Contents lists available at ScienceDirect

Asian Pacific Journal of Tropical Medicine

journal homepage:www.elsevier.com/locate/apjtm

Document heading doi: 10.1016/S1995-7645(14)60070-5

Depth of anaesthesia monitors and the latest algorithms

Tian-Ning Li*, Yan Li

Faculty of Health, Engineering and Sciences, University of Southern Queensland, Toowoomba, QLD 4350, Australia

ARTICLE INFO

Article history:
Received 10 February 2014
Received in revised form 15 March 2014
Accepted 15 April 2014
Available online 20 June 2014

Keywords:
Depth of anaesthesia
Consciousness
Electroencephalograph

ABSTRACT

This paper reviews the existing depth of anaesthesia (DoA) monitors and their algorithms and also proposes to improve their performance from four aspects. An ideal DoA monitor should be able to suggest a personalised drug dosages, to predict and provide early warnings when dosages are inappropriate, to be portable and highly cost-effective. The limitations of the existing DoA monitors commonly include unsatisfied data filtering techniques, time delay for the monitoring responses, and inflexible and low noise immunity problems. The latest research results show that their performance can be improved using up-to-date computing technology and neurophysiology. The findings in Chinese market review show that neither the imported nor the Chinese domestic DoA monitors are widely utilised at hospitals, but the demand for DoA monitors is very high. Clearly there is a high demand which encourages the development of a better DoA monitor and its mass production in China.

1. Introduction

The anesthesia depth is reflected in the change of the partial pressure of the anaesthetics in the brain[1]. It is extremely important to assess the depth of anesthesia (DoA) accurately since a precise assessment is helpful for avoiding various adverse reactions such as intraoperative awareness with recall (underdosage), prolonged recovery and an increased risk of postoperative complications for a patient (overdosage). An evidence shows that the DoA monitoring using electroencephalograph (EEG) improves patient treatment outcomes by reducing the incidences of intra-operative awareness, minimizing anaesthetic drug consumption and resulting in faster wake-up and recovery[2,3]. For an accurate DoA assessment, intensive research has been conducted in finding "an ultimate index", and various monitors were developed to assess the DoA, including central function analyzing monitor (CFAM)[4], Bispectral (BIS) monitor, Nacotrend monitor, Patient State Analyser 4000, Score of Neonatal Acute Physiology (SNAP) monitor, Auditory evoked potential (AEP) monitor, Entropy-Module, Cerebral State monitor (CSM), and Index of Consciousness (IoC) monitor. With the advanced DoA monitors, the incidences of awareness have been reduced from 1%-2% in 1980s to about 0.1% in 2010[5].

Generally, the limitations of the existing DoA monitors include unsatisfied data filtering techniques, time delay and inflexible and low noise immunity problems. The latest research results show that there are still many improvements that can be done with the existing DoA monitors. Several important factors need to be considered carefully when designing new monitors as follows: avoiding or reducing the problems of the exciting DoA monitors using the latest techniques; adding the functions of personalised drug dosage suggestion and the prediction of the DoA and early warning. New DoA monitors should be portable and highly cost-effective, so that they can also serve as devices which are compatible with other monitors in clinical use.

Electrocardiogram (ECG) monitors are still the main monitors used in clinical in China nowadays. DoA monitors

---

*Corresponding author: Tian-Ning Li, Faculty of Health, Engineering and Sciences, University of Southern Queensland, Toowoomba, QLD 4350, Australia.
Tel: +61046871381
E-mail: tianning.li@usq.edu.au

are rarely used. The imported DoA monitors are hard to be promoted, due to its high cost and language problems.

As the awareness of the significance of monitoring the DoA, the demand for DoA monitors will increase evidently in the following years. Therefore, the development and sales of DoA monitors will be promising in China. Rather than to import DoA monitors from oversea, the domestic designed and produced DoA monitors can better meet the needs of the Chinese market.

Following the introduction section, we briefly described the existing DoA monitors and provided the comparison of different DoA algorithms. The latest DoA techniques were discussed and a feasible procedure of developing DoA monitors was proposed. Then, we addressed Chinese market review on using DoA monitors. Finally, a conclusion was drawn.

2. Existing DoA monitors

2.1. Review of existing DoA monitors

Determining the DoA using EEG signals is based on the changes in signal characteristics related to increasing concentrations of anaesthetics in the blood. An intravenous agent propofol, for example, induces a continuum of neurophysiological changes, which reflect on the spectral properties of EEGs[6]. However, the EEG signals are the signatures of neural activities[7], and their high nonlinearity and nonstationarity make the EEG signals hard to be assessed. In addition, individual patients have differences in variability and various factors, for instance, the degree of stimulation and pain induced by surgery and the use of concomitant analgesic drugs. Therefore, developing an accurate DoA index is indeed a challenging work.

The BIS index (A–2000 BIS monitor; Aspect Medical Systems Inc., Newton, MA) is a single index derived from a set of time domain and frequency domain measures[8]. It is calculated from the following four parameters: (i) burst suppression ratio (BSR); (ii) quazi suppression index; (iii) relative β ratio and (iv) synch fast slow. BIS is presented as a numerical index ranging from 100 (awake) to 0 (isoelectric EEG). Values below 60 indicate that the patient is almost certainly unconscious. Although the BIS monitor has received some critical press, it is an important reference or benchmark when developing a new DoA index.

