Sample entropy analysis for estimating depth of anesthesia based on human EEG signal at different levels of unconsciousness during surgeries

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Estimation of depth of anesthesia (DoA) has always been a critical issue in light of its underlying complicated brain mechanism and its significant role in clinical operations. Electroencephalogram (EEG) is undoubtedly the most widely used signal to conduct analysis related to anesthesia. In this paper, a novel EEG based index is proposed to evaluate the DoA over 24 patients receiving general anesthesia with different level of unconsciousness. Sample Entropy (SampEn) is employed to acquire the chaotic features of EEG signal filtered by advanced nonlinear and nonstationary algorithm called multivariate empirical mode decomposition (MEMD). After extracting the SampEn from EEG series, artificial neural network (ANN) is utilized with Bispectral index (BIS) as the target. Correlation coefficient, mean absolute error and receiver operating characteristic (ROC) were used to verify the perioperative performance of our method. The comparison between before and after filtering was made as well as ANN. In order to check the accuracy and variability of the proposed methodology further, we divided all the data points into 4 groups based on BIS to represent different level of unconsciousness, and then analysis of variance (ANOVA) was applied to the corresponding index (i.e. ANN regression output) of our method. Results show that the correlation coefficient is improved to 0.79 ± 0.08 from 0.51 ± 0.17 which is significant after filtering and ANN utilization eventually. Similarly, the mean absolute error is dramatically reduced to 8.88 ± 2.46. In addition, the ultimate AUC has increased to 0.96 ± 0.04 and ANOVA analysis of 4 subgroups of different anesthetic level shows significant difference from the nearest ones. Furthermore, the ANN output is linearly correlated with the BIS, thus predicting DoA more precisely. In conclusion, the proposed method can provide a concrete basis for monitoring patients' anesthetic status during surgeries.

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Abstract: Estimation of depth of anesthesia (DoA) has always been a critical issue in light of its underlying complicated brain mechanism and its significant role in clinical operations. Electroencephalogram (EEG) is undoubtedly the most widely used signal to conduct analysis related to anesthesia. In this paper, a novel EEG based index is proposed to evaluate the DoA over 24 patients receiving general anesthesia with different level of unconsciousness. Sample Entropy (SampEn) is employed to acquire the chaotic features of EEG signal filtered by advanced nonlinear and nonstationary algorithm called multivariate empirical mode decomposition (MEMD). After extracting the SampEn from EEG series, artificial neural network (ANN) is utilized with Bispectral index (BIS) as the target. Correlation coefficient, mean absolute error and receiver operating characteristic (ROC) were used to verify the perioperative performance of our method. The comparison between before and after filtering was made as well as ANN. In order to check the accuracy and variability of the proposed methodology further, we divided all the data points into 4 groups based on BIS to represent different level of unconsciousness, and then analysis of variance (ANOVA) was applied to the corresponding index (i.e. ANN regression output) of our method. Results show that the correlation coefficient is improved to 0.79 ± 0.08 from 0.51 ± 0.17 which is significant after filtering and ANN utilization eventually. Similarly, the mean absolute error is dramatically reduced to 8.88 ± 2.46. In addition, the ultimate AUC has increased to 0.96 ± 0.04 and ANOVA analysis of 4 subgroups of different anesthetic level shows significant difference from the nearest ones. Furthermore, the ANN output is linearly correlated with the BIS, thus predicting DoA more precisely. In conclusion, the proposed method can provide a concrete basis for monitoring patients' anesthetic status during surgeries.

Keywords: multivariate empirical mode decomposition; electroencephalogram; depth of anesthesia; sample entropy; artificial neural network; ANOVA

1. Introduction

General anesthesia (GA) is a temporally drug-induced unconsciousness state, which is reversible under human's manipulation (Purdon et al. 2015). The advent of the modern general anesthesia brings huge benefits to humans in medical fields as it guarantees a safe performance

of disease diagnosis and surgery for millions of patients every year (Vutskits & Xie 2016). However, there still exists many literatures that provide strong evidence of postoperative side effect, such as derilum (Cole et al. 2002; Lepouse et al. 2006), cognitive dysfunction (Monk et al. 2008) and even postoperative mortality (Arbous et al. 2005; Bainbridge et al. 2012). Limited solutions can be adapted to deal with these problems very well because the mechanism underlying anesthesia still remains not fully understood (Uhrig et al. 2014). Therefore, optimal titration of anesthetic dose is of great importance to achieve ideally effective analgesia, unconsciousness and immobility to reduce the potential negative influence of both under and over dosing to the minimum. This, undoubtedly, poses a crucial issue that precise evaluation the depth of anesthesia (DoA) counts much in light of emerging critical requirements of patients' surgery safety and experience.

As it is known, anesthetic agents mainly rely on enhancing the activity of inhibitory cells or suppress the activity of excitatory cells. Two pervasive receptors: gamma-amino butyric acid (GABA), N-methyl-D-aspartate (NMDA) are usually induced by drugs like propofol, sevoflurane, ketamine, etc (Brown et al. 2010; Uhrig et al. 2014). Normally, there is a disruption between the neural communications during loss of consciousness (LOC). Anesthetics alter normal information processing (Chauvette et al. 2011; Purdon et al. 2013; Vizuete et al. 2014). Thus, how to assess the degree of the brain state might unfold a feasible method to represent the DoA, which is the direction researchers turn towards (Shalbaf et al. 2013). Nevertheless, it is not routinely accepted to monitor brain state in practical anesthesia care because markers that reliably reflect consciousness level changes under GA have yet to be identified (Palanca et al. 2009). Instead, indirect measures such as changes in heart rate, blood pressure, and muscle tone—along with drug pharmacokinetics, pharmacodynamics and for inhaled anesthetics, the level of exhaled anesthetic gas, are the standards for anesthesiologists to judge whether patients are adequately anesthetized (Purdon et al. 2013; Uhrig et al. 2014). Anesthesiologists primarily rely on autonomic and behavioral responses to optimize levels of anesthesia and provide appropriate analgesia. However, it performs individually for these traditional methods. Moreover, it is difficult and unreliable to analyze these signs due to the use of some

medications such as muscle relaxants (Shalbaf et al. 2013). Actually, accumulating evidence show that electrical potential in frontal cortex, namely electroencephalogram (EEG), behaves so much association with general anesthesia (KIERSEY et al. 1951; Martin et al. 1959). Brain information processing is based on the spike or action potential transmission and reception by neurons, which is one of the fundamental mechanisms underlying the central nervous system interaction (function) (Kandel et al. 2000). Subcortical areas produce weaker and difficultly detectable electrical potentials because the electric field strength decreases with the increasing distance from its source (Hämäläinen et al. 1993). However, scalp EEG patterns reflect the states of both cortical and subcortical structures due to their strongly connected structures (Ching et al. 2010). EEG is the most pervasively non-invasive signal that reflects the brain communication and states.

Fortunately, more electrophysiological measures of brain activity have been investigated to quantify anesthetic depth (Bart et al. 1971; McKeever et al. 2014; Poorun et al. 2016). Spectrum-power analysis includes decomposition of specific frequency components, compressed spectral array, the two-dimensional plot of the spectrogram and so on (Bickford et al. 1971; Billard et al. 1997). Later on, several spectral indices are proposed such as 95% spectral edge frequency (SEF) (Katoh et al. 1998). Median Frequency(MF) and Spectral Entropy (SE) (Höcker et al. 2010). Among them, the SE has already been applied to the commercial monitor Datex–Ohmeda developed by GE company. However, these methods are based on the traditional FFT to study the spectral characteristics. It assumes the data is stationary in a short period. Because the EEG presents non-stationary and non-linear features in human biological system, those methods above may ignore much valuable information. Consequently, it is reasonable to apply the nonlinear dynamics and information theory to EEG for the prediction of DoA.

