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Multiscale Entropy Analysis of Instantaneous Frequency Variation to Overcome the Cross-Over Artifact in Rhythmic EEG

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ABSTRACT Generally, for healthy adults, the entropy of electroencephalogram (EEG) signals gradually decreases from wake to sleep stages N1, N2, to N3, and increases during REM. However, some researchers found that multiscale entropy curves of sleep and wakefulness intercept, a cross-over phenomenon whose origin remains unexplored. The objective of the present work is to trace the origin of the cross-over phenomenon and to propose a workaround strategy. We simulated EEG by generating 1/f broadband signal and chirp signals with continuously varying frequencies. We then retrieved the rhythmic component from simulated EEG and real-world EEG and conducted MSE analysis of the instantaneous frequency variation (IFV) of the rhythmic component. The simulation revealed that this interception was ubiquitous in the MSE analysis of simulated EEG with rhythmic components of different frequencies. The cross-over point moved toward larger scale factors with the increasing sampling rate. We found that the MSE curve of IFV from real-world EEG for the wakefulness group was higher than that for sleep, showing no interception. These results suggest that (1) for a rhythmic signal like EEG, MSE analysis of the raw signal is highly affected by the rhythmic component, presenting artificial cross-over curves in sleep EEG study, (2) frequency variation of rhythmic components are complex signal which differs between wakefulness and sleep, in accordance with the complexity loss theory.

INDEX TERMS Multiscale entropy analysis, complexity, sleep, brain wave.

I. INTRODUCTION

It has attracted considerable attentions to quantify the ''complexity'' of physiologic time series in the attempt to distinguish different conditions, e.g., between wakefulness and sleep [1], the elderly and the young [2]. Sleep is a sophisticated non-linear and non-stationary process that involves the interaction between the brain and the rest of the body [1]. Various entropy-based methods, e.g., approximate entropy [3], sample entropy [4], permutation entropy [5], have been used to compare the complexity of wakefulness and sleep electroencephalographic (EEG) signals. It is widely accepted that the entropy of EEG signals for healthy adults gradually decreases from wake to sleep stages N1, N2, to N3, and then increases during REM [4].

However, the entropy-based measure quantifies the irregularity of time series, assigning the highest complexity values to white noise, therefore are not satisfactory in describing physiologic complexity [6], [7]. To avoid this problem, multiscale entropy (MSE) and its variants have been widely used in a variety of research fields [6]–[9] by calculating sample entropy at multiple scales of the coarse-grained versions of the original signal.

Complexity indices decrease as sleep gets deeper, and reach their lowest level when slow wave sleep occurs [1], [10]. Abásolo *et al.* [11] have found that activated brain states – wakefulness and REM sleep – are characterized by higher complexity compared with NREM sleep.

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However, in sleep studies, some researchers have found what we would call cross-over phenomenon, the MSE curve of wakefulness is higher than that of sleep at small scale factors, and lower at large scale factors. For healthy subjects, MSE curves of wakefulness and sleep present interception, although not explicitly compared [7]. Multi-scale fuzzy entropy analysis and multi-scale permutation analysis also reveal similar cross-over phenomenon while the authors intend to classify the sleep stages [12]. Shi *et al.* studied the cross-over phenomenon and have found the entropy measures are higher in the awake stage and lower in deep sleep (N3) at small scales; while the measures are lower in the awake stage and higher in deep sleep stages at large scales [8]. Miskovic *et al.* have confirmed the cross-over phenomenon with multiscale dispersion entropy analysis on wakefulness/sleep data [13].

Although some researchers interpret the cross-over phenomenon as an outcome of physiological origin [8], the underlying cause remains unclear. In this paper, we investigate the cross-over phenomenon by simulated and real data. We reveal by simulation that this interception can be caused by imperfection of MSE algorithm in dealing with time series with rhythmic components. We then retrieve rhythmic component, from which we compute the instantaneous frequency variation (IFV), and conduct MSE analysis. We find that the MSE curve of IFV for wakefulness group is higher than that for sleep, showing no interception.

II. MULTISCALE ENTROPY (MSE)

MSE has been proposed to quantify the complexity of biomedical time series [14], and is briefly summarized here. Suppose there is a finite length discrete time series $X_i : \{x_1, x_2, x_3, \ldots, x_n\}$, the length is n. Its MSE calculation has the following two steps:

1) Coarse-grain the original sequence to obtain the new sequence with different time scales:

$$y_j^\tau = \frac{1}{\tau} \sum_{i=(j-1)\tau+1}^{j\tau} x_i \, (1 \le j \le n/\tau) \tag{1}$$

τ is the time scale, also known as scale factor. The length of each time series after coarse-grained is n/τ. When $\tau = 1$, it is the original time series. The generation process of the coarse-grained sequence of scale 2 and scale 3 is shown in Fig.1 [6].

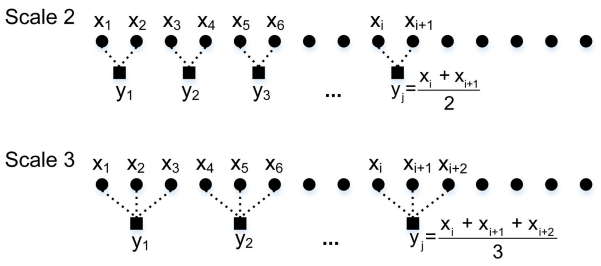

FIGURE 1. The generation process of coarse-grained sequence of scales 2 and scale 3.

