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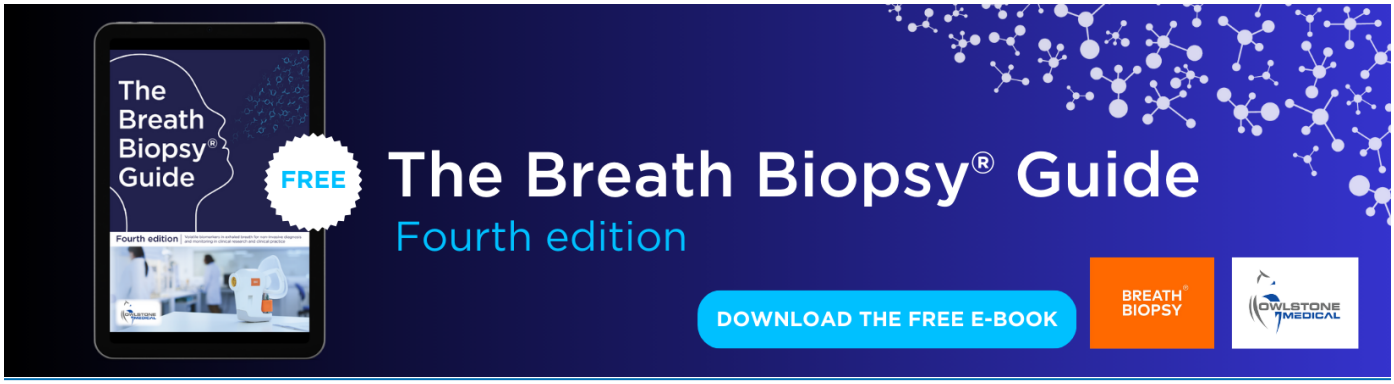

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Multiscale permutation entropy analysis of EEG recordings during sevoflurane anesthesia

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Abstract

Electroencephalogram (EEG) monitoring of the effect of anesthetic drugs on the central nervous system has long been used in anesthesia research. Several methods based on nonlinear dynamics, such as permutation entropy (PE), have been proposed to analyze EEG series during anesthesia. However, these measures are still single-scale based and may not completely describe the dynamical characteristics of complex EEG series. In this paper, a novel measure combining multiscale PE information, called CMSPE (composite multi-scale permutation entropy), was proposed for quantifying the anesthetic drug effect on EEG recordings during sevoflurane anesthesia. Three sets of simulated EEG series during awake, light and deep anesthesia were used to select the parameters for the multiscale PE analysis: embedding dimension m, lag τ and scales to be integrated into the CMSPE index. Then, the CMSPE index and raw single-scale PE index were applied to EEG recordings from 18 patients who received sevoflurane anesthesia. Pharmacokinetic/pharmacodynamic (PKPD) modeling was used to relate the measured EEG indices and the anesthetic drug concentration. Prediction probability (P_k) statistics and correlation analysis with the response entropy (RE) index, derived from the spectral entropy (M-entropy module; GE Healthcare, Helsinki, Finland), were investigated to evaluate the effectiveness of the new proposed measure. It was found that raw single-scale PE was blind to subtle transitions between light and deep anesthesia, while the CMSPE index tracked these changes accurately. Around the time of loss of consciousness, CMSPE responded significantly more rapidly than the raw PE, with the absolute slopes of linearly fitted response versus time plots of 0.12 (0.09–0.15) and 0.10 (0.06–0.13), respectively. The prediction probability P_k of 0.86 (0.85–0.88) and 0.85 (0.80–0.86) for CMSPE and raw PE indicated that the CMSPE index correlated well with the underlying anesthetic effect. The correlation coefficient for the comparison between the CMSPE index and RE index of 0.84 (0.80–0.88) was significantly higher than the raw PE index of 0.75 (0.66–0.84). The results show that the CMSPE outperforms the raw single-scale PE in reflecting the sevoflurane drug effect on the central nervous system.

(Some figures in this article are in colour only in the electronic version)

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1. Introduction

The central nervous system is the most important target for anesthetic drugs. Accordingly, measurement instruments that reflect the behavior of the brain, such as EEG (electroencephalogram), can be used to assess anesthetic effects. Due to its relatively inexpensive and easy operation, the EEG has received considerable attention in the field of anesthesia research. Analysis of the raw EEG signal can be used to extract a continuous non-invasive index of the anesthetic drug effect (Jameson and Sloan 2006, Bruhn *et al* 2006, Rampil 1998). In recent years, a number of EEG-based monitors of depth of anesthesia (DOA) have been developed (Bruhn *et al* 2006). For example, the bispectral index (BIS; Aspect Medical Systems, Newton, MA) and spectral entropy (M-entropy module; GE Healthcare, Helsinki, Finland) monitors have been used in commercial monitoring systems. The bispectral analysis is based on the power spectrum and phase spectrum, and quantifies the phase coupling between different EEG frequencies (Rampil 1998); the spectral entropy is based on the Shannon entropy of the time–frequency balanced power spectrum, from which two entropy indicators are derived: state entropy (SE) is calculated across the frequency band 0.8–32 Hz and is said to reflect the cortical state of the patient, and response entropy (RE) is calculated in the frequency range from 0.8 to 47 Hz and includes electromyogram (EMG)-dominated frequencies (Viertio-Oja *et al* 2004). However, these methods are based on Fourier transformation—which is more suitable for the analysis of linear and stationary signals.

Population neural activity has been shown to exhibit nonlinear or chaotic behaviors (Elbert *et al* 1994, Vakorin *et al* 2009). As a result, methods based on nonlinear dynamics and information theory have been proposed to analyze brain signals (e.g. Fell *et al* (1996), Richman and Moorman (2000), Bruhn *et al* (2000, 2001), de Araujo *et al* (2003), Viertio-Oja *et al* (2004), Cao *et al* (2004), Li *et al* (2007a), Mantini *et al* (2008)). In particular, approximate entropy (AE; Bruhn *et al* 2000) and permutation entropy (PE; Bandt and Pompe 2002, Cao *et al* 2004) can be used to quantify the regularity of EEG series, providing an index of the anesthetic drug effect during anesthesia (Bruhn *et al* 2000, Koskinen *et al* 2006, Jordan *et al* 2006, 2007). PE is conceptually simple, computationally efficient and artifact resistant (Olofsen *et al* 2008, Li *et al* 2008a), while the calculation of AE requires long, stationary and noiseless EEG data. Therefore, PE is more suitable than AE for application to EEG monitoring systems in practice (Li *et al* 2008a).

Recently, a new method, called multiscale entropy (MSE), has been proposed by Costa *et al* (2002, 2005) to measure the complexity of a time series. The basic idea of MSE analysis is to account for the correlations of a time series over multiple temporal scales instead of a single scale. This computational tool has been effectively used to investigate the complexity of EEG series (e.g., Escudero *et al* (2006), Park *et al* (2007), Ouyang *et al* (2009)). Brain function is regulated by complex self-regulating systems that process inputs from interacting mechanisms that operate across multiple spatial and temporal scales. The EEG is an integrated manifestation of this brain electrical activity and exhibits complex fluctuations that contain information about the underlying dynamics (Buzsáki 2006, Ouyang *et al* 2009, Fastenrath *et al* 2009). Therefore, MSE may be advantageous for exploring the dynamical characteristics inherent in brain electrical activities on multiple scales.

In this study, MSE was applied to anesthetic EEG recordings, and PE values were combined at multiple scales to develop a new index of CMSPE (composite multiscale permutation entropy) for quantifying the anesthetic drug effect on the brain. The parameter selection in the multiscale PE analysis was accomplished by artificially generating EEG series representing different anesthetic levels. Pharmacokinetic/pharmacodynamic (PKPD) modeling and prediction probability were used to evaluate the effectiveness of the CMSPE index in comparison with the raw single-scale PE index. Furthermore, correlation analysis with the RE index derived from the spectral entropy was carried out to further validate its usability.

2. Materials and methods

2.1. Subjects and EEG recordings

In this study, we tested the algorithms using EEG data from a previously published study (McKay *et al* 2006). Eighteen patients aged 18–63 years were investigated, with ASA (American Society of Anesthesiologists) physical status I or II and scheduled for elective gynecological, general or orthopaedic surgery. All subjects fasted for at least 6 h before anesthesia and received no premedication. Waikato Hospital ethical committee approval was obtained, along with written informed consent from all subjects.

A composite electrode composed of a self-adhering flexible band holding three electrodes was used to record the EEG between the forehead and temple. The sampling rate for EEG data collection was 100 Hz. The spectral entropy was measured with a plug-in M-entropy module (GE Healthcare, Helsinki, Finland). RE and SE were sampled at 0.2 s^{-1}. At the same time, the sevoflurane concentrations were measured at the mouth and sampled at 100 s^{-1}. The data were recorded on a laptop computer and stored for later off-line analysis using the MATLAB (version 7; MathWorks Inc.) computational and data analysis software.