The Nacotrend Monitor was produced by Monitor Technik in 2000, Switzerland. Compared to the BIS, the Narcotrend seems to perform better during emergence as it regains its baseline value upon discontinuation of the drug effect[9]. The Danmeter company designed the first generation of AEP monitor in 2001 and then AEP–Monitor/2. The new version applied autoregressive models with exogenous input to detect the AEP and added spectral EEG parameters to build DoA index[5]. In 2002, Physiometrix introduced the PSA–4000, which also displays a dimensionless number: the Patient State Index (PSI). While the PSI is based on similar principles to the BIS (i.e., composite index based on spectral and bispectral parameters), it differs in that it focuses on the power shift of specific frequency components between the frontal cortex and posterior lobes. In the same year, the SNAP monitor, the first Personal Digital Assistent (PDA)–based DoA monitor, was introduced by Nicolet Biomedical Monitors. It assesses high and low frequency EEGs and outputs a SNAP index that ranges from 0 to 99 (awake)[10]. The Morpheus medical company introduced the Index of Consciousness (IoC) monitor whose main algorithm is the symbolic dynamics method, which divides an EEG signal into a finite number of partitions with certain symbols and uses the alternations of symbols to determine the dynamics of the EEG. Entropy index monitoring produced by Datex–Ohmeda in 2003 was based on the acquisition and processing of raw EEGs and facial electromyography signals by using entropy algorithms to produce two parameters: state entropy (SE) and response entropy (RE)[11]. In 2004, Danmmeter devised the CSM. Its cerebral state index (CSI) is calculated using a fuzzy logic combination of four sub parameters of the EEG signals in time domain and frequency domain[12]. Besides, central function analysing monitor (CFAM)[4] which analyses EEG spectrum and amplitude is rarely used because of the limitations of the early technologies.

2.2. Comparison of different DoA monitors

In Musizza's research, a detailed comparison of different DoA monitors was reported[5]. They discussed the advantages and disadvantages of different monitors according to their algorithms at full length (See the summary in Table 1). Thus the repetitious details need not be given in this paper.

In this paper, we analyse the performance of different DoA monitors in clinical use and the functions of the latest models.

2.2.1. BIS

According to DoA monitors industry reports[13] and statistics, up to August 2013, 90% of the famous brands have BIS modules and more than 3 400 papers published are related to the BIS index. The BIS monitors are still the most popular monitor in the market. The newest BIS models have four electrodes to obtain two channels of EEG signals. The

Table 1

Comparison of DoA monitors summarized from the reference [5].

DoA monitors	Database included in the development of algorithm or for inference	Features or methods included in algorithm	Surrogate analysis	Burst suppression analysis	Index calculation
BIS	Yes	Bispectral analysis, beta-ratio	No	Yes	Weighted sum of subparameters
Narcotrend	Yes	SEF, median fr., spectral entropy, relative δ, θ, α, β, AR model	Yes	Yes	Classification function with plausibility analysis
PSA 4000	Yes	Several frequency domain features extracted from power spectrum	Yes	Yes	Plausibility analysis with surrogate testing against BSR and arousal parameters
AEP-Monitor/2	No; index based on previous studies of the algorithm	AEP, ARX model	Yes	Yes	Modulation of index based on SNR and EMG
Entropy module	No; index based on previous studies of the algorithm	Multiscale analysis, entropy, spectral entropy	No	Yes	Entropy, no inference algorithm
CSM	No; index based on previous studies of the algorithm	α, β, α-β power ratios	No	Yes	Fuzzy logic inference system
IoC	No; index based on previous studies of the algorithm	Symbol dynamics analysis	No	Yes	Fuzzy logic inference system

filter results are improved by comparing the signals of two channels. However, Nguyen-Ky *et al.* claimed that there were still some problems existing in the BIS monitors[14], including being redundant[15]; not responsive to some anaesthetic agents[16]; not robust across patients[17] and time delay[18]. In addition, the estimator requires averaged estimates at several levels of the estimation process. Stationary assumptions are imposed on a larger segment of the data[19] and performance is poor when poor signal quality[20].

2.2.2. AEP-Monitor/2

The AEP-Monitor/2 applies the autoregressive model with exogeneous input (ARX) model instead of moving time averaging (MTA) (old version) to calculate the middle latency auditory evoked potentials (MLAEP). As a result, the time delay for data collection decreases from 45–120 s to 2–6 s. However, the limitations of the AEP-Monitor/2 are that the quality of signals from the passive electrode is not good; it is only suitable for the patients who are more than 2 years old; it cannot be used for patients who have hearing impaired or severe neurological dysfunction; it cannot be applied for ear-nose-throat surgeries; and not convenient in clinical use.

2.2.3. CSM

The Danmeter CSM monitor equips with Danmeter Neuro sensors (the same as AEP). It is portable and able to connect with UP8000 monitor by wireless and it can be applied in intensive care unit (ICU) and infants' surgeries. However, some cases reveal that the CSI cannot reflect the real states of a patient.

2.2.4. Narcotrend monitor

The advantage of using the Narcotrend monitor is that its sensors are cheap. The disadvantages are that the monitor takes too large space to be applied in some small ICU or operating rooms; and the information obtained from the monitor is too complex to be understood timely.

