Sample Entropy of High Frequency Oscillations for Epileptogenic Zone Localization

Yung-Chih Su, Shun-Chi Wu*, Chien Chen*, Chen-Wei Chou, Sheng-Che Hung, A. Lee Swindlehurst, and Shang-Yeong Kwan

Abstract—For epileptic patients whose seizures are poorly controlled with medication, removing the brain region responsible for seizure onset is a treatment option. This requires the epileptogenic zone (EZ) to be accurately delineated. In this paper, a two-stage approach for EZ delineation is proposed. The algorithm starts by detecting events of high-frequency oscillations (HFOs) directly from the multi-channel intracranial electroencephalograms (iEEGs). The sample entropy is then computed for each of their channels that will be used for determining the channels correlated with the EZ. The performance of our proposed method is evaluated using the receiver operating characteristic curve analysis, and the results indicate that our proposed approach can provide an accurate estimation of the EZ.

Index Terms—epilepsy, epileptogenic zone, high frequency oscillations, sample entropy

I. INTRODUCTION

Epilepsy is a recurrent neurological disease characterized by unprovoked seizures. According to the World Health Organization fact sheet on epilepsy, around 50 million people worldwide are affected by it. For about 30% of the patients, their seizures are poorly controlled with medication alone and removing the brain region responsible for causing seizures is an alternative treatment option. This latter option requires the epileptogenic zone (EZ) to be accurately delineated and is usually performed through visual inspection by clinicians. However, manually determining the EZ in high volumes of intracranial electroencephalograms (iEEGs) is laborious and automated approaches to evaluate for the EZ through direct analysis of iEEGs are indispensable [1].

Most existing methods used to locate the EZ are associated with detecting changes of synchronization and complexity in iEEGs. Measures for synchronization include, for example, the mean phase coherence [2] and the cross-correlation coefficient [3]. iEEG channels that demonstrate excess synchronization compared to others correlate strongly with the epileptogenic focus. To describe the complexity of iEEG data, measures such as delay permutation entropy [4], approximate entropy, and sample entropy [5] are suggested. As reported in [4], epileptogenic iEEGs usually exhibit lower entropy than those from nonepileptogenic areas. In the past decade, high-frequency oscillations (HFOs) in iEEGs with frequencies ranging from 80 Hz to 500 Hz have been regarded as promising markers of epileptogenicity [6], [7], [8], [9]. They are found mostly in the regions of primary epileptogenesis rather than those of the secondary spread in patients with intractable focal epilepsy [6], [7], and surgical removal of the brain areas generating HFOs correlates with seizure free post-surgical outcomes [8]. Moreover, HFOs have durations of 30 to 100 ms, indicating that they are mostly short-lasting rhythmic events [6], [7], [9].

To exploit the “temporal” information (i.e., data complexity) used by existing techniques while taking advantage of the “spatial” information (i.e., found mostly in the regions of primary epileptogenesis) provided by HFOs, this paper considers a two-stage approach for EZ localization. Unlike studies [2], [3], [4], [5] that blindly divide large amounts of iEEG recordings into segments and compute the desired measures accordingly on each of these data segments, we first directly detect the HFO events from the multi-channel iEEGs. The sample entropy is then computed for EZ determination. The iEEG channels correlated with the EZ are finally determined to be those having normalized sample entropies lower than the decision threshold. With this approach, including nonepileptogenic related data that might deteriorate the performance of the above-mentioned measures can be avoided, and a better localization accuracy is expected.

II. METHODS

A. Clinical iEEG data

A 6-year-old patient with drug-resistant focal epilepsy was recruited in this study. The patient received subdural grid implantation with 16 electrodes for intracranial monitoring at the Taipei Veterans General Hospital for a comprehensive pre-surgical evaluation. The iEEGs were acquired with the Nicolet system (Nicolet, Viasys, USA), low-pass filtered through a built-in anti-aliasing filter with a cutoff frequency of 512 Hz and sampled at 2048 Hz. For data analysis, a bipolar montage between adjacent electrodes was used to improve the sensitivity to local electrical activities. The resulting 14-channel iEEGs were then visually inspected by a clinician, and the channels associated with the EZ were identified for later reference. This study was approved by the Institutional Review Board of Taipei Veterans General...
Hospital. All participants gave written informed consent before inclusion in the study.

B. Two-stage scheme for EZ localization

To begin, the iEEGs of each channel were passed through a Hanning window-based finite impulse response filter (of order 63) to limit their frequency range to that of interest. The upper and lower cutoff frequencies were set at 70 Hz and 260 Hz, respectively. A notch filter was applied to eliminate the 60-Hz power-line interference and its harmonics as well.

