Automated Localization of the Seizure Focus using Inter-ictal Intracranial EEG

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***Abstract*— Up to 30% of newly diagnosed epileptic patients have seizures poorly controlled with anti-epileptic drugs alone. Surgical therapy might be beneficial to patients who respond poorly to drug treatments. It is therefore very crucial to accurately localize the seizure focus. Neurologists rely heavily on seizures to determine the focus. The invasive recordings usually continue for days or weeks, which is costly, suffering, and infectiously risky for patients.**

In this paper, techniques are developed to localize the seizure focus using brief inter-ictal intracranial EEG (iEEG). A supervised learning paradigm is utilized making use of features extracted from inter-ictal iEEG on multiple referential montages. Analysis of 14 epileptic patients (implanted with depth electrodes) shows that epileptic features such as slowing, ripples, spikes, and local synchrony measures are strongly correlated to the seizure focus. In the long term, it may allow reliable localization of the seizure focus from brief inter-ictal iEEG, which in turn makes it possible for shorter hospitalizations.

I. INTRODUCTION

Epilepsy is a group of chronic disorders of the brain, which is characterized by unprovoked recurrent seizures. Around 50 million people worldwide have epilepsy, and only 70% of newly diagnosed epilepsy can be successfully controlled with anti-epileptic drugs [1]. Surgical therapy might be beneficial to patients who respond poorly to drug treatments. Regional resection may provide seizure reduction or even cure [2]. The success of surgical resection strongly depends on accurate localization of the seizure focus. Apart from medical imaging modalities such as MRI and SPECT, modern clinical practices utilize EEG (scalp or intracranial) in localizing the surgical seizure focus [3]. Intracranial EEG (iEEG) is only necessary for intractable cases when scalp EEG is non-conclusive. On the other hand, neurologists rely heavily on EEG containing seizures to determine the focus. However, due to the unprovoked and infrequent natures of seizures, the invasive recordings usually continue for days or weeks until enough seizures are captured. It is costly, suffering, and infectiously risky for patients.

In this paper, brief inter-ictal iEEG recordings are used to determine the seizure focus. Our analysis shows that inter-ictal iEEG recordings do contain much relevant information about the seizure focus. In the long term, instead of seizure EEG, neurologists may rely on brief inter-ictal iEEG to delineate the seizure focus. It would drastically reduce the time of hospitalization for intractable epileptic patients. In addition, majority of the current localization studies are about scalp EEG, and iEEG recorded with surface electrodes. In this paper, we focus on iEEG recored with depth electrodes, which would provide new insights.

To localize electrodes inside the seizure focus can be considered as a binary classification problem. Several studies have suggested that both univariate and multivariate analysis may help to delineate epileptogenic cortex ([4], [5]). In earlier work ([2], [6]), we have combined univariate feature such as slowing, and multivariate features such as Pearson correlation coefficient [7], magnitude coherence [7], phase synchrony [8], and omega complexity [9], for the purpose of localizing the seizure focus from interictal iEEG. In this paper, building upon our earlier results, we include two more univariate features, i.e., ripples [10], and inter-ictal spikes [11], in combination with slowing, cross-correlation coefficient and phase synchrony, to localize the seizure focus. We also consider more patients (14 instead of 5).

A supervised learning paradigm is utilized in which the clinical determinations of seizure focus are used for training together with input features. Specifically, adaptive boosting algorithm [12] was applied to test all possible combinations of features. Our numerical results have shown that combining features results in more accurate predictions. However, adding more features does not seem to always improve the performance. In the best combination (spikes and phase synchrony on local common average montage, and ripples on global common average montage), there are 11 cases out of 14 patients having accuracy $\geq$80%.

This paper is organized as follows. In section II, we briefly explain our inter-ictal iEEG data and techniques for signal processing. In section III, we present our numerical results, and in section IV we offer concluding remarks.

