אוניברסיטת בן-גוריון בנגב
הפקולטה למדעי ההנדסה
המחלקה להנדסה ביורפואית

Electroencephalogram data-based analysis of paroxysmal slow wave events patterns in brain pathologies

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Introduction

Slowing of brain activity observed in electroencephalography (EEG) recordings can be physiological under specific conditions such as deep sleep. However, in a series of studies the BBB Lab has recently described a new, abnormal pattern of cortical slowing in aging [1] and in patients with epilepsy and Alzheimer's disease [2], called paroxysmal slow wave events (PSWEs). Paroxysmal slow wave events (PSWEs) are defined as slow transient events, in which the network switches from apparently normal activity to brief periods of low-frequency activity (in humans, median power frequency (MPF) <6Hz for more than 5 seconds; In rats, MPF<5Hz for more than 10 seconds).

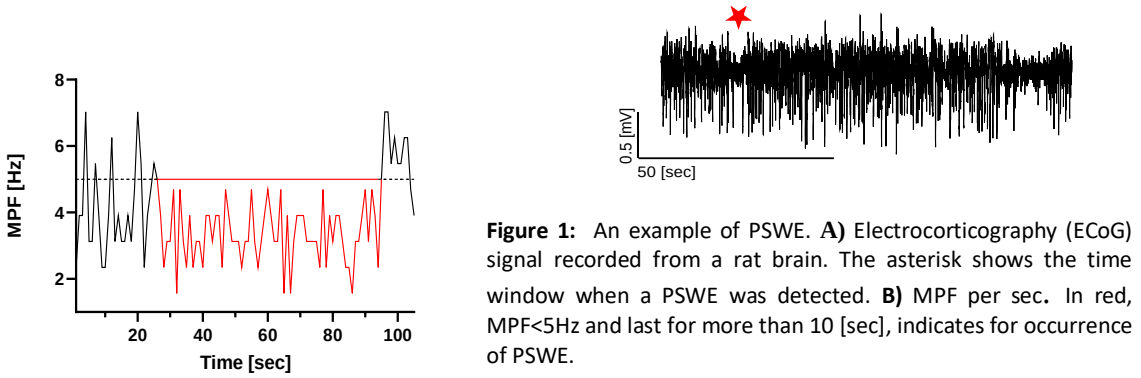

Figure 1: An example of PSWE. **A)** Electrocorticography (ECoG) signal recorded from a rat brain. The asterisk shows the time window when a PSWE was detected. **B)** MPF per sec**.** In red, MPF<5Hz and last for more than 10 [sec], indicates for occurrence of PSWE.

Occurrence and quantification of PSWEs following first seizure were confirmed as predictor for epilepsy [3]. Recent studies have also linked PSWEs occurrence to pathologies such as Parkinson's disease [4] and cognitive impairment in patients with obstructive sleep apnea [5].

Epilepsy: PSWEs are more frequent and of longer duration in epilepsy patients compared to controls [2], [4]. These events are also localized in areas where there is blood-brain barrier disruption [2]. Another study has shown that the occurrence of PSWEs in early EEG recordings from patients who later reported spontaneous seizures was significantly higher compared to seizure-free patients and healthy controls. PSWEs exhibit lower MPF and longer duration in patients who later reported spontaneous seizures compared to controls, making them a potential predictive factor for epilepsy (AUC 0.72) [3].

Cognitive impairment in patients with obstructive sleep apnea: Obstructive sleep apnea OSA patients with mild cognitive impairment (MCI) exhibited a higher frequency of PSWEs, particularly during REM sleep, compared to those without MCI. Also, the occurrence of PSWEs in specific EEG channels during REM sleep was independently associated with cognitive impairment [5].

Alzheimer's disease (AD): The occurrence per minute of PSWE is correlated with cognitive impairment (MMSE score) and was higher in Alzheimer's disease patients compared to controls of the same age [2] .

Parkinson's Disease (PD): PSWE was significantly correlated with disease duration in PD patients in all brain areas [4].

Aging: PSWE were more prevalent in older participants and those with lower cognitive performance, with these events being longer, slower, and more widespread in older individuals [6].

Until now, the characterization of these waves has been relatively general, focusing mainly on the amount of PSWE and their duration. Therefore, this study aims to provide a more in-depth characterization of these events in both the frequency and time domains, with the goal of linking them to different brain pathologies and evaluating their specific characteristics**.**

Research question

What are the spatial and temporal characteristics of paroxysmal slow wave events (PSWEs) in healthy and diseased brains?

