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Auto-Mutual Information Function of the EEG as a Measure of Depth of Anesthesia

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Abstract—**Monitoring the depth of anesthesia (DOA) is necessary in order to decrease the incident of awareness in anesthesia and to prevent delays in the recovery phase. In the last decades a number of noninvasive methods have been proposed for the analysis of the electroencephalogram (EEG) for monitoring DOA. The objective of this work was to apply auto mutual information function (AMIF) to EEGs of patients under anesthesia in order to find variables able to characterize the following 4 states: awake, sedated, anesthetized and burst suppression episodes. The results show that the single and combined AMIF parameters were able to correctly classify the states in the range 72.2% – 94.1% and 61.1% – 100%, respectively.**

I. Introduction

ANESTHESIA is defined as the state of unconsciousness, amnesia and hemodynamic, motor, and endocrinologic stability during surgery, produced by specific medication. This means that for achieving an adequate level of depth of anesthesia (DOA), usually a combination of hypnotic, analgesics, and neuromuscular blocking agents are used [1]. The relationship between drugs and desired responses of DOA is not a simple one-to-one connection, but it seems to present features of complexity and nonlinear behavior [1].

Anesthetic drugs influence both the frequency content and the amplitude of the electroencephalographic (EEG) signal. Therefore, the study of the Central Nervous System, the main target for anesthetic agents, has received a great deal of attention and EEG based methods have been widely used for estimating the DOA [2].

The EEGs during anesthesia exhibit characteristic changes when anesthetic depth increases. These changes include complex patterns of frequency slowing accompanied by amplitude increases. As DOA increases from light anesthesia to deep anesthesia, the EEG exhibits rhythmic waveforms, burst suppression pattern activity, and finally, very low amplitude isoelectric or flat-line activity [3-4].

Various signal analysis approaches have been used to quantify these pattern changes and provide an indication of loss of recall, loss of consciousness and anesthetic depth as in [5-6]. The most common technique in clinical practice is the bispectral index analysis of the EEG (BIS) [7] while other available devices are the IoC-view, applying symbolic dynamics [8], or the Auditory Evoked Potentials (AEP) index, AAI [9].

In this work, four different states of DOA of patients undergoing surgery were taken into account. There is no gold standard to measure the DOA, so indirect parameters were used to validate the results. In this analysis, the signal containing burst suppression (BS) was also considered. BS is a characteristic behavior of the EEG that appears in the deepest state of anesthesia. It is recognized by a pattern of low voltage, less than 10 µV, and a relatively shorter pattern of higher amplitude complexes.

In the present work, an analysis based on techniques of auto-mutual information function (AMIF) of EEGs was performed in order to find which variables can better discriminate between the four states: awake (Awk), sedated (Sdt), lightly anesthetized (Ansth) and deeply anesthetized (BS).

II. Materials and Methodology

A. EEG Data and Preprocessing

After informed consent for all patients and approval from the Institutional Ethics Committee, the EEG from 19 women, 18 to 60 years old, scheduled for ambulatory gynecological surgery in the Ghent University Hospital, Belgium, was recorded. For this study, one of the subset of the raw EEG waves from a previously published study [8] was post-processed. All patients received continuous infusion of propofol fixed at 300 ml/h by a computer-assisted infusion device (RUGLOOP). The DOA was measure by AAI, auditory evoked potential index, [10] calculated using the A-Line monitor (Danmeter A/S, Odense Denmark). Three electrodes were positioned: one at the mid forehead (+), one at the left forehead (reference) and one at the left mastoid (-). The difference between (+) and (-) was taken into account for this study. All

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hemodynamic data together with the AAI index were logged automatically every 10 s. The A-Line monitor provided a measure of the burst suppression ratio (BS), which represents the fraction of time where the EEG has small amplitudes. Database contains also information about AAI, assumed to define states of DOA in the present study, and CePropo, the concentration of the Propofol in the patient's brain. The AAI defines the following states [2]: Awk, when AAI index is higher than 60; Ansth, when AAI index is lower than 30; Sdt, when AAI index is between 30 and 60.

The EEG was recorded with a sampling frequency of 900 Hz, with a resolution of 16 bits and a recording time of about 15 min. A Butterworth filter of 5th order was applied to the EEGs, with a cut-off frequency of 45Hz in order to reduce the influences of the EMG and the external noise. In each state, EEG signals were segmented in windows of 1 s and 10 s. Figure 1 contains windows of 6 s of unfiltered EEG for each state of DOA of a patient.

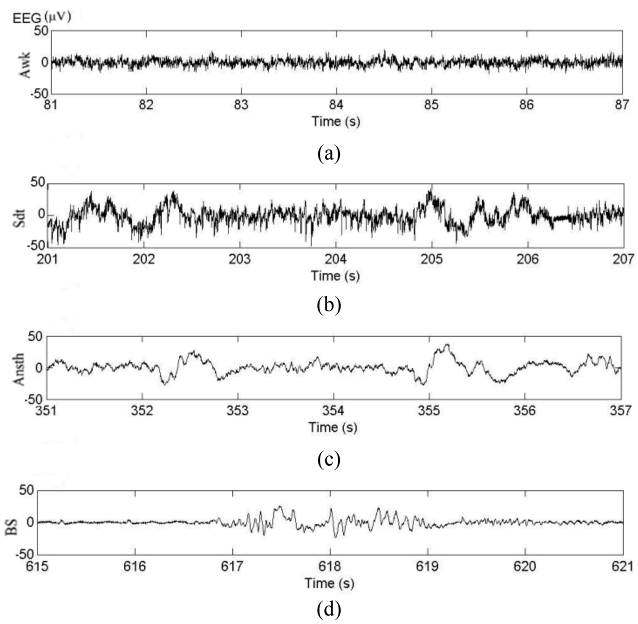

Fig. 1. Windows of 6 s of unfiltered EEG for each state of DOA of a patient: (a) Awk; (b) Sdt; (c) Ansth; (d) BS.

