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Complexity Analysis of Brain Electrical Activity

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Abstract: The characterization of brain electrical activities in terms of neuronal complexity has recently received great attention. However, traditional complexity measures which are maximized for random sequences fail to quantify the inherent long-range correlation in brain dynamics. The recently introduced multiscale entropy (MSE) analysis accounts for the complexity over multiple time scales and therefore can reveal the complex structure of the brain electrical signal. The aim of this study is to test the applicability of MSE for electroencephalogram (EEG) signal characterization and classification. Besides, the MSE method has been tested against two other entropy metrics: permutation entropy (PermEn) and Lempel-Ziv entropy (LZEn) along with sample entropy (SampEn) in the context of discriminating EEG epochs recorded from different recording regions and for different brain states. It is shown that the MSE method with sample entropy as the complexity estimator outperforms other entropy measures for the cases considered and its potential is demonstrated as a feature extraction method for more sophisticated EEG signal classification scheme.

Keywords: Multiscale entropy analysis, sample entropy, permutation entropy, Lempel-Ziv entropy, complexity analysis.

Introduction

The brain is an extremely complex biological structure consisting billions of interconnected neurons. The electroencephalography (EEG) records the collective spontaneous electrical activity of a large population of radially oriented pyramidal neurons of the cortex subsequently filtered through the skull and scalp. The filtered brain electrical signals are nonstationary, non-Gaussian and non-linear in nature, also have characteristic frequency ranges, spatial distributions, and are associated with different states of brain functions. As a result, EEG has found a widespread use in diagnostic application in many neurological diseases such as epilepsy, encephalopathies, tumors, stroke, and sleep disorders, in addition, for monitoring the depth of anesthesia in surgical operation, for brain function monitoring in intensive care units and in neuroscience, cognitive science, cognitive psychology, and psycho-physiological research [1].

To understand the neurophysiological mechanisms underlying normal and disturbed higher brain functions, traditionally linear analysis methods such as Fourier transforms and spectral analysis are used to characterize EEG. Although these methods can identify the rhythmic oscillations in the EEG signal that fall primarily within five frequency bands: delta(<4Hz), theta(4-8Hz), alpha(8-14Hz), beta(14-30Hz) and gamma(>30Hz) and the results from these linear methods are quite easy to interpret in physiological terms, they are unable to yield information of the brain's inherent nonlinear complex dynamics. Dynamical behaviour of individual neurons exhibits nonlinear phenomena such as threshold and saturation [2] resulting in the assumption that EEG signals are generated by nonlinear deterministic processes with nonlinear coupling interactions between neuronal populations [3]. As a result, nonlinear dynamics is increasingly used to analyze EEG signal in order to better characterize and understand brain functions [4].

Recently, Costa et al. [5] have introduced multiscale entropy (MSE) to measure the complexity of finite length time series. This tool can be applied both to physical and physiologic data sets and can be used with a variety of measures of entropy. Traditional entropy measures such as Shannon entropy, Kolmogorov-Sinai (KS) entropy, approximate entropy (ApEn) and sample entropy (SampEn) quantify only the regularity (predictability) of time series on a single scale by evaluating the appearance of repetitive patterns [5]. However, there is no straightforward correspondence between regularity and complexity. Neither completely predictable (e.g., periodic) signals nor completely unpredictable (e.g., uncorrelated random) signals are truly complex since at a global level they admit a very simple description. As a result, the output of complex systems is far from the two extrema of perfect regularity and complete randomness. Instead, they generally reveal structures with long-range correlations on multiple spatial and temporal scales. These multiscale features, ignored by conventional entropy calculations, are explicitly addressed by the MSE method [5].

So far MSE has been successfully applied to investigate fluctuations of the human heartbeat under pathologic conditions like erratic cardiac arrhythmia and congestive heart failure [5], EEG and MEG recordings in patients with Alzheimer's disease [3], compare the complexity of human gait time series from healthy subjects under different conditions [6], examine variations in EEG complexity in response to photic stimulation during aging [7], study complex dynamics of human red blood cell

flickering and alterations with in vivo aging [8]. All the reported results strongly support the general 'complexity-loss' theory with aging and disease.