1) Multi-channel HFO event detection: To detect HFOs, methods based on detection statistics such as root mean square [10] and short-time line length [11] are usually adopted. However, they are applied channel-by-channel, ignoring the information between channels for detection. To avoid this loss, HFO detection in this study was performed directly on the multi-channel recordings through a multi-channel detection statistic based on the Frobenius norm [12]:

$$f_n(t) = \sum_{i=1}^{m} \sum_{k=t-n+1}^{t} x_i^2(k), \quad (1)$$

where \(x_i(k)\) is the data from the \(i\)-th iEEG channel at time \(k\), \(m\) is the number of channels, and \(n\) is the length of the iEEG epoch. Using (1) for HFO detection allows the detection statistic to be calculated without eliminating the interrelations between HFOs appearing close in time on different channels. Furthermore, this detection statistic has also been shown to be more robust to noise [12]. The HFO events were detected by comparing the statistic to an adaptive threshold. Successive values larger than the threshold for a duration longer than 40 ms were considered to correspond to the existence of HFOs. This threshold was updated epoch-by-epoch based on a two-component Gaussian mixture model and was determined using information from the baseline activity. The epoch length was set to be 3 sec in this study.

2) Sample entropy and EZ determination: Due to its insensitivity to the length of the data record, the sample entropy [13], [14] is a useful method for estimating the complexity of a time series through assessing the presence of repetitive patterns therein. Suppose that \(x = [x_1, x_2, ..., x_n]\) is a time series of length \(n\) from any channel of a multi-channel HFO event, and that \(u_m(i) = [x_i, x_{i+1}, ..., x_{i+m-1}]\) is a vector of \(m\) data points (called the template) from \(1 \leq i \leq n-m+1\). The sample entropy is calculated as

$$SpEn(m, r, n) = -\ln \frac{\sum_{i=1}^{n-m} n_i^{m+1}}{\sum_{i=1}^{n-m} n_i^m}, \quad (2)$$

where \(n_i^m\) represents the number of vectors \(u_m(j)\) that match the vector \(u_m(i)\) within a tolerance \(r\). A template match with tolerance \(r\) is said to occur if \(d[u_m(i), u_m(j)] < r\), where

$$d[u_m(i), u_m(j)] = \max \{ |u_m(i+k) - u_m(j+k)| : 0 \leq k \leq m-1 \}, \quad (3)$$

the maximum difference of their corresponding scalar components. The sample entropy reflects the frequency with which each pattern appears in the time series. To obtain a reasonable entropy estimate, the value of \(m\) should lie in a range such that \(n = 10^m\) to \(20^m\) [13]. The tolerance \(r\) is usually set to be 15% of the standard deviation of the time series under consideration, and for this study we chose \(m = 2\).

For any given multi-channel HFO event, we determine the channels correlated with the EZ as follows. The localization is defined in terms of the normalized sample entropy

$$nSpEn_i^k = \frac{SpEn_i^k}{SpEn_i^{max}}, \quad (4)$$

where \(SpEn_i^k\) is the sample entropy calculated using (2) with iEEGs from the \(k\)-th channel of the \(i\)-th HFO event, and \(SpEn_i^{max}\) is the maximum sample entropy among all the channels for event \(i\). As mentioned, epileptogenic iEEGs usually show lower entropy than those from nonepileptogenic areas [4], and thus we consider the \(k\)-th channel to be correlated with the EZ if \(nSpEn_i^k < \beta\), where \(\beta\) is the decision threshold.

3) Localization accuracy: To assess the localization accuracy of the proposed scheme, the receiver operating characteristic (ROC) curve [15] was used. By comparing the identified channels by the above approach with those given by visual inspection, we could quantify the true positive rate (TPR) and false positive rate (FPR):

$$TPR = \frac{TP}{TP + FN}, \quad FPR = 1 - \frac{TN}{TN + FP}, \quad (5)$$

where TP, TN, FP, and FN are the numbers of true positives, true negatives, false positives, and false negatives for a given \(\beta\). The ROC curve for each HFO event is obtained by plotting TPR against FPR with \(\beta\) varying from 0 to 1, and the localization accuracy can be assessed by the area under the ROC curve (AUC).