All of the patients were connected to a closed anesthesia breathing circuit via a face mask, and fresh gas flow was set at 4 L min^{-1}. The patients were pre-oxygenated to the satisfaction of the anesthetist in charge. Then, sevoflurane was delivered by vaporizer at 3% for 2 min, followed immediately by 7%. The time at which spectral entropy fell to 20 or less was noted and 7% sevoflurane continued for a further 2 min. The sevoflurane was then turned off until the spectral entropy returned to a value of 70 (lightening). All data in the present study are based on this single deepening and lightening anesthetic protocol. No attempt was made to rouse the subjects and no supplemental medications were administered.

2.2. EEG preprocessing

The artifacts in raw EEG recordings, such as EOG (electrooculogram), EMG (electromyogram), etc, can obscure the underlying processes of anesthesia and make the subsequent analysis of the anesthetic drug effect difficult, especially during the awake state. To reduce these artifacts, a combined filter was used in this study (Li *et al* 2008b). First, outlier points are rejected based on the statistical properties (mean and standard deviation) of the EEG signals. Then, a notch filter is used to remove the power signal of 50 Hz. The stationary wavelet transform is used to set an appropriate threshold for removal of the EOG artifact (Krishnaveni *et al* 2006), and the empirical Bayes method for level-dependent threshold selection is used to remove white noise at all frequency bands (Johnstone and Silverman 2005). Meanwhile, wavelet coefficients in the frequency range of 0–0.5 Hz are reduced to 0 to remove the effect of the baseline drift. Finally, Kalman filtering is used to estimate adaptive autoregressive parameters and inverse filtering is used to detect and then remove EMG and other transient high-amplitude artifacts (Schlögl 2000).

2.3. Multiscale permutation entropy

Multiscale entropy was described in Costa *et al* (2002) and (2005). Given a one-dimensional discrete time series $\{x_1, x_2, \ldots, x_N\}$, first a 'coarse-graining' process is applied, constructing a consecutive coarse-grained time series, $\{y^{(s)}\}$, by averaging the data points in non-overlapping windows of length s. Each element, $y_j^{(s)}$, of the coarse-grained time series, is calculated according to the equation

$$y_j^{(s)} = \frac{1}{s} \sum_{i=(j-1)s+1}^{js} x_i, \tag{1}$$

where s represents the scale factor and $1 \leqslant j \leqslant N/s$. The length of each coarse-grained time series is equal to the length of the original time series N divided by s. For scale $s = 1$, the time series $\{y^{(1)}\}$ is simply the original time series. Next an entropy measure was calculated for each coarse-grained time series, and then plotted as a function of the scale factor s. The sample entropy measure, a refinement of AE, was used in Costa *et al* (2002, 2005). As PE is more appropriate for estimating the anesthetic drug effect than AE as previously indicated in Li *et al* (2008a), in our analysis, PE is incorporated into the MSE analysis and defined as multiscale PE.

Permutation entropy was originally proposed by Bandt and Pompe (Bandt and Pompe 2002, Bandt 2005) and has been successfully used to analyze neural signals, for instance, epileptic (Cao *et al* 2004, Li *et al* 2007b) and anesthetic EEG series (Jordan *et al* 2006, 2007, Olofsen *et al* 2008, Li *et al* 2008a). It explores the local order structure of a dynamical time series, giving a quantitative complexity measure. This method transforms a given time series into a series of ordinal patterns, each describing the order relations between the present and a fixed number of equidistant past values at a given time. Given a scalar time series $\{y_1, y_2, \ldots, y_i, \ldots, y_M\}$, an embedding procedure forms vectors $Y_t = [y_t, y_{t+\tau}, \ldots, y_{t+m\tau}]$ with the embedding dimension m and lag τ. Then, Y_t can be arranged in an increasing order. For m different numbers, there will be $m!$ possible order patterns π. For a permutation with number π, let $f(\pi)$ denote its frequency in the time series. Then, the relative frequency is $p_i(\pi) = f(\pi)/(M - (m-1)\tau)$. The permutation entropy is defined as follows:

$$H_p(m) = -\sum_{i=1}^{N-(m-1)\tau} p_i(\pi) \ln p_i(\pi). \tag{2}$$

The corresponding normalized entropy can be defined as

$$PE = H_p(m)/\ln(m!). \tag{3}$$

The PE value will be 1 when all permutations have equal probability. Conversely, PE will be small if the time series is regular. Thus, the more regular the time series, the smaller the PE value.

The calculation of PE depends on the selection of the data length M, embedding the dimension m and lag τ. Obviously, M should not be so small as to make the statistics inconclusive. However, too large an M value is not suitable for real-time application (Cao *et al* 2004). When m is too small the scheme will not work, as there are too few distinct states. On the other hand, too large an m is also inappropriate for detecting the dynamical changes in the EEG recording. Bandt and Pompe (2002) recommend $m = 3, 4, \ldots, 7$. For the lag τ, $\tau = 1$ was chosen in Bandt and Pompe (2002), while Cao *et al* (2004) tested different τ values and concluded that to some extent, the appropriate choices for both m and τ are related to the signal analyzed and its sampling frequency. In the context of the anesthetic EEG, the selection of these parameters will be discussed using simulated EEG data.

Although multiscale PE analysis can account for the relative complexity of time series over multiple scales, we need to derive a single index from the multiscale analysis to quantify the anesthetic drug effect. Through simulated EEG of different anesthetic levels, the scales that can effectively differentiate these different states can be determined, and then integrated into a composite measure (CMSPE) to estimate the effect of anesthetic drugs.

To demonstrate the superiority of multiscale PE analysis, the newly developed CMSPE index will be compared with the raw single-scale PE index, incorporating the same parameter settings (m, τ). Moreover, the performance of the new index will be compared with two previously suggested PE measures. The first one is denoted as PE(6,1), a PE index with $m = 6$, $\tau = 1$, chosen in terms of optimal statistical performance (prediction probability P_k) (Li *et al* 2008a). The second is a composite PE index (CPEI) that sums PE for $m = 3$, $\tau = 1$ and for $m = 3$, $\tau = 2$ (Olofsen *et al* 2008). The comparative results of these EEG measures on real EEG recordings during anesthesia will be given in section 3.

2.4. Pharmacokinetic/pharmacodynamic modeling

Pharmacokinetic/pharmacodynamic (PKPD) modeling, as described by McKay *et al* (2006), was performed to derive the relationship between anesthetic drug concentration

and measured EEG index (e.g. CMSPE). PKPD modeling considers two successive physiological processes to describe the relationship between drug dose and its effect. The pharmacokinetic side of the model describes how the blood concentration of the drug varies with time. The pharmacodynamic side describes the relationship between the concentration of drug at its effect site and its measured effect. Briefly, an effect site was introduced by a first-order effect-site model:

$$dC_{\text{eff}}/dt = k_{\text{eo}}(C_{\text{et}} - C_{\text{eff}}), \tag{4}$$

where C_{eff} is the effect-site concentration, C_{et} is the end-tidal concentration and k_{eo} is the first-order rate constant for efflux from the effect compartment. The relation between the estimated C_{eff} and the measured EEG index was modeled with a nonlinear inhibitory sigmoid $E_{\max}$ model:

$$\text{Effect} = E_{\max} - (E_{\max} - E_{\min}) \times \frac{C_{\text{eff}}^{\gamma}}{EC_{50}^{\gamma} + C_{\text{eff}}^{\gamma}}, \tag{5}$$

where Effect is the processed EEG measure, $E_{\max}$ and $E_{\min}$ are the maximum and minimum Effect for each individual patient, EC_{50} is the sevoflurane concentration at which Effect is midway between this maximum and minimum and γ is the slope of the concentration–response relationship. The C_{eff} was estimated by iteratively running the above model with a series of k_{eo} steps. The optimal k_{eo} was determined yielding the greatest coefficient of determination (R^2) for the measured and modeled EEG Effect for each patient. The coefficient of determination R^2 is calculated by

$$R^2 = 1 - \frac{\sum_{i=1}^{n}(y_i - \hat{y}_i)^2}{\sum_{i=1}^{n}(y_i - \bar{y})^2}, \tag{6}$$

where y_i and $\hat{y}_i$ are the measured and corresponding modeled *Effect* for a given time, respectively, and $\bar{y}$ is the average of the measurements over time. Values of the pharmacodynamic parameters γ and EC_{50} can be derived from the fitted inhibitory $E_{\max}$ curve.