2.2.5. Entropy modules

The latest E-Entropy modules can be used for the monitors with a newer version software than L-ANE03(A) or L-CANE03(A). The SE and RE can present different useful information. SE reflects the hypnotic effect of drugs on the cerebral cortex and RE serves as analgesic parameters. However, some researches reveal that BIS was seen to respond better with SE and RE in some cases[21] and the increase of the difference between SE and RE shows that the motor only responses to noxious simulation but not directly indicates the analgesia per se[22].

2.2.6. SNAP 2

The SNAP 2 can detect the useful information in low frequency band and predict the recovery of consciousness by high frequency band at the same time. But it can only analyse and present one channel raw EEG data and does not equip with paediatric sensors as BIS monitors.

2.3. Problems of existing DoA algorithms

Although the BIS monitor is the most popular one, it still received many criticisms. Other monitors based on different DoA algorithms improved the performance with different aspects. However, they are not widely used because of other various limitations. According to the review of existing DoA monitors, the following research gaps in the field are identified:

2.3.1. Unsatisfied filtering results

The filtering results were not satisfied with existing methods and it is hard to accurately evaluate the denoising results with EEG signals. Electromyography (EMG), ECG and electrooculography (EOG) cannot be removed efficiently by existing filtering methods[23]. In addition, all existing monitors were susceptible to electromagnetic (EM) interference[5]. Therefore, an efficient denoising method is urgently needed, especially in the case of denoising poor quality signals.

2.3.2. Time delay

The BIS and other existing monitors showed a long time delay after a change in a state of consciousness. The burst–suppression ratio (BSR), one important parameter for all the existing monitors, normally only represents a portion of the isoelectric EEG of 60 s (Table 2)[5], thus existing monitors are hard to avoid time delay.

Table 2
Susceptibility to EM interference and time delay[5].

DoA monitors	Susceptibility to EM interference	Estimated time delay
BIS	Moderate	63 s / 61 s
Narcotrend	Moderate	90 s /26 s
Entropy module	High	Data not available
CSM	Moderate	106 s / 55 s

2.3.3. Inflexible

Most of DoA algorithms (e.g., entropy algorithms) lack a mechanism for displaying the probability distribution. Since there is a wide variation in responses to the anaesthetic agents among individuals, the same effect–site concentrations, even if being accurately approximated, do not therefore induce similar EEG changes to all patients[24]. The BIS monitor received criticisms, such as non–responsive to some anaesthetic agents[16] and not robust across patients[17]. In addition, it is not reasonable to attempt to measure DoA changes with a single, complex parameter, but rather using multiple parameters that properly describe all the phases of the continuum from awake to very deep anaesthesia state[24]. Although most of the existing DoA algorithms used different multiple parameters to estimate DoA, the parameter selections were not flexible and they were limited in some aspects, Therefore, the existing DoA algorithms are not robust with the changes of agents or patients.

3. Discussion of the latest DoA algorithms

3.1. Latest research in DoA

EEG changes during the induction of anaesthesia are nonlinear and need, therefore, to be processed with nonlinear methods. The methods based on nonlinear dynamics theory and information theory, like entropy algorithm, have been proposed to process EEG data[11,25–30]. The approximate entropy can serve as an index of degree of conscious states or DoA[31]. However, compared with the sample entropy, it is more proper for long time series and less sensitive to the transform of complexity[32]. Multi–scale entropy (MSE) is also able to present the different states of patients using the distribution of complexity in different time scales[33].

The detrended moving–average (DMA) method is used to quantify correlation properties in nonstationary signals with underlying trends. It has been proposed to study the scaling properties of a time series[34,35]. The isomap–based estimation is designed to assess neurophysiological changes during anaesthesia and offers potentials for the development of more advanced systems for the DoA monitoring[24].

Empirical–mode decomposition (EMD) was proposed to explore the structure of EEG recordings[36,37]. The method can break a complicated signal into a series of oscillatory intrinsic mode functions (IMFs) embedded in the original signal[3]. Li *et al* have successfully established an approach centering on Hilbert–Huang transform (HHT) and EMD to analyze the EEG data for the DoA measurement[37]. Ensemble empirical–mode decomposition (EEMD), an adaptive time–frequency analysis method, is particularly suitable for extracting useful information from noisy nonlinear or nonstationary data. Unfortunately, since the EEMD is highly compute–intensive, the method does not apply in real–time applications on top of commercial–off–the–shelf computers. Aiming at this problem, a parallelized EEMD method was developed using general–purpose computing on the graphics processing unit (GPGPU), namely, G–EEMD[3]. The multivariate empirical mode decomposition (MEMD) can efficiently eliminate the noises among EMD, EEMD and complementary ensemble empirical mode decomposition (CEEMD)[32].

