury et al., 2003) have shown

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higher seizure predictability power in the scalp EEG or iEEG (see Mormann et al., 2006 for review). Seizure prediction using these measures has suggested a transition state with characteristic changes that occur minutes–hours before a seizure. However, no measure has been shown to out-perform a random predictor (Mormann, 2008). Bivariate measures have also been employed for seizure prediction, such as nonlinear interdependence (Arnhold et al., 1999), phase synchronization, cross correlation (Mormann et al., 2003). In a comparative study, Mormann et al., (2005) compared the performance of univariat and bivariate measures for seizure prediction and found a significant superiority for bivariate over univariate measures.

In general, univariate and bivariate measures can provide different, albeit complementary and relevant, information (Lehnertz et al., 2001). Therefore, for better characterizing preictal states and, consequently, for achieving a clinically acceptable performance across different patients and seizure types, multiple univariate and bivariate features ought to be used for developing seizure prediction tools (Iasemidis and Sackellares, 1996).

In the present study, we have developed a patient-specific method based on integrated univariate and bivariate measures to predict partial seizures using iEEG data. The aim is to improve seizure prediction by combining the predictability power of different measures. We also aim to identify preictal states based on spatio-temporal dynamic characteristics of the iEEG signal. To achieve these goals, the information exploited by using univariate and bivariate measures from iEEG is spatio-temporally integrated with patient-specific rules established using a sample seizure from each patient.

## 2. Methods

### 2.1. iEEG data

In this study, iEEG data of patients with medically intractable focal epilepsy were analyzed to test the performance of the developed method. The iEEG data were selected from the Freiburg Seizure Prediction EEG (FSPEEG) database including clinical and subclinical seizures (Maiwald et al., 2004) with authorization, having been recorded by a Neurofile NT digital video-EEG system (IT-Med, Usingen, Germany) with 128 channels, 256 Hz sampling rate, and a 16 bit analog-to-digital converter. Out of a total of 21 patients in the database, we included only the 11 individuals with a neocortical epileptic focus to evaluate our system, because seizure prediction in these patients is typically more challenging (Navarro and Martinerie, 2002) due to less inter-patient homogeneity, in terms of clinical manifestations and electrographic characteristics (Lee et al., 2000). It is of interest that almost two-thirds of adult epileptic patients with partial epilepsy suffer from seizures with neocortical onset (Semah et al., 1998).

Grid, strip, and depth electrodes were used to record iEEG data. For each patient in this database, only six contacts were selected by visual inspection of iEEG data by an experienced epileptologist: three near the epileptic focus, and three in remote locations. The extra-focal contacts were located at least more than two contacts distant from the focal contacts. No hyperventilation or photo stimulation had been used to provoke seizures.

In total, 316 h of iEEG data containing 49 seizures with at least 50-min pre-ictal data were analyzed. Based on identification of epileptic patterns preceding clinical manifestation of seizures in iEEG recordings, the onset and offset times of seizures had been previously determined by the epileptologist. Table 1 summarizes the details of the iEEG data used in this study.

#### 2.1.1. Optimization and testing subsets

The iEEG data of each patient were split into the optimization and test sets. The optimization set included one randomly selected sample seizure with a preictal period of 50 min and four-hour seizure-free interictal iEEG data distal to any ictal activity, referred to as the reference window or state. The optimization set was used to tune the parameters of the system in a patient-specific way. The testing set containing the remaining seizures and interictal data was used to assess the performance of the system.

### 2.2. Seizure prediction system

Fig. 1 shows a schematic of the proposed seizure prediction system. It comprises three stages: *preprocessing, feature extraction and thresholding, and rule-based decision making.*

#### 2.2.1. Preprocessing

The purpose of this stage was first to remove both high frequency noise and low frequency activity and subsequently to divide the iEEG signal into quasi-stationary segments. For this two-fold purpose, the iEEG data were band-pass filtered between 0.5 and 100 Hz using a 4th order digital Butterworth filter, and notch filtered to remove 50 Hz power line noise. Then, the filtered iEEG data were partitioned into non-overlapping 10-s segments. The choice of segment length was a trade-off between signal stationarity and having the adequate number of data points required for extracting features from the iEEG data (Mormann et al., 2006).

#### 2.2.2. Feature extraction

This stage aimed at extracting relevant features, which contained specific characteristic properties of iEEG signal, and were suitable for the seizure prediction task. After reviewing the

**Table 1**
Patient specific characteristics of the intracranial EEG data.

| Patient | Sex | Age | Seizure type | Origin | Electrodes | Number of seizures | Average seizure duration (s) | Interictal seizure-free EEG duration (h) |
|---|---|---|---|---|---|---|---|---|
| 1 | F | 15 | SP,CP | Frontal | g,s | 4 | 13.1 | 24 |
| 2 | M | 14 | SP,CP | Frontal | g,s | 5 | 92.7 | 24 |
| 3 | F | 16 | SP,CP,GTC | Frontal | g,s | 5 | 44.9 | 24 |
| 4 | F | 32 | SP,CP | Frontal | g,s | 2 | 163.7 | 24 |
| 5 | M | 44 | CP,GTC | Temporo/occipital | g,s | 5 | 113.7 | 24 |
| 6 | F | 10 | SP,CP,GTC | Parietal | g,s | 4 | 157.3 | 24 |
| 7 | M | 28 | SP,CP,GTC | Temporal | s | 5 | 86.2 | 24 |
| 8 | F | 25 | SP,CP | Frontal | s | 5 | 13.7 | 25 |
| 9 | F | 28 | SP,CP,GTC | Frontal | s | 4 | 12.5 | 24.4 |
| 10 | M | 33 | SP,CP,GTC | Tempo/parietal | d,g,s | 5 | 85.7 | 25.6 |
| 11 | M | 13 | SP,CP | Temporal | g,s | 5 | 83.1 | 24 |
| Total | | | | | | 49 | | 267 |

SP = simple partial; CP = complex partial; GTC = generalized tonic-clonic; g: grid; s: strip; d: depth.