C. Phase-locking value (PLV)

To measure the synchronization of any pair of iEEG channels, the phase-locking value (PLV) was used [2], [16]:

$$PLV(t) = \frac{1}{N} \sum_{n=1}^{N} \left| e^{i\theta(t,n)} \right|, \quad (6)$$

where \(\theta(t, n)\) is the difference between the instantaneous phases of the two signals. The instantaneous phase of each signal is obtained by computing its convolution with a complex Gabor wavelet centered at a target frequency and then extracted for time instant \(t\) and trial \(n\), over a total of \(N\) trials [16]. The PLV measures the intertrial variability of this phase difference at time \(t\). If the phase difference varies little across the trials, PLV is close to 1; otherwise, it will be near zero.
III. RESULTS AND DISCUSSION

From the randomly selected one-minute 14-channel interictal iEEGs, 27 multi-channel HFO events were detected using the approach described in Section II-B.1. Figure 1 (a) shows the sample entropies of different channels for these events. As can be seen, channels that locate inside the EZ annotated by the clinician (i.e., channels 6, 7, 13, and 14 enclosed by the red dot-dashed rectangles) tend to have lower entropy (i.e., bluer), which is consistent with what was observed in [4], [17]. To quantify the localization accuracy, we conducted the ROC analysis for all the detected events. The obtained ROC curves were then averaged over the events to obtain the mean ROC curve shown in Figure 1 (b), whose AUC value is 0.827. Generally, an AUC value of 0.7 to 0.8 is considered to be acceptable, 0.8 to 0.9 implies excellent discrimination, and above 0.9 indicates outstanding discrimination [18]. This result demonstrates the efficacy of our proposed scheme.

One thing that the existing EZ localization approaches [6], [7], [8], [9] have in common is that to compute the complexity or synchronization measure, a windowed data handling technique is typically used (i.e., iEEGs are divided into either overlapped or nonoverlapped segments). This may result in nonepileptogenic data being included in the analysis. To see whether the event-based approach can reduce the influence of nonepileptogenic related data on localization accuracy, the window-based data handling approach was implemented as well. We segmented the multi-channel iEEGs with a nonoverlapping window of size 150 ms (roughly the duration of an HFO event [19]), and sample entropies of various data segments were calculated as shown in Figure 2 (a). As can be seen, the channels inside the EZ still possess lower entropy even though they are less discriminative compared with those not belonging to the EZ. The mean ROC curve for all the data segments is shown in 2 (b), resulting in an AUC value of only 0.689. This demonstrates the influence of nonepileptogenic related data on localization accuracy.

To illustrate the robustness of the approaches based on different data handling techniques (i.e., event- or window-based), the distributions of their obtained AUC values are presented using boxplots as shown in Figures 1 (c) and 2 (c). The red bars in the boxplots indicate the median AUC values and the lower and upper borders of each box correspond to the 25% and 75% percentiles, respectively. The whiskers cover the entire range of the AUC values, and the data points (marked by red crosses) above the third quartile or below the first quartile by 1.5 interquartile ranges are seen as possible outliers. It is clear that the AUC values of the event-based approach are much higher and more concentrated than those obtained by the window-based approach.

Finally, the methods based on PLV were also implemented for the same one-minute iEEGs. For the event-based method, since each detected event had different duration, the data from both sides of each event were discarded so that all the events to be used for PLV calculation were of the same duration (i.e., 100 ms). The multi-channel iEEGs were divided into 20% overlapped segments of 150 ms duration. Then, the pairwise PLVs were calculated for various events or data segments, which were averaged to form the mean PLV matrix following the procedure of [2]. The resulting mean PLV matrices are depicted in Figures 3 (a) and (b) for the event- and window-based approaches, respectively. In both cases, the channel pair exhibiting the highest phase

![Figure 1](image1.png)

![Figure 2](image2.png)
synchrony is 1 and 2 rather than those belonging to the EZ (enclosed in the red rectangles). We also noted that the high phase synchrony values always occurred among nearby electrodes including the epileptic channel pair 6 and 7 and others although some of these pairs may be artifacts. As pointed out in [16], neighboring electrodes will record the same field potential due to volume conduction and are thus trivially synchronous. These kinds of artifacts are difficult to remove from the pathological synchronization and might thus limit the capability of PLV for EZ localization.

IV. CONCLUSION

This paper has presented a two-stage approach for EZ localization with multi-channel iEEGs. To begin, the multi-channel HFO events are detected with the Frobenius norm statistic that allows interrelations among electrodes to be exploited. Next, the sample entropy is computed for the data from various channels of HFO events. The channels correlated with the EZ are determined with a threshold-value of 0.2 on the PLV matrices. The entropies lower than the decision threshold are regarded as correlated with the EZ. To evaluate the performance of the proposed scheme, iEEGs from a drug-resistant focal epileptic patient were used. Compared to existing approaches that use the window-based data segmentation technique or PLV, our proposed scheme provides better EZ determination (i.e., higher AUC values) and less AUC variations. Our next step will apply the proposed scheme to iEEGs from more epileptic patients to determine its robustness against variability among patients.

REFERENCES