As one of the most popular choices in the time–frequency–transformations, wavelet transformation normally includes integral wavelet and orthonormal wavelet transformations. The former one is usually used for time–frequency analysis (TFA) and the later one enjoys a great popularity in the research of multi–resolution analysis (MRA). In 2001, wavelet decomposition of the EEG was adopted to assess the hypnotic state of anesthetized patients undergoing surgery. The results show that the technique could differentiate clearly between the anesthetized state and the awake "baseline" state[38]. Gifani *et al* claimed the DoA could be discriminated precisely using the detrended fluctuation analysis (DFA) on different scales of wavelet coefficients and quantifying the relative drift between the lines generated by DFA[39]. In 2006, wavelet entropy (WE) was designed to characterize the dynamical properties of EEGs and the results show that the WE measure distinguished the awake and asleep state in anaesthesia with a high accuracy of 95%[40]. Stationary wavelet transform (SWT) was used to analyse a single-channel (frontal) EEG signal to obtain a wavelet-based anaesthetic value for central nervous system monitoring (WAVCNS). The results show WAVCNS offers faster tracking of transitory changes at induction and emergence, with an average lead of 15–30 s compared with the BIS. In addition the WAVCNS regains its pre induction baseline value when patients are responding to verbal command after emergence from anaesthesia[41]. Through wavelet analysis technique, a steady-state index was developed to obtain steady-state information of the system response (inputs-output) which is useful for modelling the drugs combined effect[42]. Based on the features extracted using wavelet analysis, a radial-basis function (RBF) network is trained to calculate the index for DoA assessment[43]. Nguyen-Ky *et al* proposed a double wavelet-based de-noising algorithm to denoise the raw data and proposed to assess DoA based on discrete wavelet transform (DWT) and power spectral density (PSD) function[20,44,45]. The result shows that the proposed index reflected the patient's transition from consciousness to unconsciousness with the induction of anaesthesia in real time[46]. They also applied the wavelet transform on EEG signals to obtain a new index (namely WAI) which shows the conscious level of a patient. In 2012, Liang *et al* applied the Hurst exponent and wavelet transform in multiscale rescaled range analysis (MRRA) algorithms and received a satisfactory result[47].

Variational Bayesian framework was used to extract high order spectral features of EEG signals. The results show that better classification can be achieved with higher order spectral features in two third of anaesthetic agents[48]. In 2007, Rezek *et al* presented an autoregressive class of polyspectral models in the variation Bayesian framework[19]. Their results showed that the estimated higher order spectra significantly improved DoA assessment. A Bayesian dynamical model for quantifying probability of response and probability of correct response simultaneously was applied to trinary behavioural data from 10 human subjects undergoing general anaesthesia. This method served as an example of responses to auditory stimuli at varying levels of propofol anaesthesia ranging from light sedation to deep anaesthesia in human subjects[49]. Kortelainen et al. developed an algorithm based on Bayesian information criterion (BIC) for the assessment of the switch-like change in the signal characteristics occurring just before the awakening[50]. The result shows it detected the sudden change in the EEG related to the moment of awakening with a precision comparable to careful visual inspection. Based on Bayesian method, the MAP was applied to de-noise the wavelet coefficients based on a shrinkage function and the new Bayesian threshold shown better performance than the larger posterior mode (LPM) one. The effect of sample *n* and variance *r* on the maximum posterior probability (MPP) is studied. Compared with the BIS index, the new BDoA index could estimate the patient's hypnotic state in the case of poor signal quality[45].

To develop a reliable denoising method, the component of the noise should be analysed firstly. The external (environmental) noise and the physiological noise are the two main noise sources of EEG signals. The external noise is normally composed by AC power line noise and electromagnetic noise from the equipment and recording rooms. The physiological noise, such as EMG, ECG, EOG and skin potentials, is difficult to avoid during the recording process[51]. Based on previous studies, there is no accurate description (traits and magnitude) of the noise in EEG signals; but three types of noise, including Gaussian white noise, spiking noise and specific frequency noise, can be summed up[44,51–53]. To obtain high quality denoised EEG signals, external environmental noise should be eliminated using efficient methods during data recording process[51]. Algorithms based on known EMG, ECG and EOG data (e.g., adaptive filtering[54] and blind source separation[55]) are developed to remove these interferences from EEG signals. The other types of noise are eliminated using advanced denoising methods (*eg*., signal averaging, filtering). Normally, the frequencies below 0.01 Hz (caused by sweating and drifts in electrode impedance) and those above 100 Hz (caused by contraction of muscles) are filtered out[51]. The noise from electricity lines (50 or 60 Hz) can be eliminated by notch filters. Although most of the existing DoA monitors have artefact detection and removal modules, the denoising results are not satisfied by researchers.

To eliminate the EMG, AC power line, electrode disturbance and other disturbances, the wavelet transform noise rejection methods including wavelet decomposition and reshape, wavelet threshold values and wavelet max-module method were applied in EEG signal denoising[56]. The newest outcomes include an adaptive threshold technique to remove spikes and low-frequency noise from raw EEG data and the results revealed the output EEG signal is almost noiseless when using the hard threshold[44]; a new Bayesian wavelet threshold based on the maximum a posterior (map) is applied to de-noise the wavelet coefficients[45] and it performed better than the wavelet threshold based on LPM[57]. The experiments also proved that the de-noising algorithm did not filter out any important information regarding the DoA. However, these methods are mainly based on the Fourier transform, and their denoising results of EEG signals (which is not cycle or steady) are not that good[58]. While the Hilbert-Huang transform (HHT) shows better performance in EEG signal denoising, the empirical-mode decomposition, one important part of HHT, is highly compute-intensive and may lead to time delay in some cases.

To reduce the time delay, an adaptive window length technique in T Nguyen-Ky *et al*'s paper[44] was applied to compute the optimum length of the sliding window and the results show that the new index can reflect the changes between consciousness and unconsciousness during emergence from anaesthesia in nearer to real time. Correspondingly, there is a remarkable time lag with the BIS index. In T Nguyen-Ky *et al*'s later study[45], a new index BDoA was proposed based on the MPP values, which performed better in detecting the anaesthesia states' change from awake to light, moderate and deep anaesthesia than the BIS index.