2.5. Statistical analysis

To evaluate the correlation between the measured EEG index (CMSPE) and underlying anesthetic drug effect (sevoflurane effect-site concentration C_{eff}), the prediction probability (P_k) statistics was applied, as described in Smith *et al* (1996), Vanluchene *et al* (2004), Koskinen *et al* (2006) and Ellerkmann *et al* (2004). As a nonparametric, scale-independent measure, P_k, can be computed for any degree of coarseness and can fully use the available data without imposing additional arbitrary constraints. Given two randomly selected data points with distinct C_{eff}, P_k describes the probability that the EEG index correctly predicts which of the data point is the one with the higher (or lower) C_{eff}. The prediction probability P_k is defined as

$$P_k = \frac{P_c + P_{\text{tx}}/2}{P_c + P_d + P_{\text{tx}}}, \tag{7}$$

where P_c, P_d and P_{tx} are the respective probabilities that two data points—drawn at random, independently and with replacement from the population—are a concordance, a discordance or an x-only tie. A P_k value of 1 means that the EEG index is perfectly concordant with the underlying anesthetic depth C_{eff}; a P_k value of 0.5 means that the EEG index is not superior to that obtained by chance. Considering the negative monotonic relation between the sevoflurane concentration and the measured EEG index, the resultant P_k value is replaced by $1 - P_k$.

To further assess its performance, the CMSPE index was correlated with the RE index in the M-entropy module. In this paper, the performance of the CMSPE index and raw single-scale PE index was compared pairwise using the Student t-test or Wilcoxon test where appropriate. The Kolmogorov–Smirnov test was used to determine whether data sets were normally distributed. All tests were two tailed with a specified statistical significance level p, and data are presented as mean (95% confidence interval), if not specifically stated.

3. Simulations and results

In this section we first artificially generated EEG series corresponding to different anesthetic levels. These artificial EEG signals were used to determine the optimum parameters for the computation of PE and appropriate scales for integration into the CMSPE index. Then, the CMSPE index was applied to real EEG recordings during sevoflurane anesthesia. PKPD modeling and the prediction probability statistics were used to evaluate the effectiveness of the CMSPE index over the raw single-scale PE. In addition, correlation analysis with the RE index in the M-entropy module was conducted to further validate the performance of the proposed index.

3.1. Simulations of EEG series of different anesthetic levels

For most commonly used general anesthetic drugs, such as sevoflurane and propofol, a significant and common effect is the enhancement of γ-amino-butyric acid (GABA) activity (Olofsen *et al* 2008, Antkowiak 1999). As described by Olofsen *et al* (2008), there are four main components of anesthetic-induced EEG changes. First, EEG loses power in the high-frequency range. Secondly, large waxing and waning 'spindle-like' waves appear, whose frequency is often related to the anesthetic drug concentration. Thirdly, large amplitude delta and sub-delta waves may be seen. Finally, deep anesthesia gives rise to the burst suppression pattern (Jameson and Sloan 2006). Figure 1(A) shows an EEG recording during sevoflurane induction. The concurrent end-tidal sevoflurane concentration is given in figure 1(D). The frequency content changes of the EEG signal are demonstrated in the spectrogram, as shown in figure 1(B). As the sevoflurane concentration increases, and then decreases, the EEG spectrogram presents obviously different frequency contents.

Three 10 s EEG epochs are extracted, labeled as I (awake EEG), II (light anesthetic EEG, with mixed spindle-like activity and slower delta waves), III (deep anesthetic EEG, with pure high-amplitude delta waves), respectively. The enlarged EEG waveforms and corresponding power spectra

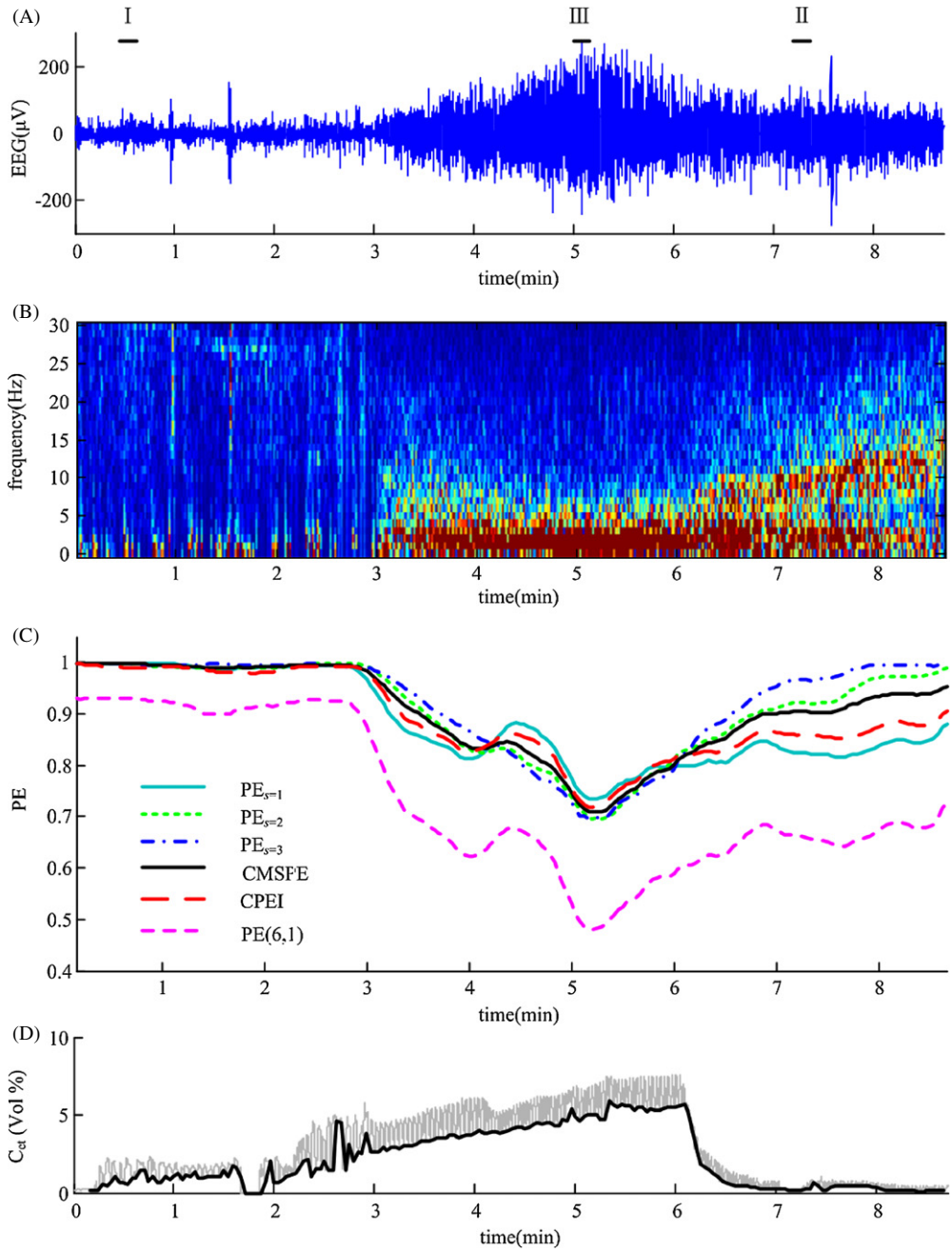

Figure 1. An EEG recording from a patient and corresponding EEG measures versus time. (A) A preprocessed EEG recording. The sample frequency is 100 Hz. Three example EEG epochs represent the awake state (I), the light anesthetic state with mixed spindle-like activities and slower delta waves (II), and the deep anesthetic state with pure high-amplitude delta waves (III). (B) The spectrogram computed by short-time Fourier transform using a Hamming window with a length of 1 s and 50% overlapping. (C) Time course of PE measures with an embedding dimension $m = 3$, lag $\tau = 1$ at scale $s = 1, 2, 3$ (PE$_{s=1,2,3}$) and the CMSPE (combined multiscale PE) index, as well as the PE index with $m = 6$, $\tau = 1$(PE(6,1)) (Li *et al* 2008a) and CPEI (Olofsen *et al* 2008); the interval is of 10 s and the overlapping size is 7.5 s. (D) End-tidal sevoflurane concentration (C_{et}) during the same time course.

are shown in figure 2(A). The spectral estimation is conducted using the Burg method with auto-regression (AR) and order optimally selected by Schwarz's Bayesian criterion (SBC; Schwarz 1978) by running the ARfit algorithm (Schneider and Neumaier 2001). On average, SBC chose the correct model order most often and led to the smallest mean-squared prediction error of the fitted AR models (Lütkepohl 1985). In the following, we use the AR parameters obtained from the three *real* EEG epochs to artificially generate *simulated* series; then, these simulated series are used to select parameters for computation of the CMSPE index—which are finally tested on other real EEG recordings.