II. METHODS

In this section, we briefly explain the inter-ictal iEEG data being studied in this paper. Topics such as de-noising and pre-processing of the signal are addressed as well. Most importantly, we introduce a supervised learning paradigm used in this study, involving the classification algorithm, and the epileptic EEG features of our interest.

A. Epileptic Inter-ictal Intracranial EEG

14 drug-resistant patients with focal epilepsy underwent depth electrode implantation at Massachusetts General Hospital. The position of the electrodes was selected exclusively for clinical reasons. In each case, multiple 1-hour records at

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least 24 hours away from seizures were used. Neurophysiologists defined the seizure focus as the area showing the first ictal activity using seizure EEG, which was carried out independently from this study.

With 500Hz sampling rate, the iEEG recordings were band-pass filtered between 1 and 200Hz. A notch filter was applied as well to remove the 60Hz power-line interference. Before computing features, each EEG signal was normalized (mean subtracted, divided by standard deviation). In addition, the EEG analysis was performed on 3 different referential montages, including mono-polar, local common average (average of local contacts of the same electrode), and global common average (average of all the contacts of the same patient). Each depth electrode contains multiple contacts (6 or 8). For each univariate feature, the average among feature values of local contacts was used as the representative for a given electrode. For pairwise synchrony features, the average of feature values of all pairs of local contacts was used for a given electrode. The features varied considerably across patients necessitating a normalization procedure. We further divide each electrode-wise feature by the average of feature values of all the electrodes for a given record.

B. Adaptive Boosting

In this study, binary adaptive boosting algorithm (AdaBoost) was applied as the classifier to delineate the seizure focus. AdaBoost is a general method for generating a strong classifier out of a pool of weak classifiers [12]. The weak classifiers are trained sequentially, and for classifier with index m, AdaBoost computes the weighted classification error:

$$\varepsilon_m = \sum_{n=1}^{N} d_n^{(m)} \mathcal{I}(y_n \neq h_m(x_n)), \qquad (1)$$

with x_n denoting the observation, y_n the desired label, h_m the predicted label, $\mathcal{I}$ the indicator function, and $d_n^{(m)}$ the weight of observation. AdaBoost then increases weights for observations misclassified while reducing those correctly classified. Training of AdaBoost can be viewed as stage-wise minimization of the exponential loss

$$\sum_{n=1}^{N} w_n \exp(-y_n f(x_n)), \qquad (2),$$

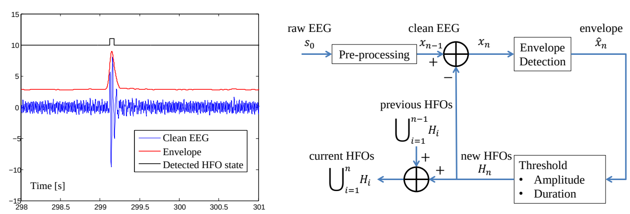
with w_n denoting the normalized observation weights, $f(x) = \sum_{m=1}^{M} \alpha_m h_m(x)$ the prediction score for new data, and $\alpha_m = 0.5 \log \frac{1-\varepsilon_m}{\varepsilon_m}$ the weights of the weak predictions.

C. Epileptic EEG Features

Each depth electrode can be viewed as sample point defined by epileptic EEG features. In this paper, we have exploited features such as ripples, inter-ictal spikes, slowing, cross-correlation coefficient, and phase synchrony. In addition, a novel method has been developed for ripple detection.

*1) **High Frequency Oscillations**:* High Frequency Oscillations (HFOs) are special EEG patterns recorded from intracranial electrodes in patients with intractable epilepsy (see Fig. 1a). According to frequency range, HFOs are further divided into 3 subcategories, referred to as ripples (80-250Hz), fast ripples (250-500Hz) and very fast ripples (>500Hz). HFOs can be characterized by oscillations of at least 4 cycles, with a typical duration of 80-100ms for ripples, and 30-50ms for fast ripples [13]. HFOs are believed to be associated with the seizure focus [10], with higher rates of HFOs observed in the seizure focus from inter-ictal iEEG [14].

