A Spectral Clustering Approach for the Classification of Waveform Anomalies in High-Dimensional Brain Signals

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***Abstract*— Transient electrophysiological anomalies in the human brain have been associated with neurological disorders such as epilepsy, may signal impending adverse events (e.g, seizurse), or may reflect the effects of a stressor, such as insufficient sleep. These, typically brief, high-frequency and heterogeneous signal anomalies remain poorly understood, particularly at long time scales, and their morphology and variability have not been systematically characterized. In continuous neural recordings, their inherent sparsity, short duration and low amplitude makes their detection and classification difficult. In turn, this limits their evaluation as potential biomarkers of abnormal neurodynamic processes (e.g., ictogenesis) and predictors of impending adverse events. A novel algorithm is presented that leverages the inherent sparsity of high-frequency abnormalities in neural signals recorded at the scalp and uses spectral clustering to classify them in very high-dimensional signals spanning several days. It is shown that estimated clusters vary dynamically with time and their distribution changes substantially both as a function of time and space.**

***Index Terms*— Spectral clustering, brain signals, high-frequency abnormalities**

I. Introduction

Anomalies in the brain's electrical activity have been associated with a broad range of neurological and neuropsychiatric disorders. Although the underlying biological processes that give rise to these anomalies are not fully understood, a large body of literature has shown that they can occur at the signal or network levels and may be localized to the affected region or be widespread in large parts of the brain. Epilepsy, autism spectrum disorders and schizophrenia are examples of relatively common disorders (each affecting $>1\%$ of the US population) that impact the morphology and spectral content of neural signals [1], [2], [3], [4]. In the field of epilepsy where scalp encephalograms (EEG) are routinely used for diagnostic purposes, signal anomalies has been reported across the EEG spectrum, particularly at frequencies $\leq$50 Hz, (e.g., [1], [5], [6], [7]).

More recently, transient, low-amplitude ($\leq 10\ \mu$V) and short-duration ($\leq$100 ms) waveforms with characteristic frequencies ($>$80 Hz) have also been identified in human EEG. These anomalies were first identified in invasive recordings [8] and have since been associated both with seizure evolution and specifically with the epileptogenic region (the brain area that is indispensable for generating seizures), [9], [10]. A growing number of studies have also reported transient signal anomalies in noninvasive EEG [11], [12], [13], [15], but their origin, characteristics and variability remain poorly understood. It is unclear whether they are specifically associated with seizure evolution (ictogenesis) or represent a signature of the epileptic brain, or both. This is in part due to the focus of most prior studies on relatively short data. To assess their specificity to ictogenesis and distinguish them from physiological high-frequency activity, these anomalies need to be estimated in continuous EEGs that contain multiple interictal and peri-ictal epochs of interest, physiological states (wakefulness/sleep).

The detection and classification of high-frequency (HF) anomalies in in *noninvasive* signals is of significant interest, particularly as potential biomarkers of seizure evolution. In contrast to invasive EEG, which is available to a small fraction of patients who are candidates for epilepsy surgery, scalp EEG is a ubiquitous diagnostic tool and available to most patients. Scalp EEG is also routinely used to measure activity in other settings, such as sleep studies. Disordered sleep may also be associated with HF anomalies in the brain. Depending on their origin in the brain, role and time of occurrence, the morphology of HF waveforms may vary significantly within and across patients. Their detection in very high-dimensional signals and classification is computationally very expensive. To improve computational efficiency, easy-to- implement detection and classification is desirable.

This paper presents a novel algorithm for the detection and classification of HF abnormalities in very high-dimensional neural signals. Across scientific fields, a number of algorithms have been proposed for clustering experimental data ([16], [17], [18], [22] among many others). All have advantages and shortcomings, in terms of their complexity, robustness and computational cost. Spectral clustering [20] has been shown to outperform other methods, is straightforward to implement, requires no a priori assumptions (beyond the specification of the number of graph partitions) and is relatively computationally efficient [19], [21]. The proposed algorithm leverages the transience and sparsity of HF anomalies in neural signals to improve the computational efficiency of clustering without the need to process entire recordings spanning multiple days. Estimated clusters are compared to those based on k-means clustering. In addition to the latter's extensive use, previous work has also identified theoretical relationships between the two approaches [18].

