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Monitoring the Depth of Anesthesia from Rat EEG using Modified Shannon Entropy Analysis

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Abstract— **In this paper, an entropy based method for quantifying the depth of anesthesia from rat EEG is presented. The proposed index for the depth of anesthesia called modified Shannon entropy (MShEn) is based on Shannon entropy (ShEn) and spectral entropy (SpEn) which are widely used for analyzing non-stationary signals. Discrimination power (DP), as a performance indicator for indexes, is defined and used to derive the final index for the depth of anesthesia. For experiment, EEG from anesthetized rats are measured and analyzed by using MShEn. MShEn shows both high stability and high correlation with other indexes for depth of anesthesia.**

I. INTRODUCTION

The therapeutic index, a ratio of the dose that kill 50% of population to the effective dose for 50% of population, of general anesthetics is only $3-4$, whereas the indexes for many drugs are on the order of several hundreds, implying that anesthetics are powerful poisons [1]. Due to this narrow margin, patients often undergo intraoperative awareness, postoperative recall and aftereffects. Therefore, patients should be continuously monitored throughout surgeries in order to use proper amount of anesthetic agent.

Results from both human and animal studies demonstrate that changes in EEG during anesthesia reflect hypnotic state of the subject. In recent years, monitoring the depth of anesthesia based on EEG signal has been an active research topic. Many methods for quantifying the level of consciousness have been proposed and some of them are commercialized. Bispectral index (BIS) monitor [2] from Aspect Medical Systems, Entropy monitor [3] from Datex Ohmeda and NeuroSENSE monitor [4] from NeuroWave Systems are the well-known results. Despite these results, the research on monitoring the level of consciousness based on EEG is still active as those monitors sometimes provide wrong indexes under certain circumstances [5].

Since EEG from conscious subject tends to show unpredictable and dynamic behavior compared to EEG from anesthetized subject, entropy and complexity have been extensively studied as a measure of level of consciousness. Among many different ways of defining complexity and entropy, researchers have found that spectral entropy (SpEn), wavelet entropy, approximate entropy (ApEn), and Lempel-Ziv complexity have large correlation with depth of anesthesia [6]. As a comparison of these methods, in [7], SpEn, ApEn, complexity, fractal dimension and BIS are calculated from EEG of 150 patients undergoing general anesthesia. SpEn performed best of the entropy and complexity measures, and similar to BIS. On the other hand, Shannon entropy (ShEn) has not been widely used to measure the level of consciousness from EEG signal.

In this work, modified Shannon entropy (MShEn) is proposed as a measure of the depth of anesthesia from EEG signal. ShEn is modified based on the data set from rat EEG measurement in a way to discriminate EEG data from awake subject and anesthetized subject. Despite its computational simplicity, the experimental results show that it outperforms other entropy measures in discriminating EEG signals from different states.

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II. MODIFIED SHANNON ENTROPY (MSHEN) : CONCEPT AND DERIVATION

Following approach is used to derive an entropy based measure for depth of anesthesia. First, two data sets are defined as follows and are extracted from the measurement results in order to derive an index for depth of anesthesia. The experimental procedure for obtaining EEG data is explained in Section III.

- $\mathbf{D_{AW}}$ (awake state) : 30 epochs recorded from 8 awake rats. The length of each epoch is $16s$.
- $\mathbf{D_{AN}}$ (deep hypnotic state): 30 epochs recorded from 3 rats in deep hypnotic state. The length of each epoch is $16s$. Isoelectric EEG is often observed.

Each epoch is normalized by its RMS value. This is inevitable when evaluating anesthetic depth from EEG signal, as amplitude of EEG is vulnerable to measurement conditions such as contact impedance of electrodes. Let f be a function that maps an observed EEG vector $\mathbf{x}$ to an index that represents the depth of anesthesia

$$f : \mathbf{x} \longrightarrow f(\mathbf{x}) = \text{Index for Depth of Anesthesia} \tag{1}$$

and discrimination power (DP) is defined as follows as an index for evaluating the function f, where the conceptual explanation about DP is presented in Fig. 1.

$$DP = \frac{|MEAN(f(\mathbf{D_{AW}})) - MEAN(f(\mathbf{D_{AN}}))|}{(STD(f(\mathbf{D_{AW}})) + STD(f(\mathbf{D_{AN}})))/2} \tag{2}$$

We define our goal as to find a function f that maximizes DP by modifying entropy measures based on DP test results.