To enhance the flexibility and robustness of a DoA index, a novel technology using the spectral features of EEG was presented for separating the anaesthetic effects of propofol and an ultrashort-acting opioid, remifentanil. The results show that the feature set is able to detect the impacts of propofol and classify whether remifentanil has been coadministered or not. As a result, the determination of the clinical state of the patient becomes more accurate[24].

The latest DoA algorithms are summarized in Table 3.

Table 3

Summary of latest DoA algorithms.

Algorithms	Derivative algorithms	Reference
Entropy	Entropy	[11,25-30]
	Approximate entropy	[31]
	Sample entropy	[32]
	Multi-scale entropy	[33]
DMA	MDMA	[20]
Isomap-based estimation	Isomap-based estimation	[24]
EMD	Empirical-mode decomposition	[36,37]
	EEMD	[37]
	G-EEMD	[3]
	MEMD	[32]
	CEEMD	[32]
Wavelet	Wavelet	[38,42]
	DFA	[39]
	Wavelet entropy	[40]
	WAVCNS	[41]
	RBF	[43]
	DWT	[20,44-46]
	MRRA	[47]
Bayesian	Bayesian	[48]
	Variation Bayesian	[19,49]
	BIC	[50]
	MAP	[45]
	MPP	[45]

3.2. *Improving DoA monitors*

When designing new DoA monitors, several important factors need to be considered carefully as follows.

3.2.1. *Avoiding or reducing the problems in exciting DoA monitors*

According to the latest review, a new DoA monitor should avoid or reduce the unsatisfied filtering and time delay problems, so that the new product can detect the changes of patient's anaesthesia stages timely and it is still able to perform well even the quality of EEG signals is poor.

3.2.2. *Suggesting of drug dosage*

The flexibility and robust of a new DoA monitor should be improved. The monitor can accurately assess the impact of different types of drugs and suggest the dosage of anaesthetic agents.

3.2.3. *Predicting and early warning*

With advanced prediction algorithms, new monitors should be able to predict the trend of DoA index in the following period and provide early warning when inconsistent.

3.2.4. *Portable and high cost-effective*

Considering the space limitations of an operating room, a new DoA monitor could also serve as modules which are compatible with other monitors in clinical use. All the older generation of monitors have EEG modules which can present two to four channels of EEG patterns. However, because of the complexity of EEG patterns, they are difficult to use for timely diagnosis and are not popular. A new monitor should present useful information succinctly. Although some latest monitors (*eg*., CSM and SNAP2) are portable and convenient in some extent, further improvements for their compatibility and more functions are still needed to be added in. Besides, high cost-effective is also a significant factor for promoting the use of DoA monitors.

4. Chinese DoA market review

4.1. *Increase awareness towards the DoA monitoring*

With the advanced DoA monitors, the incidence of awareness has been reduced from 1%-2% in 1980s to about 0.1% in 2010[5]. However, since DoA monitors are not widely used in clinical in China and most of the DoA assessments depend on anaesthetists' empirical experience, the incidences of intraoperative awareness in China (0.72%-2.00%) is much higher than the international average[59]. The intraoperative awareness is considered as major medical causality in developed countries. However, there are currently no clear regulations to define the intraoperative awareness in China nowadays. As the increase of Chinese people's awareness to health and medical knowledge, the intraoperative awareness causes an increasing number of medical disputes inevitably. Accurately assessing the DoA is becoming a significant issue to be addressed in the near future in China.

4.2. Chinese DoA Market

DoA monitors are widely used in general anaesthesia. According to statistics, on average, there were recently about 90 million cases of surgeries with general anaesthesia (not including eye surgeries) per year in China[60]. Taking Shanghai as an example, there are 530 000 cases in 2005, 880 000 cases in 2009 and 1.26 million cases in 2012[59,60]. The number of cases increases yearly. It is predicted that the annual amount will reach 155 million during the period from 2014 to 2018. It is better to allocate one DoA monitor in every operating room, so the demand of DoA monitors for each hospital will be more than one. According to the data from Chinese National Bureau of Statistics[60], by the end of 2011, there were 1 399 third-grade hospitals, 6 468 second-grade hospitals and 5 636 first-grade hospitals in China. Only a few third-grade class-A hospitals have been equipped with DoA monitors. There is potentially a large market demanding DoA monitors in China.

4.3. Existing DoA products and vendors in China

Although the demand for DoA monitors in China keeps increasing, the available products in China are very limited. There are only about 20 companies serving as agents to sell the imported DoA monitors according to a market review. Because of the high price and various barriers to get into hospitals, the imported DoA monitors are not easy to be promoted in China. There are no improvements in Chinese manufactured DoA monitors because most of the key techniques are adopted from overseas[59]. In China, the price negotiation during purchasing process is complex and unreasonable. Chinese products are not widely used in China either. According to China Food and Drug Administration, only eight types of products have obtained the national production license. Seven out of eight DoA monitors are based on the techniques imported. One is from bispectral algorithms; three from CSI algorithms, two from IoC algorithms and one by nonlinear algorithms (Entropy modules). Totally, 10 types of monitors are produced by eight companies. Two of them obtained the national production license in 2010, one in 2011, six in 2012 and one in 2013. On average, the selling of each product is around 60 per year. This indicates the sales of Chinese DoA monitors are not good.