II. Materials and Methods

A. Electrophysiological data

All scalp EEG data were collected at the Comprehensive Epilepsy Center, Beth Israel Deaconess Medical Center (BIDMC), as part of clinically indicated studies. Data were

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recorded using a clinical 10-20 EEG system, with a sampling rate of 500 samples/s and were high-pass filtered using a 3rd order elliptical filter with cutoff at 80 Hz, 0.5 dB ripple in the passband and 20 dB attenuation in the stopband. All data were re-referenced to an average reference montage prior to analysis. The study was approved by the institutional review board. Data from 4 adult patients [2 males and 2 females, age 41-48 years, respectively] with diagnosed focal epilepsy and seizures originating in the left temporal lobe were analyzed. Recordings spanned ∼51 to ∼65 h. Continuous EEGs are typically contaminated by multiple artifacts associated with eye-blinking (high-amplitude, low-frequency), and/or muscle activity (high-amplitude and broadband). The artifact suppression algorithm in [14] was used to pre-process the data but it is possible that residual, muscle-related HF activity can still be detected in high-pass filtered signals. Such activity may, in fact, be part of a distinct data cluster. A representative example of segments containing non-random, non-artifactual HF waveforms of interest are shown in Figure 1.

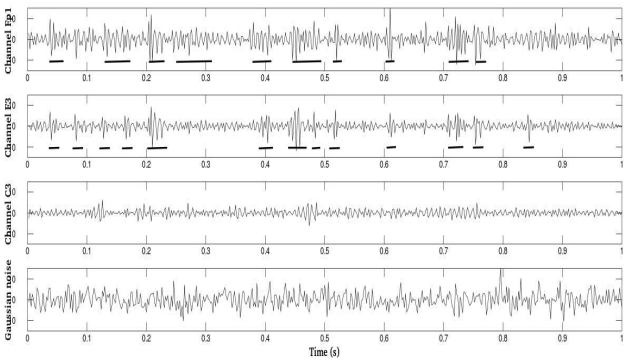


Fig. 1. One-second interictal (non-seizure) segment from electrodes Fp1 (top panel), F3, C3 and a Gaussian noise signal (bottom panel). HF abnormalities are present in electrodes Fp1 and F3 but not C3.

B. Clustering algorithm

The proposed approach is summarized in Figure 2. At frequencies >80 Hz, signals of biological origin measured at the scalp have low amplitudes. In prior work [12], [13] HF anomalies with duration ≤50 ms have been estimated. EEG signals were, thus, segmented into 50 ms intervals and a randomness test (runs test) was applied sequentially to each interval, with the null hypothesis being that it only contains noise. Segments for which the null hypothesis was rejected were flagged for further processing, thus substantially reducing the data dimensionality (typically to ≤ 5% of the raw data). In the second step, a similarity measure between non-random waveforms within and across electrodes was used to assess their pairwise similarity. A wide range of such measures (linear and non-linear) have been proposed, both in the time and frequency domains. The selection of an optimal similarity measure is beyond the scope of this preliminary investigation, so the match filter (MF)[23] was used to compare pairs of identified waveforms (with signal-to-noise ratio (SNR) gain as the measure of similarity and maximum gain obtained when a signal is filtered with its time-reverse replica). Although time consuming, the MF provides a measure of pattern similarity. There are many other similarity measures [19], which may be estimated at lower computational cost (given that the MF involves a relatively expensive convolution). Although this step is not necessary in k-means clustering, it is necessary for constructing the similarity matrix based on which spectral clustering will be performed.