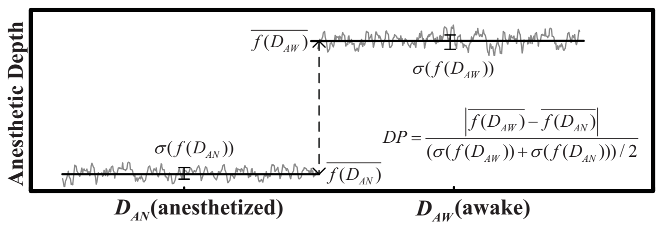

Fig. 1. Description of DP. DP quantifies the degree of discrimination for two sets of data.

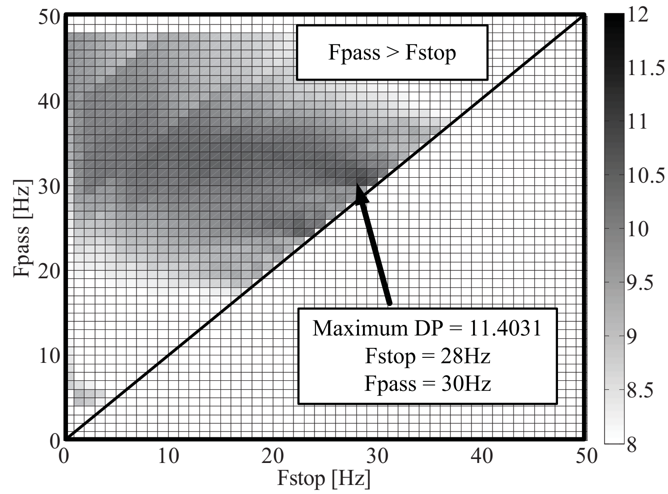

Fig. 2. DP of ShEn calculated after high-pass filtering the signal with different pass-band and stop-band frequencies is calculated. DP is maximized when $F_{pass} = 30Hz$ and $F_{stop} = 28Hz$.

A. Entropy measures used for EEG analysis

1) Shannon Entropy (ShEn): ShEn [8] quantifies the histogram of a signal as (3), where a_i is the discrete set of signal amplitude and $p(a_i)$ is the probability that amplitude a_i occurs.

$$ShEn = \frac{-\sum_{i=1}^{k} p(a_i) \log p(a_i)}{\log k} \tag{3}$$

The DP of ShEn is 0.7413, implying that it has little information about the depth of anesthesia. This limitation is from the fact that ShEn does not contain any frequency domain information where amplitude information in each epoch in the data sets is removed by normalizing it with its RMS value.

2) Spectral Entropy (SpEn): SpEn can be calculated as follows, where f_i is the discrete set of frequency and $PSD(f_i)$ is the normalized power spectral density at f_i.

$$SpEn = \frac{-\sum_{i=1}^{k} PSD(f_i) \log PSD(f_i)}{\log k} \tag{4}$$

The DP of SpEn is 9.4076, proving its high performance on discriminating EEG signals from different states.

3) Approximate Entropy (ApEn): ApEn [9] measures the unpredictability or repeatability of a signal. Given a signal $\mathbf{X} = \{x_1 x_2 x_3 \cdots x_N\}$, ApEn is calculated as follows. First, a positive integer m and a positive real number r_f are determined. Second, $N - m + 1$ vectors are constructed as $\mathbf{X_m}(i) = \{x_i x_{i+1} x_{i+2} \cdots x_{i+m-1}\}$ and the distance between two vectors is defined as follows.

$$Dist(\mathbf{X_m}(i), \mathbf{X_m}(j)) = \max(|\mathbf{X_m}(i) - \mathbf{X_m}(j)|) \tag{5}$$

Next, $C_i^m(r_f)$ is defined as $1/(N - m + 1)$ times the number of vectors $\mathbf{X_m}(j)$ falling within vector distance r_f of $\mathbf{X_m}(i)$. Finally, the ApEn is defined as follows :

$$ApEn = \frac{\sum_{i=1}^{N-m+1} \log C_i^m(r_f)}{N-m+1} - \frac{\sum_{i=1}^{N-m} \log C_i^{m+1}(r_f)}{N-m}. \tag{6}$$

The DP of ApEn is 7.7795.