In the past decades, the concept of entropy has been widely recognized in medical and neurological fields from the Approximate Entropy (ApEn) (Bruhn et al. 2000; Pincus et al. 1991) to Shannon Entropy (Bruhn et al. 2001; Shannon et al. 1951). The entropy concept is derived

from the time series. They calculate the irregularity of time series and reflect the randomness and complicity in time domain. Especially, it applies to non-stationary data, which overcomes the drawbacks of many spectral methods. Sample Entropy (SampEn), a kind of improved algorithm of previous entropy methods (Richman & Moorman 2000), estimates the probability that the data series are closely correlated in a dataset, within a given tolerance. It has been applied to many biomedical dynamics such as heart rate variability and EEG analysis (Chu et al. 2017; Huang et al. 2013; Shalbaf et al. 2012). Although related researches have been studied somehow, including our previous works, they ignore the variability in different anesthetic level to some extent. Unconsciousness does not mean an unresponsive state simply. It is much associated with the concentration level of anesthetic agents, which will affect the neuron activity and brain network, leading to some phenomena, like burst suppression or postoperative cognition dysfunction (Purdon et al. 2015). This might be avoided if we can control the DoA precisely with appropriate drug dose. It is worthwhile to study further to assess the DoA in different levels.

Artificial neural network (ANN) is an advanced modeling tool in statistics, machine learning and cognitive science (Alpaydin 2014; Kriegeskorte 2015). It is inspired by biological neural networks in performing all the units' functions. Neural network models are part of theoretical neuroscience and computational neuroscience, thus making it optimal for non-linear, distributed, parallel and local processing and adaptation. In summary, neural network is a powerful solution for data regression by training the input data aimed at targets. It can automatically adjust the node connecting weight and bias to achieve desired results. In biomedical fields, it plays an important role for the complex physiological data analysis (Amato et al. 2013).

In this paper, EEG analysis to estimate the DoA was conducted further. We use the most commonly used commercial Bispectral index (BIS; Aspect Medical Systems, Newton, MA, USA) (Rampil et al. 1998) as a gold standard to evaluate our method performance due to its relatively high accuracy in GABA receptor anesthetic situation and approval by US Food and Drug

Administration (FDA). The range of the recorded BIS is from 0 (suppression state of EEG) to 100 (Awake). The BIS index shows significant advantages such as comprehensive clinical validation (Johansen et al. 2000; Luginbühl et al. 2003). However, its algorithm still remains unreleased and has some specific weak points comprehensively discussed in Section 4, thus posing a need for a better open source methodology. Here, we focus on patients receiving GABA receptor dependent anesthetic agent aimed at BIS as gold standard first, i.e. BIS behaves precisely for this kind of anesthetic. Totally, 24 datasets of EEG data from are analyzed to evaluate the DoA. First, multivariate empirical mode decomposition (MEMD; a non-linear, non-stationary method) is applied to filter the noise, and then SampEn features are extracted from specific combination of intrinsic mode function (IMF), generated from MEMD. Next, ANN is used to train the features for regression in order to optimize the performance. Finally, the capability is evaluated by comparison between ANN outputs with BIS gold standard. In order to analyze this method capability in more detail, analysis of variance (ANOVA) analysis is undertaken for data pairs of four subgroups.

2. Materials and methods

2.1 Subjects

Ethical approval was granted by the Research Ethics Committee of the National Taiwan University Hospital (NTUH) (No: 201302078RINC). All written informed consents were obtained from involved patients. In this study, patients were recruited from NTUH, who received the regular surgery under general anesthesia (i.e. no access to high risk operations related to brain, heart, lung etc.). Those who had alcohol, smoking or other medical illness affecting the data recording were excluded. Finally, 24 patients (age 20-80 years old) are eligible in this study.

2.2 Data recording

The surgery lasts from 30 minutes to 4 hours regularly. It is widely classified into 3 conditions: awake, maintenance (i.e. LoC) and recovery. Prior to the operation, pulse oximetry, Electrocardiography (ECG) sensor and blood pressure cuff are established when patients are awake. The vital signs (Heart Rate, SpO2, Pulse Rate and Blood Pressure) play an important role in anesthesiologists' assessment of DoA along with medical decisions in clinical practice. They

will be shown on the physiological monitor MP60 (Philip, IntelliVue, US). Although these signals are not analyzed in this study, they count much to surgery successful running. LoC is usually induced by intravenous propofol, inhaled desflurane or sevoflurane, which are GABA dependent. After unconsciousness is confirmed by anesthesiologists through response to the verbal commands or stimulus, general anesthesia with laryngeal mask airway (LMA) is used to transfer the drug to keep the unconsciousness (maintenance period). By the end of the surgery, anesthesiologists use some anti-anesthetic and analgesia to terminate the anesthesia procedure.

As to EEG recording, conductive paste is used to optimize contact between the frontal scalp skin and EEG sensor BIS™ Quatro Sensor (Aspect Medical Systems, Newton, US) with low impedance under 5k ohm. EEG sensor is connected to MP60 as well through BIS module. Raw EEG continuous waveform data including the routine signals mentioned above were recorded onto a laptop via serial port RS-232 using the collection software developed by Borland C++ Builder 6 developing environment kit (Borland Company, C++ version 6). The EEG data was acquired at sampling rate of 125 Hz. The intermittent BIS value is obtained every 5 seconds.

2.3 Data preprocessing

All the clinical administration data and physiological data were sorted in order. And then the EEG data experienced converting data format, labeling the event time point, etc. All cases data were then visually inspected roughly to abandon the specific segments of artifact resulting in waveform saturation (e.g., electrical artifact caused by medical equipment or body movement). After that, 5s of data epoch was used to conduct the MEMD analysis and 30 s segment of the reconstructed signal is used for the SampEn calculation, and the window step size was set 5 s to in order to be consistent with BIS value for further comparison.

2.4 Data analysis

2.4.1 Filtering by MEMD

EEG is easily contaminated by artifacts such as Electromyography (EMG), Electrooculography (EOG), and electric circuit noise (Huang et al. 2013). It is definitely necessary to filter the signal

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to reduce the computation error. Considering the nonlinear and nonstationary characteristics of EEG, a method called empirical mode decomposition (EMD), is proposed by Huang et al. in 1998 (Huang et al. 1998). The EMD method decomposes signal into a series of intrinsic mode functions (IMF). The extraction procedure of an IMF from signal is named as sifting. Find all the local extrema and then generate the upper envelope by drawing a cubic spline line via all the local maxima; conduct the similar steps for the local minima to produce the lower envelope.

All the data should fall the range between the upper and lower envelopes. The first component h_1 is obtained by computing difference between the data and mean:

$$X(t) - m_1 = h_1 \quad (1)$$

m_1 denotes the mean. h_1 can only be treated as a proto-IMF. In the next step, h_1 is treated as data:

$$h_1 - m_{11} = h_{11} \quad (2)$$

After sifting up to k times, h_1 becomes an IMF that is

$$\mathrm{h}_{1(\mathrm{k}-1)} - \mathrm{m}_{1\mathrm{k}} = \mathrm{h}_{1\mathrm{k}} \quad (3)$$

Then, the 1st IMF is acquired as $\mathrm{h}_{1\mathrm{k}}$:

$$\mathrm{C}_1 = \mathrm{h}_{1\mathrm{k}} \quad (4)$$

Repeat the steps above for residual generated by previous loop to get successive IMFs.

Finally, signal is decomposed as:

$$\mathrm{X(t)} = \sum_{\mathrm{i}=1}^{\mathrm{N}} \mathrm{c_i\,(t)} + \mathrm{r_N(t)} \quad (5)$$

where $\mathbf{N}$ is the number of IMFs, $\mathbf{c_i(t)}$ is the ith IMF and $\mathbf{r_N(t)}$ is the residual. A combination of different IMFs can reconstruct a signal to eliminate the artifact. However, EMD induces mode mixing problem. In 2010 an improved EMD called MEMD is presented by Rehman Mandic (Rehman & Mandic 2009) and noise assisted MEMD (N-A-MEMD) is also introduced by them (Ur Rehman & Mandic 2011). The new N-A-MEMD solves the mode mixing problems, and also can be applied to single channel data by adding Gaussian noise together, which constitute a multi-channel data. The definition is as follows:

$$\mathrm{m(t)} = \frac{1}{\mathrm{K}} \sum_{\mathrm{i}=1}^{\mathrm{K}} \mathrm{e^{\theta i}(t)} \quad (6)$$

where $e^{\theta i}(t)$ is the multivariate envelope curves of the whole set of direction vector, K is the length of the vectors, and $m(t)$ is calculated by means of the multivariate envelope curves.