A k-nearest neighbor graph $W(i,j)$ was estimated, assuming a connection (edge) $w_{i,j}$ between nodes v_i and v_j if either node is in the neighborhood of the other (to obtain an undirected graph). From this, the diagonal degree matrix $D(i,i) = d_i = \sum_j w(i,j)$ was calculated. To partition the graph into k partitions (or k clusters when using the k-means algorithm) we arbitrarily assumed $k = 10$ when clustering waveforms *within* an individual EEG electrode and $k \leq 30$ when clustering all waveforms *across* all electrodes. Depending on their location in the brain, HF abnormalities may differ substantially between EEG signals both in morphology and spectral content. To account for potentially heterogeneous waveforms, a higher number of clusters was assumed when data across electrodes were combined. Partitions of vertices $A_i, i = 1,...,k$ were estimated by minimizing the k-normalized *Ncut* defined as: $Ncut(A_1,...,A_k) = \frac{1}{2}\sum_{i=1}^{k} \frac{W(A_i,\bar{A}_i}{\sum_i d_i}$, with $\bar{A}_i$ the complement of A_i. This amounts to solving the generalized eigenvalue problem $(D-W)y = \lambda Dy$, where $D-W$ is the Laplacian matrix (for details see [24]).

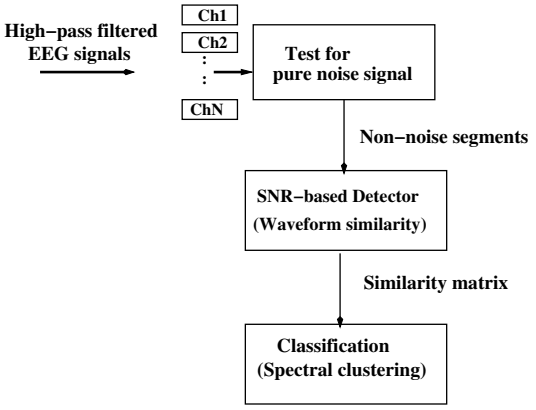
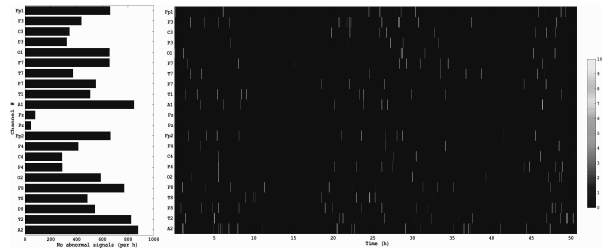


Fig. 2. Diagram of proposed algorithm.

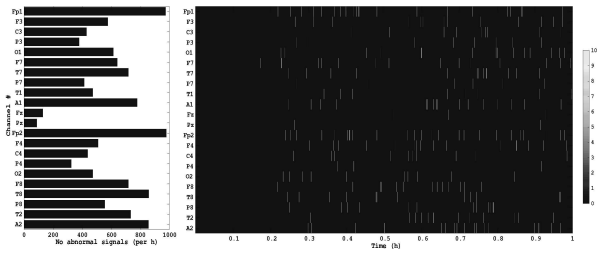
III. Results

The proposed algorithm was applied to continuous recordings, focusing predominantly on the occurrence of signal abnormalities in seizure-free (interictal) periods. One patient had data from 22 EEG electrodes and the other from 28 electrodes). Identified waveforms were sparse, non-localized and heterogeneous. An example of their spatial distribution in a period of >50 h and a shorter (1-h) sub-interval starting at 20 h from the beginning of the recordings is shown in Figure 3. The rate of occurrence of these waveforms in individual electrodes is shown in left panels. In general, electrodes along the midline, followed by central (C2, C4)

and occipital electrodes (O1, O2) had the lowest rates of HF waveforms. Otherwise, these waveforms occurred bilaterally. At shorter time scales (e.g,, 1-h) frontal electrodes had the higher rate of transient HF signals. In this example, artifactual (e.g. related to muscle-activity) signals were not excluded. However, for both patient recordings and across electrodes, the first identified cluster contained waveforms suspected to be residual muscle-related artifacts.