2) Calculate the Sample Entropy (SE) value of the corresponding sequence of each scale to obtain MSE:

$$MSE\,(\tau) = SampEn\,(\tau, m, r, n) \tag{2}$$

where, m, r and n are the embedding dimension, similarity tolerance and data length respectively as in SE. r is calculated by $r = c * \sigma$, σ is the standard deviation of the original sequence X_i. c is the tolerance factor as a percentage of σ with typical value in the range of 0.1-0.3.

III. PROPOSED STRATEGY

Biological signals are often non-stationary and nonlinear. Their instantaneous variations in amplitude and frequency may include rich dynamic characteristics and can be extracted from its analytic form [15]. We propose an analysis process, MSE analysis on instantaneous frequency variation (MSE-IFV) of rhythmic brain activity as follows:

- *Step 1.* A 4th order Butterworth bandpass filter is adopted to extract the rhythmic component from the original signal. A zero-phased filter process is used to ensure the performance of Hilbert transform in Step 2. The main rhythmic component of sleep EEG stages is shown in Table 1. When the EEG stage is awake in silence, the rhythmic component of EEG dominates in 8∼13Hz (α wave). EEG's amplitude of S1 stage decreases and its rhythmic component concentrates in 4∼7Hz (θ wave), with a minor of α wave. EEG of S3 stage focus on 0.5∼3Hz (δ wave), with high amplitude [16].

TABLE 1. The main feature frequency of sleep EEG stages.

EEG stage	Main rhythmic component
Wake	8∼13Hz
S1	4∼7Hz
S3	0.5∼3Hz

- *Step 2.* Hilbert transform is used to compute the instantaneous frequency of the rhythmic component extracted in Step 1.
- *Step 3.* MSE analysis for the instantaneous frequency of the rhythmic component extracted in Step 2.

Schematic diagram of MSE-IFV for sleep EEG signal is shown in Fig. 2.

IV. EXPERIMENTS AND RESULTS

A. SIMULATION SIGNAL GENERATION

We generated three types of signals.

1) 1/f signal. The 1/f signal (data length 20000 points) was generated using the Matlab toolbox powernoise.m provided by [17].

2) Pure rhythmic signal. We chose 10 Hz and 2 Hz sinusoidal signals as pure rhythm signals. The length of each signal was 20000 points.

3) A signal with frequency variation. The signal whose frequency changed from 30 Hz to 1 Hz were generated with the Matlab toolbox chirp.m. The time series had 20000 points.

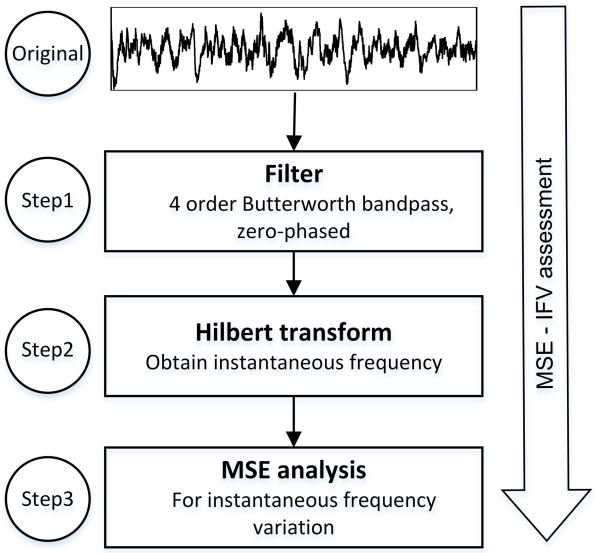

FIGURE 2. Schematic diagram of MSE-IFV method of EEG signal.

B. REAL-WORLD SLEEP DATASET

The sleep EEG data files were extracted from the Sleep-EDF Expanded Database (SC*) of the public repository physionet [18]. The dataset included 153 recordings that were obtained in a 1987-1991 study of age effects on sleep in healthy Caucasians aged 25-101 [19]. All subjects showed no somatic, neurologic, or psychiatric disorders. But some persons from the senior age group were found to have visual or hearing loss. The 153 PSG recordings for almost 24 hours, approximately 8-hour overnight recordings were sampled at 100 Hz. The PSG recordings include dual-channel EEG from Fpz-Cz and Pz-Oz, horizontal electromyogram, submental EMG, and an event marker. Its associated hypnogram files contain sleep stages corresponding to each subject according to the R&K classification with an epoch size of 30 seconds. These stages consist of sleep stages '1', '2', '3', '4', 'W', 'R', 'M', and '?', which represent S1, S2, S3, S4, Wake, REM, movement, and not scored respectively.

For the accuracy of the MSE algorithm, the recording would be discarded if the data length was less than 10000 samples. Therefore the S4 stage was discarded. S2 stage presents multiple rhythmic components (K-complex wave and spindle wave), therefore was also discarded in this study. In summary, the EEG (Fpz-Cz) of 3 stages (Wake, S1 and S3) of 10 subjects (26-35 years) were used in this work. In order to ensure the validity of this study, the segments of datasets for different stages were selected randomly.