4) Lempel-Ziv Complexity (LZC): LZC [10] is a measure of number of patterns in a given sequence of symbols. For calculation of LZC for a sequence of symbols $\mathbf{X} = \{x_1 x_2 x_3 \cdots x_N\}$, the sequence is decomposed into consecutive blocks as $\mathbf{X} = B_1, B_2, B_3, \cdots B_n$. B_1 is set to x_1 and B_i ($i \geq 2$) is defined as the minimal size of block that has not shown in B_j ($1 \leq j < i$). Finally, the complexity is defined as $LZC = \frac{n}{N} \log_\alpha N$, where α is the number of symbols. The DP of LZC is 4.8526 and the DP test result for various entropies and their specifications are summarized in Table. I.

B. Proposed Modified Shannon Entropy (MShEn)

As aforementioned, the limitation of using ShEn of EEG as a measure of the depth of anesthesia comes from the fact that it does not reflect any frequency domain information. Therefore, it can be expected that ShEn may provide more information about the depth of anesthesia, once it is modified to reflect frequency domain information.

Our approach to modify ShEn is to calculate entropy from the high frequency component of EEG signal, based on the report that loss of consciousness after anesthetic administration showed a marked drop in high frequency band activity. EEG signal is filtered by an FIR high-pass filter, to calculate entropy from high frequency component. In order to find an optimum high-pass filter that maximizes DP, many high-pass filters with different frequency responses are tested and the result is shown in Fig. 2. F_{pass} and F_{stop}, which are the filter design parameters, are used to represent the characteristic of the filter where the order of the filters is fixed to 15. It can be seen that the maximum DP of 11.4031 is achieved when $F_{pass} = 30Hz$ and $F_{stop} = 28Hz$.

For further improvement of DP by modifying the index to reflect more frequency domain information, SpEn is multiplied to the ShEn from high-pass filtered signal. Before the multiplication, the entropy values are linearly mapped into

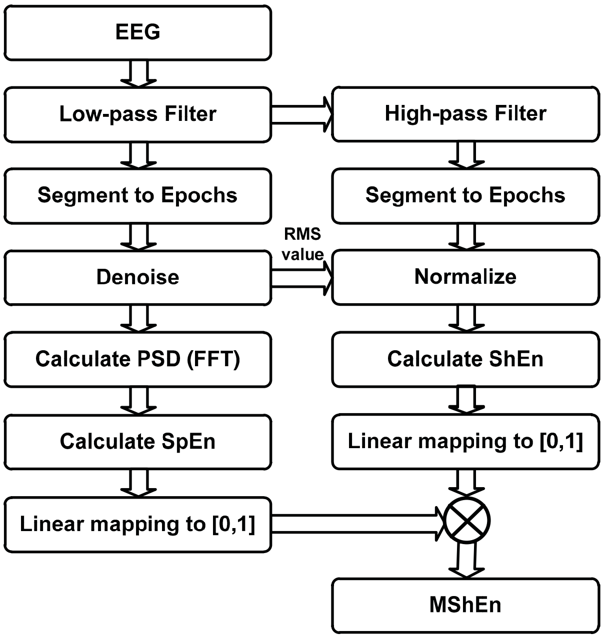

Fig. 3. The proposed algorithm for calculating MShEn. ShEn is calculated after high-pass filtering the signal and SpEn is multiplied to the result.

Method	DP	Parameter	Value
ShEn	0.7413	number of histogram bins, k	64
SpEn	9.4076	number of channels, k	16
ApEn	7.7795	Embedding dimension, m	2
		Filtering level, r_f	0.2STD
LZC	4.8526	number of symbols, α	3
MShEn	**13.2497**	number of histogram bins, k	64

TABLE I
SPECIFICATION AND DISCRIMINATION POWER OF SHEN, SPEN, APEN, LZC AND PROPOSED MSHEN.

