34th Annual International Conference of the IEEE EMBS
San Diego, California USA, 28 August - 1 September, 2012

A Network Analysis of the Dynamics of Seizure

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Abstract—**Seizures are events that spread through the brain's network of connections and create pathological activity. To understand what is occurring in the brain during seizure we investigated the time progression of the brain's state from seizure onset to seizure suppression. Knowledge of a seizure's dynamics and the associated spatial structure is important for localizing the seizure foci and determining the optimal location and timing of electrical stimulation to mitigate seizure development.**

In this study, we analyzed intracranial EEG data recorded in 2 human patients with drug-resistant epilepsy prior to undergoing resection surgery using network analyses. Specifically, we computed a time sequence of connectivity matrices from iEEG (intracranial electroencephalography) recordings that represent network structure over time. For each patient, connectivity between electrodes was measured using the coherence in the band of frequencies with the strongest modulation during seizure. The connectivity matrices' structure was analyzed using an eigen-decomposition. The leading eigenvector was used to estimate each electrode's time dependent *centrality* (importance to the network's connectivity). The electrode centralities were clustered over the course of each seizure and the cluster centroids were compared across seizures. We found, for each patient, there was a consistent set of centroids that occurred during each seizure. Further, the brain reliably evolved through the same progression of states across multiple seizures including characteristic onset and suppression states.

I. Introduction

Epilepsy affects 50 million people worldwide [1], and 30% remain drug-resistant [2]. Although seizure is usually considered to be a hypersynchronous state that entrains different regions of the brain, more recent research suggests the dynamics of seizure are more complex [3]. Earlier work on the structure of brain activity during seizure activity focused on classifying different types of seizures. These studies quantified the time dependent properties of seizures either through supervised methods and visual inspection [4] or through measuring the spectral properties of scalp and intracranial EEG recordings [5]. In Schiff et al. [6], it was found that seizures had distinct dynamical states using canonical discrimination analysis in both scalp and intracranial recordings. They found in most cases initiation and termination stage dynamics that were distinct from the dynamics of the middle of seizures. There has also been modeling results using nonlinear models of the cortex that indicate that seizure may result from the presence of global bifurcations in the chaotic dynamics of the brain that are capable of generating multistable states [7-8]. This multistability could generate a progression of seizure states more complex than merely the seizure focus driving the rest of the brain into a synchronous state. Derchansky et al. [9] studied *in vitro* seizure activity in hippocampus slices using both electrode recordings and voltage sensitive dye. They found bidirectional seizure activity between different regions of the hippocampus. This result also suggests that seizure is a dynamic process with feedback between regions rather than a passive unidirectional event.

Recently, the application of network analysis to the study brain activity has proven to be a powerful technique for better understanding the complex interactions that occur between brain regions [10] and specifically to the study of seizures [3]. Schindler et al. [11] studied the temporal evolution of the multivariate correlation structure in seizures recorded from 60 patients. They found using the eigenvalue spectrum that the correlation decreases during the first half of seizure and increases toward termination. Using a network analysis of the clustering coefficient and path length during seizure [12] found that during seizure the brain became more organized in comparison to interictal periods. Ortega et al. [13] studied the synchronization properties between electrodes using multiple measures and found clusters of synchronized activity in patients with temporal lobe epilepsy that may be involved in the neuronal circuits associated with seizure. Kramer et al. [14] also used a network analysis of electrode recordings in humans during seizure and found that the connectivity changes during seizure. They found an increase in coupling at seizure onset compared to interictal periods and in [15] found that the topology of the network progressed through different states during seizure.

Here, we further develop the network analysis of iEEG data during seizure states by examining the eigenvectors of the network connectivity matrix. But, rather than treat the eigenvectors only as an abstract representation of the brain state, we exploit the property that they are related to the immediate features of the network through their interpretation as measures of the network's eigenvector centrality. This method has the advantage of incorporating information from all electrodes rather than pair-wise techniques and is computationally more efficient than social network measures.