4.4. The prospect of Chinese DoA monitors

Though the market of DoA monitors in China is not satisfied by investors recently, the prospect of Chinese DoA monitors will be exciting because of the increasing awareness towards the DoA monitoring and the fact that the demand is much greater than the supply. Another important factor is that the research and development costs for DoA monitors are high but the cost of the production is low. So the market of DoA monitors will be lucrative once the mass production is in action. Based on a market review, the market price of Chinese domestic DoA monitors is from 230 000 RMB to 380 000 RMB per unit. The price of imported DoA monitors is about €12 000 but the import tariffs are high. Supposed the profit for one new Chinese domestic monitor is 50 000 RMB, there are around 10 000 third-grade and second-grade hospitals and 50% of them would demand setup two monitors on average. The Chinese market capacity will be 500 million RMB approximately.

5. Conclusion

This paper conducts a comprehensive review about existing DoA monitors and their algorithms in China. The results show that the limitations of existing DoA monitors include (i) EMG and other high-frequency electrical artifacts are common and interfere with EEG interpretation. (ii) Data processing time produces a lag in the computation of the depth-of-anaesthesia monitoring index. (iii) The EEG effects of anaesthetic drugs are not good predictors of movement in response to surgical stimulus because the main site of action for anaesthetic drugs to prevent movement is the spinal cord. The currently available monitoring algorithms do not account for all anaesthetic drugs, including ketamine, nitrous oxide and halothane. The use of DoA monitoring in children is not as well understood as in adults.

Efforts in solving or answering the above questions should be encouraged and promoted. In particular, the review suggests improving the existing DoA monitors in four aspects. They are drug dosage indication, prediction and early warning, and portable and high cost-effective.

The review on Chinese domestic market also reveals that the demand for DoA monitors is much higher than the supply. However, there are various barriers for imported DoA monitors, and Chinese monitors have not yet been widely accepted. The market of using DoA monitors will be lucrative once mass production is in operation.

Conflict of interest statement

We declare that we have no conflict of interest.

References

[1] Nakamura M, Sanjo Y, Ikeda K. Predicted sevoflurane partial pressure in the brain with an uptake and distribution model: Comparison with the measured value in internal jugular vein blood. *J Clin Monit Comput* 1999; **15**(5): 299–305.

[2] Bowdle TA. Depth of anesthesia monitoring. *Anesthesiol Clin* 2006; **24**(4): 793–822.

[3] Chen D, Li D, Xiong M, Bao H, Li X. GPGPU-aided ensemble empirical-mode decomposition for EEG analysis during anesthesia. *IEEE Trans Inf Technol Biomed* 2010; **14**(6): 1417–1427.

[4] Maynard D, Jenkinson J. The cerebral function analysing monitor Initial clinical experience, application and further development. *Anaesthesia* 1984; **39**(7): 678–690.

[5] Musizza B, Ribaric S. Monitoring the depth of anaesthesia. *Sensors* 2010; **10**(12): 10896–10935.

[6] Kortelainen J, Koskinen M, Mustola S, Seppänen T. Time-frequency properties of electroencephalogram during induction of anesthesia. *Neurosci Lett* 2008; **446**(2): 70–74.

[7] Sanei S, Chambers JA. EEG signal processing. Wiley-Interscience; 2008.

[8] Pomfrett C, Pearson A. EEG monitoring using bispectral analysis. *Engin Sci Educ J* 1998; **7**(4): 155–157.

[9] Schmidt GN, Bischoff P, Standl T, Jensen K, Voigt M, Esch JS. Narcotrend® and Bispectral Index® monitor are superior to classic electroencephalographic parameters for the assessment of anesthetic states during propofol-remifentanil anesthesia. *Anesthesiology* 2003; **99**(5): 1072–1077.

[10]Willmann K, Springman S, Rusy D, Daily E. A preliminary evaluation of a new derived EEG index monitor in anesthetized patients. *J Clin Monit Comput* 2002; **17**(6): 345–350.

[11]Viertiö-Oja H, Maja V, Särkelä M, Talja P, Tenkanen N, Tolvanen-Laakso H, et al. Description of the Entropy algorithm as applied in the Datex-Ohmeda S/5 Entropy Module. *Acta Anaesthesiol Scand* 2004; **48**(2): 154–161.

[12]Jensen E. Cerebral state monitoring and pharmacodynamic modelling by advanced fuzzy inferencestate of the art. Präsentation vorgestellt auf: AMCA; 2005.

[13]Aspect. Analysis of the competitors of BIS 2013. [Online] Available from: http://www.docin.com/p-511924648.html

[14]Nguyen-ky T, Wen P, Li Y. An improved Chaos method for monitoring the depth of anaesthesia. In: *2013 International Conference on Computing, Management and Telecommunications (ComManTel) IEEE* 2013; p. 321–325.

[15]Schneider G, Schöniger S, Kochs E. Does bispectral analysis add anything but complexity? BIS sub-components may be superior to BIS for detection of awareness. *Br J Anaesth* 2004; **93**(4): 596–597.

