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Early Detection of Human Epileptic Seizures Based on Intracortical Local Field Potentials

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Abstract

The unpredictability of re-occurring seizures dramatically impacts the quality of life and autonomy of people with epilepsy. Reliable early seizure detection could open new therapeutic possibilities and thus substantially improve quality of life and autonomy. Though many seizure detection studies have shown the potential of scalp electroencephalogram (EEG) and intracranial EEG (iEEG) signals, reliable early detection of human seizures remains elusive in practice. Here, we examined the use of intracortical local field potentials (LFPs) recorded from 4×4-mm² 96-microelectrode arrays (MEA) for early detection of human epileptic seizures. We adopted a framework consisting of (1) sampling of intracortical LFPs; (2) denoising of LFPs with the Kalman filter; (3) spectral power estimation in specific frequency bands using 1-sec moving time windows; (4) extraction of statistical features, such as the mean, variance, and Fano factor (calculated across channels) of the power in each frequency band; and (5) cost-sensitive support vector machine (SVM) classification of ictal and interictal samples. We tested the framework in one-participant dataset, including 4 seizures and corresponding interictal recordings preceding each seizure. The participant was a 52-year-old woman suffering from complex partial seizures. LFPs were recorded from an MEA implanted in the participant's left middle temporal gyrus. In this participant, spectral power in 0.3–10 Hz, 20–55 Hz, and 125–250 Hz changed significantly between ictal and interictal epochs. The examined seizure detection framework provided an event-

wise sensitivity of 100% (4/4) and only one 20-sec-long false positive event in interictal recordings (likely an undetected subclinical event under further visual inspection), and a detection latency of 4.35 ± 2.21 sec (mean $\pm$ std) with respect to iEEG-identified seizure onsets. These preliminary results indicate that intracortical MEA recordings may provide key signals to quickly and reliably detect human seizures.

I. INTRODUCTION

Approximately 50 million people in the world suffer from epilepsy, with approximately 3 million in the United States alone [1]. The seemingly unpredictable nature of seizures has significant negative effects on the autonomy of people with epilepsy and their quality of life. Reliable early seizure detection could, especially when integrated with novel seizure abortion approaches [2–4], significantly improve the quality of life of these people.

Prior studies on early seizure detection have focused primarily on scalp electroencephalogram (EEG) and intracranial EEG (iEEG) signals. Several approaches based on these signals have been attempted using spectral features and related wavelet decompositions [5–8], line-length [9, 10], and other linear and nonlinear measures [11]. However, to date, reliable early seizure detection based on EEG and/or iEEG signals remains elusive in practice [12].

Here we explore a different approach based on local field potentials (LFPs) recorded from *intracortical* microelectrode arrays. Specifically, we examine the use of LFPs recorded from a 96-microelectrode array (96-MEA) on a 4×4 -mm² platform (the NeuroPort System; Blackrock Microsystems, Salt Lake City, UT USA) implanted in neocortex of a participant with focal epilepsy undergoing pre-resection surgery monitoring [13]. Our long-term goal is to develop and test a real-time closed-loop seizure intervention system that integrates intracortical recordings of ensembles of single neurons and LFPs with more conventional macroscopic iEEG signals.

II. Methods

A. Data Description and Approach Outline

This study and neural recordings were carried out with approval of Institutional Review Boards at local Partners Human Research Committee and Brown University as well as informed consent of the participant. The participant was a 52-year-old female, who suffered from complex partial seizures and occasional secondary generalized seizures.

In addition to standard electrocorticography grids (ECoG), a 96-MEA was implanted in her left middle temporal gyrus. The MEA was approximately 2 cm distant from the nearest ECoG electrode where seizure onsets were identified. In this study, we focused on LFPs recorded during four seizures and 168.9-min of interictal (between seizures, normal) time. Interictal recordings before each of the seizures included approximately a 40-min period, excluding 10-min prior to its onset.

The early seizure detection framework explored here is outlined in Figure 1. It consists of sampling, pre-processing, feature extraction, and support vector machine (SVM) classification. The detection scheme was based on spectral power features which were particularly tailored for this participant.

B. Sampling: LFP Extraction

Intracortical neural electrical signals in the 96-MEA were recorded broadband (0.3 Hz – 7.5 kHz) and sampled at 30 kHz [13]. LFPs were extracted by further low-pass filtering (250 Hz cutoff) and down-sampling at 1 kHz.

C. Pre-processing: Kalman-Filter Denoising and Artifact Removal

Pre-processing is crucial in reducing or removing noise and artifacts in neural signals, thus improving the algorithm's detection rate. In this study, two pre-processing steps were applied: Kalman-filter denoising of LFPs (see Figure 2) and artifact rejection. We assume that the recordings consist of noisy observations of a true underlying LFP state according to the following state-space model [14]:

$$\begin{aligned} x_{k+1} &= \begin{bmatrix} 1 & \Delta T \\ 0 & 1 \end{bmatrix} x_k + v_k \\ y_k &= \begin{bmatrix} 1 & 0 \end{bmatrix} x_k + w_k, \end{aligned}$$

where x_k denotes the true LFP state, y_k denotes the observations (measurements), and $v_k \sim N(0, Q)$ and $w_k \sim N(0, \sigma_w^2)$ are uncorrelated; The state noise covariance matrix was set to

$$Q = \begin{bmatrix} \frac{\Delta T^4}{4} & \frac{\Delta T^3}{2} \\ \frac{\Delta T^4}{4} & \Delta T^2 \end{bmatrix} \sigma_v^2,$$

$$\text{with } \frac{\sigma_v^2}{\sigma_w^2} = 2^{-20}.$$

Transient LFP artifacts in the dataset typically contained high power in 60 Hz and higher harmonics. 1-sec long segments with 120 Hz power above a pre-specified threshold were labeled as artifacts and removed from the analysis.