II. Methods

A. Experimental Data

We analyzed data collected from two patients (previously monitored with intracranial electrodes as part of their pre-surgical evaluation at the Johns Hopkins University Epilepsy Center) in this study. Patient A was recorded continuously for 5.58 days during which 3 clinical seizures were recorded. Patient B was recorded continuously over 5.55 days during which 4 clinical seizures occurred. The decisions regarding

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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.

Intracranial 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 have subdural grid arrays, subdural strips or depth electrode arrays in various combinations as determined by the clinical assessment. Subdural grids have 20-64 contacts per array and 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. Since 2001, about 20-30 patients per year have required invasive monitoring with subdural grid arrays for assessment of partial seizures. The data previously recorded for clinical purposes are stored in a database compliant with Health Insurance Portability and Accountability (HIPAA) regulations.

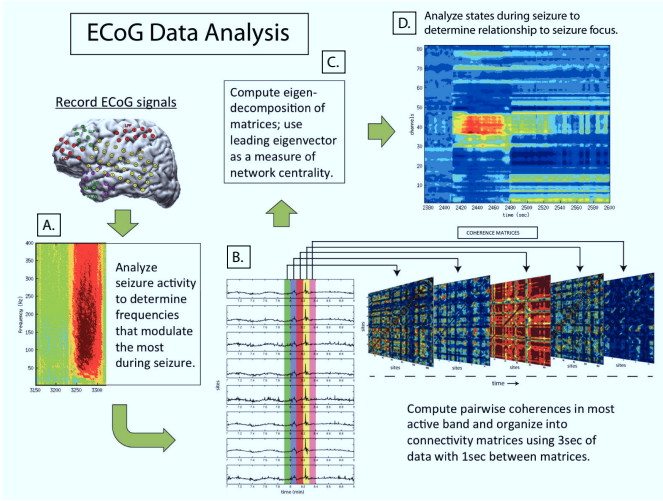

Figure 1: Schematic of intracranial EEG data analysis.

B. *Data Analysis*

Figure 1 illustrates the data processing steps undertaken to determine the centrality, or importance, of nodes in the iEEG network during seizure. We describe each step of the processing below.

B1. Determining the Frequency Band for Each Patient (Figure 1A)

For each patient the mean inter-ictal power was computed using nonoverlapping 3sec windows from all non-annotated inter-ictal recordings. The spectrograms of the recordings during all seizures were normalized by the mean inter-ictal power spectrum to generate the r-spectrum, defined as

$$\text{R}-\text{spectrum} = \frac{\text{Ictal Power (frequency)}}{\text{Interictal Power (frequency)}} \qquad (1.)$$

During seizure, the r-spectrum was equal to one for frequencies that did not modulate and greater than one for frequency that increased during seizure relative to the inter-ictal activity. The r-spectrum was analyzed according to the mean over the traditional EEG frequency bands (Delta 1-4Hz, Theta 4-8Hz, Alpha 8-13Hz, Beta 13-25Hz, Gamma 25-90Hz, and High Gamma 90-200Hz). The frequency band that showed the greatest modulation across all seizures was selected to form the connectivity matrices as described in section B2.

B2. Computing Network Connectivity over Time (Figure 1B)

The network connectivity was measured by computing all pairwise coherences, C_{ij}, between electrodes and the averaged over the largest modulated frequency band,

$$C_{ij} = \frac{|P_{ij}|^2}{P_{ii}\,P_{jj}}, \qquad (2.)$$

where P_i is the Fourier transform of the time series recorded at electrode i, P_{ii} and P_{jj} are the power at electrodes i and j, and P_{ij} is the cross-power. These pairwise coherences were organized into a connectivity matrix that described the entire network. Connectivity matrices were computed every second using a sliding 3 sec window for each estimate. The diagonal of each connectivity matrix was set to be all zeros to indicate that each electrode is not considered to be connected to itself.