$[0, 1]$. Finally, an entropy based index for depth of anesthesia, named modified Shannon entropy (MShEn), is obtained and the overall procedure for the calculation of MShEn is shown in Fig. 3. The DP of MShEn is 13.2497, which is much higher than that of other entropy based measures. It should be noted that even small increase in DP, in analogous to the effect of SNR on BER in communication systems, may result in significant increase in the reliability of the index.

III. EXPERIMENTS

A. Subject Strains

Male and female Sprague Dawley rats aged from 6 to 10 weeks and weighing 150-250 grams were used in the experiment. Rats were group housed in transparent Plexiglas cages ($38cm \times 25cm \times 19cm$) and freely accessible to food and water. The temperature was held constant at $21 \pm 2°$C and the humidity was maintained between $16 \pm 2\%$. The experimental protocols were approved by Institutional Animal Care and Use Committee, KAIST, Korea.

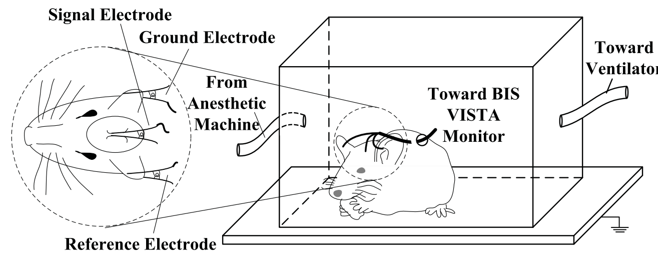

Fig. 4. Experimental setup and top view of the rat head with the electrodes. The signal electrode is clipped on the scalp and the ground and the reference electrodes are clipped on the right and left ear, respectively. Electrolyte is pasted on the electrodes.

B. Experimental Procedure

Before the measurement, the scalp hair of the rats was shaved while the rats were anesthetized with 2.5-3.5 mL/Kg mixed anesthetic agent(volumetric ratio 4:1 of zoletil and rompun, respectively) administered intraperitoneally. All rats had three to five days of relaxation period after shaving. The EEG signal was recorded by BIS VISTA monitor (Version 3.00), which also provides useful indexes such as BIS, EMG and spectral edge frequency (SEF). Copper alligator clips were used as the electrodes for measuring EEG, as the BIS electrodes are designed to be used for human. Signal electrode, the reference electrode and the ground electrode were clipped to the middle of scalp, the left ear and the right ear, respectively. After attachment of the electrodes, electrolyte was pasted at the contact points in order to ensure high conductivity.

The rats were under the inhalation anesthesia by anesthesia machine with enflurane. During the measurements, the rats were kept in a chamber as shown in Fig. 4. For continuous change in the concentration of the anesthetic gas, the gas from anesthesia machine was delivered to the chamber instead of directly delivering the gas to the rats. Artificial respirator in the anesthesia machine was not used since the tidal volume of the respirator is not appropriate for rats.

During measurements, the flow rate and concentration of anesthetic agents were controlled with 3 steps. First, 0.5 LPM of oxygen mixed with 5% of enflurane was provided for inducing anesthesia for 15-20 minutes. Second, the delivery of anesthetic gas was stopped for maintaining deep anesthesia for 5-10 minutes. Finally, 0.4 LPM of pure oxygen was supplied into the chamber for awakening the rat. Measurements were ended when the rat became conscious and started to move.

IV. RESULT & DISCUSSION

Once EEG signal is obtained from BIS VISTA monitor, signal processing is performed on a PC using MATLAB R2010a. In order to enhance the signal integrity while minimizing the signal distortion in desired frequency band, an FIR low-pass filter is designed to have linear phase response and a zero at $60Hz$. Denoising technique using wavelet transform is employed to reject low frequency artifacts such