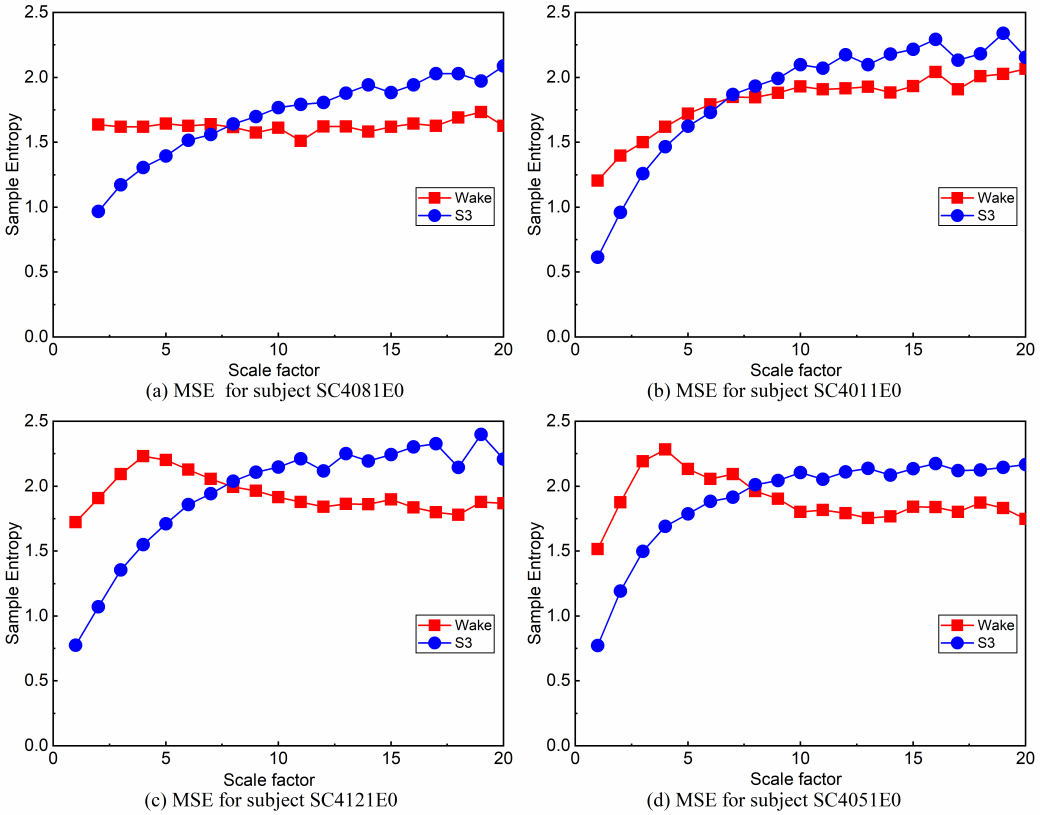

FIGURE 3. MSE results for 4 healthy subjects sleep EEG between the Wake stage and the S3 stage. (a), (b), (c) and (d) denotes that MSE analysis of subject SC4081E0, SC4011E0, SC4121E0 and SC4051E0. Wake: wakefulness. S3: sleep stage 3.

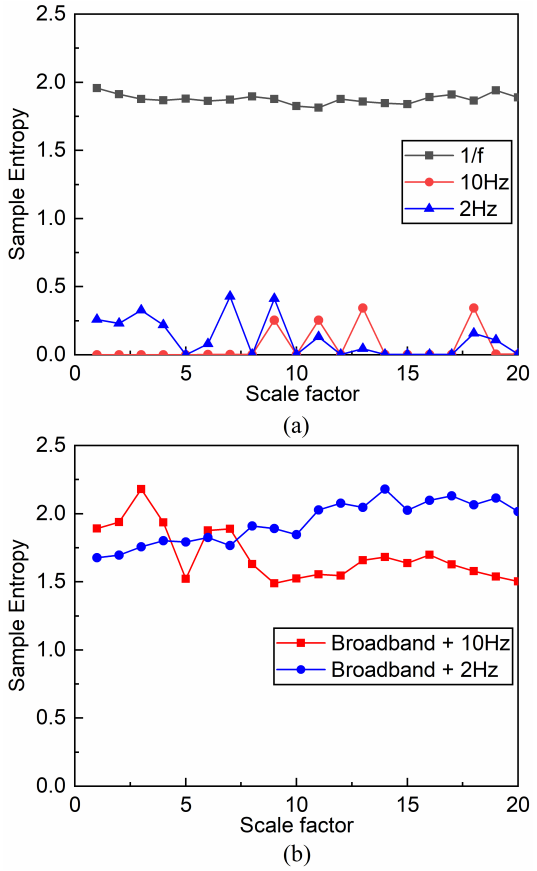

FIGURE 4. MSE analysis for simulated signals (Sampling rate: 100Hz). (a): MSE analysis for simulated broadband 1/f signal, 10Hz and 2Hz sinusoidal signal separately. (b): MSE analysis for simulated mixed signal of broadband 1/f, 10Hz and 2Hz sinusoidal signals. When analyzed separately, entropy values are small for sinusoidal signals (a), while mixed with broadband 1/f, entropy values are largely affected (b). The cross-over phenomenon is evident: Comparing with mixed signal of 2Hz sinusoidal wave, mixed signal of 10Hz sinusoidal wave is higher at small scale factors and lower at large scale factors.