Across the recordings there was a static dominant set of coherences present in the data. In the interest of measuring the changes in connectivity during seizure, each entry in the connectivity matrices were standardized (subtract the mean and divide by the standard deviation) using their inter-ictal activity. After standardizing, each entry in the connectivity matrix was positive or negative reflecting the number standard deviations the instantaneous coherence was above or below that pair of electrodes' mean coherence. In order to retain the interpretation as a connectivity matrix, whose values must be positive, the standardized entries were transformed using an inverse logit function,

$$h(x) = \frac{e^x}{1+e^x}, \qquad (3.)$$

which maps the real numbers to the interval [0,1].

B3. Computing Eigenvector Centrality (EVC) over Time (Figure 1C)

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

$$EVC(i) = \lambda^{-1} \sum_{j=1}^{N} A_{ij}\, EVC(j), \qquad (4.)$$

where A is the connectivity matrix, λ is the leading eigenvalue of A and the EVC is then the leading eigenvector of A. The leading eigenvectors of connectivity matrices were calculated numerically at each second during the recordings from the connectivity matrices. The dynamics of the centralities were used to define the network state. In contrast to a multivariate model, the leading eigenvector of A_{ij} is a computationally efficient method to identify the nodes that are most influential on the network as a whole. The centrality is solved implicitly, describing the simultaneous dependence among nodes. While in a multivariate model the predictor is an explicit function of a collection of regressors.

B4. Determining the Seizure States (Figure 1D)

For each of the patients, the time dependent EVCs were used to infer a progression of brain states during the course of multiple seizures. The discrete seizure states were found by using a K-means algorithm. The summed distance of each data point to its assigned centroid was computed for a range of number of clusters, *K*. The number of clusters was the smallest value of *K* for which the summed distance showed only a small change with the addition of more clusters. The cluster centroids were vectors whose entries were the centralities of the set of electrodes. The centroids of the clusters for each seizure were compared with those from all other seizures in the same patient and determined to be the same if their projection after being normalized was greater than 0.95. After identifying corresponding centroids between different seizures, the progression of states in multiple seizures was compared with a common set of patient specific centroids.

III. Results

The step-by-step analysis of the seizure states for one patient (Patient A) is described in detail. The results from a second patient (Patient B) are also summarized. Both patients had seizures that originated in the temporal lobe and all seizures examined here began as complex partial seizures that then progressed to generalized seizures.

C1. Seizure Centrality Analysis of One Seizure

In Figure 2, the steps involved in the analysis of one seizure recorded in Patient A are shown to demonstrate our method. In Figure 2A, the unprocessed voltage recordings from a selection of the total number of electrodes (88 total electrodes) are plotted (seizure onset occurred at t = 2773s and termination at t = 3140s). In Figure 2B, the EVCs for each electrode as a function of time are plotted during the seizure.

The summed distances of each data point from its centroid are plotted as a function of K, the number of clusters. The summed distance has a break at four clusters, which was used as the total number of clusters for this seizure (each seizure was allowed to have a different number of clusters). In Figure 2D the EVCs (from Figure 2B) are shown grouped into four clusters.

C2. Seizure Centrality Analysis of Two Patients

In Figure 3, the time progression of the brain states of Patient A (described in Section B) and of a second patient labeled, Patient B (94 total electrodes) are described. For each patient multiple seizures were examined. After clustering each seizure, we took the inner product of all normalized centroids Once all corresponding centroids were found and related across seizures we then refer to them as 'states' (If a centroid only appears in one seizure and is not repeated, it is still considered a state but one that only occurs in one seizure). On the left hand side of Figure 3 the results for Patient A are plotted. For Patient A all centroids appeared in multiple seizures. All three seizures analyzed began in the State 1, progressed to State 2 and returned to State 1. At this point, seizures 2 and 3 visited State 3 and State 4 while seizure 1 remained in State 1. All three seizure returned to State 1 at suppression.