[16]Johansen JW, Sebel PS, Sigl JC. Clinical impact of hypnotic-titration guidelines based on EEG bispectral index (BIS) monitoring during routine anesthetic care. *J Clin Anesth* 2000; **12**(6): 433–443.

[17]Hall J, Lockwood G. Bispectral index: comparison of two montages. *Br J Anaesth* 1998; **80**(3): 342–344.

[18]Kuizenga K, Wierda J, Kalkman C. Biphasic EEG changes in relation to loss of consciousness during induction with thiopental, propofol, etomidate, midazolam or sevoflurane. *Br J Anaesth* 2001; **86**(3): 354–360.

[19]Rezek I, Roberts SJ, Conradt R. Increasing the depth of anesthesia assessment. *IEEE Eng Med Biol Mag* 2007; **26**(2): 64–73.

[20]Nguyen-Ky T, Wen P, Li Y. An improved detrended moving-average method for monitoring the depth of anesthesia. *IEEE Trans Biomed Eng* 2010; **57**(10): 2369–2378.

[21]Vanluchene A, Struys M, Heyse B, Mortier E. Spectral entropy measurement of patient responsiveness during propofol and remifentanil. A comparison with the bispectral index. *Br J Anaesth* 2004; **93**(5): 645–654.

[22]Takamatsu I, Ozaki M, Kazama T. Entropy indices vs the bispectral index™ for estimating nociception during sevoflurane anaesthesia. *Br J Anaesth* 2006; **96**(5): 620–626.

[23]Johansen JW. Update on bispectral index monitoring. *Best Pract Res Clin Anaesthesiol* 2006; **20**(1): 81–99.

[24]Kortelainen J, Vayrynen E, Seppanen T. Depth of anesthesia during multidrug infusion: separating the effects of propofol and remifentanil using the spectral features of EEG. *IEEE Trans Biomed Eng* 2011; **58**(5): 1216–1223.

[25]Bein B. Entropy. *Best Pract Res Clin Anaesthesiol* 2006; **20**(1): 101–109.

[26]Bruhn J, Lehmann LE, Röpcke H, Bouillon TW, Hoeft A. Shannon entropy applied to the measurement of the electroencephalographic effects of desflurane. *Anesthesiology* 2001; **95**(1): 30–35.

[27]Bruhn J, Röpcke H, Rehberg B, Bouillon T, Hoeft A. Electroencephalogram approximate entropy correctly classifies the occurrence of burst suppression pattern as increasing anesthetic drug effect. *Anesthesiology* 2000; **93**(4): 981–985.

[28]Cao Y, Tung W-w, Gao JB, Protopopescu VA, Hively LM. Detecting dynamical changes in time series using the permutation entropy. *Phys Rev E Stat Nonlin Soft Matter Phys* 2004; **70**(4 Pt 2): 046217.

[29]Fell J, Röschke J, Mann K, Schäffner C. Discrimination of sleep stages: a comparison between spectral and nonlinear EEG measures. *Electroencephalogr Clin Neurophysiol* 1996; **98**(5): 401–410.

[30]Li X, Sleigh J, Voss L, Ouyang G. Interpretation of anesthetic drug effect using recurrent dynamics of EEG recordings. *Neurosci Lett* 2007; **424**: 47–50.

[31]Fan SZ, Yeh JR, Chen BC, Shieh JS. Comparison of eeg approximate entropy and complexity measures of depth of anaesthesia during inhalational general anaesthesia. *J Med Biol Eng* 2011; **31**: 359–366.

[32]Wei Q, Liu Q, Fan SZ, Lu CW, Lin TY, Abbod MF, et al. Analysis of EEG via multivariate empirical mode decomposition for depth of anesthesia based on sample entropy. *Entropy* 2013; **15**(9):

3458–3470.

[33]Liu Q, Wei Q, Fan SZ, Lu CW, Lin TY, Abbod MF, et al. Adaptive computation of multiscale entropy and its application in EEG signals for monitoring depth of anesthesia during surgery. *Entropy* 2012; 14(6): 978–992.

[34]Arianos S, Carbone A. Detrending moving average algorithm: A closed-form approximation of the scaling law. *Physica A* 2007; 382(1): 9–15.

[35]Xu L, Ivanov PC, Hu K, Chen Z, Carbone A, Stanley HE. Quantifying signals with power-law correlations: A comparative study of detrended fluctuation analysis and detrended moving average techniques. *Phys Rev E Stat Nonlin Soft Matter Phys* 2005; 71(5): 051101.

[36]Sweeney-Reed C, Nasuto S. A novel approach to the detection of synchronisation in EEG based on empirical mode decomposition. *J Comput Neurosci* 2007; 23(1): 79–111.

[37]Li X, Li D, Liang Z, Voss LJ, Sleigh JW. Analysis of depth of anesthesia with Hilbert-Huang spectral entropy. *Clin Neurophysiol* 2008; 119(11): 2465–2475.

[38]Bibian S, Zikov T, Dumont GA, Ries CR, Puil E, Ahmadi H, et al. Estimation of the anesthetic depth using wavelet analysis of electroencephalogram. In: *Engineering in Medicine and Biology Society, 2001 Proceedings of the 23rd Annual International Conference of the IEEE*. IEEE; 2001; p. 951–955.

[39]Gifani P, Rabiee H, Hashemi M, Ghanbari M. Extraction of anesthesia depth using self similarity and fluctuation analysis on the wavelet coefficients of EEG. In: *The 3rd IEE International Seminar on Medical Applications of Signal Processing (Ref No 2005-1119)*. IET; 2005; p. 7–12.