(a) EEG recordings spanning >50 h.



(b) EEG recordings spanning 1 h.

Fig. 3. (a) Distribution of non-random HF waveforms across EEG electrodes in a ∼51-h seizure-free period from patient #1 (right panel) and their rate of occurrence (per h) in individual electrodes-specific rate of occurrence.

Examples of identified waveforms in 3 different clusters are shown in Figure 4. Overall, those with similar characteristic frequency and signatures (e.g., sinusoids) were classified in the same cluster, while those with distinct characteristic frequencies (>20 Hz apart) and similar morphology were classified in different clusters, as were those with distinct signatures (e.g., bursts versus sinusoids). A higher (but not statistically distinct) number of bursts was estimated in electrodes covering the clinically identified seizure onset.

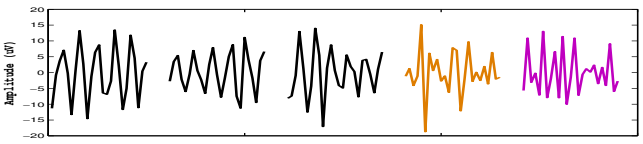


Fig. 4. Examples of transient HF waveforms in distinct clusters. Three waveforms of similar morphology and characteristic frequency were classified in the same cluster (black). Higher-frequency signals with similar signatures were classified in different clusters (black versus purple) and so were signals containing bursts (brown).

Electrode-specific clusters of identified HF waveforms in 2-h interictal (≥12 h removed from a seizure) and peri-ictal (1-h prior to 1-h after a seizure) intervals for 2 patients are shown in Figures 5 and 6. The first cluster, containing waveforms suspected to be artifactual is not shown but all other clusters are shown. Waveforms were typically clustered in a small number of statistically distinct clusters, typically 1-2 clusters in interictal intervals and ≤5 clusters in peri-ictal intervals. As expected, a significantly higher number of transient waveforms were identified in peri-ictal intervals, although their spatial specificity was unclear, occurring in broad areas of the brain beyond the epileptogenic region. Electrodes along the midline, followed by central and occipital, had the lowest number of HF signals.

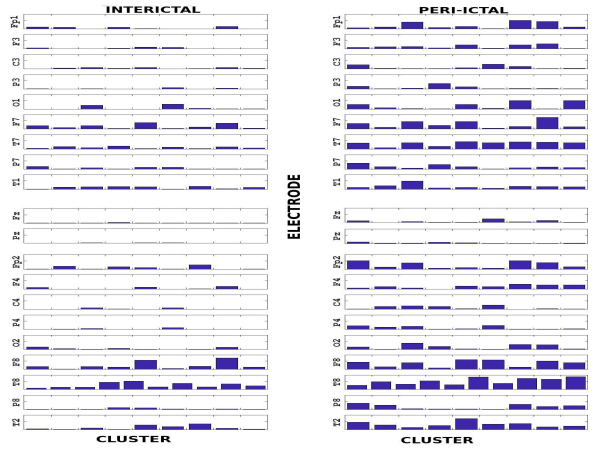


Fig. 5. Distribution of identified waveforms in 9 clusters, as a function of electrode, in a 2-h interictal segment (left) and preictal segment (right), respectively, from Patient #1. Ear electrodes A1 and A2, are not shown.