As pointed out in [1], the neural networks in the brain possess a structure which is intermediate between complete randomness (for example, gas) and perfect order (for example, crystal). So, it is apparent that MSE method should be applied to characterize brain electrical activity. The major aim of this study is to apply MSE to characterize EEG signals recorded extracranially in healthy subjects with eyes open and closed, and intracranially in epilepsy patients both during seizure-free intervals and epileptic seizures and thus compare the classification of different brain states with some other nonlinear methods particularly Lempel-Ziv entropy and permutation entropy. Besides, the MSE method is also tested against the above two entropy statistic along with sample entropy to determine the superiority of sample entropy in terms of classification accuracy. The structure of this paper is as follows. First, MSE and other nonlinear methods are introduced and followed by a brief summary of the EEG data and the statistical analysis method used. The results of the entropy analysis and classification are reported afterwards and finally the relevant results are discussed and conclusions are drawn.

Quantitative Complexity Estimators

In this paper, a set of different nonlinear entropy estimators has been applied to quantify the complexity of the EEG time series in multiscale entropy (MSE) analysis. They are sample entropy (SampEn), permutation entropy (PermEn) and Lempel-Ziv entropy (LZEn). All the methods are suitable for analysis of time series of limited length.

A. Multiscale Entropy Analysis

Costa et al. [5] proposed multiscale entropy (MSE) as a meaningful physiologic complexity measure which evaluates the relative complexity of normalized time series across multiple scales. Briefly, the MSE methodology has two steps:

- Multiple coarse-grained time series are generated from the original time series $\{x_1, x_2, \ldots, x_N\}$ by averaging the data points within non-overlapping windows of increasing length ε, also known as scale factor. The elements of the coarse-grained time series of scale factor ε are calculated as the equation below:

$$y_j^{\epsilon} = \frac{1}{\epsilon} \sum_{i=(j-1)\epsilon+1}^{j\epsilon} x_i \qquad where, 1 \le j \le \frac{N}{\epsilon} \tag{1}$$

- SampEn is calculated for each coarse-grained time series, and then plotted as a function of the scale factor.

In this paper, sample entropy is not only considered alone as complexity estimator in MSE method. Two other popular complexity estimator namely, permutation entropy and Lempel-Ziv entropy are also compared to establish the superiority of the sample entropy in the multi-scale framework.

B. Sample Entropy

Richman and Moorman [9] introduced the sample entropy (SampEn) which represents the conditional probability that two sequences of *m* consecutive data points, which are similar to each other within a tolerance level *r* will remain similar when next consecutive point is included, provided that self matches are not considered in calculating the probability. It is largely independent of time series length and displays relative consistency over a wide range of operating conditions. For a time series $\{x(n)\} = x(1), x(2), \ldots, x(N),$ SampEn is defined as [9] in Table 1.

C. Permutation Entropy

Bandt and Pompe [10] took an ordinal approach to quantify complexity of time series. They introduced permutation entropy (PermEn) that measures the local order structure of the time series in phase space. The use of ordinal statistics (rank) makes PermEn less sensitive to noise embedded in phase space. In Table 1, PermEn is computed as [10] for a time series $\{x(n)\} = x(1), x(2), \ldots, x(N)$.

D. Lempel-Ziv Entropy

Another approach to quantify complexity of time series is to use the theory of symbolic dynamics. To compute the Lempel-Ziv complexity [11, the original time series is first mapped onto a finite symbol sequence. One popular approach is to convert the time series into a binary (0:1) sequence by comparing with a threshold X_{th}, i.e., whenever the original time series samples are larger than X_{th}, it maps onto *1*, otherwise to *0*. Usually the median of the series is used as the threshold X_{th} due to its robustness to outliers. The resulting symbol sequence $\{S_i\}$ with *i=1, ..., N* is then went through the Lempel-Ziv parsing [11] algorithm to estimate the size $c(\{S_i\})$ of its vocabulary. In this algorithm, the symbol sequence $\{S_i\}$ is scanned from left to right and its complexity counter $c(\{S_i\})$ is increased by one unit every time a new subsequence of consecutive symbols is encountered and the scanning proceeds regarding the following symbol as the starting of the next symbol sequence. To obtain a complexity measure that is independent of the sequence length, $c(\{S_i\})$ should be normalized by the expected asymptotic value for a random sequence of symbols of length *N* which is $N/\log_\alpha N$, where α is the number of symbols (for binary sequence it is 2). Thus, the normalized Lempel-Ziv complexity or Lempel-Ziv entropy is,

