Computing Network-based Features from Intracranial EEG Time Series Data: Application to Seizure Focus Localization

Stephanie Hao[1,2], Sandya Subramanian[1,2], Austin Jordan[1,2], Sabato Santaniello[2], Robert Yaffe[2], Christophe C. Jouny[3], Gregory K. Bergey[3], William S. Anderson[4], and Sridevi V. Sarma[2]

***Abstract*— The surgical resection of the epileptogenic zone (EZ) is the only effective treatment for many drug-resistant epilepsy (DRE) patients, but the pre-surgical identification of the EZ is challenging. This study investigates whether the EZ exhibits a computationally identifiable signature during seizures. In particular, we compute statistics of the brain network from intracranial EEG (iEEG) recordings and track the evolution of network connectivity before, during, and after seizures. We define each node in the network as an electrode and weight each edge connecting a pair of nodes by the gamma band cross power of the corresponding iEEG signals. The eigenvector centrality (EVC) of each node is tracked over two seizures per patient and the electrodes are ranked according to the corresponding EVC value. We hypothesize that electrodes covering the EZ have a signature EVC rank evolution during seizure that differs from electrodes outside the EZ. We tested this hypothesis on multi-channel iEEG recordings from 2 DRE patients who had successful surgery (i.e., seizures were under control with or without medications) and 1 patient who had unsuccessful surgery. In the successful cases, we assumed that the resected region contained the EZ and found that the EVC rank evolution of the electrodes within the resected region had a distinct "arc" signature, i.e., the EZ ranks first rose together shortly after seizure onset and then fell later during seizure.**

I. INTRODUCTION

Over 50 million people worldwide are affected by epilepsy, which is characterized by chronically recurrent seizures resulting from excessive electrical discharges from groups of neurons [1]. Of these patients, nearly one third have drug-resistant epilepsy (DRE), i.e., despite using at least two anti-epilepsy drugs at the highest allowed dosage, they still experience seizures [2], [3].

DRE is costly, both financially and psychologically. The lifetime cost of caring for DRE patients can be as high as $12.5 billion, with the majority of these costs stemming from patients experiencing uncontrollable seizures even with medication [4]. The physical burden of DRE is just as great, with patients often unable to care for themselves due to impairment in cognitive performance and barriers in societal activities, such as education and working. This can lead to multiple behavioral, psychological, social, financial and legal issues [5]–[8]. A viable solution to this problem is the surgical resection of the epileptogenic zone (EZ), the smallest region responsible for generating the recurrent seizure activity [9]. This only works, however, if the EZ is correctly localized and resected. Prior to surgery, clinicians must determine both the location of the EZ and the possible side effects of resection. Before surgery, non-invasive methods such as scalp EEG, video-EEG, neuropsychological tests, speech-language studies, and brain imaging (MRI, PET, Ictal SPECT) are used. While a focal MRI lesion is the best indication for surgical resection [10], a quarter of patients that have focal epilepsy have MRIs that are normal [11]–[13].

If the above methods cannot determine the location of the EZ, clinicians may perform an invasive evaluation, involving placement of subdural grid arrays and subsequent prolonged extra-operative monitoring in a dedicated monitoring unit. This is a costly procedure and can lead to multiple infections and neurological deficiency [13]. While this method increases the chance of identifying the correct EZ, failure still occurs due to (i) a smaller sampling of the brain region due to safety issues of implanting electrodes into the brain, and (ii) incorrect identification of EZ signatures from intracranial EEG (iEEG) recordings [14].

This study focuses on patients who are selected for iEEG implantation with a strong pre-implantation hypothesis of the location of the EZ, minimizing the spatial sampling limitation. Our goal is to accurately identify the EZ in DRE patients. Several studies have analyzed iEEG data and the role of the EZ, either by examining each channel individually to determine the onset and location of seizures [15], [16] or by representing the brain as a network and examining the temporal evolution of the connectivity among channels [17]–[21]. These studies, though, did not specifically look at the role of the EZ within the network. Studies [22]–[27], instead, retrospectively analyzed the connectivity of the clinically identified EZ during inter-ictal periods and at seizure onset, but they did not characterize the EZ during seizures.