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Unlike the traditional method with constant amplitude and frequency in a harmonic component, an IMF represents a simple oscillatory mode as a counterpart and has variable amplitude and frequency over time. According to our the previous study (Huang et al. 2013), we reconstruct the EEG signals by summing IMF2 and IMF3 after decomposition as the filtered signals owing to its better discrimination ability of different states of anesthesia.

2.4.2 Sample Entropy Analysis

Based the non-stationary characteristic of EEG, SampEn is appropriate to quantify the data's degree of irregularity. More complicated series generates higher value. The SampEn, proposed by Richman and Moorman in 2000 (Richman & Moorman 2000), aims to improve ApEn to measure the complexity of physical time series more precisely. It follows the steps:

Step 1, obtain a time series with N points $\{X(i),\ 1 \le i \le N\}$, set parameters r and m, representing tolerance and embedding dimension, respectively.

Step 2, the m-dimension template vector $X_m(i)$ is defined as

$$X_m(i) = \{X(i), X(i+1), \dots, X(i+m-1)\}, \qquad 1 \le i \le N-m+1 \tag{7}$$

Step 3, calculate the distance between two vectors:

$$d[X_m(i), X_m(j)] = \max(|X_m(i+k) - X_m(j+k)|) \qquad 0 \le k \le m-1,\ i \ne j \tag{8}$$

Step 4, let B_i be the number of vectors $X_m(j)$ within r of $X_m(i)$, then

$$B_i^m(r) = \frac{1}{N-m+1} B_i \tag{9}$$

$$B^m(r) = \frac{1}{N-m} \sum_{i=1}^{N-m} B_i^m(r) \tag{10}$$

Step 5, Set $m = m + 1$, and repeat Step 1 to Step 4, we can get

$$A^m(r) = \frac{1}{N-m} \sum_{i=1}^{N-m} A_i^m(r) \tag{11}$$

Finally, SampEn is gained by

$$SampEn = -ln \frac{A^m(r)}{B^m(r)} \tag{12}$$

Before computing SampEn, three important parameters need to be set, namely, the length of the time series (N), tolerance *r* and dimension m. *N* was chosen to be 3750 points (30 s). Various theoretical and clinical applications have described the validity of $m = 1 \text{ or } 2$ and r with a range from $0.1 * std \; to \; 0.2 * std$, where *std* means standard deviation. We employed parameters as $m = 2$ and $r = 0.1 * std$ in this study.

2.4.3 Artificial neural network

In order to symbolize DoA more accurately, ANN is employed to conduct the data regression. By resembling the biological nervous interaction system, ANN is a highly appropriate tool for nonlinear regression and classification tasks. It is composed of three parts; input layer, hidden layers and output layer. Learning and regression effect are accomplished via the connection weight between nodes, which can be adjusted during the data training. From an engineering perspective, 3 to 4 layers are mostly used (Kourentzes et al. 2014; Ripley & Ripley 2001). Under the consideration of computation time, we employ the backpropagation neural network (BPNN) with 4 layers: 1-9-18-1. It means 1 input layer in this study, 2 hidden layers with 9 and 18 nodes each and 1 output layer. The commonly recognized BIS index was regarded as the target while the entropy features act as input data. The input samples data were randomly divided into training (70%), validation (15%) and testing datasets (15%) to adjust he weights and bias to generate the eventual model.

2.5 Statistical analysis

To verify SampEn capability for decimating the anesthesia stages, we used Parametric Paired Student's t-test. For the intact surgery assessment of DoA, the receiver operating characteristic curve (ROC) is calculated to obtain area under curve (AUC), which is often used in medical field when diagnosing diseases. The BIS binary threshold to distinguish the condition between anesthesia and awake is set as 65 (Johansen & Sebel 2000; Kreuer et al. 2001). To evaluate the ANN effect, the comparison between the non-ANN results and ANN regression output is made. Pearson correlation coefficient, mean absolute error (MAE) and AUC with EACL were computed with BIS as the gold standard. Moreover, the DoA states are classified into 4 groups (Johansen & Sebel 2000), ANOVA analysis is undertaken for data pairs of BIS and corresponding SampEn to study the performance in details. Statistical analysis was performed using SPSS Statistics (IBM v22, US) and MATLAB (Mathworks R2014b, US).

The whole workflow diagram is shown in Fig. 1. First, the valid subjects are selected and then the preprocessing is conducted. Afterwards, MEMD is applied to filter the data, constructing new data by combing the IMF2 and IMF3. Then, SampEn features are extracted from data

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segments for all cases followed by ANN modeling. Finally, the results are statistically compared with BIS to evaluate the performance, including the perioperative analysis evaluation and detailed sub-level group ANOVA analysis.

3. Results

3.1 Discrimination of different anesthetic stages

General anesthesia can be categorized into three stages: pre-operation (i.e. awake), LoC, emergence from anesthesia (recovery) as the time goes through the whole operation. Awake stage denotes the period before anesthetic injection. Patients keep very clear awareness. Then LoC is induced by drug slowly, eventually followed by a stable unconsciousness state. By the end of operation, the patients gradually recover from the as the drug volume decreases. Therefore, it is worthwhile to distinguish the stages prior to the tracking DoA for the whole surgery. 2 mins separate segment is extracted from three stages for each patient, respectively. By applying window size 30 s and window step 5 second, 24 data points are calculated for each stage and then average them. Figure 2 shows the SampEn percentile distribution of the three stages over the 24 patients. It is can be observed that SampEn during the LoC is lower than the others. It makes sense that the SampEn drops from awake to LoC and then increases when recovering. The results ($p < 0.05$) statistically demonstrates the significant difference between unconsciousness and consciousness states. The mean value and standard deviation of SampEn among the three stages is 1.78±0.16, 1.36 ± 0.13 and 1.79 ± 0.11. One point; the awake stage; is not significantly different from recovery stage ($p = 0.85$), which means the consciousness return after surgery. Therefore, SampEn can distinguish the anesthetic status along the EEG traces during surgical operations.

3.2 MEMD filter performance

As discussed previously, the non-stationary and non-linear characteristics of physiological signal (i.e. EEG in this study) requires a more robust and appropriate method to get rid of the weakness of traditional FFT methods, MEMD is applied to reconstruct the signal. One representative patient SampEn derived from both combination signal (i.e. IMF2+ IMF3) and raw

EEG data are presented in Fig. 3 together with gold standard BIS index. By roughly visual evaluation, it is obvious that filtered outcome behaves better than the raw one. And statistically, we compute the Pearson correlation coefficient between the perioperative SampEn and BIS for both filtered signal and raw signal in Fig. 4. It shows a significant increase from 0.51 ± 0.17 to 0.72 ± 0.09 ($p < 0.05$). Thus, the MEMD filtering improves the accuracy of SampEn as an index to symbolize DoA.

3.3 ANN regression model performance

In order to improve the capability of SampEn to predict the DoA, non-linear regression model ANN is established to optimize the method performance. Figures 5 and 6 give the Pearson correlation coefficient and mean absolute error between non-ANN group and ANN group based on the filtered signal and raw signal. It is significantly different between the two groups in conditions, which demonstrate the ANN regression effect. It should be noted that correlation coefficient value between filtered data and BIS is improved to 0.79 ± 0.08 from 0.72 ± 0.09 while it changed from 0.51 ± 0.17 to 0.60 ± 0.16 for raw data. For mean abssolute error, regression process much reduces the value between the output and BIS target (i.e. 8.88 ± 2.46 vs 47.23 ± 7.84 (filtered data via ANN) and 9.92 ± 2.08 vs 46.88 ± 7.73 (raw data via ANN)).