Higher order AR models can be used to model the real EEG signals to provide a 'test-bed' to compare the performance of different EEG measures (Sleigh *et al* 2001, Wright *et al* 1990). Simulated EEG series corresponding to the awake, light and deep anesthetic states are generated by filtering Gaussian noise with the filters specified by the fitted

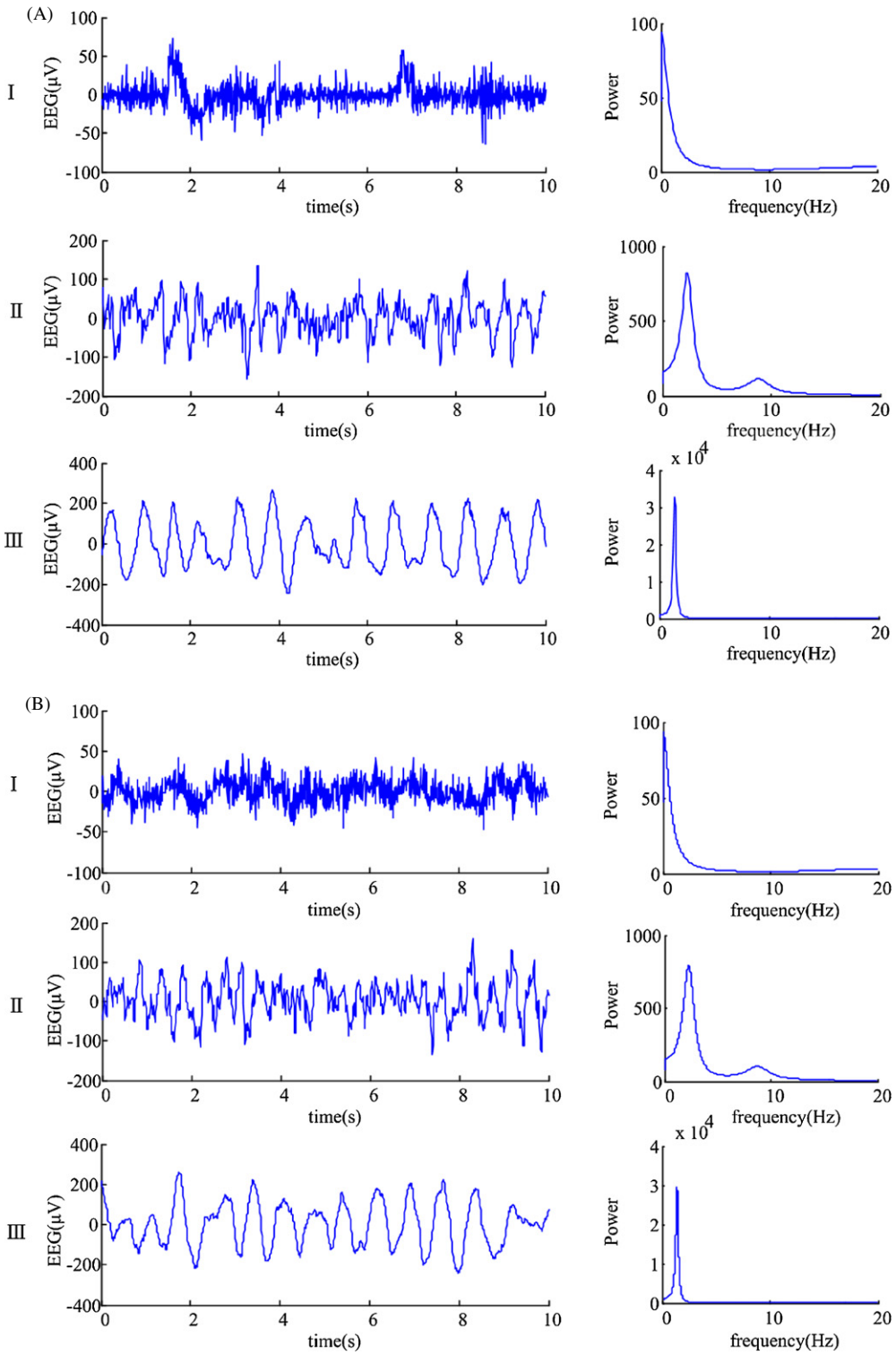

Figure 2. Example EEG series and the artificially simulated series. (A) The three example EEG epochs labeled as anesthetic states I, II, III in figure 1, and their power spectra estimated by the Burg method. (B) Three simulated EEG series corresponding to the awake (I), light (II) and deep (III) anesthetic states, generated by AR models determined by the real EEG series in (A). The waveforms and the spectra are similar with those of real EEG signals in (A).

AR model parameters above. At each state, 20 simulated series with the length of 2×10^4 data points were generated, with the first 2×10^3 points skipped due to their transients. Figure 2(B) shows three modeled EEG series simulating different anesthetic levels, and their power spectra. The waveforms and spectra are similar to the real EEG signals in figure 2(A).

Now using the simulated EEG series, we examine how PE values with different embedding dimension m, lag τ and data length M can differentiate the three different states. It

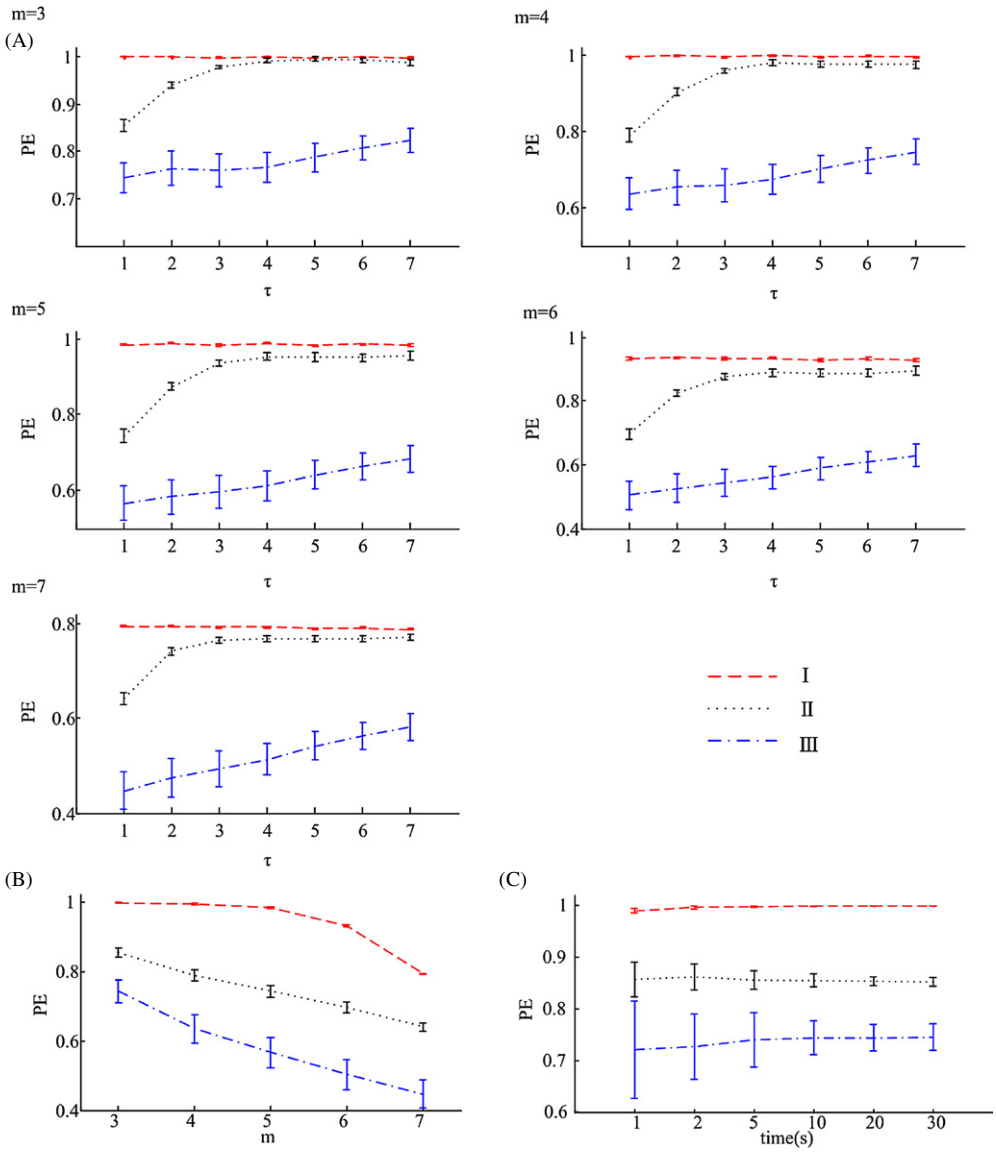

Figure 3. Parameter selection of PE to differentiate among the awake (I), light (II) and deep (III) anesthetic states. (A) PE values with different lags $\tau(\tau = 1\text{–}7)$ in the cases of $m = 3\text{–}7$, respectively. (B) PE values of $\tau = 1$ with different embedding dimensions $m = 3\text{–}7$. (C) PE values with different data lengths M (in the form of seconds). Entropy values are given in mean ± SD (20 realizations for each anesthetic state).

is expected that the entropy value in the awake state will be maximum, lower during the light anesthetic level and minimum in the deep anesthetic state. Figure 3(A) shows the PE value changes with different lag τ of $m = 3\text{–}7$. In all cases of m, it is obvious that at larger τ ($\tau > 2$), the awake and the light anesthetic level can not be differentiated well, compared with the cases at smaller τ; clearly, when $\tau = 1$, the three levels can always be distinguished. Further, at $\tau = 1$, the changes in PE values with different embedding dimension m are shown in figure 3(B). As m increases, the PE values at all three levels decrease. The ability to discriminate the three anesthetic states for PE values with different m is almost equivalent and PE values with $m = 3$ give a satisfactory result. The effect of data length M on PE is illustrated in figure 3(C). Using shorter data segments results in larger variations in PE values, and when $M > 500$ (5 s), consistent results (with relatively smaller variations) can be obtained. Therefore, for the sake of simplification and convenience, we set $m = 3$, $\tau = 1$ and $M = 1000$ to compute the PE index in the following analyses.