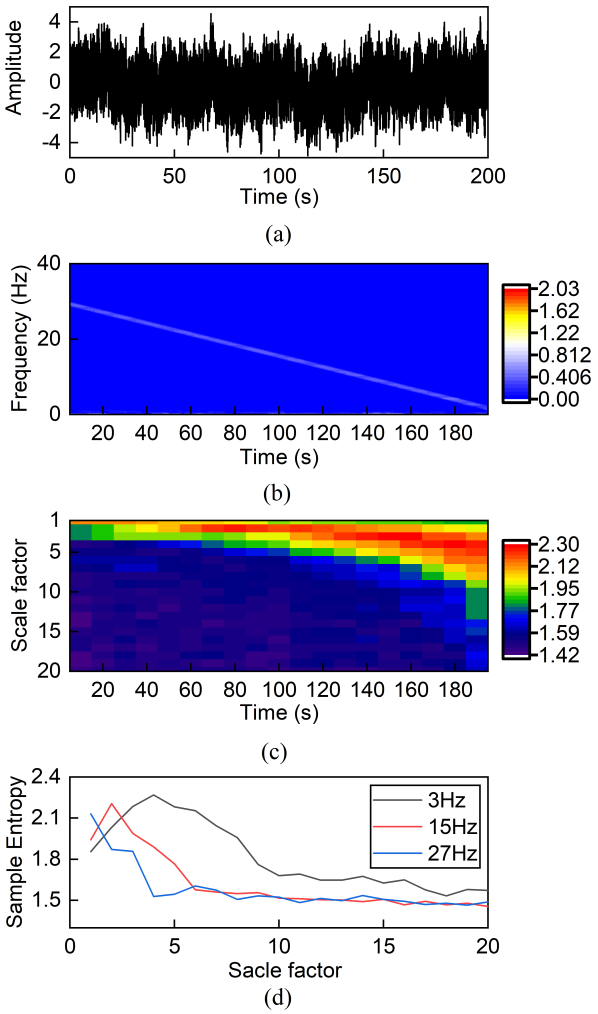

FIGURE 5. The mixed signal of broadband 1/f and chirp signal whose frequency change from 30Hz to 1Hz, the power spectrum density, and the MSE estimation over the changed frequency. Sampling rate for the mixed signal is 100 Hz. (a): Time series of simulated mixed signal of broadband 1/f and rhythm. (b): Power spectrum of simulated mixed signal of broadband 1/f and rhythm over frequency. (c): MSE of simulated mixed signal of broadband 1/f and rhythm over frequency using sliding window method. (d): MSE values corresponding to 3Hz, 15Hz and 27Hz mixed signals are extracted from (c).

C. STATISTICAL ANALYSIS

The distribution of datasets was tested using Shapiro–Wilk Normality test. If the dataset followed a normal distribution, independent sample t-test was used to test the significant differences between the 2 stages (Wake, S3); if not, non-parametric Mann-Whitney test was employed. One-way ANOVA was performed to examine if the significant differences existed between the 3 stages (Wake, S1 and S3) at each scale factor. For analysis that yielded significant group differences, post hoc tests were performed (Bonferroni p value) to determine the specific nature of the stage differences. All statistical analyses were carried out using SPSS (version 20), and a significant level of 0.05 was applied for all analyses.

D. CROSS-OVER PHENOMENON IN MSE OF REAL-WORLD SLEEP EEG

MSE method was applied to estimate the sleep EEG signals from the Sleep-EDF Expanded Database (10 subjects). Fig.3 only shows MSE curves of 2 stages (Wake, S3) for subject SC4081E0, SC4011E0, SC4121E0 and SC4051E0, representing the experimental results of all subjects. Comparing the S3 stage, the MSE values of the Wake stage is larger at small scales, and is smaller at large scales. The cross-over phenomenon exists between the Wake stage and the S3 stage.

E. CROSS-OVER PHENOMENON IN MSE OF THE SIMULATED RHYTHMIC SIGNALS

Fig.4 shows MSE estimation for simulated signals. Fig.4 (a) shows MSE values of 10Hz and 2Hz pure rhythm signals are closer to 0, and the broadband 1/f signal is assigned higher complexity. Then the mixed signal of the broadband component and the rhythmic component for MSE estimation. The mixed signal is considered as