Given the lack of a complete definition, subjectivity is inevitable, sometimes resulting in poor agreement among reviewers. In addition, manually marking HFOs is highly time-consuming [10]. As a result, we are motivated to develop an automated HFO detector. Due to the small sampling rate (500Hz), only ripples are of our interest for this study. As preparation, each iEEG channel was high-pass filtered at 80Hz in advance.



(a) (b)

Fig. 1: (a) HFO with envelope obtained via Hilbert Transform, and (b) Block diagram of the proposed iterative ripple detector.

The proposed ripple detector consists of 3 major techniques:

- ***Envelope detection via Hilbert Transform***
  The envelope $\widehat{x}$ (see Fig. 1a) of a given time series x can be obtained via Hilbert Transform [15], defined by
  $$\widehat{x}(t) = |x(t) + i(\frac{1}{\pi} P \int_{-\infty}^{\infty} \frac{x(\tau)}{t-\tau} d\tau)|. \qquad (3)$$
  Morphological features such as amplitude and duration are well reserved by the envelope $\widehat{x}$.
- ***Thresholds upon amplitude and duration***
  According to definition in [13], only waveforms with amplitude larger than 5 multiples of the standard deviation σ_n of the current input signal x_n, and duration within 80-100ms, are considered as HFOs.
- ***Method of Iteration***
  The detection process is iterative as shown in Fig. 1b, such that HFOs newly detected in current stage H_n are removed from the previous input signal x_n, to initiate the new loop of detection. The iteration stops when there are no more HFOs newly detected.

The performance of the proposed ripple detector is validated using a piece of 30-min long inter-ictal iEEG with total 797 HFOs manually annotated by 2 experts (85% agreement). It ended up with 97% sensitivity, 95% specificity, and running time of 33s.

Feature	Mono-polar			Local Common Average			Global Common Average		
	Focus	Normal	p-values	Focus	Normal	p-values	Focus	Normal	p-values
	mean±std	mean±std		mean±std	mean±std		mean±std	mean±std	
slowing	1.09±0.20	0.97±0.13	1.3E-12	1.05±0.16	0.98±0.13	5.7E-07	1.05±0.16	0.98±0.13	9.5E-05
HFO	1.61±1.63	0.70±0.81	1.5E-09	2.00±1.67	0.68±1.00	2.4E-20	1.77±1.11	0.76±0.79	1.0E-20
spike	1.44±2.03	0.73±1.04	2.73E-04	1.66±1.22	0.79±0.73	1.1E-12	1.51±0.98	0.84±0.79	2.77E-11
xCorr	1.23±17.16	0.93±21.19	0.44	-11.37±134	4.9±172.83	0.11	233.54±5270	-72.25±1692	0.45
phase	0.90±0.25	1.03±0.26	4.3E-06	0.90±0.31	1.03±0.34	5.5E-05	0.87±0.31	1.04±0.34	1.8E-06

TABLE I: Statistic characteristics of (normalized) epileptic EEG features.

*2) **Inter-ictal Spikes:*** Inter-ictal spikes are brief, morphologically defined events observed in EEG of patients with epilepsy [11] (see Fig. 2). Inter-ictal spikes are highly correlated with epilepsy and can be used for diagnostic purpose ([16], [17]).

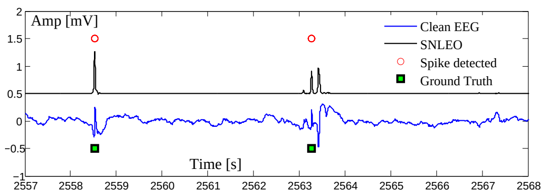


Fig. 2: Inter-ictal spike detection via Smoothed NLEO.