In this study, we analyze the connectivity of the brain network and the role of the EZ during seizure in three DRE patients with different surgical outcomes, (see Table I: 2 seizures per patient, each seizure considered from 60 s before onset to 60 s after termination), by analyzing iEEG recordings and eigenvector centrality (EVC) [28]. The EVC is tracked over each seizure and the iEEG electrodes are ranked according to the corresponding EVC value. Rank

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[1]Undergraduate students

[2]Institute for Computational Medicine, Department of Biomedical Engineering, Johns Hopkins University, 3400 North Charles Street, Baltimore MD, USA

[3]Department of Neurology, Johns Hopkins School of Medicine, 600 North Wolfe Street, Baltimore, MD 21287, USA

[4]Department of Neurosurgery, Johns Hopkins School of Medicine, 600 North Wolfe Street, Baltimore, MD 21287, USA

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TABLE I
PATIENT INFORMATION

ID	Age (y)	Sex	Sz. Type	Sz. Length (s) mean±SD	Res.	Out.
2	17	F	CPS:GTC	94±7.1	OL	succ
3	14	M	CPS:GTC	180±27	n/a	succ
8	29	F	CPS	94±7.0	R-OL, R-TL, PL	fail

Sz = seizure; Res. = resected area; Out. = outcome; R = right lobe; TL = temporal lobectomy; OL = occipital lobectomy; PL = parietal lobectomy; CPS = complex partial seizure; GTC = generalized tonic clonic seizure; succ = success; fail = failure; n/a = not available

1 and N indicate the most and least central electrodes, respectively (for N electrodes). We hypothesize that the electrodes covering the EZ have a characteristic EVC rank evolution during seizures that differs from electrodes outside the EZ. To test this, we first examined iEEG recordings from 2 DRE patients who had a successful surgery. Under the assumption that the clinically resected region contained the true EZ, we found that the EVC rank evolution of the electrodes within the resected region exhibited an "arc"-like signature, i.e., the EZ first increases in rank to be the least connected region and then it drops in rank to become the most connected region. We do not predict to see this signature in the DRE patient that had an unsuccessful surgery.

II. METHODS

A. Experimental Data

We analyzed iEEG recordings from 3 DRE patients monitored with subdural and depth electrodes as part of their presurgical evaluation at the Johns Hopkins University Epilepsy Center (Table I). The decisions regarding the need for invasive monitoring and the placement of electrode arrays were made independently of this project and solely based on clinical necessity. Acquisition of data for research purposes was done with no impact on the clinical objectives of the patient stay.

iEEG recordings are typically used when scalp or sphenoidal-ictal records do not indicate a clear lateralized seizure onset, if functional mapping is required because of the proximity of eloquent areas to a planned resection, or if further seizure localization (e.g. within the frontal lobe) is required. Patients are monitored by subdural grids (20-64 contacts per array), which are used in combination as indicated along with subdural strips (4-8 contacts) or depth arrays. Intracranial contact locations are documented by post-operative CT and co-registered with MRI. The data were previously recorded for clinical purposes and stored in a HIPAA compliant database.

Board-certified electroencephalographers (up to three) marked, by consensus, the unequivocal electrographic onset of each seizure and the period between seizure onset and termination. The seizure onset was indicated by a variety of stereotypical electrographic features, which include, but were not limited to, the onset of fast rhythmic activity, an isolated spike or spike and wave complex followed by rhythmic activity, or an electrodecremental response [29]. Concurrently with the examination of the ECoG signals, changes in the patient's behavior were also sought from the video segment of video-EEG recordings.

For each patient, we combined (i) surgical notes of the electrodes corresponding to the resected regions of the brain and (ii) postoperative follow up information describing how the resection affected the patient's seizures. If a patient stopped having seizures after surgery or the seizures could be managed with medication after their surgery, then we denoted the surgery as a success. In these cases, we assumed the resected area contained the EZ. For our purposes, we considered it to be the EZ.

Fig. 1. Processing steps to derive the EVC rank signature of the EZ.