Goals

The main goal is to investigate and differentiate the characteristics of PSWE across neurological conditions to enhance diagnostic accuracy and understanding of their clinical implications.

- **Classification of patient groups** Investigate the utility of PSWE features for effectively classifying patient groups, focusing on distinguishing between different neurological conditions (such as epilepsy and non-epilepsy states) and exploring their potential diagnostic value.
- **Differentiation of pathological and physiologic states**: Explore and categorize different subtypes of PSWEs for differentiation between healthy and diseased brains, and understand the diverse manifestations and clinical implications of PSWEs across various neurological disorders
- **Comparative analysis across disorders:** Conduct comparative analyses of PSWE features across different neurological disorders, such as epilepsy and Alzheimer's disease, to identify commonalities and distinct patterns that may aid in differential diagnosis and enhance understanding of disease-specific pathophysiology.
-

Methods

1. Research data

In this research, I first utilized a group of subjects from 'The TUH EEG Epilepsy Corpus' (TUEP). This group was manually validated based on their records to confirm the diagnosis of epilepsy or the absence thereof. The data comprises 156 subjects diagnosed with epilepsy and 184 subjects without epilepsy. Each patient had EEG data recorded using the conventional 10-20 method with 19 electrodes, with a minimum recording duration of 20 minutes. The sampling rate for data is uniform across all patients, set at 250 Hz [7].

2. Preprocessing

The preprocessing was performed based on Makoto's preprocessing pipeline [8] and previous studies [9],[11],[14], and written in MATLAB by a research member in my lab. The preprocessing includes:

1.1 DC removal: performed by reducing the signal average for each electrode.

1.2 BPF 1-45 Hz: Consistent with a previous studies [9],[11],[14] , the PSWEs were characterized after using a band-pass filter (BPF) applied to frequencies ranging from 1 to 45 Hz. Consequently, event detection was performed within the same frequency range to maintain consistency.

1.3 Re-reference the data to average: approximation of scalp potentials that is independent of reference location in a location of the head.

3. PSWEs

The analysis was conducted individually for each electrode, with PSWE events identified as occurrences detected in at least two different electrodes to avoid noise. To calculate the MPF, I buffered the signal into 1-second windows using MATLAB (according to the sampling rate). For each window, I calculated the power spectrum of the signal, sorted the power spectrum values in ascending order, found the cumulative sum of the sorted values, and determined the frequency at which the cumulative sum crossed half of the total power (i.e., 50% power).

4. Features calculation

Based on previous studies, approximately 40 PSWE features have been calculated [3] [10] [11] (the extended list can be found in the appendices). The code segments the data into epochs of 2 sec (according to the sampling rate) with a 1 sec overlap. The size was chosen based on previous studies [10], so that it would allow local stationary assumptions and satisfactory temporal and frequency resolution. For every PSWE epochs, the features are computed separately for each electrode, followed by calculating the mean across electrodes and patients.

5. Features selection

To simplify complex models and prevent overfitting, dimension reduction algorithms reduce the number of features while retaining essential information. Instead of feature extraction, I used feature selection algorithms to preserve the interpretability of the model by retaining original features. This approach selects the most relevant features, reducing dimensionality while improving the model's generalization and training efficiency by discarding irrelevant or redundant features.

To address the challenge of high-dimensional datasets and prevent overfitting, I implemented feature selection algorithms. This method focuses on identifying and retaining the most relevant features from the original dataset while systematically removing those that are irrelevant or redundant. By doing so, feature selection enhances computational efficiency, as it reduces the complexity of the model, leading to faster training and evaluation times. Moreover, this approach maintains the interpretability of the model by preserving the original features, which are crucial for understanding the underlying relationships within the data. By focusing on these key features, the model is better equipped to generalize to new data, thereby improving its overall performance and reliability in real-world applications.

Feature selection based on two algorithms:

5.1 Correlation-Based filter approach: [12]

The purpose of this algorithm is to select a subset of features by prioritizing those with the highest relevance to the target variable while removing highly correlated and redundant features.

1. Calculate the SU and ranked them according to the decreasing value of their relevance.
2. Take the first feature from the list (names X, the most relevance), and remove all the features that has high correlation with the selected feature X. Threshold=0.9
3. Set the next remaining feature in the list as X and repeat step 2 for all the remaining features in the list.