$$LZEn = [\log_\alpha N \times c(\{S_i\})]/N$$

Table 1: Sample Entropy & Permutation Entropy Definition

Sample Entropy	*Permutation Entropy*
• Form $N-m$ vectors $X_m(1), X_m(2), \ldots, X_m(N-m)$ defined by $X_m(i) = [x(i), x(i+1), \ldots, x(i+m-1)]$where $i = 1, 2, \ldots, N-m$. These vectors represent m consecutive x values, commencing with the i-th point. • Define the distance between $X_m(i)$ and $X_m(j)$ as the maximum norm, $d[X_m(i), X_m(j)] = \max_{k=1,\ldots,m}\{\lvert x(i+k-1) - x(j+k-1)\rvert\}$ • For a given $X_m(i)$, count the number of j ($1 \le j \le N-m, j \ne i$), denoted as B_i, such that $d[X_m(i), X_m(j)] \le r$. Then, for $1 \le i \le N-m$, $B_i^m(r) = \frac{1}{N-m-1} B_i$ • Define $B^m(r)$ as $B^m(r) = \frac{1}{N-m}\sum_{i=1}^{N-m} B_i^m(r)$ • Then increase the dimension of the vectors to $m+1$ and calculate A_i as the number of $X_{m+1}(i)$ within r of $X_{m+1}(j)$, where j ranges from 1 to $N-m(j \ne i)$. • Define $A_i^m(r)$ as $A_i^m(r) = \frac{1}{N-m-1} A_i$ • and $A^m(r)$ as $A^m(r) = \frac{1}{N-m}\sum_{i=1}^{N-m} A_i^m(r)$ • Thus, $B^m(r)$ is the probability that two sequences will match for m points, whereas $A^m(r)$ is the probability that two sequences will match for $m+1$ points. • Then $SampEn$ is estimated by, $SampEn(r, m, N) = -ln[\frac{A^m(r)}{B^m(r)}]$ where r is the tolerance level, m is the pattern length and N is the length of the time series.	• Form vectors $X_n = [x(n), x(n+1), \ldots, x(n+m-1)]$ where $n = 1, 2, \ldots, N-m+1$ with the embedding dimension m and lag 1. • Arrange any vector X_n in increasing order such that $x(n) \le x(n+1) \le \ldots \le x(n+m-1)$. • For m different numbers, there will be $m!$ possible order patterns π, which are also called permutations. Find its frequency in the time series and denote it as $f(\pi)$. • Then the relative frequency is $p(\pi) = f(\pi)/(N-m+1)$. • Thus $PermEn$ is estimated by, $PermEn(m) = -\sum_{m=1}^{m!} p(\pi)\ln p(\pi)$. • And the normalized permutation entropy is $PermEn = PermEn(m)/\ln(m!)$

Data

The EEG data used in this study are obtained from the EEG database available publicly from the University of Bonn and described in detail in [2]. In brief, the complete dataset was comprised of five sets denoted A-E, each consisting 100 single-channel EEG epochs of duration 23.6 seconds each recorded with a sampling rate of 173.61 Hz. The first two sets A and B were obtained from EEG recorded extracranially using a standardized electrode placement scheme from five healthy volunteers with eyes open and closed respectively. The last three sets were obtained from EEG recorded intracranially using depth electrodes from five epileptic patients undergoing presurgical evaluations. Epochs in sets C and D were taken during seizure free intervals respectively from the hippocampal formation of the opposite hemisphere of the brain and within the epileptogenic zone. The epochs of set E were selected from all recording sites exhibiting ictal activity and thus contain seizure activity. As a pre-processing step, the downloaded data has been filtered using a band-pass filter with settings 0.53-40 Hz (12 dB/octave).

Statistical Analysis

To evaluate the statistical difference of the calculated entropy statistics of different sets, Student's t-test as well as the Mann-Whitney U test (also known as Wilcoxon rank sum test) has been applied. For more than two groups, one-way ANOVA (analysis of variance) which is a generalization of the Student's t-test for more than two groups is used as a parametric test whereas Kruskal-Wallis test, an extension of the Mann-Whitney U test for three or more groups is used as nonparametric one.

A multiple comparison procedure is also followed the ANOVA and Kruskal-Wallis test to find the information about which pairs of means/medians are significantly different, and which are not. In all cases, differences are considered statistically significant and the null hypothesis is rejected if the *p* value is lower than 0.01.