In order to evaluate the rate of inter-ictal spikes for each EEG channel, non-linear energy operator (NLEO) is applied to perform the spike detection. NLEO is widely used to estimate the energy content of a linear oscillator in AM-FM modulation. Due to its accentuation of high frequencies and computational efficiency, NLEO is believed to be the "ideal" spike detector in biomedical analog signal processing ([18]). Mathematically, NLEO of discrete time series $x(t)$ is defined as

$$\Psi(x) = x^2(n) - x(n+1)x(n-1). \quad (4)$$

NLEO is further smoothed by Gaussian kernel to achieve sufficient reduction of interference without loosing much time resolution. In the end, hard threshold defined in [19] i.e., constant multiples of mean of smoothed NLEO $\widetilde{\Psi}(x)$, is applied and only large enough peaks resulting from local maxima (spikes started with rising flanks) are kept (see Fig.2).

*3) **Slowing:*** Signals recorded from damaged cortex often seem to be "slower", i.e., containing more power at low frequencies [2]. Relative power is used to quantify this slowing effect by computing the ratio of power from [1 8Hz] to that from the entire band [1 200Hz].

*4) **Local Synchrony:*** Pairwise cross-correlation and Hilbert phase [8] are computed to study the magnitude and phase synchrony measures respectively.

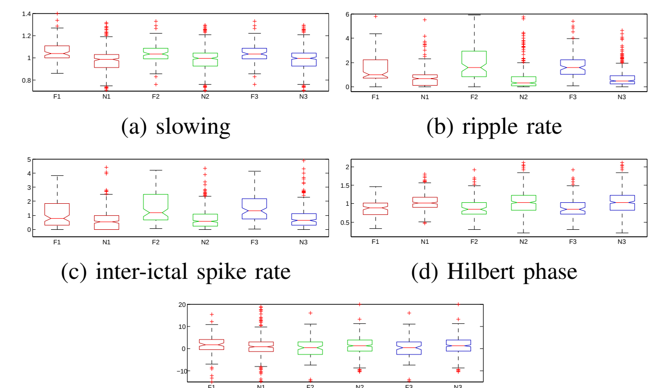
III. Results

The statistic characteristics of individual epileptic EEG feature, and p-values of Mann-Whitney test are summarized in Tab. I, with boxplots shown in Fig. 3. AdaBoost was applied to test all possible combinations of features. In each case, classification rate, specificity, and sensitivity were computed through leave-one-patient out cross-validation.

Accumulative leave-one-patient out cross-validation results with increased no. of features are shown in Tab. II. It can be seen that combining features results in more accurate

Features	Err	Sens	Spec
HFO_3	21%	70%	83%
$phase_2$-HFO_3	14%	64%	93%
$spike_2$-$phase_2$-HFO_3	**14%**	**69%**	**93%**
$spike_2$-$phase_2$-HFO_2-HFO_3	15%	67%	92%
$slowing_1$-$xCorr_2$-$phase_2$-$spike_2$-HFO_3	15%	71%	89%
$d = 6$	16%	71%	87%
$d = 7, 8$	19%	56%	88%
$d = 9$	20%	56%	87%
$d = 10, 11, 12$	17%	59%	90%
$d = 13$	17%	65%	89%
$d = 14$	17%	59%	90%
$d = 15$ (All)	19%	60%	88%

TABLE II: Classification results with increased no. of features d (the best combination only), with subscripts $_{1,2}$ and $_3$ denoting different referential montages as in Fig. 3.