B. Network Analysis

In this study, we search for an EEG signature of the EZ in patients who had successful surgeries by computing the network centrality of each electrode over seizures (first processing step shown in Fig. 1). Network centrality for each node was computed every second using a 3 s window sliding every second (from 60 s before seizure onset to 60 s after seizure termination) for 2 seizures. For each window, the brain network was represented by a connectivity matrix [28], by computing the pairwise cross-power in the gamma frequency band (30-90 Hz), i.e.,

$$A_{ij} = \int_{30}^{90} \big(P_i(f) \cdot P_j(f)\big) df \tag{1}$$

where P_i and P_j are the magnitudes of the Fourier transform of the time series in the window recorded from electrodes i and j, respectively. The gamma frequency band often exhibited the most modulation in power between non-seizure and seizure periods and has been thought to be correlated to neuronal spiking and fMRI activity and thus carries information in such invasive recordings [30]–[32].

The importance of each electrode to the network connectivity was measured by the strength and number of connections it makes with other electrodes referred to as centrality. We used the eigenvector centrality (EVC) to measure the connectivity of each electrode. The EVC of an electrode is defined as the sum of the EVCs of all other electrodes weighted by their connectivity. The EVC of all electrodes is computed implicitly as [28]

$$EVC(i) = \lambda \sum_{j=1}^{N} A_{ij}\, EVC(j) \tag{2}$$

where λ is the leading eigenvalue of A and the EVC is the leading eigenvector of A. In simple terms, the EVC of a node in the network (electrode) is proportional to the sum of EVCs of its neighbors (nodes it is connected to). That is,

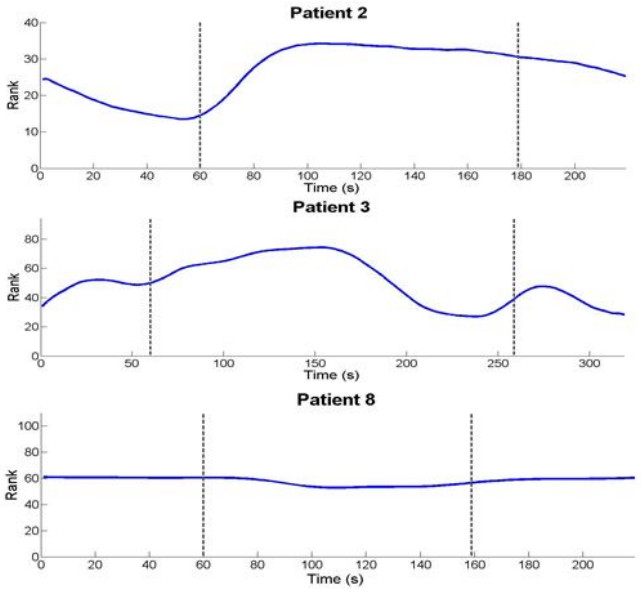

Fig. 2. Rank evolution signals during seizure of the electrodes within the resected region for each DRE patient included in the study.

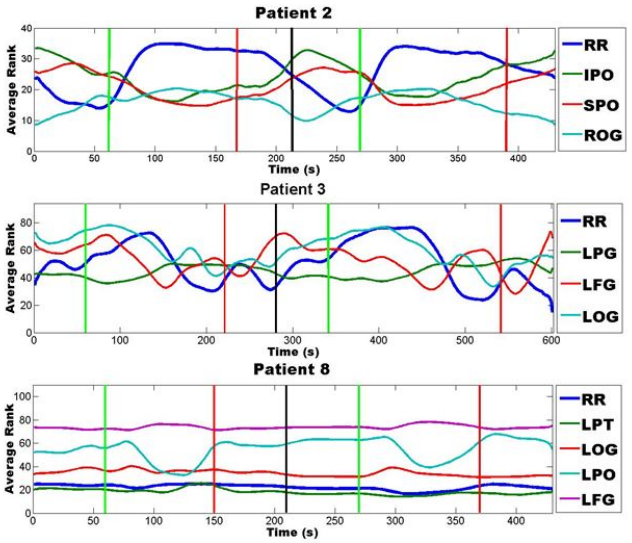

Fig. 3. Rank evolution signals during seizure of all electrodes, grouped by region of the brain, for each DRE patient included in the study. Green and red vertical lines represent the start and end of seizure respectively, and black vertical lines represent the change in seizure events. The resected region (RR) is the rank in dark blue. IPO = inferior parietal-occipital; SPO = Superior parietal-occipital; ROG = Right occipital head region; LPG = Left parietal; LFG = Left Frontal; LOG = Left occipital; RFG = Right frontal; ROG = Right occipital; RPO = Right parietal-occipital; RAT = Right anterior temporal; RPT = Right posterior temporal.

a node is important if it is (i) connected to a few nodes that are themselves very important or if it is (ii) connected to a very large number of not-so-important nodes.