On the right hand side of Figure 3 the results from Patient B

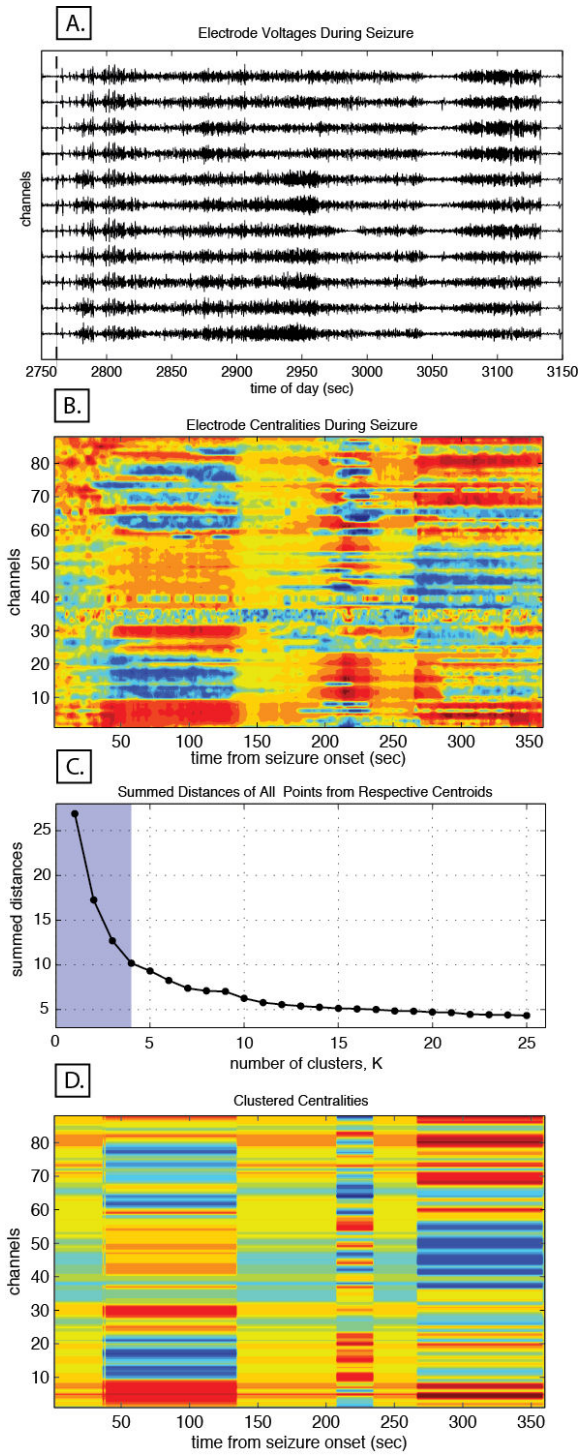

Figure 2: A) Voltages from electrodes on the seizure focus during seizure. B) The time dependent eigenvector centralities (EVC) of each electrode during seizure. C) Summed distance of all data points from their respective centroids. D) The clustered EVCs using four clusters.

are plotted. As was the case for Patient A, all centroids appeared in multiple seizures. Three of the four seizures began in State 5 and progressed to State 1, while seizure 2 began directly in State 1. Similar to Patient A, all four seizures followed very similar dynamics, across all seizures there existed centroids that consistently appeared in different seizures, and all seizures terminated in the same state, State 3.