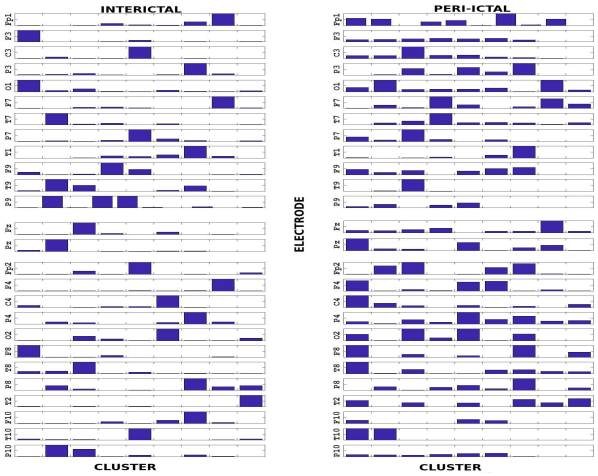
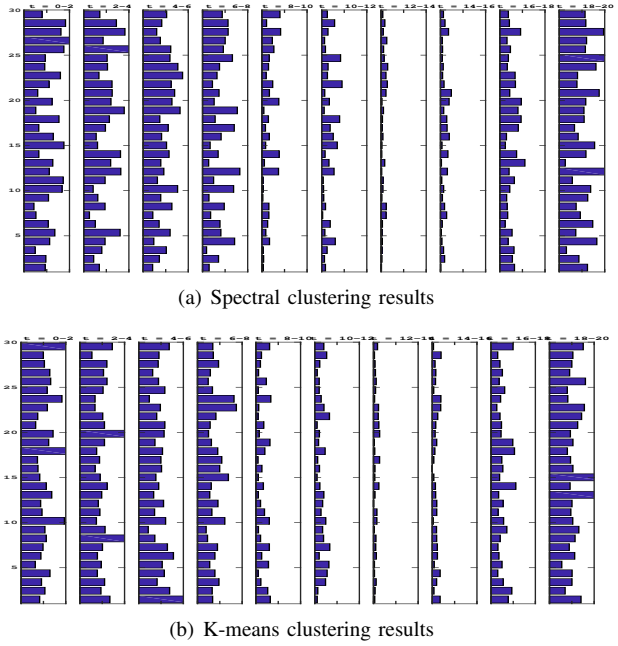


Fig. 6. Distribution of identified waveforms in 9 clusters, as a function of electrode, in a 2-h interictal segment (left) and preictal segment (right), respectively, from Patient #4. Additional electrodes F9, T9, P9 and F10, T10, P10 are shown.

Finally, when signals from all electrodes were combined prior to clustering, a larger number of statistically distinct clusters were estimated even in interictal intervals, although typically ≤10. The distributions of identified waveforms in 30 clusters over a period of 20 hours, using spectral clustering versus k-means clustering are shown in Figure 7. In both cases, a small number of statistically distinct clusters were identified (6-8 with spectral clustering, 4-5 with k-means clustering). When waveforms were examined in each

cluster, the smaller number of k-means clusters contained mixtures of waveforms with statistically distinct characteristic frequencies (>20 Hz apart), indicating that k-means may be less sensitive to the frequency content of individual waveforms compared to spectral clustering. Both approaches distinguished signals with different morphologies.



(a) Spectral clustering results

(b) K-means clustering results

Fig. 7. Distribution of interictal HF waveforms in 30 clusters, identified via spectral (a) and k-means clustering (b), as a function of time, in 2-h intervals (total of 20 hours).

IV. Conclusion

This paper has explored the classification of heterogeneous pathological HF waveforms in noninvasive EEG (up to 65 h) from 4 epilepsy patients by proposing an algorithm based on spectral clustering that leverages the sparsity of HF activity in scalp EEG to reduce the data dimensionality, and uses match-filtering to assess the similarity of identified waveforms. Comparisons of identified clusters with those obtained used k-means clustering indicate that spectral clustering may be more sensitive to waveforms with distinct frequency characteristics but similar signatures. The results also suggest that HF signal abnormalities are sparse in type, spatially distributed and can be classified using a relatively small number of clusters ($\leq$10 when examined across electrodes and $\leq$5 when examined within the same electrode) even in periods of significantly increased HF activity potentially associated with seizure evolution. Clearly these findings are preliminary and based on a very small number of patients. Further studies using extensive simulations to control signal morphology and frequency content and compare findings across different clustering approaches and/or based on different similarity measures for constructing the similarity graph are planned.

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