5.2 Forward feature selection and K-fold cross validation:

Forward feature selection is a technique used to identify the most relevant subset of features by incrementally adding features that enhance model performance. The process begins with no features and progressively incorporates those that contribute most significantly to model performance. Model performance is assessed using the Area Under the Receiver Operating Characteristic Curve (AUC-ROC), a metric that summarizes the overall effectiveness of a binary classification model. The AUC-ROC value ranges from 0 to 1, with higher values indicating better model discrimination. At each iteration of the forward feature selection process, the performance of the model is evaluated with the inclusion of an additional feature. The feature that yields the greatest improvement in performance, is selected. This iterative process continues until the improvement in AUC-ROC falls below a predefined threshold of 0.001.

To evaluate model performance robustly, k-fold cross-validation is employed. This technique partitions the dataset into k (k=5) subsets, trains the model on k−1 of these subsets, and validates it on the remaining subset. This process is repeated k times to ensure a comprehensive assessment of the model's generalization capabilities. Given the relatively

small size of the dataset, cross-validation aids in mixing the groups and training on various subsets. Subsequently, the models are combined into an expert system, which classifies instances as either epileptic or non-epileptic based on the majority vote from the individual models (i.e., if 3 out of 5 models classify an instance as epileptic, the system does as well).

To train the model, I divided the data into three subsets: training set, validation set, and testing set. The training set is used to train the model, while the validation set is utilized to tune the parameters of the feature selection algorithm and assess its generalization. The testing set, kept separate from the training set, is employed to evaluate the model's performance. Typically, a standard split is 80-20, where 80% of the data is allocated for training and the remaining 20% is reserved for testing purposes. The validation set comprises 20% of the training data. The separation was conducted randomly while ensuring a balanced distribution between the classes.

Preliminary Results

As detailed in the methodology section, in this study I analyze data from 'The TUH EEG Epilepsy Corpus'. Following pre-processing, forward selection was employed on to identify the most optimal subsets of PSWE's features. Preliminary results focus on the classification of epilepsy and non-epilepsy based on PSWE features. Figure 2 presents an example of the area under the curve (AUC) of the ROC, chosen as the optimal criterion, plotted against the number of features included in the model. The performance of the algorithm was evaluated on the testing data, which remained unseen for all five models. After testing various classification techniques (SVM, decision trees, logistic regression, etc.), the 'Coarse Tree' method yielded the best results, with a sensitivity of 76.47%, a specificity of 68.57%, and an overall accuracy of 72.46% (Figure 3). I also examined the distribution of features among the classes, revealing that some features differ significantly between the groups. The effect size was assessed using Cohen's *d* coefficient, with a large effect size (above 0.8) found in Harmonicity, relative power in theta, and median MPF (Figure 4). All Cohen's *d* coefficients and p-values can be found in the appendices.