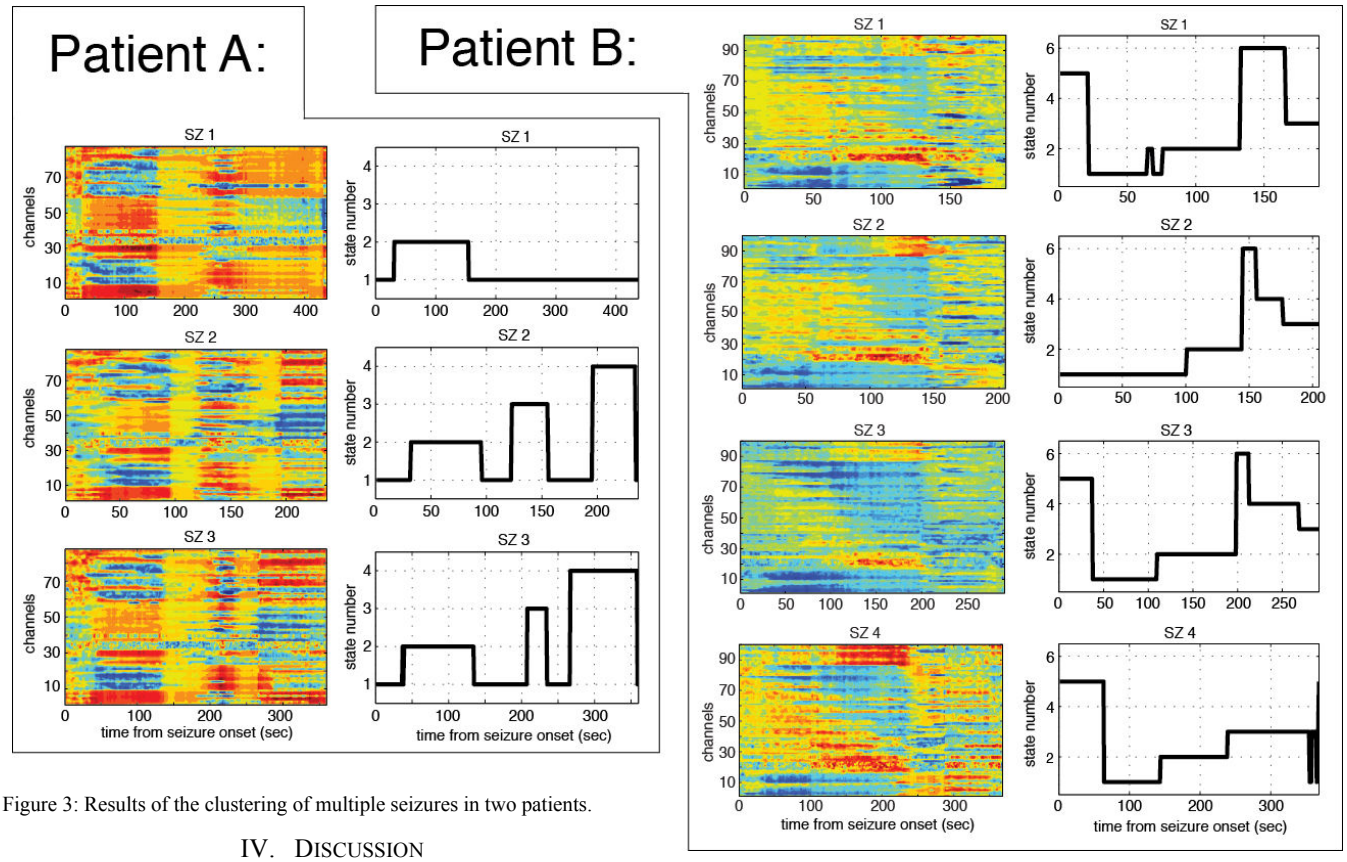

Figure 3: Results of the clustering of multiple seizures in two patients.

IV. Discussion

This analysis revealed that, within a patient, the dynamics of seizures have very regular structure. Although the timing of state changes in each seizure is not identical, the progression through states shows a consistent pattern. Further, in both patients there were characteristic seizure entry and exit states. The properties of these states may contain information about how seizures are initiated and terminated.

The structure of seizure dynamics and the associated centralities of each state may also be used to identify the seizure focus and guide the placement of electrodes for seizure intervention using electrical stimulation.

Acknowledgment

S. V. Sarma was supported by the Burroughs Wellcome Fund CASI Award 1007274 and the National Science Foundation CAREER Award 105556.

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