Further, we investigated the selection of scales for incorporation into the CMSPE index. The multiscale PE analysis is applied to the simulated EEG series with the length of 10^4 points. The PE values as a function of scale factor s are illustrated in figure 4. As s increases, the PE values at different anesthetic levels show different changes. At $s = 2, 3$, the three anesthetic levels are most widely separated; however, when $s \geqslant 4$, the PE value of the EEG in the awake state begins to decrease and may overlap with that in the light anesthetic state. Therefore, the PE values at scales $s = 2, 3$ are incorporated into scale $s = 1$ (raw single-scale PE) to derive the CMSPE index for estimating the effect of anesthetic drug. We define

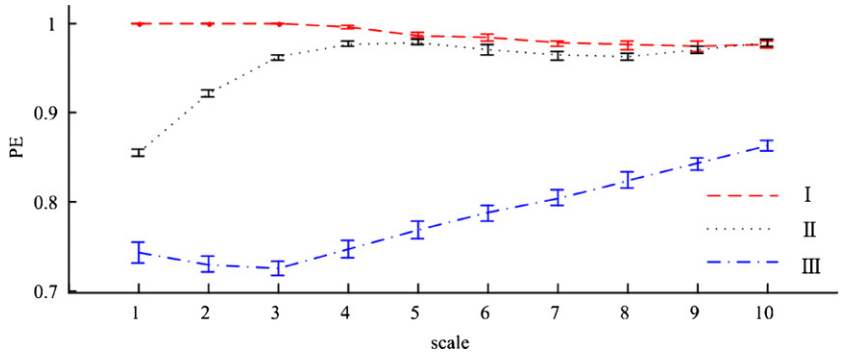

Figure 4. Multiscale PE analysis of simulated EEG series of awake (I), light (II) and deep (III) anesthetic levels. PE ($m = 3$, $\tau = 1$, $M = 10^4$) is calculated for scales $s = 1$–10. The PE index at scale $s = 1$ is just the raw single-scale PE index. The PE values at scales $s = 2$, 3 are incorporated into it to construct a unitary CMSPE index.

Table 1. Parameters of PKPD models.

Parameters	$t_{1/2}k_{eo}$(min)	γ	E_{max}	E_{min}	EC_{50}	R^2
$PE_{s=1}$	2.19 ± 1.52	6.74 ± 2.15	0.99 ± 0.01	0.82 ± 0.03	1.22 ± 0.31	0.94 ± 0.04
$PE_{s=2}$	1.40 ± 0.45	5.45 ± 3.61	0.99 ± 0.01	0.86 ± 0.03	1.60 ± 0.35	0.89 ± 0.08
$PE_{s=3}$	0.82 ± 0.29	9.35 ± 4.33	0.99 ± 0.01	0.87 ± 0.06	2.15 ± 0.54	0.83 ± 0.14
CMSPE	1.89 ± 0.66	4.27 ± 2.50	0.99 ± 0.01	0.85 ± 0.04	1.62 ± 0.57	0.90 ± 0.07
PE(6,1)	2.30 ± 1.39	6.31 ± 3.24	0.93 ± 0.01	0.62 ± 0.03	1.27 ± 0.32	0.96 ± 0.02
CPEI	1.80 ± 0.83	6.22 ± 2.96	0.99 ± 0.01	0.84 ± 0.03	1.45 ± 0.30	0.91 ± 0.07
M-entropy RE	1.88 ± 0.57	6.57 ± 5.85	0.83 ± 0.07	0.47 ± 0.15	1.90 ± 0.84	0.85 ± 0.08

$t_{1/2}k_{eo}$ = blood effect-site equilibration constant;
γ = slope parameter of the concentration–response relation;
E_{max} = EEG parameter value corresponding to the maximum drug effect;
E_{min} = EEG parameter value corresponding to the minimum drug effect;
EC_{50} = concentration that causes 50% of the maximum effect;
R^2 = maximum coefficients of determination;
PE = permutation entropy;
$PE_{s=1,2,3}$ = PE with at scale $s = 1,2,3$;
CMSPE = combined multiscale PE;
PE(6,1) = PE with embedding dimension $m = 6$, lag $\tau = 1$, adopted in Li *et al* (2008a);
CPEI = a composite PE index summing up PE with $m = 3$, $\tau = 1$ and that with $m = 3$, $\tau = 2$ (Olofsen *et al* 2008);
M-entropy RE = response entropy in the M-entropy module.

the CMSPE index as the averaged PE values at scale $s = 1$, 2, 3. This new measure accounts for the complexity property of EEG signals at multiple scales, giving a more complete description of the underlying anesthetic effect.

3.2. Application to real EEG signals

In this section, the CMSPE index is applied to real EEG signals after pre-processing. An EEG recording from one patient, its spectrogram, the EEG measures and concurrent end-tidal sevoflurane concentration versus time are shown in figure 1. The CMSPE and $PE_{s=1,2,3}$ (PE at scale $s = 1$, 2, 3) can be seen in figure 1(C). The $PE_{s=1}$ is the raw single-scale PE. To consistently track the transient changes in the EEG recording, these measures are computed over a window of 10 s with an overlap of 7.5 s. As can be seen from these plots, CMSPE and $PE_{s=1,2,3}$ all track the gross changes in EEG with increasing anesthetic drug effect. However, as the drug concentration increases over 4–5 min, the EEG loses power in high frequencies and theta waves increase, as shown in the spectrogram in figure 1(B); the raw PE ($PE_{s=1}$) shows an anomalous upward trend, while this increase is minimized in $PE_{s=2}$ and $PE_{s=3}$. Thus, little abnormality remains in the resulting CMSPE index. Also, at around 7–8 min, the sevoflurane concentration decreases, resulting in an increase in the high frequency content of the spindle-like activity; $PE_{s=1}$ shows no increase, but the CMSPE responds well. For comparison, two other PE measures, PE(6,1) and CPEI, versus time are also shown in figure 1(C). The former shows a similar tendency to $PE_{s=1}$, while the latter falls between $PE_{s=1}$ and $PE_{s=2}$.

A further example is shown in figure 5 from another patient. This example shows a more complex time series, with transitions from awake to deep anesthesia, a lightening phase, followed by a return to deep anesthesia. These changes are clearly shown in the spectrogram in figure 5(B). The CMSPE accurately tracks these changes. However, the deep–light anesthetic state transition in the period from 4 to 8 min did not produce a notable increase in $PE_{s=1}$, and erroneously increased during the subsequent return to deep anesthetic state.

Figure 6 shows the change in the raw single-scale PE (figure 6(A)) and CMSPE (figure 6(B)) around the time of