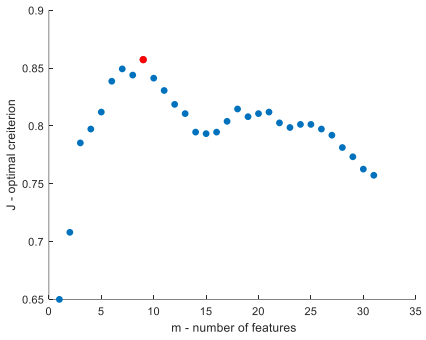

Figure 2: Example of Forward feature selection algorithm

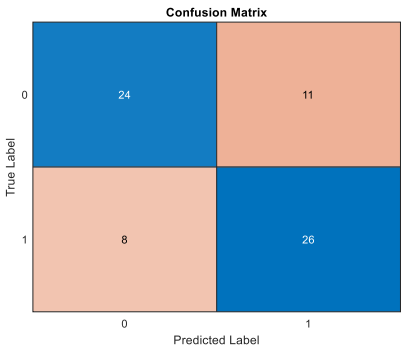

Figure 3: Classification model performance

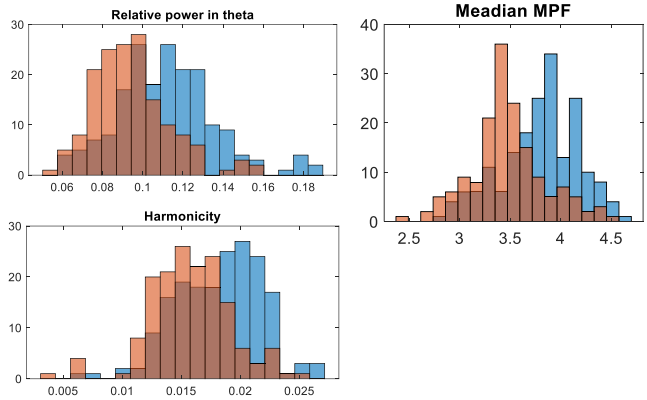

Figure 4: Features distributions

Future plans

Our future plans involve leveraging advanced unsupervised methodologies to unravel the underlying mechanisms of PSWE. To date, our efforts have focused on the classification of PSWE on a per-patient basis. We hypothesize that PSWE can be categorized into distinct types—pathologic and physiologic—each with its own unique characteristics. The next phase of our research will concentrate on identifying and differentiating these PSWE subtypes through the application of unsupervised learning techniques. This approach aims to provide deeper insights into the heterogeneity of PSWE, thereby enhancing our understanding of its role in epileptic pathophysiology. Specific future methodologies can be found in the appendix.

Reference

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Appendices:

Table 1: schedule

Literature review	done
Pre-processing	done
PSWEs detection	done
Feature extraction	done
Classification per patients – Epilepsy Vs. Non-epilepsy	
Statistics analysis using t-test and Cohen's d effect	done
Dimensionality reduction using features selection algorithms (FFS + Correlation)	done
Classification model (SVM, decision tress, logistic regression) + Expert system using k-fold cross validation	done
Looking for event classification using the model	done
Classification per event – pathologic Vs. physiologic	
Unsupervised algorithms- K means using different combination of features	done
Dimensionality reduction using PCA (Principal Component Analysis)	done
Unsupervised algorithms - Gaussian mixture models (GMM) and Expectation-Maximization (EM)	done
Future plans	
Looking over the reports of the events classified as special – what can we learned?	1-2 weeks
Looking for dynamic changes of the features over time	September - October
Looking for space changes of the features – electrodes, brain areas and their connection to the pathologies	November-December
Looking for differences between brain pathologies – classification per patients and per events (adding different data)	January- March
Deep learning methodologies	April-May

PSWE features:

1. Energy of the signal: the energy of a signal is a measure of its total power or strength over a given period of time, $E = \frac{1}{N}\sum_{n=1}^{N} \mathrm{x_n^2}$
2. Maximal amplitude: the absolute highest peak – indicates the presence of high amplitude discharge, $MA = \max(|x_n|)$
3. Amplitude integral: corresponding to local excitability and synchronicity, $AI = \frac{x_1}{2} + \sum_{n=2}^{N-1} x_n + \frac{x_N}{2}$

Amplitude distribution features:

4. Standard deviation: $\sigma = \sqrt{\frac{1}{N}\sum_{\mathrm{n=1}}^{\mathrm{N}}(x_n - \bar{x})^2}$
5. Skewness: measure the degree of asymmetry in the amplitude distribution, $S = \frac{\frac{1}{N}\sum_{\mathrm{n=1}}^{\mathrm{N}}(x_n-\bar{x})^3}{\left[\frac{1}{N}\sum_{\mathrm{n=1}}^{\mathrm{N}}(x_n-\bar{x})^2\right]^{\frac{3}{2}}}$
6. Kurtosis: describes the relative peakedness or flatness of amplitude distribution, $K = \frac{\frac{1}{N}\sum_{\mathrm{n=1}}^{\mathrm{N}}(x_n - \bar{x})^4}{\left[\frac{1}{N}\sum_{\mathrm{n=1}}^{\mathrm{N}}(x_n - \bar{x})^2\right]^2}$
7. Curve length: sensitive to changes in amplitude and frequency, $CL = \sum_{n=2}^{N} |x_n - x_{n-1}|$
8. Harmonicity: estimates the proportion of harmonic components in the power spectrum. Design to identify the presence of rhythmic synchronized patterns, $H = \max\{\Gamma\}: \Gamma_m = \sum_{n=0}^{N-m-1} x_n \cdot x_{n+m} \;;\; m = 0,1,\dots,N-1$
9. Zero crossing: refers to the points in a signal where the amplitude changes its sign, crossing the zero axis. Zero crossing rate is an estimation of instantaneous frequency, meaning measure of how often these transitions occur within a signal over a specified period of time, $ZC = \sum_{n=2}^{N}(x_n \cdot x_{n-1} \leq 0)$
10. Fractal dimension: a curve is called fractal if it displays self-similarity and can be split into portions, each of which is a scale-reduced copy of the whole. The fractal dimension of a curve indicates the degree of its complexity.
11. Peak: $P = \frac{\max|x_n|}{\sigma}$