3.4 Receiver operating characteristic analysis

To evaluate the our method accuracy, the ROC analysis is conducted for raw EEG SampEn, filtered EEG SampEn, ANN derived SampEn based on raw EEG and ANN derived SampEn based on filtered EEG. AUC is widely used to assess the medical diagnosis rate or classification accuracy. It is the area under ROC curve with a range from 0.5 to 1. The better classification of one method owns, the larger the value is. We calculate the AUC for the four types of ROC curve over 24 cases. One representative case ROC curve is shown in Fig. 7, which exemplify the proposed methods best capability (raw EEG SampEn has the lowest AUC, suggesting weakest discrimination rate). The statistical comparisons results were calculated between MEMD filtering and ANN regression effect. It demonstrates the SampEn after filtering possesses higher value with 0.95 ± 0.04 from 0.81± 0.13. And ANN regression based on filtered data performs

best (i.e. 0.96 ± 0.04), It is significant higher than others ($p < 0.05$). Furthermore, the AUC demonstrate effect of the filtering and regression effect to some extent, which are illustrated by Pearson Coefficient and mean absolute error in previous sections.

3.5 ANOVA analysis of 4 data pair subgroups

By taking the BIS value as gold standard, four groups can be classified, which are Phase 1 (0~40, deep anesthesia), Phase 2 (40~65, general anesthesia), Phase 3 (65~85, light anesthesia) and Phase 4 (85~100, awake). The corresponding SampEn is automatically divided into these phases. Thus, there are 33895 data pairs (i.e. ANN SampEn and BIS) along the whole procedure over 24 patients. Statistical analysis was performed by one-way analysis of variance on ranks (ANOVA on ranks) and Student-Newman-Keuls test for pairwise comparisons. The results show a general decrease trend and a significant difference compared with its previous subgroups ($p < 0.05$) in Fig. 8. Also, in Table 1, the SampEn value distribution is presented. For all phase groups, the majority fall into the corresponding phase value range except Phase 3, which means the light anesthesia. This can be more clearly observed in Fig. 9 of the scatter plot between ANN SampEn and BIS. It shows general linear relationship between the two variables.

4. Discussion

In this paper, a novel method for estimation of DoA is proposed. By extracting EEG signal features, we acquire the Entropy fluctuation patterns along with anesthetic levels. ANN is established to achieve regression effect by taking BIS index as a DoA reference. Distribution of the index of our methods in 4 different groups (phases) shows roughly linear relationship with BIS. Results illustrate capability of proposed method signify the DoA over 24 patients.

EEG plays a vital role for brain related study like epilepsy, Parkinson's diseases well as aesthesia (Le Van Quyen et al. 2001; Ly et al. 2016; Vlisides & Mashour 2017). It might provide the most effective non-invasive method for diagnosis and treatment. During anesthesia, EEG traces show dominant low frequency and high amplitude oscillations while the high frequency components decrease for common medication, thus providing us the opportunity to develop EEG based

method to track the DoA automatically (Purdon et al. 2015). However, EEG is so weak to be contaminated by EOG, EMG baseline drift and nonlinear distortion of the amplitude, etc (Liu et al. 2017). Also due to its non-stationary and non-linear properties, traditional filtering method may not work well. In our procedure, MEMD produce a good artifact cancelation capability. By comparison the correlation coefficient in Fig. 4, the filtered effect is improved from 0.51 ± 0.17 to 0.72 ± 0.09 significantly. Although the MEMD is an improved EMD method (Rehman & Mandic 2009), it still consumes much computation time. Therefore, it is hard to be applied to real-time situation presently. This deficiency might be overcome thanks to the hardware development. Another point is the principle of choosing the combination of IMFs (Huang 2014; Komaty et al. 2014). The decomposition result changes individually because EEG signal might vary from patient to patient although IMF2+IMF3 are selected based on our previous study (Huang et al. 2013). There might be better combinations. This property details should be analyzed more clearly, i.e different anesthetics, age group, etc. Another solution is we can try something like ICA (Long & Sheng 2014), wavelet (Mamun et al. 2013) to explore the potential better artifact rejection method (Khatwani & Tiwari 2013).

Entropy is a good concept for series randomness analysis (Fast 1962). It is becoming a powerful analysis tool for information process of EEG activity recently (Al-Kadi et al. 2013; Chu et al. 2017). Entropy implies the degree of irregularity of a system, lowering the entropy values during anesthesia significantly shown in Fig. 3. However, we choose factors empirically. It is worthwhile to study the rationale to improve the accuracy further. Results should be compared with a range of these parameters. Moreover, EEG signal naturally exhibits complicated variations, which come from complex self-regulating systems over multiple temporal scales. So, advanced multiscale entropy and permutation entropy can be considered as alternative methods (Chu et al. 2017; Shalbaf et al. 2013).

ANN is employed to model the estimation of DoA. It should be admitted that it is very complicated to make ANN function properly. In ANN result section, the accuracy is truly improved though not very much. However, it is unknown that whether the more sophisticated

structure ANN can perform better. In the data mining fields, the ANN or deep ANN is widely discussed to do the mining analysis (Kriegeskorte 2015). We may change the structure or training function type to get better regression results. Nevertheless, the amount of data definitely needs to be increased. This is also what we are handing with now.

There are several limitations in our work. First, BIS receives some controversy (Avidan et al. 2008). It means it might not reflect the patients' status correctly, especially for Ketamine, nitrous oxide, which are NMDA dependent anesthetic agents and induce anesthesia by enhancing inhibitory receptors, opposite to GABA dependent ones such as propofol, desflurane by suppressing the excitatory nervous circuits (Uhrig et al. 2014). This, on the other hand, explains why BIS (i.e. EEG) is not required as a compulsory standard in practical operation. Second, BIS has some time delay (Shalbaf et al. 2013) and deficiency for pediatric [1]. So, Expert Assessment of Consciousness Level (EACL), which comes from experienced anesthesiologists' comprehensive evaluation under consideration of multiple clinical indicators used in practice, would be referred to be as the gold standard for our method aimed at minimizing the disadvantage and maximizing the universality. Third, 24 patients receive the GABA receptor drugs, of which anesthetic level is relatively very accurate to be represented by BIS (i.e. this is also why we can choose BIS as a gold standard here for our methodology first). This implies that our method has not been applied to other agent with different anesthesia mechanism such as ketamine, nitrous oxide mentioned above. This needs to be confirmed whether it works as well taking new gold standard to compare with BIS, thus proving rationale of our methodology. Fourth, our data only comes from adults. It has huge difference between adults and infants from clinical view point (Schechter et al. 1986). This poses potential weakness for application on children. In addition, it should be admitted that our definition of 4 groups of different anesthetic level should be questionable. Whether it is should be categorized more precisely might be clarified. And analysis with respect to this should be more comprehensive. Finally, estimation of DoA with a single parameter such as EEG measure does not work well over time. DoA monitoring reliability might be improved by taking the Autonomic nervous system activity into consideration (Cohen et al. 1990). Therefore, there still is no single perfect index, for which

there have been many trials to integrate several modes of observations to increase the accuracy of DoA evaluation. To sum up, these challenges open many possibilities for researches to explore more advanced DoA assessment in future.

5. Conclusions

In this paper, a novel method protocol based on entropy concept for estimation of DoA via EEG signals has been proposed. The SampEn feature derived from EEG is proved to be able to distinguish the selective traditional 3 stages of anesthesia firstly. And then, the feasibility of MEMD to filter EEG data and regression effect of ANN model has been demonstrated. By taking the BIS value as the gold standard, good performance of the entire perioperative DoA assessment has been verified in aspects of ROC. More importantly, ANOVA analysis over 24 GABA dependent anesthetic induced patients under different anesthetic level has been conducted, which shows clear linear relationship with gold standard. In consequence, results exhibit very high accuracy of DoA estimation, providing a basis for DoA evaluation.

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Figure 1(on next page)

The diagram of general workflow.

N-A-MEMD: noise assisted multivariate empirical mode decomposition; IMF: intrinsic mode function; ANN: artificial neural network; BIS: bispectral; DoA: depth of anesthesia; RoC:receiver operating characteristic; ANOVA: analysis of variance.