[40]Ye Z, Tian F, Weng J. EEG signal processing in anesthesia-using wavelet-based informational tools. In: *27th Annual International Conference on Engineering in Medicine and Biology Society IEEE-EMBS*. IEEE; 2006; p. 4127–4129.

[41]Zikov T, Bibian S, Dumont GA, Huzmezan M, Ries CR. Quantifying cortical activity during general anesthesia using wavelet analysis. *IEEE Trans Biomed Eng* 2006; 53(4): 617–632.

[42]Castro A, Almeida FG, Amorim P, Nunes CS. A wavelet based method for steady-state detection in anesthesia. In: *Engineering in Medicine and Biology Society, 2009 EMBC 2009 Annual International Conference of the IEEE*. IEEE; 2009; p. 954–957.

[43]Taslimi P, Rabiee HR, Shakouri G. An empirical centre assignment in RBF network for quantification of anaesthesia using wavelet-domain features. In: *NER'09 4th International IEEE/EMBS Conference on Neural Engineering*. IEEE; 2009; p. 510–513.

[44]Nguyen-Ky T, Wen P, Li Y, Gray R. Measuring and reflecting depth of anesthesia using wavelet and power spectral density. *IEEE Trans Inf Technol Biomed* 2011; 15(4): 630–639.

[45]Nguyen-Ky T, Wen P, Li Y. Consciousness and depth of anesthesia assessment based on Bayesian analysis of EEG signals. *IEEE Trans Biomed Eng* 2013; 60(6): 1488–1498.

[46]Ghanatbari M, Mehridehnavi A, Rabbani H, Mahoori A, Mehrjoo M. A comparative study of the output correlations between wavelet transform, neural and neuro fuzzy networks and BIS index for depth of anesthesia. In: *2010 IEEE Symposium on Industrial Electronics & Applications (ISIEA)*. IEEE; 2010; p. 655–659.

[47]Liang Z, Li D, Ouyang G, Wang Y, Voss LJ, Sleigh JW, et al. Multiscale rescaled range analysis of EEG recordings in sevoflurane anesthesia. *Clin Neurophysiol* 2012; 123(4): 681–688.

[48]Rezek I, Roberts SJ, Siva E, Conradt R. Depth of anaesthesia assessment with generative polyspectral models. *In: Fourth International Conference on Machine Learning and Applications*. IEEE; 2005; p. 6

[49]Wong KFK, Smith AC, Pierce ET, Harrell PG, Walsh JL, Salazar AF, et al. Bayesian analysis of trinomial data in behavioral experiments and its application to human studies of general anesthesia. In: *Engineering in Medicine and Biology Society, EMBC, 2011 Annual International Conference of the IEEE*. IEEE; 2011; p. 4705–4708.

[50]Kortelainen J, Vayrynen E, Jia X, Seppanen T, Thakor N. EEG-based detection of awakening from isoflurane anesthesia in rats. In: *Engineering in Medicine and Biology Society (EMBC), 2012 Annual International Conference of the IEEE*. IEEE; 2012; p. 4279–4282.

[51]Repovš G. Dealing with noise in EEG recording and data analysis. In: *Informatica Medica Slovenica*. 2010; p. 18–25.

[52]Ryynanen O, Hyttinen J, Malmivuo J. Study on the spatial resolution of EEG-effect of electrode density and measurement noise. In: *Engineering in Medicine and Biology Society, 2004 IEMBS'04 26th Annual International Conference of the IEEE*. IEEE; 2004; p. 4409–4412.

[53]Zandi AS, Dumont GA, Yedlin MJ, Lapeyrie P, Sudre C, Gaffet S. Scalp EEG acquisition in a low-noise environment: A Quantitative assessment. *IEEE Trans Biomed Eng* 2011; 58(8): 2407–2417.

[54]He P, Wilson G, Russell C. Removal of ocular artifacts from electro-encephalogram by adaptive filtering. *Med Biol Eng Comput* 2004; 42(3): 407–412.

[55]Romero S, Mañanas MA, Barbanoj MJ. A comparative study of automatic techniques for ocular artifact reduction in spontaneous EEG signals based on clinical target variables: a simulation case. *Comput Biol Med* 2008; 38(3): 348–360.

[56]Yu L. EEG de-noising based on wavelet transformation. In: *3rd International Conference on Bioinformatics and Biomedical Engineering ICBBE*. IEEE; 2009; p. 1–4.

[57]Cutillo L, Jung YY, Ruggeri F, Vidakovic B. Larger posterior mode wavelet thresholding and applications. *J Stat Plan Inference* 2008; 138(12): 3758–3773.

[58]Zhang L, Wu D, Zhi L. Method of removing noise from EEG signals based on HHT method. In: *2009 1st International Conference on Information Science and Engineering (ICISE)*. IEEE; 2009; p. 596–599.

[59]Hong W, Zhang Z, Song J, zhang T, Liu X, Chen N, et al. Current situation and prospect of the method and instruments for monitoring the depth of anesthesia. *Chin J Biomed Engin* 2011; 30(5): 781–786.

[60]China NBoSo. China Statistic Yearbook. 2013. [Online]. Available from:http://www.stats.gov.cn/.