D. Feature Extraction: Mean, Variance and Fano Factor of Spectral Power Across MEA Channels

Visual inspection of pre-processed LFP spectrograms suggested that changes in *spectral power* in specific bands could easily and reliably indicate seizure onsets. Specifically, spectral power in 0.3–10 Hz, 20–55 Hz, and 125–250 Hz changed significantly after seizure onset in this participant's dataset (Figures 2 and 3). The spectral power was computed in 1-sec windows with 0.5-sec overlap between consecutive windows. The multitaper spectral power estimation method [15] was used with 9 tapers and a time-bandwidth product equal to 5; the software package Chronux was used for the estimation [16].

Detection features were derived from *temporal* and statistical properties (such as the *mean*, *variance*, and *Fano factor* across the MEA channels) of the estimated spectral power. For each of the 3 specified frequency bands, we computed the mean of the power across all of the recorded MEA channels. Similarly, we also calculated the variance and the Fano factor for each band. The variance and the Fano factor indicated how homogeneous changes in power appeared across the MEA channels. These 9 statistical features were further normalized into z-scores. Statistical features from 9 consecutive 1-sec time windows, corresponding to 5-sec, were then concatenated to capture the temporal profile of power

changes, as similarly done in [8]. We used the first 20-sec period of each seizure to extract features for the ictal class.

E. Classification: Cost-Sensitive SVM-Classification

Datasets for seizure detection and prediction are typically highly imbalanced in the sense that there are far fewer ictal samples than interictal. In order to account for this imbalance, we employed *cost-sensitive* support vector machines (SVMs; software package LIBSVM [17]). Cost-sensitive SVMs set a higher misclassification cost (penalty) for ictal than for interictal samples. The cost parameter was set to 2^{15} and the cost weight, as determined as the ratio between the number of ictal and interictal samples [18], was set to 159. We used linear SVMs and a *leave-one-seizure-out cross-validation* (LOSO CV) scheme for out-of-sample testing [5, 7, 8, 10, 19].

III. Results

We assessed seizure detection performance with two types of analyses: event-wise and sample-wise detection. In the event-wise, *i.e.* a seizure occurrence is considered one event, the examined framework achieved 100% sensitivity (4/4) and one approximately 20-sec-long false positive event. Upon further visual inspection, we conjectured that this false positive event corresponded to a subclinical undetected seizure. The detection latency was 4.35 ± 2.21 sec (mean $\pm$ std). Seizure onsets were determined according to ECoG inspection.

In the sample-wise detection analysis, a single feature set was classified as an ictal or interictal sample. TABLE I summarizes the sample-wise analysis by presenting a confusion matrix and related statistics including the sensitivity, specificity, and positive and negative predictive values.

IV. Discussion

Our preliminary analysis indicates that intracortical LFPs recorded from MEAs are promising neural signals for reliable early detection of human epileptic seizures. In the examined one-participant dataset, the adopted framework achieved 100 % sensitivity and one 20-sec-long false positive event. We also demonstrated the high detection rate on a sample-by-sample basis.

The event-wise and sample-wise analyses did not involve any post-processing of the SVM classification outputs. Inclusion of a post-processing step, such as Kalman-filter denoising, might improve even further detection performance [19]. We also note that this high detection performance was achieved with a set of only 9 features, far fewer than the actual number of channels. This lowers the complexity of the algorithm and improves the feasibility of an actual real-time device for human seizure detection.

The seizure detection problem, as well as prediction [19, 20], typically involves highly imbalanced datasets, *i.e.* substantially larger number of interictal than ictal samples. To handle this imbalance issue, we used cost-sensitive SVMs. SVMs with the Synthetic Minority Oversampling TEchnique (SMOTE) [21] and the Granular SVMs with Repetitive Undersampling (GSVM-RU) [22] may be effective alternative methods to handle imbalanced classification tasks.

We plan to extend the analysis of this framework for early seizure detection based on intracortical LFPs to datasets including more participants and a large diversity of seizure types. We also plan to include other neural signals, such as single neuron action potentials

and multiunit activity, which are readily available in the intracortical MEA recordings studied here.

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Figure 1.
Outline of the seizure detection approach based on intracortical LFPs.

Figure 2.

Effect of Kalman-filter denoising of LFPs. Top panel: raw LFP time-trace (cyan) and Kalman-filtered LFPs (blue) are shown. Seizure onset is at time zero. Middle and bottom panels: spectrograms of raw LFPs (middle) and Kalman-filtered LFPs (bottom). Kalman-filter denoising may enhance spectral features and improve discriminability of interictal and ictal epochs. In particular, Kalman filter denoising enhanced the discriminability by smoothing low frequency power in the interictal epoch (white-dotted region) and by attenuating high frequency power in the ictal period (gray-dashed region). Power is in dB.

Figure 3.

Spectral power across channels in the 3 specified bands (left panels) and the corresponding statistical features (mean, variance and Fano-factor) computed across the MEA channels (right panels). Statistical features are z-scored. Seizure onset is at time zero. Power is in dB.

Table I

Sample-wise detection rate

	Actual ictal	Actual interictal	
Classified as ictal	120	32	Pos. pred. value = 0.789
Classified as interictal	8	20278	Neg. pred. value $\approx$ 1.000
	Sens. = 0.938	Spec. = 0.998	