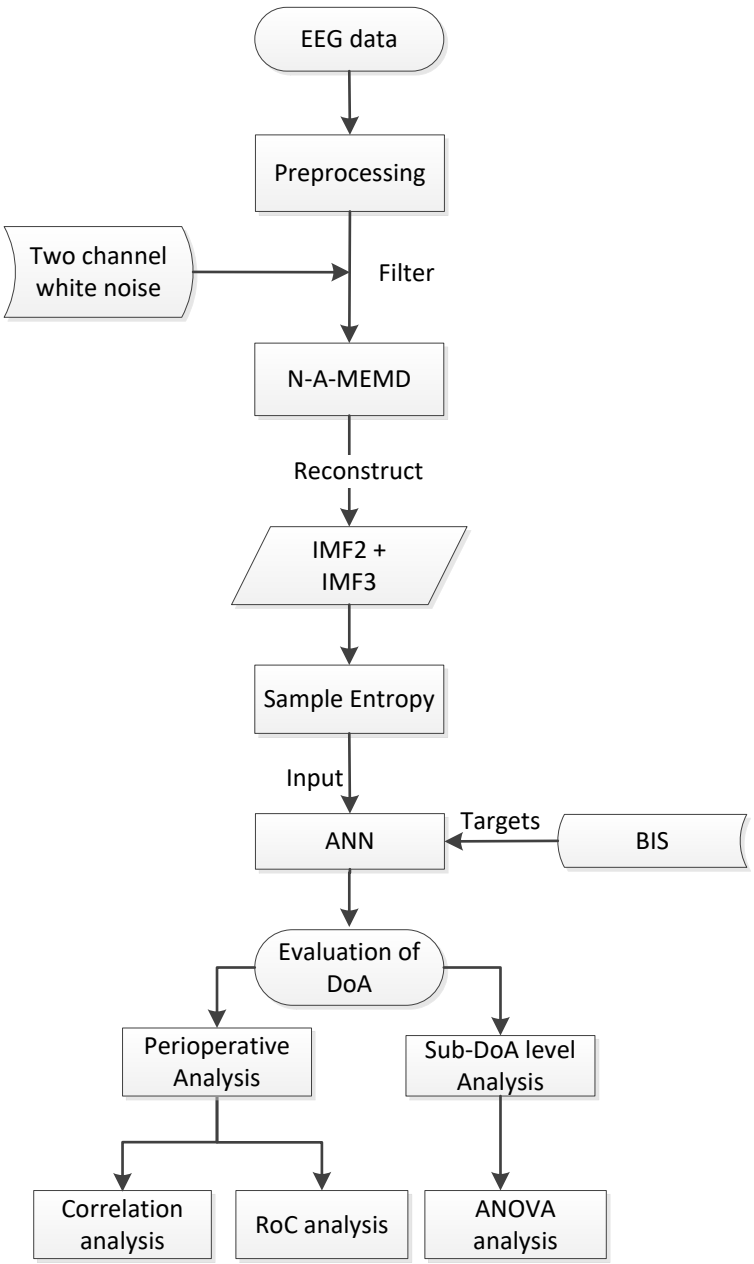

EEG data
Preprocessing
Two channel white noise
Filter
N-A-MEMD
Reconstruct
IMF2 + IMF3
Sample Entropy
Input
ANN
Targets
BIS
Evaluation of DoA
Perioperative Analysis
Sub-DoA level Analysis
Correlation analysis
RoC analysis
ANOVA analysis

Figure 2(on next page)

Boxplot of Sample Entropy over 3 anesthetic stages.

Loc: Loss of consciousness; SampEn: sample entropy.

Asterisk (*) : significant difference ($p < 0.05$); n.s: not significant.

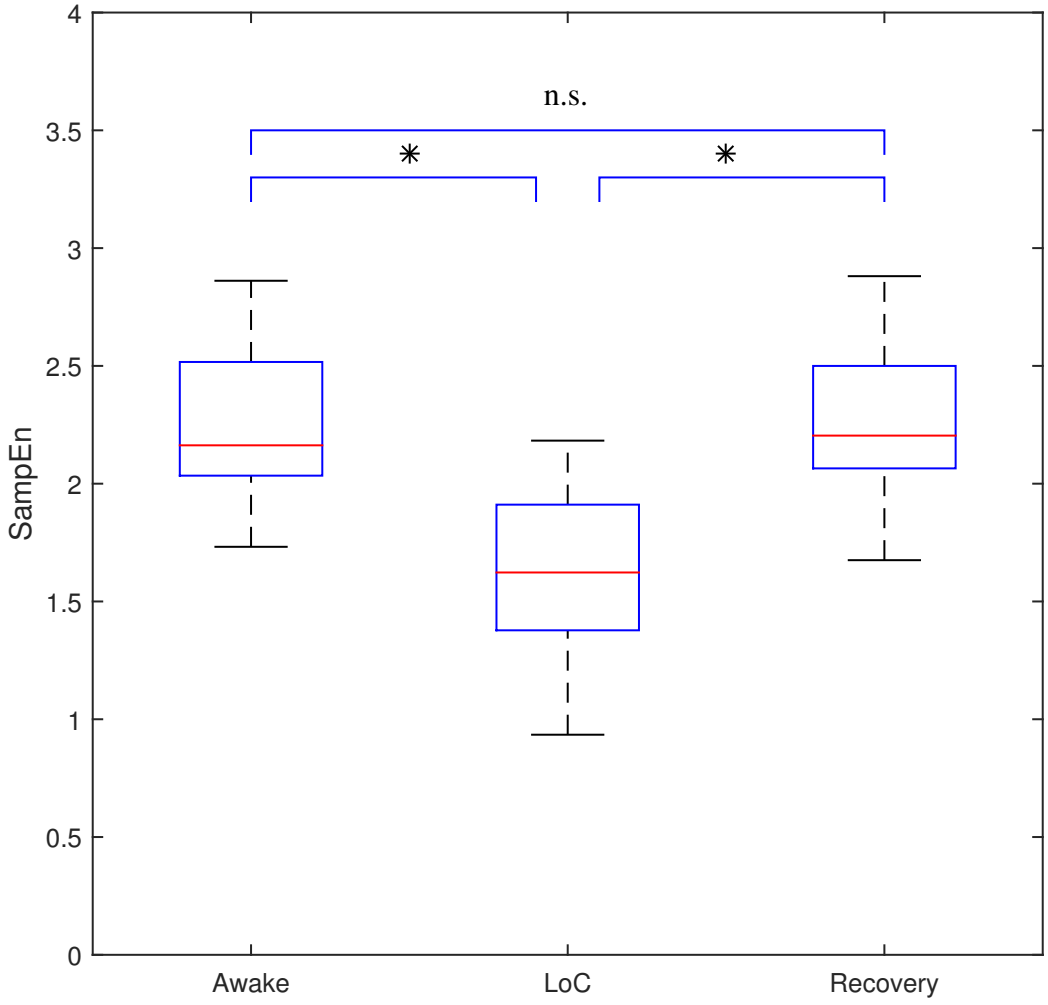

n.s.
*
*
SampEn
4
3.5
3
2.5
2
1.5
1
0.5
0
Awake
LoC
Recovery

Figure 3(on next page)

One representative case filtering effect by multivariate empirical decomposition (MEMD)

A) BIS value recorded during surgery, B) SampEn from raw EEG data and (C) SampEn from filtered data.