non-linear energy features: $ne(i) = data(i)^2 - data(i-1) \cdot data(i+1)$

Estimate both the amplitude envelope and the instantaneous frequency of broad band signals with varying amplitude and frequency components [11].

12-15. mean NE , STD NE, Kurtosis NE, Skewness NE.

Frequency domain features:

16-20. STD FFT, Kurtosis FFT, Skewness FFT, median FFT, sum FFT.

Relative power in brain waves: Relative power refers to the proportion of power within a specific frequency band relative to the total power across all frequency bands in a signal. It provides valuable insights into the relative contribution of different frequency components within the signal.

21. Relative power in delta: 0.5-3 Hz, $FT = \sum_{\text{all freq}} f_j \;;\; \delta = \frac{1}{FT} \cdot \sum_{j=0.5}^{3} f_j$
22. Relative power in theta: 3-8 Hz, $FT = \sum_{\text{all freq}} f_j \;;\; \theta = \frac{1}{FT} \cdot \sum_{j=3}^{8} f_j$
23. Relative power in alpha: 8-12 Hz, $FT = \sum_{\text{all freq}} f_j \;;\; \alpha = \frac{1}{FT} \cdot \sum_{j=8}^{12} f_j$

24. Relative power in beta: 12-20 Hz, $FT = \sum_{\text{all freq}} f_j \; ; \; \beta = \frac{1}{FT} \cdot \sum_{j=12}^{20} f_j$
25. Relative power in low gamma: 20-30 Hz, $FT = \sum_{\text{all freq}} f_j \; ; \; \gamma_{\text{low}} = \frac{1}{FT} \cdot \sum_{j=12}^{20} f_j$
26. Relative power in beta: 30-100 Hz, $FT = \sum_{\text{all freq}} f_j \; ; \; \gamma_{\text{high}} = \frac{1}{FT} \cdot \sum_{j=12}^{20} f_j$

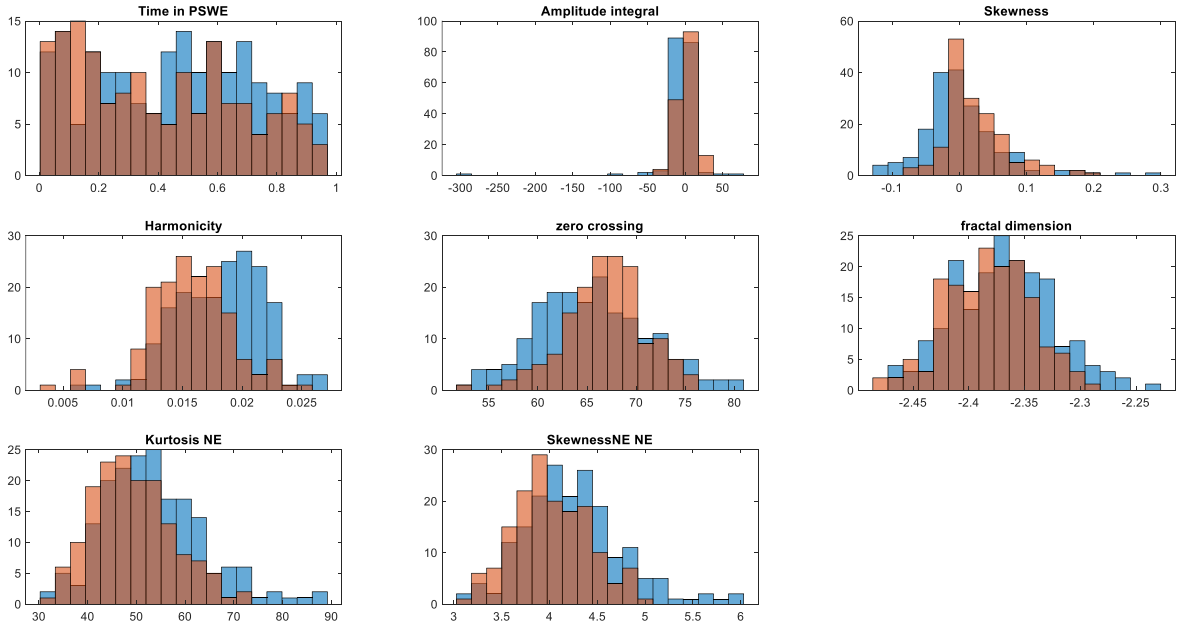
Other features per patients:

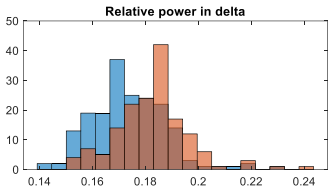
27. Number of PSWE
28. Mean number of channels that pick up PSWEs - calculate the mean number of channels that pick up the events. It offers an indication of the spatial distribution or involvement of channels in capturing PSWEs within the patient's recordings.

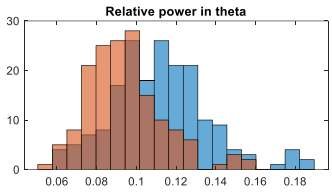
29-30. Max, min num of PSWE per electrode

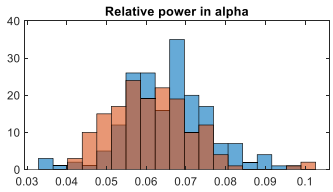
31. Occurrence per minute – the time of PSWEs as percentage of the total time of the signal.
32. Mean MPF – PSWEs defined when the MPF is lower than 6 Hz for at least 5 sec. This feature looks for the mean of the MPF of specific event (ranges between 1 to 6 Hz).
33. Time in PSWE
34. Mean of event duration – This feature calculates the average duration of PSWEs for a specific patient, providing insight into the typical length of these events within the patient's recordings.
35. Median duration
36. Mean MPF per segmen
37. STD of MPF, median MPF, highest MPF

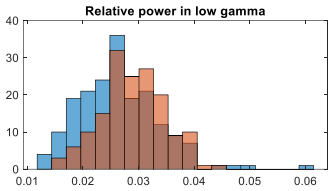
Features distributions:

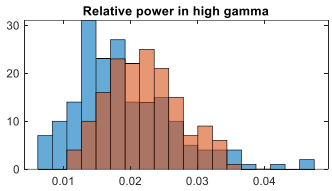


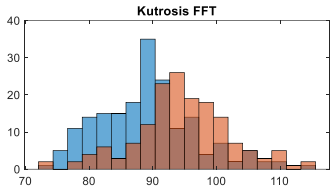


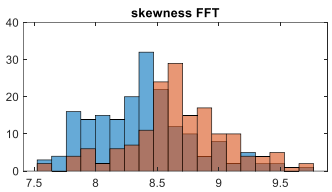


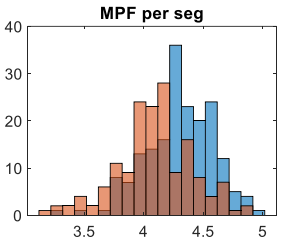


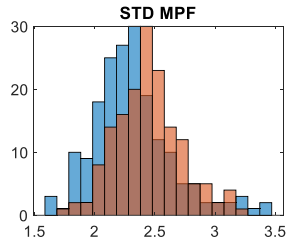


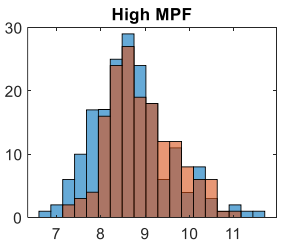


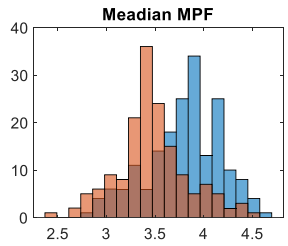












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-0.29561777	true	0.006523102	Amplitudeintegral
-0.37736565	true	0.000538449	Skewness
0.689296345	true	5.67214E-10	Harmonicity
-0.253507748	true	0.019486898	Zerocrossing
0.305886012	true	0.004897796	fractledimnsion
0.469820887	true	1.79875E-05	KutrosisNE
0.487338816	true	8.83145E-06	SkewnessNE
-0.720096193	true	1.04442E-10	KutrosisFFT
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