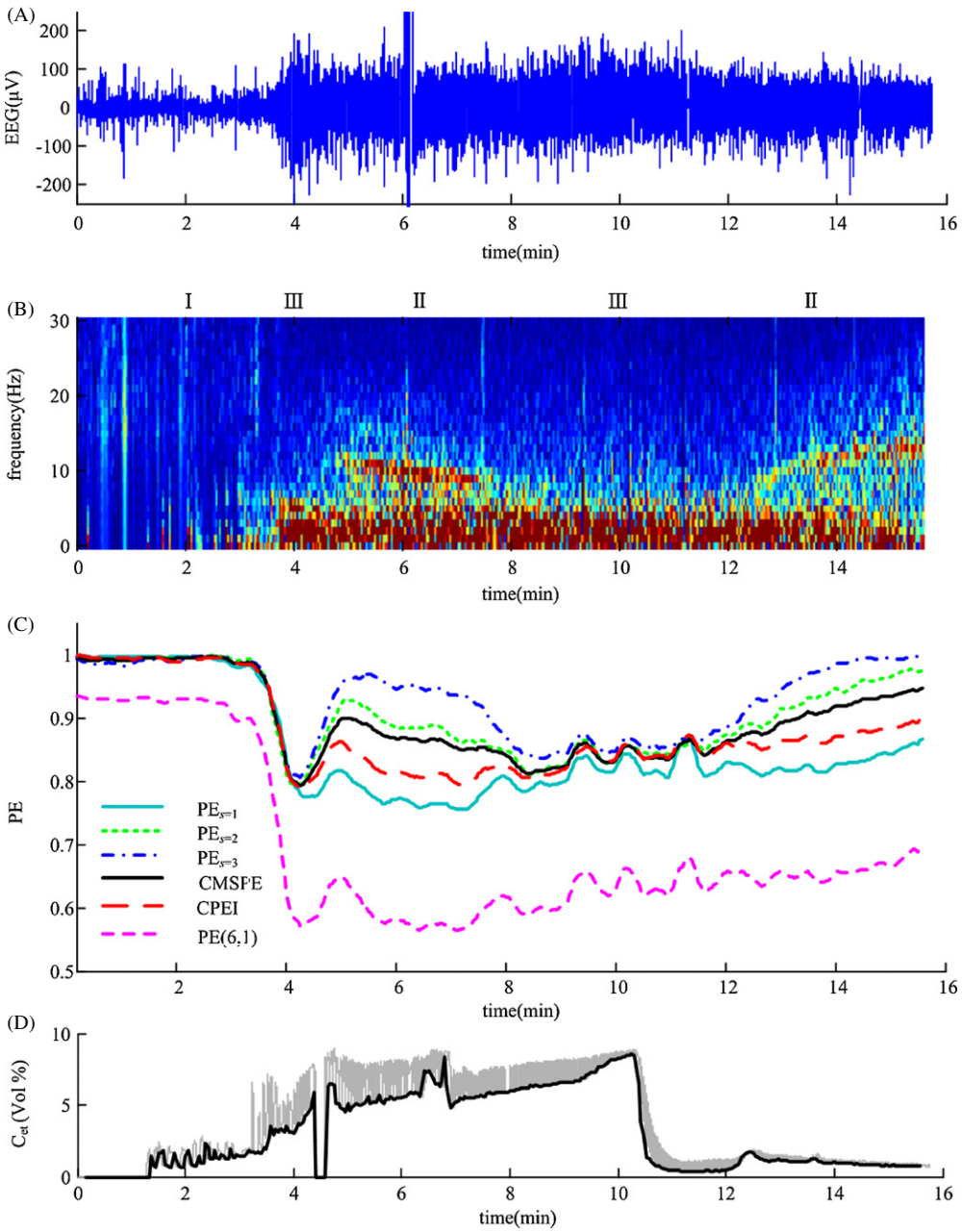

Figure 5. An EEG recording from another patient and corresponding EEG measures versus time. (A) A preprocessed EEG recording. The sample frequency is 100 Hz. (B) The spectrogram. A complex state transition, awake–deep–light–deep–light anesthesia, is clearly seen. (C) Time course of PE$_{s=1,2,3}$ and the CMSPE as well as PE(6,1) and CPEI. The CMSPE can accurately track the variations of EEG. (D) End-tidal sevoflurane concentration (C_{et}) during the same time course.

loss of consciousness (LOC), from LOC –30 s to LOC +30 s for all 18 patients. LOC typically occurred before the rapid decrease in the entropy values. The absolute slope values of the linear-fitted polynomials versus time for PE$_{s=1}$ and CMSPE are 0.10 (0.06–1.13) and 0.12 (0.09–0.15), respectively, as shown in figure 6(C). The difference, although small, is statistically significant ($p < 0.05$, paired t-test), suggesting that the multiscale PE measure can respond to changes in the drug effect more rapidly.

To compare the performance of the raw single-scale PE and CMSPE, PKPD modeling was conducted to correlate the EEG measures and the sevoflurane concentration. The method produced acceptable PKPD models for all the entropy measures. The modeled parameters yielding the greatest coefficient of determination (R^2) are listed in table 1. In the table, data are given as mean ± SD. The value $t_{1/2}k_{eo} = \ln 2/k_{eo}$ is the estimated effect-site equilibration half life, and γ is the slope parameter of the concentration–response relation. As the scale factor s increases, $t_{1/2}k_{eo}$ decreases and γ increases, mainly due to the faster response of the PE to changes in the EEG frequency content. The resulting modeled parameters for the CMSPE index were similar to those of the M-entropy RE index. Plotting the effect-site sevoflurane concentration (C_{eff}) against the measured EEG index showed

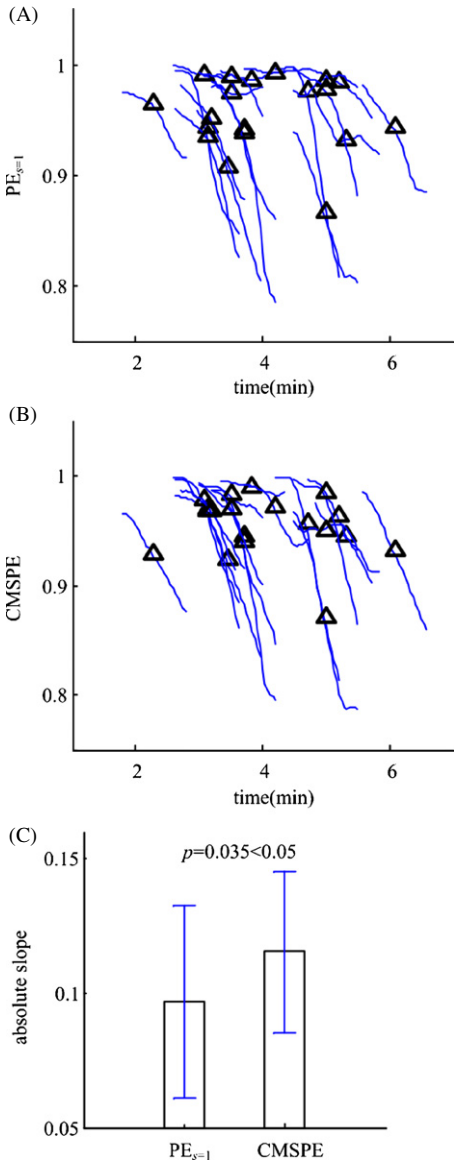

Figure 6. PE analysis around the time point of loss of consciousness (LOC) (from LOC –30 s to LOC +30 s for all subjects ($n = 18$). (A) The raw single-scale PE ($PE_{s=1}$) versus time. (B) The CMSPE index versus time. (C) Statistical analysis of the absolute slope of the linear polynomial fitted for the two entropy measures. The bar height indicates the mean value, and the lower and upper lines are the 95% confidence interval of the entropy values ($n = 18$).

the necessity of using the sigmoid $E_{\max}$ model. Figure 7 shows the best fit, median fit and worst fit relations for the CMSPE index in (A), and the corresponding fits for the $PE_{s=1}$ index in (B).

The prediction probability P_k was used to assess the performance of the CMSPE index to correctly differentiate between different effect-site sevoflurane concentrations. Individual P_k values for all patients are shown in figure 8(A). The P_k values of $PE_{s=1}$ and CMSPE were 0.85 (0.80–0.86) and 0.86 (0.85–0.88). The difference between these was statistically significant ($p = 0.025 < 0.05$, paired t-test). This suggests that CMSPE has a stronger capacity to track the sevoflurane effect-site concentrations over the entire range of data points. Also, the P_k values for CMSPE are higher than those for PE(6,1) of 0.85 (0.81–0.87) ($p = 0.065 < 0.1$, paired t-test) and CPEI of 0.83 (0.82–0.86) ($p = 0.033 < 0.05$, paired t-test).

To further demonstrate the applicability for estimating the sevoflurane effect, the CMSPE index was correlated with the RE index in the M-entropy module. The modeled PKPD parameters for the RE index were also shown in table 1. The P_k values of RE was 0.84 (0.82–0.87), slightly lower than those of CMSPE. The correlation analysis of CMSPE, raw PE ($PE_{s=1}$), PE(6,1) and CPEI with the RE index for each patient is shown in figure 8 (B). The correlation coefficients for the comparison between CMSPE and RE were 0.84 (0.80–0.88), while those with $PE_{s=1}$, PE(6,1) and CPEI were 0.75 (0.66–0.84), 0.78 (0.71–0.86) and 0.81 (0.74–0.87), respectively. The CMSPE:RE correlation was statistically higher than both the $PE_{s=1}$:RE correlation ($p = 0.018 < 0.05$, paired t-test) and the PE(6,1):RE correlation ($p = 0.041 < 0.05$, paired t-test). The CMSPE:RE correlation was slightly higher than the CPEI:RE correlation.

4. Discussion and conclusion

In this study, multiscale permutation entropy analysis was applied to anesthetic EEG recordings to describe the effect of sevoflurane on the brain. A new measure, denoted as CMSPE, which combined permutation entropy information of EEG series at multiple scales, was proposed. Its effectiveness was assessed by PKPD modeling and prediction probability statistics, and further by correlation analysis with the RE index in the M-entropy module.