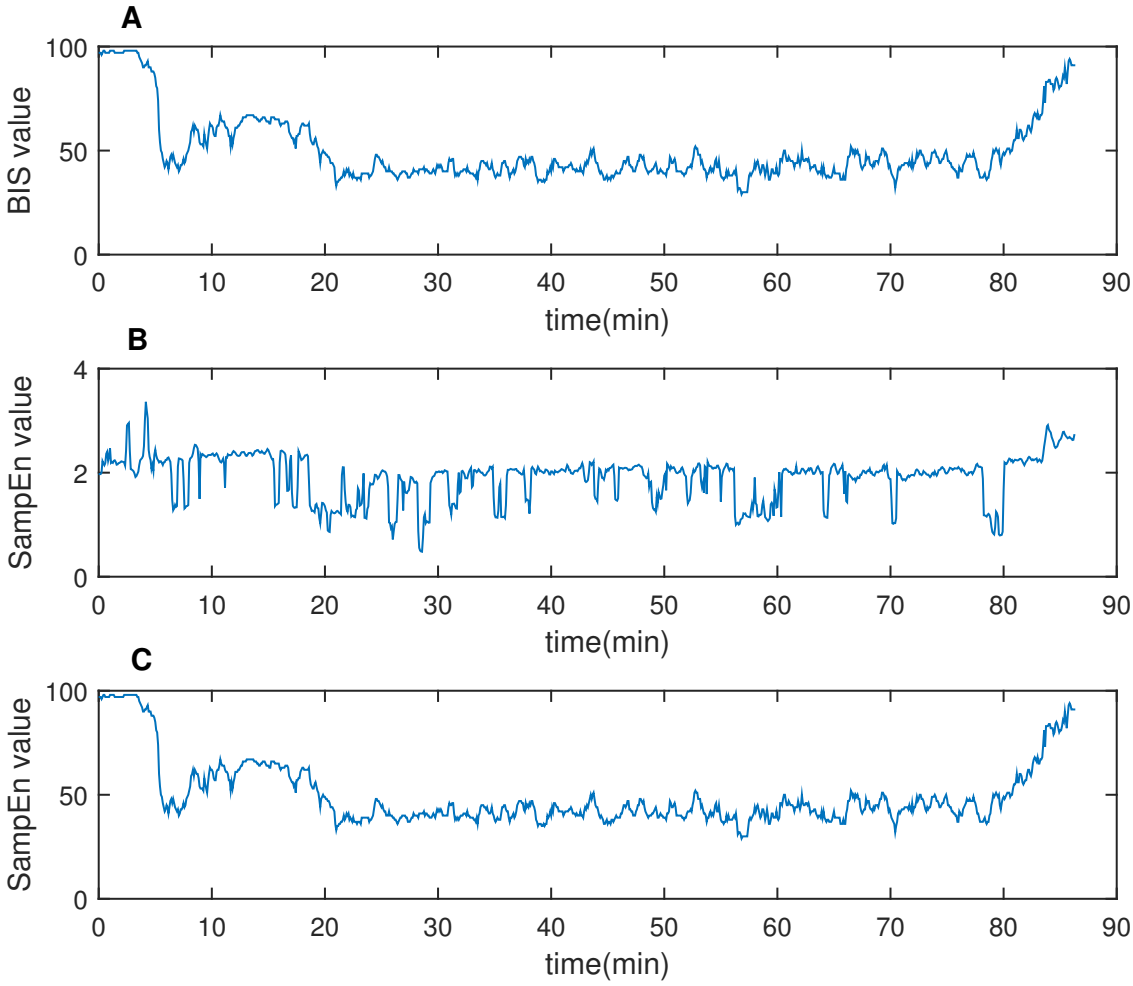

A
BIS value
100
50
0
0 10 20 30 40 50 60 70 80 90
time(min)
B
SampEn value
4
2
0
0 10 20 30 40 50 60 70 80 90
time(min)
C
SampEn value
100
50
0
0 10 20 30 40 50 60 70 80 90
time(min)

Figure 4(on next page)

Correlation coefficient between SampEn and BIS for both raw EEG data and filtered data by N-A-MEMD.

Asterisk (*) : significant difference ($p < 0.05$);

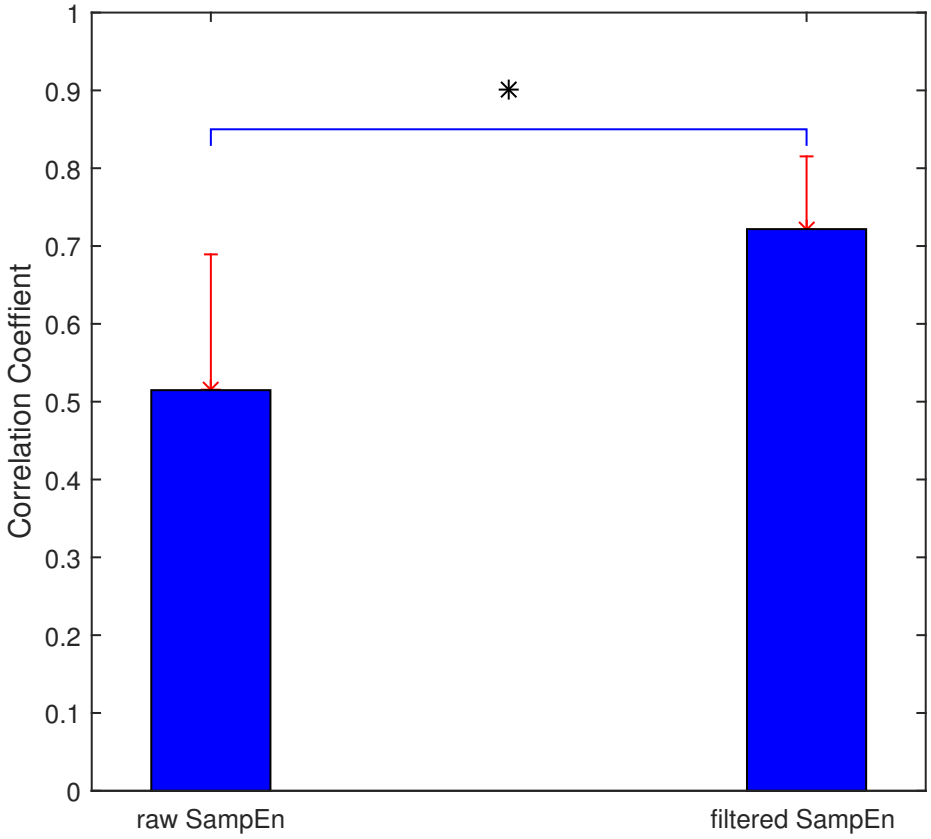

1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
Correlation Coeffient
*
raw SampEn
filtered SampEn

Figure 5(on next page)

Correlation coefficient comparison before and after ANN.

A) shows ANN regression effect for SampEn from raw EEG; B) shows ANN regression effect for SampEn from the filtered EEG