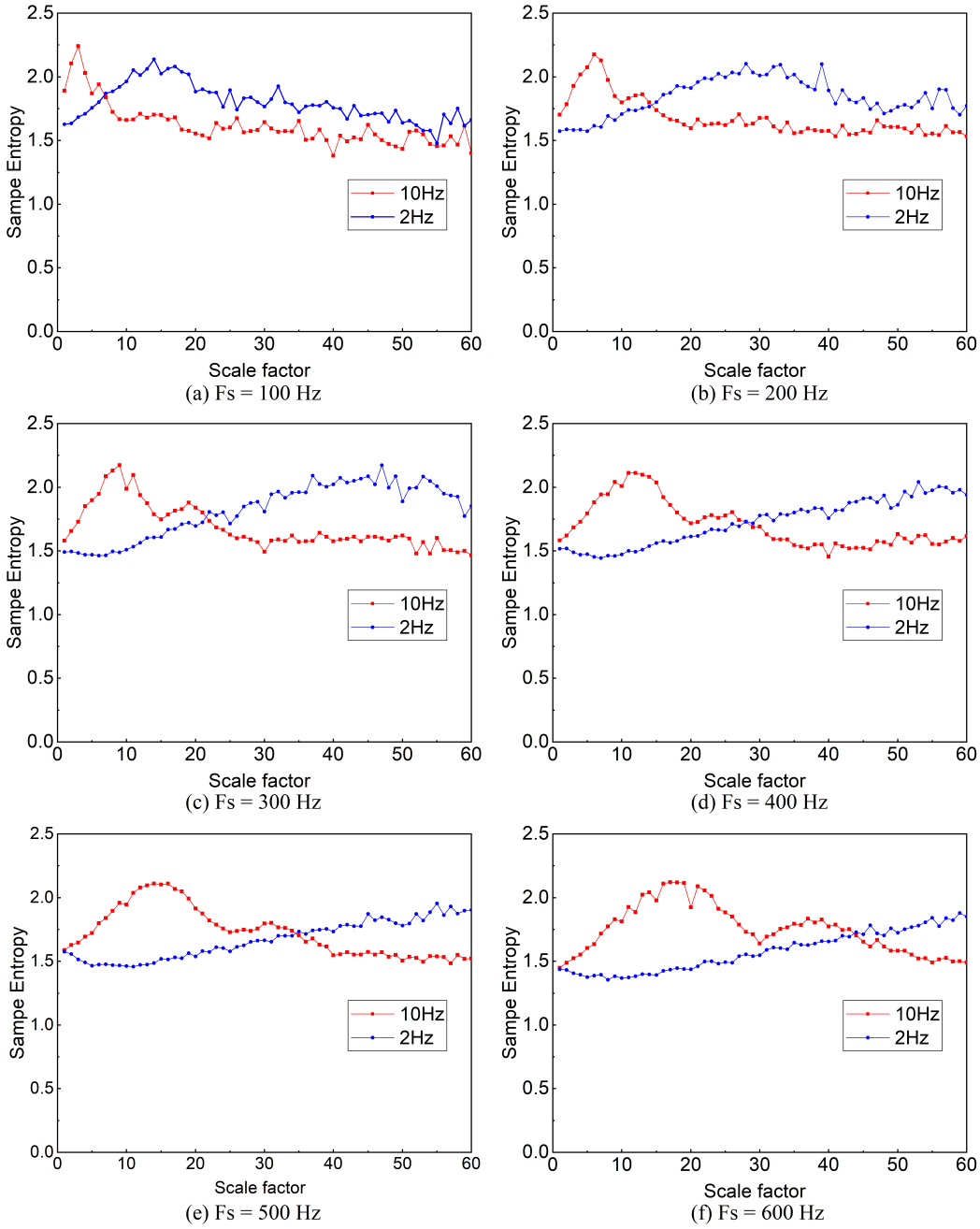

FIGURE 6. MSE analysis of mixed signal of broadband 1/f and sinusoidal signals (10Hz vs. 2Hz) at different sampling rates. The length of dataset is 10000. The cross-over point moves towards larger scale factors as the sampling rate increases.

simulated EEG signals. Comparing with the mixed signal of 2Hz sinusoidal wave, mixed signal of 10Hz sinusoidal wave is higher at small scale factors and lower at large scale factors. The cross-over phenomenon of the 2-mixed signals appears in MSE curves (Fig.4 (b)). When the rhythmic signal is analyzed separately, such as sinusoidal signals, entropy values are assigned small. While the rhythmic signal is mixed with broadband signal, entropy values are largely affected.

F. EFFECT OF RHYTHMIC BRAIN ACTIVITY ON MSE

Fig.5 shows that a mixed signal of broadband 1/f and chirp signal whose frequency changes from 30Hz to 1Hz, the power spectrum density, and the MSE estimation over the changing frequency. With the frequency of signal changing from 30Hz to 1Hz, MSE values of the mixed signal of 1/f and rhythm change. At smaller scale factors, MSE values are higher. At larger scale factors, MSE values decrease gradually. In the process of the signal's frequency changing from 30Hz to 1Hz,