The computation of PE requires the selection of appropriate parameters values for embedding dimension m, lag τ and data length M; these are dependent on the signal to be analyzed and its sampling frequency (Cao *et al* 2004). In this paper the parameter selection was based on the effect of anesthesia on the EEG. Three sets of simulated EEG series, representative of awake, light anesthesia and deep anesthesia, were generated by AR models, with model coefficients determined by modeling typical EEG epochs extracted from a real-EEG recording during sevoflurane anesthesia. As demonstrated in figure 3, the parameters of $m = 3$, $\tau = 1$, $M = 1000$ in the computation of PE were optimal for differentiating between awake, light and deep anesthetic levels.

Multiscale entropy analysis can be used to describe the complexity of a time series over multiple scales, and the plots of entropy values versus scales can be used to characterize the underlying physiological process (Costa *et al* 2002, 2005). To derive a unitary index reflecting the anesthetic drug effect, the information contained in multiple scales should be integrated. From the multiscale PE analysis (figure 4) of our simulated EEG series, $PE_{s=1}$, $PE_{s=2}$ and $PE_{s=3}$ gave correctly ordered and significantly different entropy values corresponding to the three anesthetic EEG levels, so the PE values at scale $s = 1, 2, 3$ were incorporated into the CMSPE index. Moreover, the multiple PE analysis requires an adequate length of data to provide reliable statistics. This must be balanced by the requirement of estimating the anesthetic drug effect in the

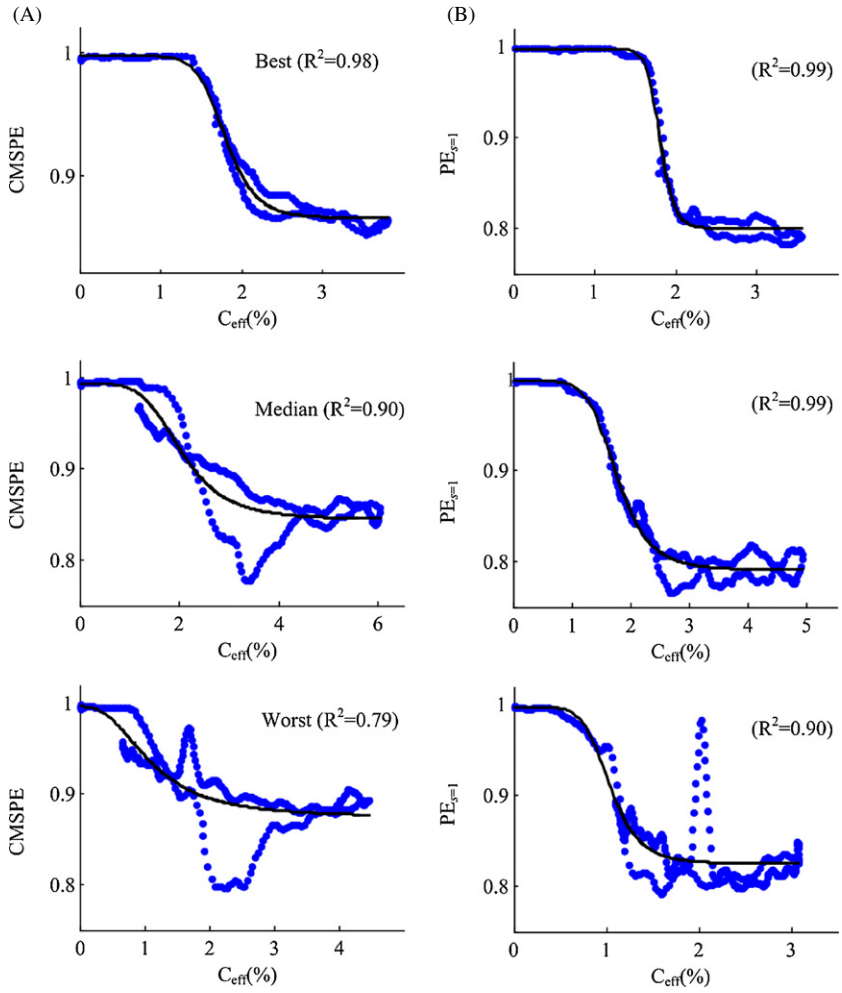

Figure 7. Dose–response curves between the CMSPE index (A) or corresponding raw PE Index ($PE_{s=1}$) (B) and the sevoflurane effect-site concentration (C_{eff}) for best fit, median fit and worst fit, with the greatest coefficient of determination (R^2) shown in the upper-right part of the figures. The dots are the measured EEG entropy values. The lines are the PKPD-modeled entropy values.

real-time application. With this in mind, the epoch length to compute the CMSPE index was set at 10 s; thus, a data length of ∼3.3 s at scale $s = 3$ could also give acceptable entropy values, as indicated in figure 3(C).

When applied to real EEG recordings with sevoflurane anesthesia, the PE values at scale $s = 1$, 2, 3 and CMSPE values can all track the gross changes in the EEG recordings. However, the CMSPE index was superior to the single-scale PE in reflecting subtle transitions between light and deep anesthetic states (see figures 1(C) and 5(C)). In addition, PE at larger scales give a faster response to changes in EEG, as compared to the raw single-scale PE, as indicated from the PKPD-modeled parameters $t_{1/2}k_{eo}$ and γ in table 1, and also from the PE analysis around the time of LOC (figures 6(A) and (B)). The reason may be explained as follows.

In figure 9(A), the frequency dependence of PE values at different scales was demonstrated. The simulated signals were generated by passing Gaussian white noise through the pass-band filter with different centre frequencies, from 2 to 30 Hz with a step of 2 Hz. The sampling frequency was set to 100 Hz. The frequency response of PE at scales $s = 2$, 3 is different from that at raw scale $s = 1$, and the frequencies around which the PE values decrease are related to the frequency at which the signal is sampled. When the patient becomes anesthetized, the EEG power in the high frequency band (∼10 Hz) decreases, and that in the low frequency band (<5 Hz) increases. With decreasing frequencies, the steeper reduction in PE at $s = 2$, 3 equates to a faster response to EEG changes than at $s = 1$. Thus, the incorporation of PE values at $s = 2$ or (and) $s = 3$ into the raw single-scale PE can render a faster response to EEG changes.

Further, the PE values at a higher scale are closely correlated with those at the raw scale, but with a higher delay τ. Figure 9(B) shows the frequency dependence of raw PE with different delays $\tau = 1$, 2, 3. From these plots, the raw PE with $\tau = 2$ is similar to $PE_{s=2}$ with $\tau = 1$, and that with $\tau = 3$ is close to $PE_{s=3}$ with $\tau = 1$. Thus, multiscale PE is basically equivalent to the integration of single-scale PE with multiple delay times τ. This idea is proposed in Olofsen *et al* (2008), where a composite PE index (CPEI), with the simple addition of PE with $\tau = 1$ and $\tau = 2$, was proposed to better track the anesthesia-related EEG changes. Obviously, the frequency dependence of CPEI is almost equal to that of the combination of the PE values at scale $s = 1$ and $s = 2$.

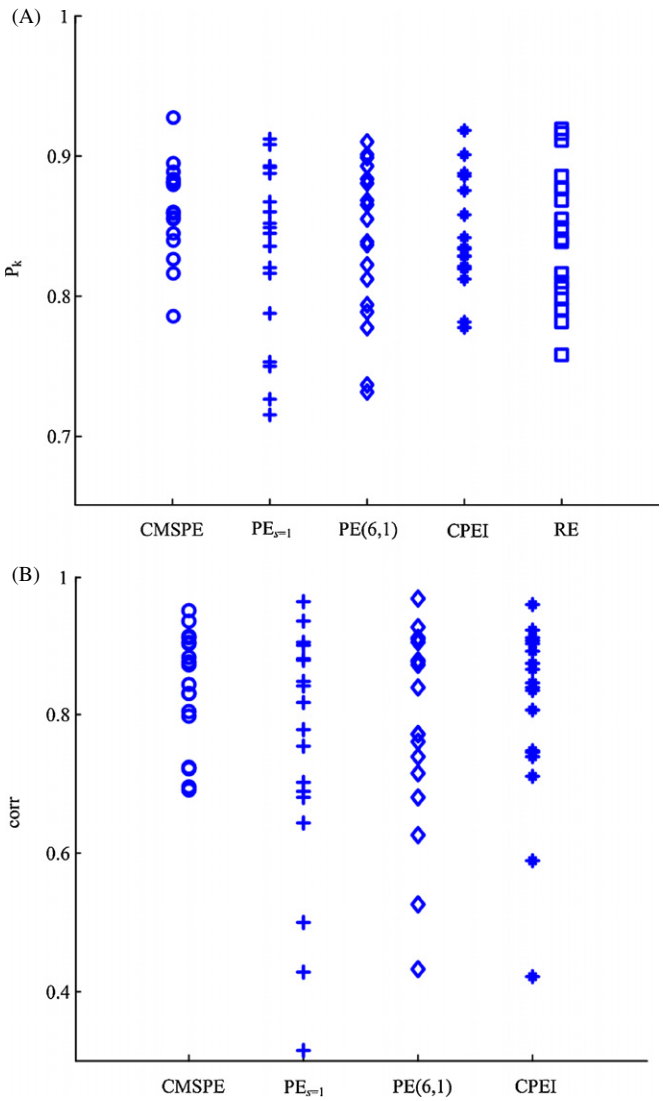

Figure 8. Statistical analysis of all patients ($n = 18$) for CMSPE and other indices. (A) Prediction probability (P_k) values for CMSPE, $PE_{s=1}$, PE(6,1), CPEI and RE index in the M-entropy module. (B) Correlation coefficients of the RE index with CMSPE, $PE_{s=1}$, PE(6,1) and CPEI.