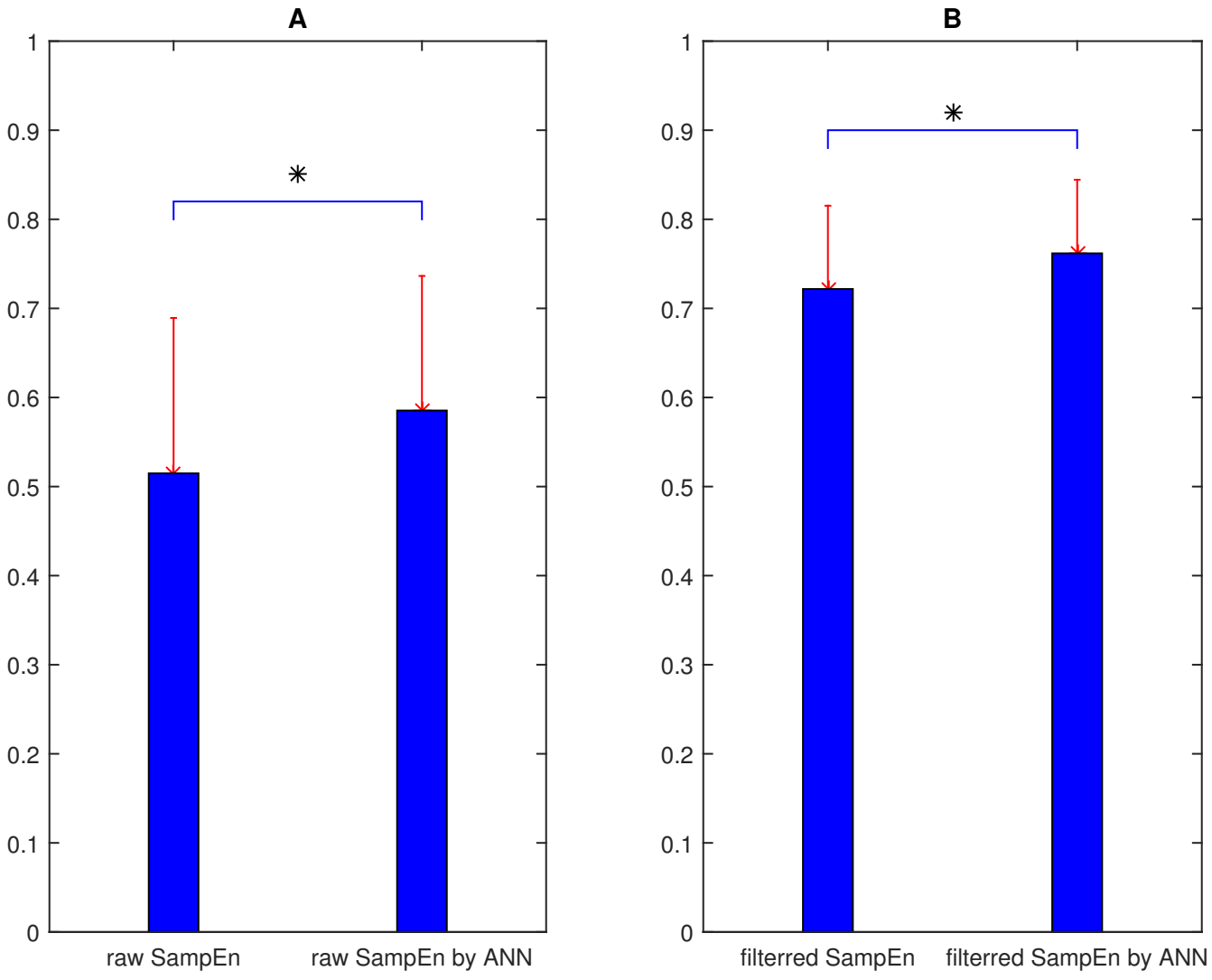
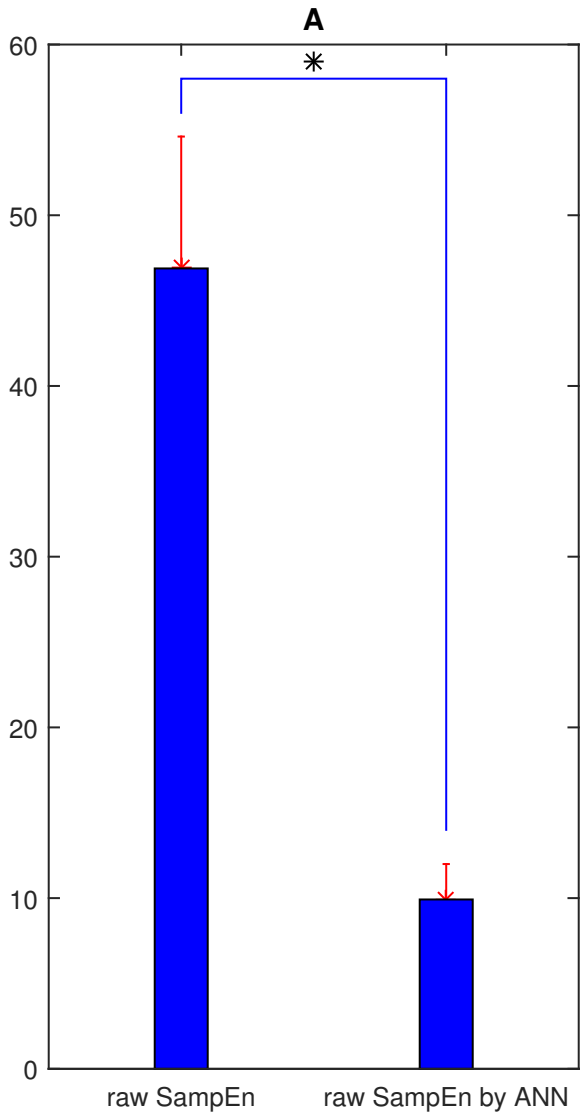

A
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
*
raw SampEn
raw SampEn by ANN
B
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
*
filterred SampEn
filterred SampEn by ANN

Figure 6(on next page)

Mean absolute error comparison before and after ANN.

shows ANN regression effect for SampEn from raw EEG; B) shows ANN regression effect for SampEn from the filtered EEG


A
60
50
40
30
20
10
0
raw SampEn
raw SampEn by ANN

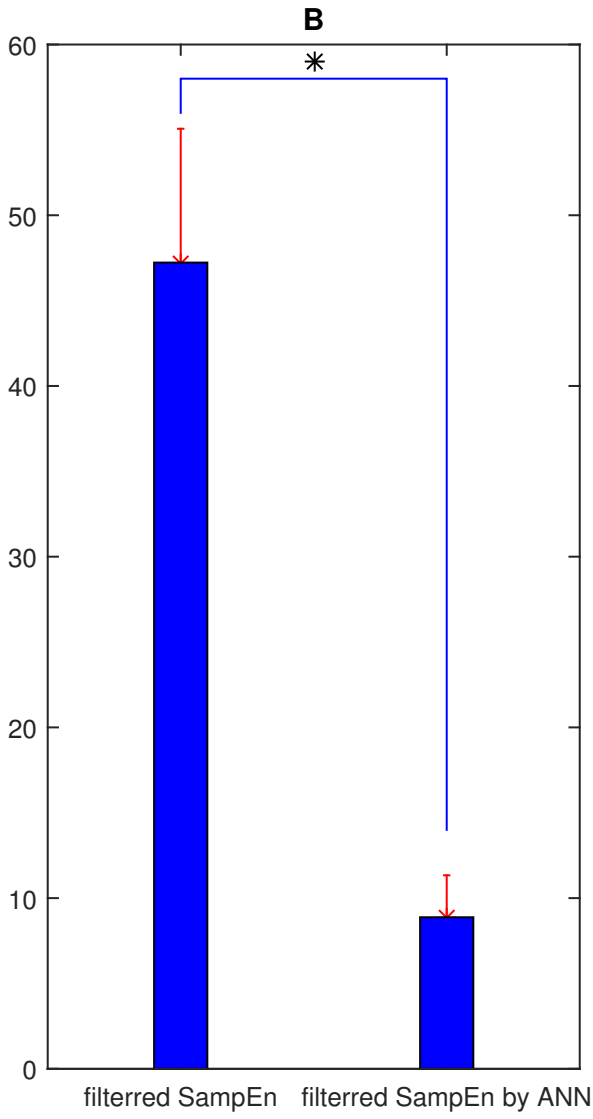

B
60
50
40
30
20
10
0
filterred SampEn
filterred SampEn by ANN

Figure 7 (on next page)

Receiver operating characteristic (ROC) curve of a representative subject.

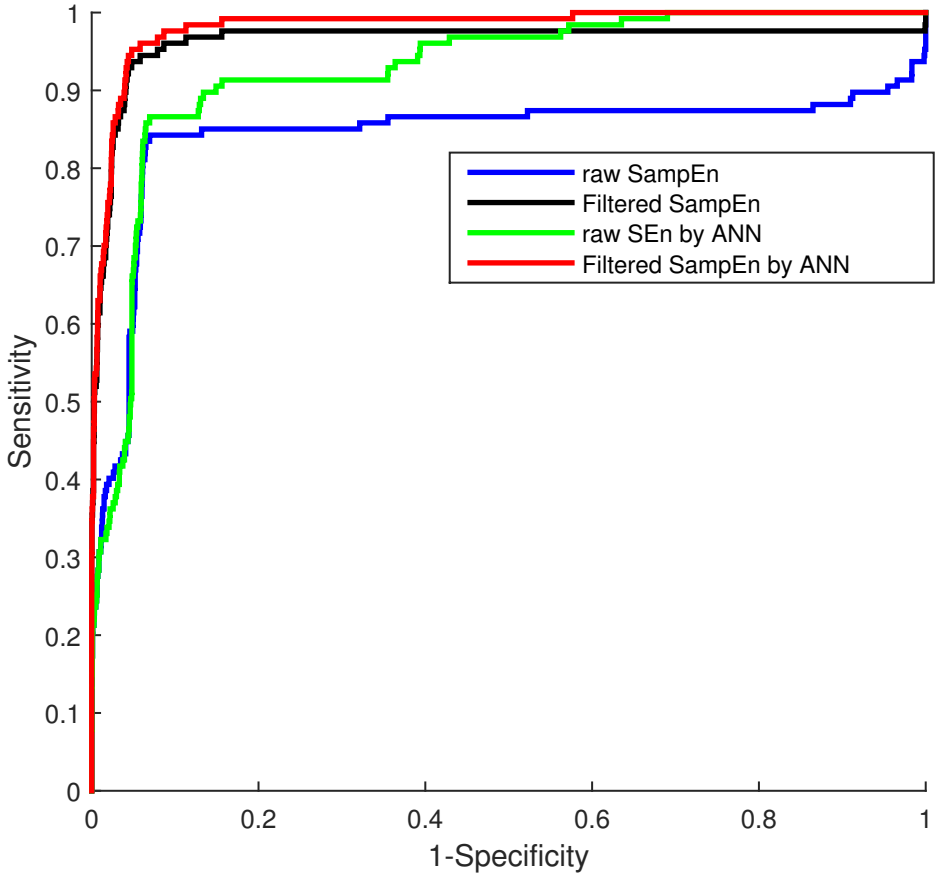

raw SampEn
Filtered SampEn
raw SEn by ANN
Filtered SampEn by ANN
Sensitivity
1-Specificity
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
0
0.2
0.4
0.6
0.8
1

Figure 8(on next page)

BIS phases and corresponding filtered SampEn values after ANN for 24 patients.