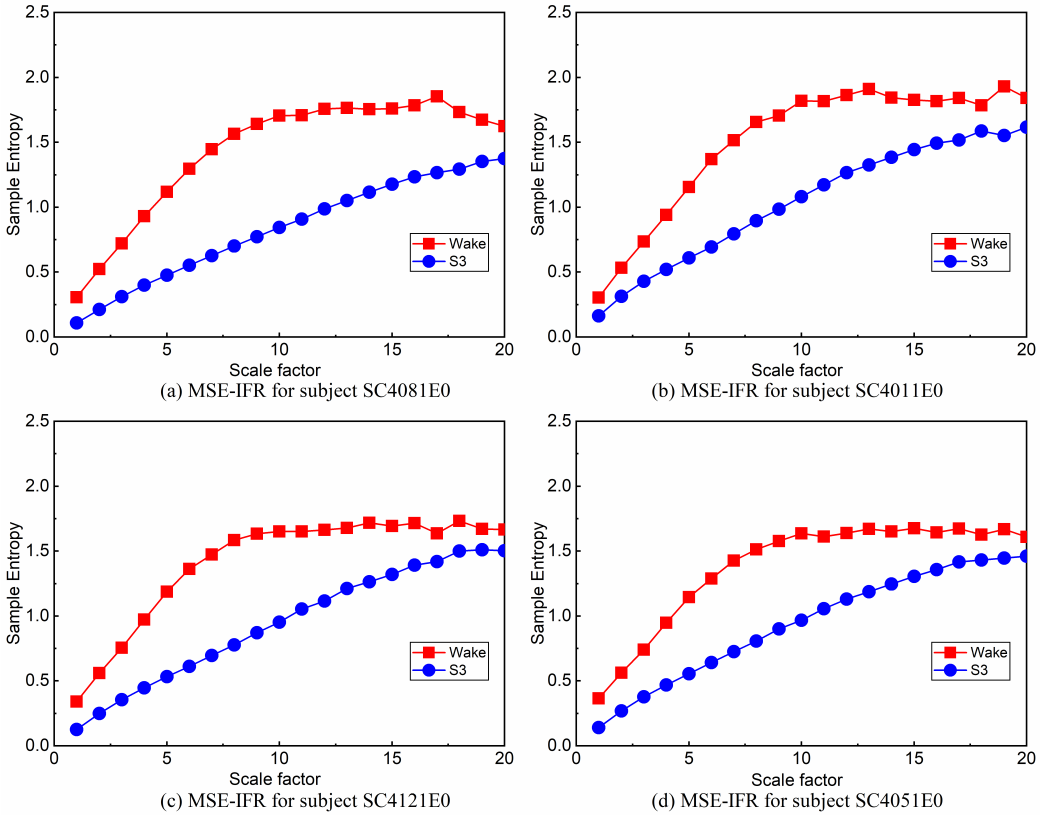

FIGURE 7. MSE-IFV of sleep EEG signals for the same subjects as Fig. 3 between the Wake Stage and the S3 Stage. (a), (b), (c) and (d) denote that MSE analysis of subject SC4081E0, SC4011E0, SC4121E0 and SC4051E0. Wake: wakefulness. S3: sleep stage 3.

TABLE 2. Statistical test results for subject SC4081E0, SC4011E0, SC4121E0 and SC4051E0.

Subject	Sleep stage	Normality test (Shapiro-Wilk)			Normal distribution	Statistical test choose	p Value (Two-Sided)
		Statistical	df	Sig.			
SC4081E0	Wake	0.782	20	0.000	No	Mann-Whitney test	0.000
	S3	0.944	20	0.285	Yes		
SC4011E0	Wake	0.767	20	0.000	No	Mann-Whitney test	0.001
	S3	0.925	20	0.126	Yes		
SC4121E0	Wake	0.725	20	0.000	No	Mann-Whitney test	0.001
	S3	0.933	20	0.176	Yes		
SC4051E0	Wake	0.733	20	0.000	No	Mann-Whitney test	0.001
	S3	0.927	20	0.136	Yes		

the MSE values can be affected by changing frequency in Fig.5 (c). Fig.5 (d) shows that MSE values corresponding to 3Hz, 15Hz and 27Hz mixed signals are extracted from Fig.5 (c) respectively. The MSE values corresponding to 3Hz, 15Hz and 27Hz respectively appear cross-over phenomenon in curves. It is clear that the cross-over is not an isolated case, but a universal phenomenon.

G. EFFECT OF SAMPLING FREQUENCY ON MSE

Fig.6 shows that the MSE curves of mixed signal of broadband 1/f and sinusoidal signals (10Hz vs. 2Hz) at different sampling rates. The result shows that the increasing sampling frequency (from 100Hz to 600Hz) is related to the scale factor at which the cross-over point moves towards the larger scale factor. While the sampling rate reaches a certain value, the cross-over point is located at a scale factor that is larger than 20.

H. MSE-IFV OF SLEEP EEG

We proposed MSE-IFV (details in Methods part) to solve the cross-over phenomenon. Fig.7 shows that MSE-IFV analyzing result of the Wake stage and the S3 stage. Fig.7 only shows MSE curves of 2 stages (Wake, S3) for subject SC4081E0, SC4011E0, SC4121E0 and SC4051E0, representing the experimental results of all subjects. The MSE values of the Wake stage is higher than the S3 stage at all scales. It's clear that the 2 stages are separate without cross-over phenomenon for the four subjects (Mann-Whitney test, $p <$

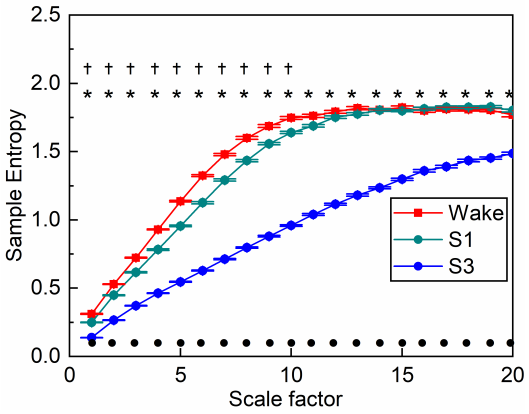

FIGURE 8. MSE-IFV for the 10 subjects (aged 26-35 years) among Wake, S1 and S3 stages. † Comparison of the Wake stage versus the S1 stage. ∗ Comparison of the Wake stage versus the S3 stage. • Comparison of the S1 stage versus the S3 stage. Wake: wakefulness. S1: sleep stage 1. S3: sleep stage 3.

0.001, p = 0.001, p = 0.001 and p = 0.001); the statistical test output is shown in Table 2.

Subsequently, we randomly choose 10 subjects for MSE-IFV analysis. The instantaneous frequency of the main rhythmic component from the Wake, S1, and S3 of 10 subjects is analyzed. The one-way ANOVA is used to examine the significant differences of the 3 stages (Wake, S1, and S3) from scale 1 to scale 20, except scale 14 and scale 16. The 3 stages do not all follow normal distribution at scale 14 and scale 16. Therefore the Mann-Whitney test is used to examine the significant differences for the 3 stages. The corresponding statistical test results are shown in Table 3 and Table 4. The significant differences among the 3 stages at different scale factors are displayed in Fig.8. From scale 1 to scale 10, the 3 stages have significant differences (one-way ANOVA, $p < 0.001$), and the Post Hoc tests show the relationship of the means among the 3 stages: Wake > S1 > S3 ($p < 0.01$, $p < 0.001$, $p < 0.001$).