This is the reason that the performance of CPEI lay between those of $PE_{s=1}$ and $PE_{s=2}$ in figures 1(C) and 5(C), as well as in the modeled PKPD parameters in table 1.

However, though similar, the new developed CMSPE index differs from the CPEI in some important aspects. First, the new index is designed to explore the complexity of EEG series at multiple scales, which is driven by the fact that the EEG signal inherently exhibits complex fluctuations that originate from complex self-regulating systems operating across multiple spatial and temporal scales (Buzsáki 2006). The next and most importantly, the scales at which the PE values are incorporated into the CMSPE index are determined by simulated EEG series representative of awake, light and deep anesthetic states.

Through the prediction probability (P_k) statistics, it was shown that the CMSPE index correlated more closely with the sevoflurane effect-site concentration derived by PKPD modeling than the single-scale PE index. Furthermore, the comparative analysis with the RE index used in the M-entropy module further substantiated the effectiveness of the CMSPE index. Modeled PKPD parameters were similar for CMSPE and correlated well with RE. We computed the RE index as described in Viertio-Oja *et al* (2004) and applied to the preprocessed EEG recordings with the same window size and overlapping as in the PE computation. This may be the cause of the difference in the PKPD parameter k_{eo} with previously published results (Ellerkmann *et al* 2004, McKay *et al* 2006), as the time delay in the computation of EEG indices can affect the value of k_{eo} (Ellerkmann *et al* 2004, Olofsen and Dahan 1999). Moreover, the developed CMSPE index is superior to two previously proposed PE indices of PE(6,1) (Li *et al* 2008a) and CPEI (Olofsen *et al* 2008), indicating that the parameter settings in the computation of PE and construction of CMSPE are justifiable.

However, the following three points should be noted and need to be further explored.

First, to integrate the information of PE on multiple scales into the CMSPE index, we simply define the CMSPE index as the averaged PE values at selected scales. The resulting CMSPE index performs better than the raw single-scale PE index and two previously proposed PE measures, demonstrating the superiority of multiscale PE analysis. However, more deliberate selection of the weighting coefficients of PE at multiple scales would be preferred and will be the subject of future work. Our plan is to find the optimal weighting coefficients to achieve the best possible performance (i.e. in terms of the prediction probability (P_k) statistics).

Second, the description of burst suppression in the EEG is a shortcoming with our current CMSPE index. As previous results have indicated, when the EEG changes into a burst suppression pattern, the PE values increase (Li *et al* 2008a), mainly due to noise during the suppression period (Olofsen *et al* 2008). Introduction into the PE index of an additional pattern-'tied' with a certain threshold level may correct for this; however, the choice of this threshold needs to be cautiously considered (Olofsen *et al* 2008). A similar strategy to that incorporated in the BIS monitoring system may be preferable for combination with the CMSPE index, such as described in Särkelä *et al* (2002) and Viertio-Oja *et al* (2004).

Third, in order to assess the performance of the measured CMSPE index to reflect underlying anesthetic states, we use two evaluation methods: the prediction probability (P_k) statistics to evaluate the correlation with sevoflurane effect-site concentration C_{eff}, estimated from PKPD modeling, and correlation analysis with the existent RE index in the M-entropy module. As the actual anesthetic level of the patients cannot be measured directly, we have to estimate it from drug concentration or patient responses, etc. While the scoring of the patient responses to verbal and physical stimuli is very subjective, the PKPD modeling with the simultaneously recorded drug delivery dose as inputs can derive the effect-site drug concentration C_{eff} as the estimate of the underlying anesthetic drug effect. The combination of the prediction probability (P_k) statistics and PKPD modeling has been

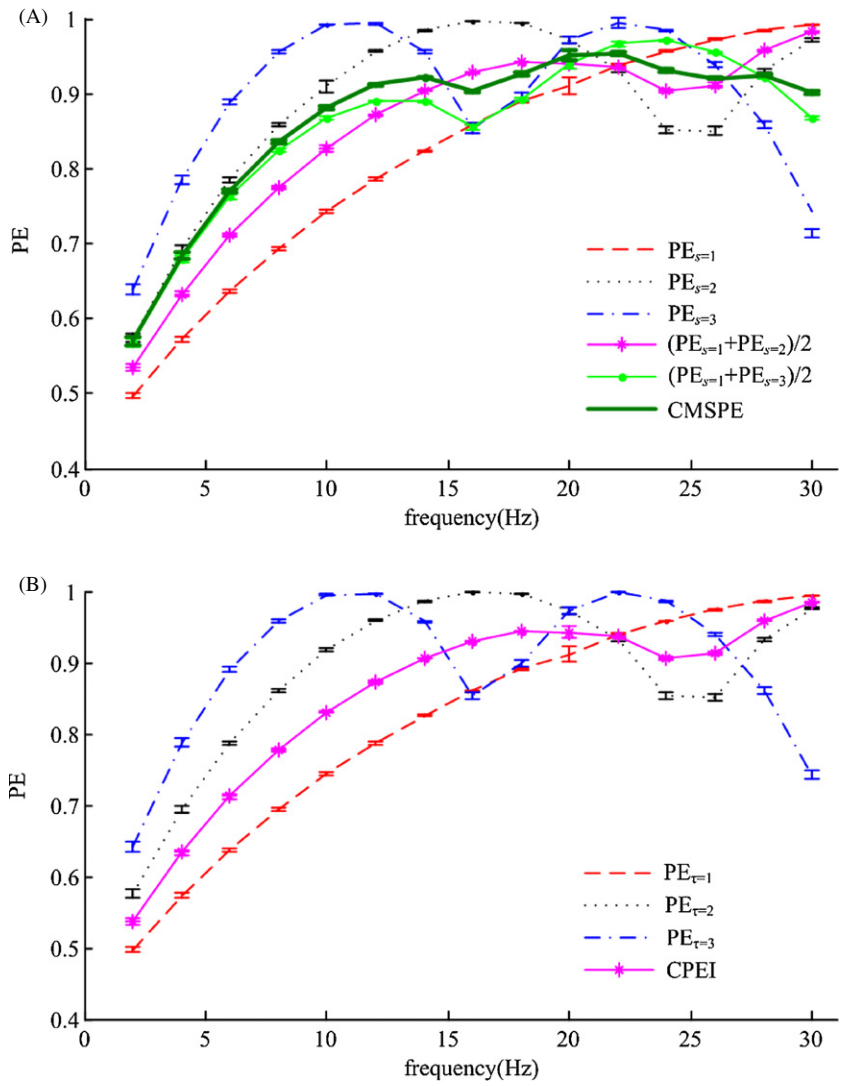

Figure 9. (A) The frequency dependence of PE values with $m = 3$, $\tau = 1$, at different scales $s = 1, 2, 3$ and the combination of different scales. The simulated signals were generated by passing Gaussian white noise through the pass-band filter with different centre frequencies, from 2 to 30 Hz with a step of 2 Hz. The sampling frequency was set to 100 Hz. (B) The frequency dependence of the raw single-scale PE values of $m = 3$ with different delays $\tau = 1, 2, 3$, and that of CPEI, with the simple addition of PE with $\tau = 1$ and $\tau = 2$. The PE value at a higher scale is closely correlated to single-scale PE values, but with a higher delay τ.

widely used in related studies (e.g. Ellerkmann *et al* (2004), Vanluchene *et al* (2004) and Li *et al* (2008b)). Comparative analysis with existent, commonly used EEG indices give a further indication of the performance of the CMSPE index. Currently, the BIS and spectral entropy are the most widely used EEG monitors (Bruhn *et al* 2006). BIS is a composite index composed of four sub-parameters, and the strategies for combining these sub-parameters have not been made public; the spectral entropy algorithm computes the SE and RE indices, and the computation of these two indicators is detailed in Viertio-Oja *et al* (2004). We compute the RE index as a 'test-bed' to assess the performance of the CMSPE index with the same preprocessing to eliminate the effect of denoising on the final performance.

In conclusion, the multiscale PE analysis accounts for the complexity of anesthetic EEG series at multiple scales and can derive an improved EEG index (CMSPE) to track the effect of the anesthetic drug sevoflurane on the brain. The CMSPE index outperforms the raw single-scale PE index in terms of the prediction probability and correlation coefficients with the RE index in the M-entropy module. It is suggested that CMSPE should be further explored and incorporated into a monitoring system for the depth of anesthesia.

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