Simulation Results

Unless otherwise specified, the values of the parameters used to calculate SampEn are N=4097, m=2, and r=0.15 which are chosen on the basis of various previous studies indicating good statistical reproducibility [9]. For MSE, as the length of each coarse-grained sequence is ε (scale factor) times shorter than the length of the original series, so the highest scale factor calculated for analysis is 20. In that case the coarse-grained sequence has more than 200 data points which is well within the SampEn signal length requirement (10^m to 20^m) [9]. For PermEn to satisfy the condition of m! <200 at highest scale factor, the value of m=5 is chosen.

A. Entropy Analysis of EEG

SampEn, PermEn and LZEn values are computed for the entire 500 EEG epochs in the five data sets described earlier. Table 2 shows the different entropy statistic for the different EEG sets.

Table 2: Summary of different entropy statistic measured in different sets

Entropy statistic		Set A	Set B	Set C	Set D	Set E
SampEn	Mean	1.0591	0.9348	0.7084	0.6528	0.6102
	Median	1.0106	0.9415	0.6981	0.6703	0.6179
	Max	1.4785	1.2725	1.0514	0.8880	1.0153
	Min	0.8274	0.7192	0.5003	0.2010	0.3123
	STD	0.1409	0.1320	0.1142	0.1418	0.1281
PermEn	Mean	0.7619	0.7049	0.7038	0.6727	0.6449
	Median	0.7558	0.7099	0.7089	0.6655	0.6469
	Max	0.8509	0.8131	0.7993	0.7773	0.8268
	Min	0.6955	0.6243	0.5572	0.5331	0.5216
	STD	0.0314	0.0471	0.0505	0.0514	0.0536
LZEn	Mean	0.5414	0.5327	0.3480	0.3347	0.3877
	Median	0.5287	0.5404	0.3456	0.3427	0.3837
	Max	0.6942	0.6356	0.5477	0.4657	0.5800
	Min	0.4335	0.4218	0.2080	0.1347	0.2343
	STD	0.0575	0.0525	0.0589	0.0720	0.0773

From the table, it is clear that epileptic EEG (set E) is the least complex among the five data sets as it yields the least value of SampEn and PermEn statistic. To find the statistical significance of the differences among the different entropy values of the five sets, one-way ANOVA and Kruskal-Wallis test is used. Afterwards, multiple comparison procedure is applied on the result of the previous two tests to find the significant differences among different pairs. The result is shown in Table 3 where the entries represent the pairs which cannot be significantly differentiated according to the above two statistical tests.

Table 3: Result of the two statistical tests

Entropy statistic	One-way ANOVA test	Kruskal-Wallis test
SampEn	C-D, D-E	A-B, C-D, D-E
PermEn	B-C	B-C, D-E
LZEn	A-B, C-D	A-B, C-D, C-E, D-E

After that, the multiscale procedure is applied with three entropy estimates. The result is shown in Fig. 1. For MSE analysis using SampEn (Fig. 1(a)), the MSE curves of sets A and B have similar patterns: a local maximum at scale factor 5 followed by decreasing entropy values. On the other hand, the MSE curves of sets C and D have a similar shape: steep increase followed by a smoother increase whereas MSE curve of set E increases until scale factor 8 and then decreases slightly. And for all scale factors, the curve of set E remains quite below from the others which prove the fact that EEG complexity decreases in seizures. From the statistical point of view, for most of the scale factors the SampEn values are significantly different among the sets for at least four sets. It is found by using one-way ANOVA and Kruskal-Wallis test followed by multiple comparison procedure. However, the LZEn measures (Fig. 1(b)) cannot differentiate in terms of MSE curves between sets A (healthy volunteer, eyes open) and B (healthy volunteer, eyes closed), and sets D (epileptogenic zone) and C (hippocampal formation of opposite hemisphere) and the PermEn measures (Fig. 1(c)) cannot discriminate any sets after scale factor 10.

B. Classification

In this section, the ability and effectiveness of the entropy measures studied in this paper are examined in the context of EEG classification. Every EEG epoch in the five different sets mentioned earlier has a desired label of the set from which it is taken and the classifier aims to correctly label each of the 500 EEG epochs. Two cases are considered here: the five-class case and the simplified three-class case, which groups classes A and B, and classes C and D. The classification is performed on the

feature vectors generated from the EEG epochs using SampEn, PermEn and LZEn individually and then with the multi-scale framework where the vector contains the entropy values for all the scale factors used.