A total of 2031 data pairs were obtained. Data are presented as mean ± SD; SampEn values obtained during the different phases were compared by one-way ANOVA on ranks and Student-Newman-Keuls test for pairwise comparisons. The asterisk (*) indicates that SampEn in each phase are significantly different with $P<0.05$ when compared to the values of the preceding phase.

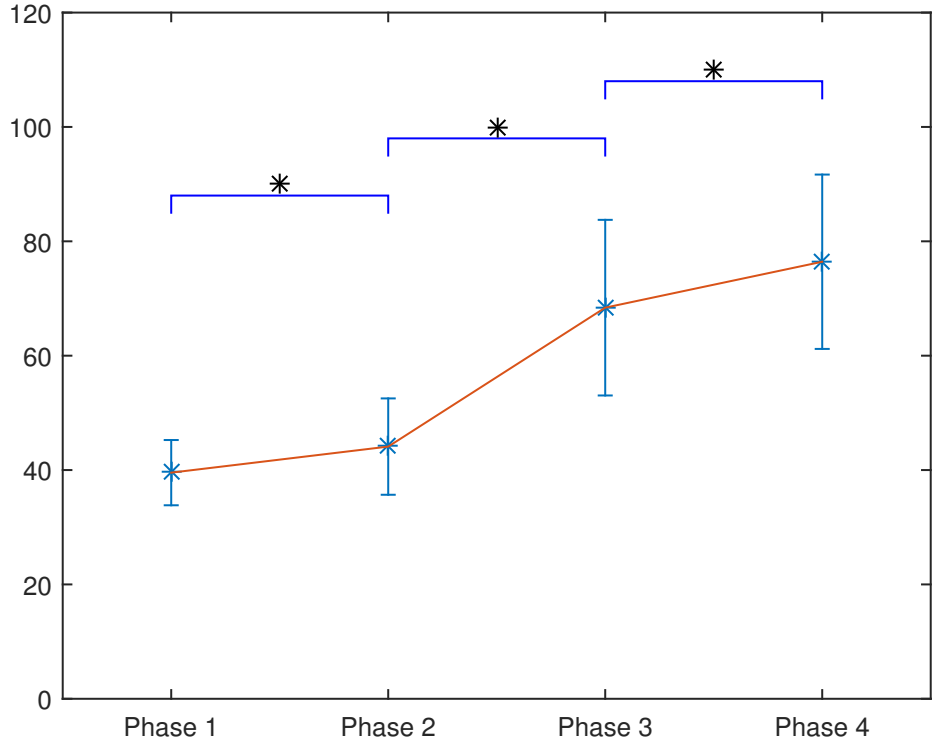

120
100
80
60
40
20
0
Phase 1
Phase 2
Phase 3
Phase 4

Figure 9(on next page)

Scatter plots of BIS value and corresponding filtered SampEn values after ANN for 24 patients.

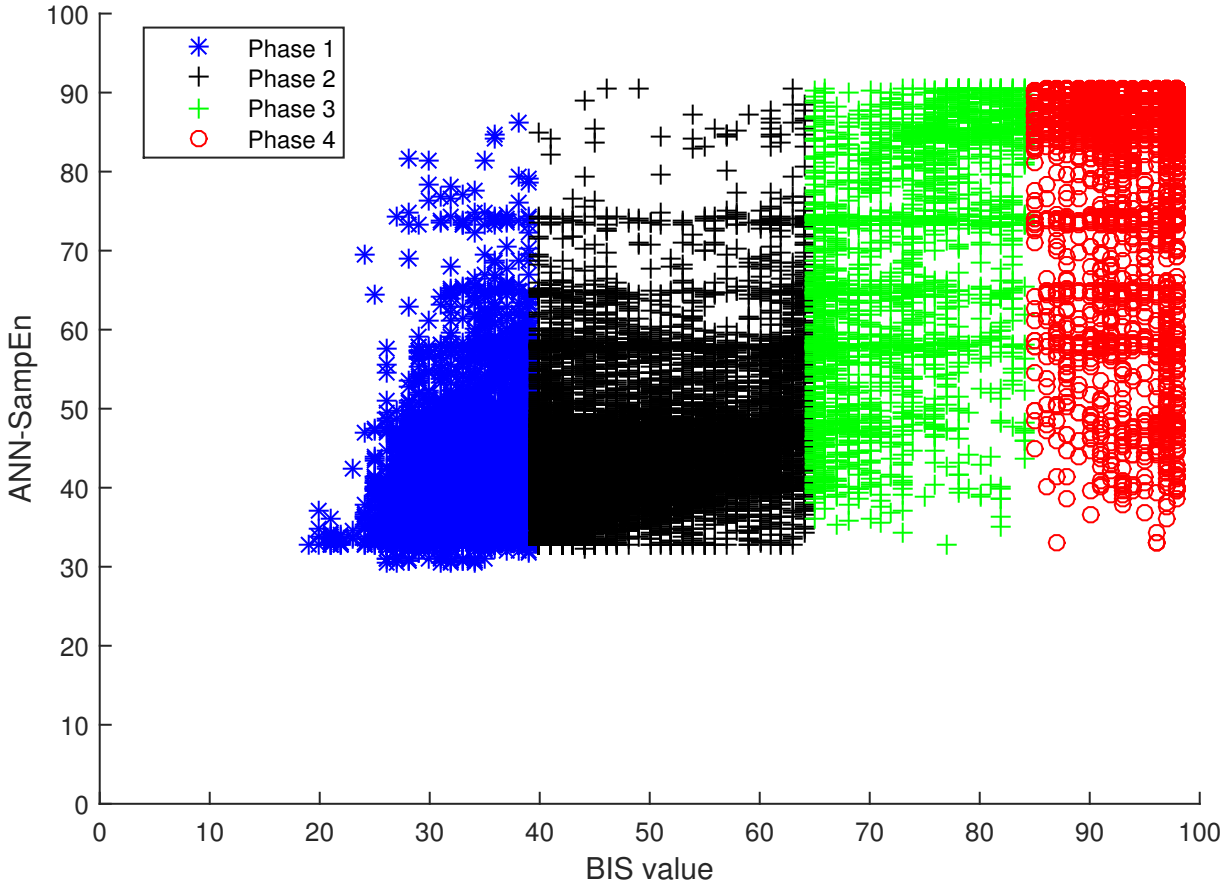

Phase 1
Phase 2
Phase 3
Phase 4
ANN-SampEn
BIS value
0
10
20
30
40
50
60
70
80
90
100

Table 1(on next page)

Filtered SampEn via ANN sub-group value distribution.

1

2

BIS Level	n	0-40	40-65	65-85	85-100
BIS 0-40	15467	9171 (59.3%)	6219 (40.2%)	76 (0.5%)	1 (0%)
BIS 40-65	13952	4218 (30.2%)	9466 (67.8%)	248 (1.7%)	20 (0.1%)
BIS 65-85	2274	47 (2.1%)	958 (42.1%)	851 (37.4%)	418 (18.4%)
BIS 85-100	2202	24 (1.1%)	547 (24.8%)	623 (28.3%)	1008 (45.8%)

3