At the next 10 scales, for scale 11, scale 12, scale 15, scale 17, scale 18 and scale 20, the data of 3 stages follow normal distribution, and there are significant differences in the 3 stages (one-way ANOVA, $p < 0.001$). The Post Hoc Tests show that there is no significant difference between the Wake stage and the S3 stage ($p > 0.05$), but the relationship of the mean for the 3 stages is: Wake > S3 ($p < 0.001$); S1 > S3 ($P < 0.001$). For scale 13, scale 14, scale 16 and scale 19, the data of 3 stages do not follow normal distribution, and there are significant differences in the 3 stages (Kruskal-Wallis test, $p < 0.001$). The Mann-Whitney test shows that there are no significant differences between the Wake stage and the S3 stage ($p > 0.05$), and the relationship of the medium among the 3 stages is: Wake > S3 ($p < 0.001$); S1 > S3 ($P < 0.001$).

In summary, Fig.8 shows that there are significant differences between the Wake stage and the S1 stage from scale 1 to scale 10; there are significant differences between the Wake stage and the S3 stage at all scale factors (1-20); and there are significant differences between the S1 stage and the S3 stage at all scale factors (1-20).

TABLE 3. Summary of post Hoc tests of stage differences at 20 scale factors.

Scale factors	Comparison of stages	Mean difference	Bonferroni p-value (two-sided)
Scale 1	Wake-S1	0.6274	0.000
	Wake-S3	0.17349	0.000
	S1-S3	0.11075	0.000
Scale 2	Wake-S1	0.8120	0.000
	Wake-S3	0.26438	0.000
	S1-S3	0.18317	0.000
Scale 3	Wake-S1	0.10686	0.000
	Wake-S3	0.35053	0.000
	S1-S3	0.24367	0.000
Scale 4	Wake-S1	0.14737	0.000
	Wake-S3	0.46705	0.000
	S1-S3	0.31968	0.000
Scale 5	Wake-S1	0.18096	0.000
	Wake-S3	0.59030	0.000
	S1-S3	0.40933	0.000
Scale 6	Wake-S1	0.19865	0.000
	Wake-S3	0.69614	0.000
	S1-S3	0.49749	0.000
Scale 7	Wake-S1	0.18649	0.000
	Wake-S3	0.76559	0.000
	S1-S3	0.57906	0.000
Scale 8	Wake-S1	0.16629	0.000
	Wake-S3	0.80376	0.000
	S1-S3	0.63746	0.000
Scale 9	Wake-S1	0.12946	0.005
	Wake-S3	0.80692	0.000
	S1-S3	0.67745	0.000
Scale 10	Wake-S1	0.10678	0.019
	Wake-S3	0.78761	0.000
	S1-S3	0.68083	0.000
Scale 11	Wake-S1	0.07364	0.273
	Wake-S3	0.72241	0.000
	S1-S3	0.64877	0.000
Scale 12	Wake-S1	0.03958	1
	Wake-S3	0.67760	0.000
	S1-S3	0.63803	0.000
Scale 15	Wake-S1	0.2296	1
	Wake-S3	0.52397	0.000
	S1-S3	0.50101	0.000
Scale 17	Wake-S1	-0.1458	1
	Wake-S3	0.41910	0.000
	S1-S3	0.43368	0.000
Scale 18	Wake-S1	-0.01665	1
	Wake-S3	0.37402	0.000
	S1-S3	0.39066	0.000
Scale 20	Wake-S1	-0.3226	1
	Wake-S3	0.28286	0.000
	S1-S3	0.31512	0.000

All stages follow normal distribution, one-way ANOVA is performed.

V. DISCUSSION

Some researchers have found what we would call cross-over phenomenon, i.e., the MSE curve of wakefulness is higher than that of sleep at small scale factors, and lower at large scale factors, presenting curve interception [7], [8], [12], [13], [20]. Most of the authors did not discuss the cross-over phenomenon. Consistent with previous studies, we confirmed the cross-over phenomenon in most cases after conducting the MSE analysis for real-world wakefulness/sleep EEG. Fig. 3 shows 4 examples.

TABLE 4. Mann-Whitney test for 3 stages in scale 13, scale 14, scale 16 and scale 19.

Scale factors	Comparison of stages	Statistical test choose	Mean/Medium difference	p Value (two-sided)
Scale 13[a]	Wake-S1	Mann-Whitney test	0.0195	0.545
	Wake-S3	Independent sample t-test	0.6365	0.000
	S1-S3	Mann-Whitney test	0.6032	0.000
Scale 14[a]	Wake-S1	Mann-Whitney test	-0.0282	0.545
	Wake-S3	Independent sample t-test	0.5716	0.000
	S1-S3	Mann-Whitney test	0.5759	0.000
Scale 16[a]	Wake-S1	Mann-Whitney test	-0.0581	0.45
	Wake-S3	Independent sample t-test	0.439	0.000
	S1-S3	Mann-Whitney test	0.4549	0.000
Scale 19[a]	Wake-S1	Mann-Whitney test	-0.0284	0.65
	Wake-S3	Independent sample t-test	0.3502	0.000
	S1-S3	Mann-Whitney test	0.3593	0.000

[a] denotes that the 3 stages do not all follow normal distribution at the scale factor. So the Mann-Whitney test is used to examine the differences for the 3 stages.

Although some researchers attribute the cross-over phenomenon to physiological mechanism [8], the mechanism underlying this phenomenon remains unrevealed.