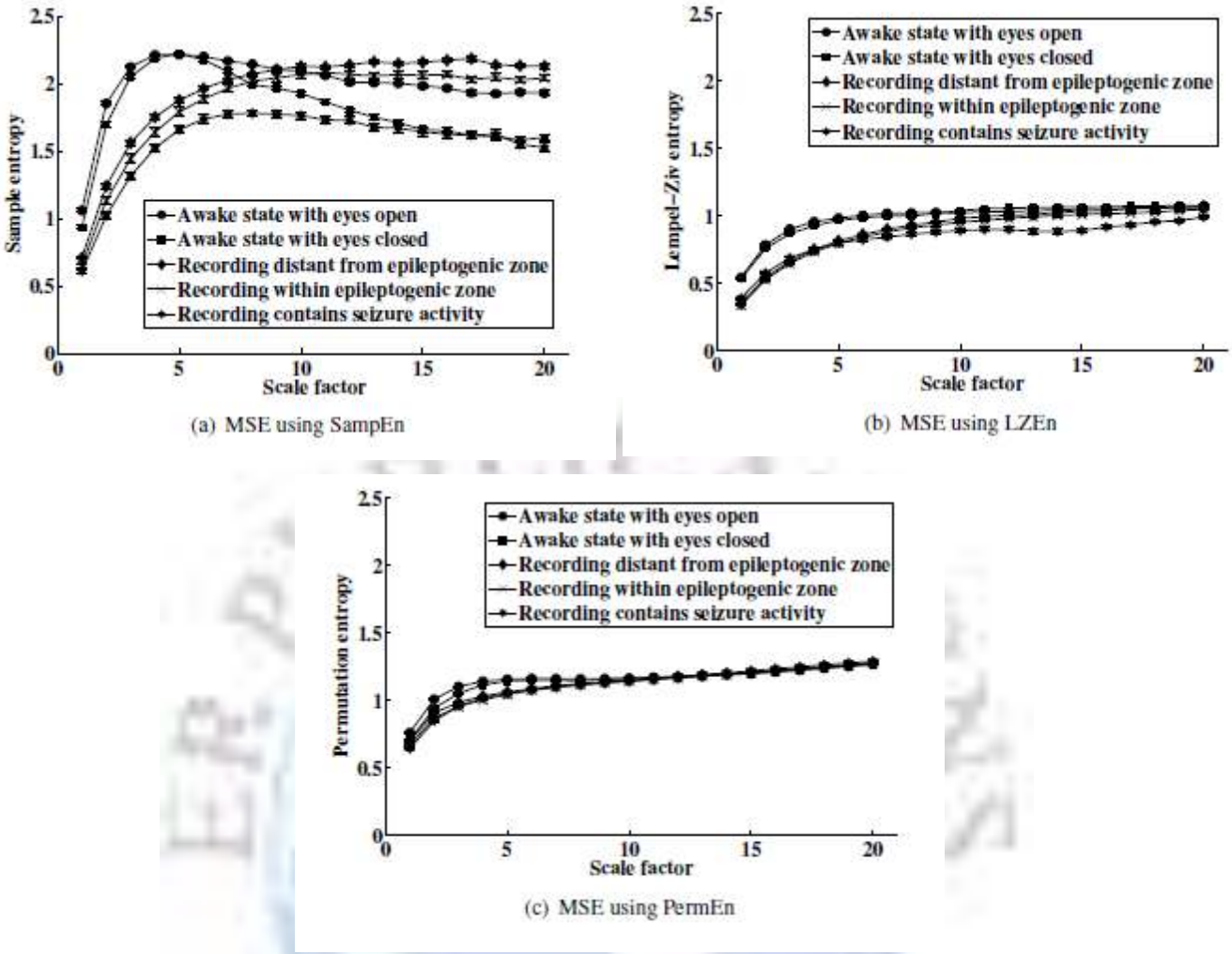

Figure 1: Multiscale entropy analysis using different entropy estimators. Symbols represent the mean values of entropy for each set and the bars represent the standard error

Though there exists a great deal of classification methods, nearest neighbour classification (NNC) and leave-one-out classification (LOOC) from the supervised classification (as the desired labels are known a priori) paradigms are chosen for this investigation. These two methods can be interpreted as a lower and upper bound of possible classification systems. In NNC, the class prototypes are determined as the average of the feature vectors of all EEG epochs belonging to a certain set. The EEG epoch is classified to the class of its nearest neighbor, with the epoch being assigned to the class label of the prototype which is nearest in Euclidean norm to its feature vectors. In LOOC, the label of an EEG epoch (testing epoch) is determined by leaving out that epoch from the set and considering the remaining set of feature vectors as the set of labelled prototypes (training epochs). The label of the testing epoch is set equal to that of the nearest neighbour prototype in Euclidean norm sense. The classification accuracy is expressed as the fraction of correct classifications and is shown in Table 4 for single scale entropy metrics and in Table 5 for multiple scale framework for the different case setup. The classification performances for the MSE method with SampEn as the complexity measure outperform all the other entropy measures in single scale as well as for multiple scales for both case setups.