(a) slowing (b) ripple rate (c) inter-ictal spike rate (d) Hilbert phase (e) x-Correlation

Fig. 3: Boxplots of (normalized) epileptic EEG features, with F denoting the focus channels, N the normal channels, and indices 1, 2, 3 denoting different referential montages monopolar, local common average, and global common average.

predictions. Our experiments have shown that adding more features does not seem to improve the performance. On the contrary, with more than 4 features the performance gradually starts deteriorating, probably due to overfitting ([2], [20]). Tab. III considers individual records from different patients. Due to space constraints, we limit ourselves to results with the most discriminative combination of features (see Tab. II). Out of 14 patients, there are 11 cases having accuracy $\geq$80%. The performance varies across patients: in the best case (P1, 3, 13, and 14), the classification accuracy are all 100%; while for some cases (P2, 5, and 10), the classification sensitivity is very low even totally off. In addition, our results appear to be state independent: it matters not whether the patient is awake or asleep.

spike$_2$-phase$_2$-HFO$_3$					
Patient	**Record**	**State**	**Err**	**Sens**	**Spec**
P1	1	asleep	0%	100%	100%
	Average		**0**%	**100**%	**100**%
P2	1	awake	20%	0%	100%
	2	asleep	20%	0%	100%
	Average		**20**%	**0**%	**100**%
P3	1	asleep	0%	100%	100%
	2	awake	0%	100%	100%
	3	asleep	0%	100%	100%
	4	awake	0%	100%	100%
	5	awake	0%	100%	100%
	6	asleep	0%	100%	100%
	Average		**0**%	**100**%	**100**%
P4	1	awake	0%	100%	100%
	2	asleep	0%	100%	100%
	3	awake	20%	50%	100%
	4	asleep	0%	100%	100%
	Average		**5**%	**88**%	**100**%
P5	1	awake	60%	0%	100%
	2	asleep	60%	0%	100%
	3	awake	30%	40%	100%
	4	asleep	60%	0%	80%
	Average		**53**%	**10**%	**85**%
P6	1	awake	10%	50%	100%
	2	asleep	0%	100%	100%
	3	awake	20%	50%	88%
	4	asleep	0%	100%	100%
	Average		**8**%	**75**%	**97**%
P7	1	asleep	20%	50%	88%
	2	awake	30%	0%	88%
	3	asleep	20%	50%	88%
	Average		**22**%	**33**%	**88**%
P8	1	awake	20%	50%	88%
	2	asleep	20%	50%	88%
	3	asleep	20%	50%	88%
	Average		**20**%	**50**%	**88**%
P9	1	awake	0%	100%	100%
	2	asleep	17%	100%	100%
	3	awake	0%	100%	100%
	4	asleep	0%	100%	100%
	Average		**4**%	**100**%	**94**%
P10	1	awake	30%	0%	78%
	2	asleep	50%	0%	56%
	3	awake	50%	0%	56%
	Average		**43**%	**0**%	**63**%
P11	1	awake	20%	0%	100%
	2	asleep	20%	0%	100%
	3	awake	20%	100%	75%
	4	asleep	20%	100%	75%
	Average		**20**%	**50**%	**88**%
P12	1	awake	14%	100%	80%
	2	asleep	0%	100%	100%
	3	awake	14%	100%	80%
	4	asleep	0%	100%	100%
	Average		**7**%	**100**%	**90**%
P13	1	awake	0%	100%	100%
	2	asleep	0%	100%	100%
	3	awake	0%	100%	100%
	4	asleep	0%	100%	100%
	Average		**0**%	**100**%	**100**%
P14	1	awake	0%	100%	100%
	2	asleep	0%	100%	100%
	3	awake	0%	100%	100%
	4	asleep	0%	100%	100%
	Average		**0**%	**100**%	**100**%

TABLE III: Classification results for individual records obtained by AdaBoost algorithm, with the best feature combination in Tab. II.

IV. CONCLUSIONS

In this paper, techniques are developed to automatically localize the seizure focus using brief inter-ictal intracranial EEG by exploiting various epileptic EEG features. For future work, we hope to organize a multi-center trial in which brief inter-ictal data are used to determine the seizure focus, and a recommended resection is offered prospectively. Outcomes in terms of both seizure freedom and complications will be analyzed. We also plan to incorporate brief intra-operative recordings (only a few mins) into our algorithm.

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