To investigate the mechanism of the cross-over phenomenon, we conducted a simulation study. Real EEG signals contain both the narrow band rhythmic component and the broadband 1/f-like component. Therefore, we used the mixed signal of rhythmic and broadband components to simulate the EEG. In conventional MSE analysis, the single broadband 1/f signal was assigned high MSE values and remained steady; MSE values of the single sinusoidal component (10Hz or 2Hz) were close to 0 (Fig. 4a). Therefore, the mixed signal of 1/f component and a sinusoidal component with different frequency should in theory remain the same complexity. However, when broadband 1/f signal adds to the fixed frequency signal, the cross-over phenomenon appears in the MSE curves of mixed signal - the MSE curve of mixed signal with 10Hz is higher than that of mixed signal with 2Hz at small scale factors, and lower at large scale factors (Fig. 4b). The result indicated that the cross-over phenomenon in MSE might be artificially caused by rhythmic activities with different frequencies.

To systematically study the effect of the frequency on the cross-over artifact in MSE, we further simulated a chirp signal with continuous changing frequency from 30 Hz to 1 Hz, mixed with 1/f component. According to complexity theory [1], [11], sinusoidal time series (despite its frequency) should present near-zero complexity. However, it's obvious that as frequency decreases, MSE values span wider (Fig. 5c), resulting in ubiquitous cross-over artifact (Fig. 5d). The result suggests that the cross-over phenomenon in MSE can be caused by a non-physiological mechanism: it can be artificially caused by the algorithm for its imperfection in dealing with rhythmic component.

We have also found that the increasing sampling frequency (from 100 Hz to 600 Hz) is related to the position of cross-over point, which moves towards larger scale factors (Fig. 6). In Shi *et al.*'s research [8], the cross-over phenomenon occurs at large scales (0.25 s-2 s) beyond regular scale factor range (1-20). Our finding is in accordance with their study for they have used a high sampling rate (512 Hz).

Heart rate and heart rate variation are the common indicators of electrocardiogram. Heart rate focuses on the number of heartbeat per minute [21]. Heart rate variation refers to the beat-to-beat alterations in heart rate, and reflects the variation in autonomic nervous system, such as blood glucose, blood pressure, sweat, digestion, etc. [22], [23]. Similarly, EEG signals contain rhythmic and non-rhythmic components, and the instantaneous frequency of rhythmic component may have rich dynamic characteristics. Therefore we proposed a so-called MSE-IFV method, in which, we retrieved rhythmic component from EEG and computed the instantaneous frequency of the rhythmic component, and conducted MSE analysis of IFV.

We conducted MSE-IFV of the real-world sleep EEG to resolve the cross-over artifact. We extracted the characteristic frequency of the Wake stage (8-13Hz) and the S3 stage (0.5-3Hz) for MSE analysis of IFV. The result showed that the cross-over phenomenon disappeared (Fig. 7), and the curves for the two stages separated completely from subject SC4081E0, SC4011E0, SC4121E0 and SC4051E0 (Mann-Whitney test, $p < 0.001$, $p = 0.001$, $p = 0.001$, $p = 0.001$). We randomly chose the 3 stages (Wake, S1and S3) of 10 subjects (aged 25-101) for MSE-IFV analysis (Table 2). Fig. 8 shows that the relationship of the mean or medium for the 3 stages (Wake, S1 and S3) is: Wake $>$ S1 $>$ S3 (one-way ANOVA, $p < 0.05$) from scale 1 to scale 10, but from the scale 11 to scale 20, only the mean or medium of the Wake stage is higher than that of the S3 stage (Mann-Whitney test/Independent sample t-test, $p < 0.05$). Compared with previous studies [8, 12], the MSE-IFV can effectively separate the 3 stages at most scales, therefore avoid the cross-over artifact. The result suggests that the new idea may be a potential solution to the cross-over artifact found in the MSE analysis of wakefulness/sleep studies.

The theory of complexity loss in aging and disease postulates that the healthy systems reveal a high complexity, which breaks down with aging and disease, due to the reduced adapting capacity of organisms to the stresses of everyday

life [24]. We argue that, in case of sleep, organisms shut down or reduce some activities, which should lead to a similar complexity loss in sleep than that in wakefulness. The complexity loss should present a lower MSE curve for sleep than wakefulness. However, we have shown in this paper that due to the imperfection of MSE algorithm, the cross-over phenomenon occurs. There are two ways to deal with it. First, one can improve the MSE algorithm that has robust performance without vulnerability to the strong rhythmic component. Second, one can also conduct the MSE on rhythmic variation itself, which has been shown complex in nature.

VI. CONCLUSION

In this paper, we have revealed by simulation that cross-over artifact in wakefulness/sleep studies is caused by imperfection in MSE algorithm in dealing with a mixed signal of prominent rhythmic component and 1/f-type broadband component. We have proposed a new analysis strategy, MSE-IFV, namely MSE analysis for instantaneous frequency variation in the original EEG, to work around the algorithm's imperfection. MSE-IFV successfully separates the wakefulness/sleep stages in accordance with the complexity loss theory and may provide an alternative tactic in MSE analysis of a broad range of physiological time series with dominant rhythmic component.

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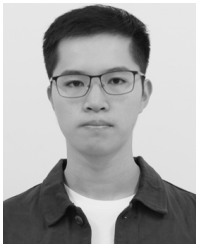

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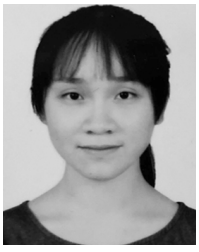

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