Discussion and Conclusions

In this study, recently introduced multiscale entropy (MSE) method with sample entropy as the complexity statistic is compared with other entropy estimators like permutation entropy (PermEn) and Lempel-Ziv (LZEn) in context of EEG signal characterization and classification. All of the entropy estimators provide a quantitative metric for the complexity measurement of different brain state. The complexity of EEG recordings of healthy volunteers with eyes open (set A) are found significantly ($p<0.01$) higher than the recordings with eyes closed (set B) using SampEn (in t-test only) and PermEn (both t-test and Mann-Whitney U test) measures but LZEn measure cannot significantly differentiate between this two sets in any test. Moreover, MSE method with sample entropy as the complexity estimator significantly detects high degree of complexity in set A compared to set B for most of the scale factors.

Table 4: The classification accuracy for the different single scale entropy measures

	NNC			LOOC		
	SampEn	LZEn	PermEn	SampEn	LZEn	PermEn
3-class case	65.4	72	54.20	64.4	73.80	45.20
5-class case	41.2	40.20	38.40	40.8	34.80	29.00

Table 5: The classification accuracy for the different entropy measures in the Multiscale entropy framework

	NNC			LOOC		
	SampEn	LZEn	PermEn	SampEn	LZEn	PermEn
3-class case	84.8	77.60	70	90	80.40	87.20
5-class case	67.2	49.80	55.20	69.2	53.80	68.80

These results are in agreement with the Hebb's concept of cell assemblies in brain function. The brain electrical activity (i.e., EEG) is generated from individual cell assembly activities. In eyes closed state, as there are no cognitive tasks involved, the number of independent, parallel functional processes active in the brain is less and brain goes into a passive state of relaxation. As a result, the neuronal networks display a state of synchrony and most of the neuronal groups within a cortex area oscillate at a certain frequency. This is associated with an increase in alpha frequencies in the brain waves. This makes EEG signals structure more regular and thus reduces its complexity. On the other hand, the task of processing large amount of visual information in eyes open state require more oscillating cell assemblies to change their oscillation patterns away from the preceding predominant one. This makes the EEG signal more irregular and thus increases complexity [1, 7].

All entropy measures were able to find significant (t-test and Mann-Whitney U test, $p< 0.01$) decrease of complexity in seizure activity (set E) compared to normal EEG (eyes open or closed) recordings. This indicates a reduction in the intra-cortical information flow and lower neuronal process in the brain. The result is in agreement with the previous studies on dimensional analysis of EEG that epileptic seizures are emergent states with reduced dimensionality compared to normal state. It was observed in [12] that neuronal hyper-synchrony, a phenomenon during which the number of independent variables required to describe the dynamical system is smaller than other times, underlies seizures. This reduction of the system's degree of freedom indicates either a strongly coupled system or the inactivation of previously active networks or a loss of dynamical brain responsiveness to the environmental conditions. Besides, the findings of our study support the more general concept of multiscale complexity loss with aging and disease which also reduces the adaptive capacity of biological organization at all levels [13].

Moreover, the classification result shows that the MSE method with sample entropy as complexity statistic provides a sufficiently detailed characterization of the EEG to discriminate among the different sets. The performance of a classifier is expected to lie between 84% and 90% in 3-class case. However, performance degrades for a more detailed classification in 5-class case which further dissociates between sets A and B and sets C and D. Among the single scale entropy measures, LZEn performs better (72%-73.8%) in 3-class case.

To conclude, the recently introduced multiscale entropy analysis (MSE) method has been examined against two other entropy statistics to reveal the hidden characteristics of the EEG signals. Compared with other traditional single scale entropy metrics, our study suggests that MSE with sample entropy as the complexity estimator can detect the long-range correlation and multiscale complexity in the brain and thus efficiently distinguish different dynamical properties of brain electrical activity. This method also has the potential to be used to extract features for more sophisticated EEG signal classification based on neural networks or support vector machines and hence characterize different brain conditions.

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