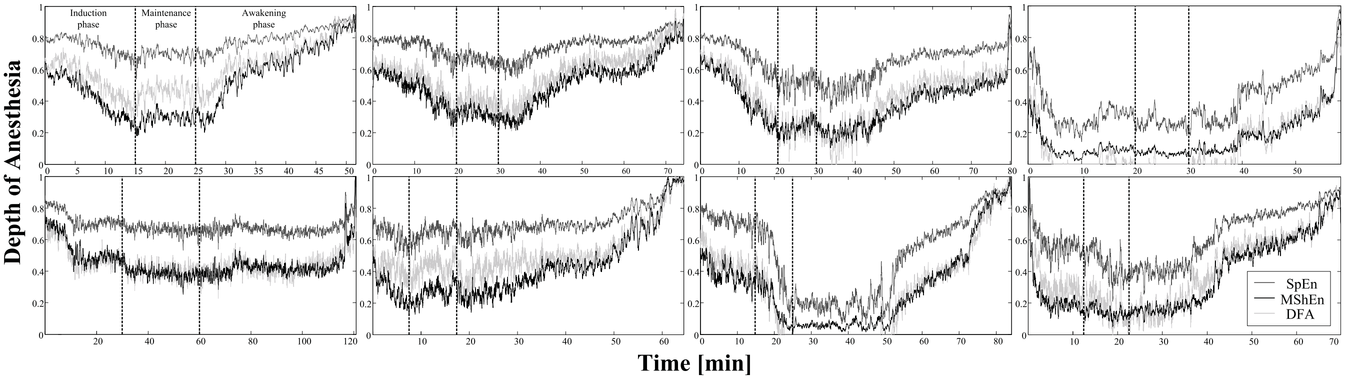

Fig. 5. Time coures of MShEn, SpEn and DFA calculated from EEG of anesthetized rats are shown. 3 phases (induction phase, maintenance phase and awakening phase) of the measurements are separated by dotted lines.

as motion artifacts due to breathing [11]. After denoising, the signal is segmented into 16s epochs with 14s overlapping with adjacent epochs. SpEn is evaluated from each epoch by using a 16 channel uniform filter bank. On the other hand, segmented epoch is filtered by high pass filter with the 3dB frequency of $29.6Hz$. Filtered epoch is normalized with the RMS value of unfiltered epoch. Then the ShEn is measured with 64 bin histogram of the normalized signal. Finally, SpEn and ShEn are linearly mapped into $[0, 1]$ and MShEn is obtained by multiplying them.

The time courses of depth of anesthesia evaluated for 8 measurements are presented in Fig. 5. For comparison, scaling exponent from detrended fluctuation analysis (DFA) [12] and SpEn, which are verified methods for evaluating depth of anesthesia from EEG signal, are engaged. Both SpEn and DFA are linearly mapped into $[0, 1]$ to compare with MShEn. The Pearson correlation coefficient between DFA and MShEn is 0.9683 and that between MShEn and SpEn is 0.9751. Although BIS VISTA monitor which was used for the measurement of EEG signal also provides its own index BIS for anesthetic depth, BIS is excluded in the comparison. The reason is that the BIS value was invalid for most part of the measurements, probably due to the differences between human and rat and low signal quality.

MShEn responds to the change in the flow rate and concentration of anesthetic gas in a few minutes in some cases, but not in some other cases. This is also true for other indexes for depth of anesthesia. More specifically, fast response is observed in the cases that the minimum value of MShEn is over 0.2. However, in the cases that MShEn reached near 0, MShEn and other indexes start to increase after delivering pure oxygen to the chamber for $3 - 20$ minutes. This latency is probably due to the long time taken for eliminating the agent from the body, as the spontaneous-breathing of the rats were weak during deep anesthesia. In order to discriminate whether the latency is from the rats or from the limitation in the indexes, experimental protocol should be modified to use artificial respirator rather than relying on spontaneousbreathing of the rats.

V. Conclusion

An entropy based index for evaluating depth of anesthesia from rat EEG is introduced. The index is mostly based on ShEn, which is not widely used for analyzing depth of anesthesia due to its low performance on discriminating signals with different spectrums. Nonetheless, high DP is achieved by modifying ShEn to reflect frequency domain information. Experimental results from rat EEG show that not only MShEn shows high correlation with other indexes for depth of anesthesia but also it achieves low variability over wide range of depth of anesthesia.

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