The leading eigenvectors of the connectivity matrices were calculated numerically at each second during the recordings from the connectivity matrices. Finally, the EVC vector for each second was converted to a ranked vector containing values 1 to N in order to see changes in connectivity more clearly. A 1 was placed in the component of EVC that had the largest centrality and an N was placed in the component of EVC that had the smallest centrality.

III. RESULTS

We computed the centrality ranks of the resected region for each of our patients, following the steps shown in Fig. 1. Patient 2 had 6 electrodes spanning its resected region, patient 3 had 12 electrodes, and patient 8 had 43 electrodes.

For each of the patients that were identified to be a success (patients 2 and 3), we found that there was a distinct arc signature of the resected region, as shown in Fig. 2A-B. Mainly, after the onset of seizure, the rank of the electrodes rose to become less connected in the network. Shortly before the end of seizure, the rank drops to become more connected in the network. This signature was especially prominent in patient 3, whereas patient 2 did not fall prominently prior to the end of seizure.

For the patient who had an unsuccessful surgery (patient 8), we did not see an arc signature in the rank evolution of the resected region. Rather, the rank appeared to move in the opposite direction, suggesting that the resected region is not the correct location of the EZ (Fig. 2C). In all cases, we did not see the signature when examining the average rank of the non-resected region. Patient 3 did have one region that was similar to our signature (Fig. 3), but upon further examination, all electrodes resected from that patient came from that region of the brain.

Overall, our preliminary findings appear to show that the EZ exhibits a distinct signature during seizure, which may be useful in directing clinicians towards identifying a more accurate EZ. Further studies will need to be conducted in order to support our findings.

IV. CONCLUSIONS AND FUTURE WORK

From these preliminary results, there seems to be a distinct rank signature associated with the EZ of the DRE patients included in our study, i.e., the EZ seems to follow a specific pattern of shifting importance in the network through the course of seizure. Namely, it goes from being relatively central prior to onset to drastically decoupling from the network at or shortly after onset, and then mid to late seizure, it comes back to being relatively central in the network.

This signature appears to be unique to the EZ, as it is not seen in other regions of the brain in these patients. This signature also seems to be identifiable based on limited data. Our analysis, in fact, was conducted by using only two seizures for each patient, but the pattern is very consistent. Based on this, the next step would be to assess the feasibility of using this signature as a way to blindly identify the EZ based on iEEG data from a new set of patients. This would involve processing the raw data in the same manner as done here, by computing connectivity matrices based on cross-power in a frequency band, performing an eigenvalue decomposition on each one, and using the first eigenvectors to compute a rank signal for each electrode through time. From here, electrodes can be grouped together by their rank evolutions during seizure, resulting in clusters that each have

a shared rank signature that is distinct from that of the other clusters. This clustering algorithm will have to be optimized to identify the correct number of clusters for each patient. Finally, the average rank signal of each cluster can be compared to the signature gleaned from these preliminary results (the arc signature) to identify the cluster(s) most likely to contain the EZ. This predicted EZ can be compared to histological results from the resected region of the brain to verify whether the predicted region was indeed epileptogenic. Some patients may yield no EZ clusters, possibly indicating that their seizures are not localized to one specific area, a larger region of the brain needs to be sampled, or a number of other factors.

A computational tool that can aid clinicians in identifying the EZ can be very valuable for several reasons. Even in cases when a clear EZ cannot be clearly identified, this can be a warning sign to clinicians that surgery may not be the best solution for that patient, or that other factors must be carefully assessed before arriving at any decision. Decreasing the number of failed surgeries can cut medical costs and save the patient severe emotional distress. These preliminary results also indicate that data from fewer seizures may be sufficient to identify the EZ, further decreasing costs and hospital stays associated with pre-surgical monitoring. Finally, correct identification of the EZ can improve surgical outcomes and improve patient quality of life after surgery.

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