B. Auto Mutual Information function

Mutual information (MI) can measure the nonlinear as well as linear dependence of two variables. It is a metric derived from Shannon's information theory to estimate the information gained from observations of one random event on another [11], and measuring both linear and nonlinear dependences between two time series [12]. It can be regarded as a nonlinear equivalent of the correlation function. Usually, MI is measured between two different systems X and Y. AMIF on the other hand is calculated between two measurements taken from a single time series $x(t)$. AMIF estimates the degree to which a delayed series $x(t+\tau)$ can be predicted from $x(t)$.

Let X be a discrete random variable which takes a finite number of possible values x_1, x_2, x_3..., x_n with probabilities $P(x_1)$, $P(x_2)$, $P(x_3)$..., $P(x_n)$ respectively, such that $P(x_i) \geq 0$, $i = 1, 2, 3 \ldots n$. AMIF can be defined as the MI between random variables X_i and $X_{i+\tau}$.

$$AMIF_{xx}(\tau) = \sum_{x_i \epsilon X} \sum_{x_{i+\tau} \epsilon X} P_{xx}(x_i, x_{i+\tau}) \, log_2 \left(\frac{P_{xx}(x_i, x_{i+\tau})}{P_x(x_i) P_x(x_{i+\tau})} \right) \tag{1}$$

This function describes how the information of a signal (AMIF value at $\tau=0$) decreases over a prediction time intervals (AMIF values at $\tau>0$). In the case of a completely regular (deterministic) signal, the AMIF would remain at the maximum value of $\tau=0$ for all τ. In the case of an uncorrelated random signal, the AMIF would become zero for all $\tau>0$. Increasing information loss is related to decreasing predictability, and increasing complexity of the signal. In this work, AMIF was calculated using a discrete time delay $0 \leq \tau_i \leq 100$ samples. In order to characterize DOA, cumulative area ($CumArea_{\tau i}$), partial area ($PartArea_{\tau i}$) and peak decay ($PDecay_{\tau i}$) were defined from AMIF:

$$CumArea_{\tau_i} = \int_0^{\tau_i} AMIF(\tau) d\tau \tag{2}$$

$$PartArea_{\tau_i} = \int_0^{\tau_i} AMIF(\tau) d\tau - \int_0^{\tau_{i-1}} AMIF(\tau) d\tau \tag{3}$$

$$PDecay_{\tau_i} = AMIF(0) - AMIF(\tau_i) \tag{4}$$

The mean value of each variable calculated in all windows along the state was considered for the analysis. For each variable, the number of states correctly classified for all patients was studied in order to find the value of τ_i that allows a better classification.

C. Statistical Analysis

A nonparametric test was applied by using U of Mann-Whitney test and a significance level p-value <0.05 was taken into account. Variables that satisfy this condition were taken into account for building a quadratic discriminant function able to classify adjacent state of DOA. The leaving-one-out cross-validation method was performed. Cross-validation involves partitioning a sample of data into complementary subsets, performing the analysis on one subset (the training set), and validating the analysis on the other subset (the validation set). To reduce variability, multiple rounds of cross-validation were performed using different partitions, and the validation results are averaged over the rounds.

The ability of the variables to describe DOA was evaluated using prediction probability (P_k), which compares the performance of indicators having different units of measurements [13]. The P_k coefficient is a statistic commonly used to measure how well an index predicts the state of the patient. A P_k of 1 represents a perfect prediction and 0.5 is not better than tossing a fair coin. In this way, the P_k is a performance which indicates the correlation between

DOA indicator value and observed anesthetic depth, taking into account both desired performance and the limitations of the data. The P_k avoids the shortcomings of other measures. For example, as a nonparametric measure, P_k is independent of scale units and does not require knowledge of underlying distributions.

In the present work, the P_k was computed for the 3 variables that provided the best classification in terms of the discriminant analysis, using the previously defined states of DOA and the concentration of the drug CePropo as references of the actual state of the patient. In order to assess the performance of the proposed variables, the P_k of CePropo is also computed when the DOA states are used as reference. Similarly, when CePropo is the reference considered, the P_k of the proposed variables is compared with the P_k of the AAI.

III. Results

Variables that allow the best classification of the segments in their correct states were found out to be the $CumArea_{10}$, $PartArea_2$, $PDecay_5$. Tables I and II show the mean value and standard error of those variables for windows of 1 s and 10 s, respectively. The p-values of each variable comparing adjacent states of DOA are contained in Table III and IV.

TABLE I
VALUES OF VARIABLES: ONE-SECOND SEGMENT

Variable	Awk mean (SE)	Sdt mean (SE)	Ansth mean (SE)	BS mean (SE)
$CumArea_{10}$	12.1 (0.043)	16.2 (0.052)	18.1 (0.033)	15.5 (0.043)
$PartArea_2$	1.61 (0.004)	2.01 (0.004)	2.17 (0.002)	1.93 (0.004)
$PDecay_5$	1.98 (0.005)	1.47 (0.006)	1.25 (0.003)	1.56 (0.005)

SE, standard error

TABLE II
VALUES OF VARIABLES: TEN-SECOND SEGMENT

Variable	Awk mean (SE)	Sdt mean (SE)	Ansth mean (SE)	BS mean (SE)
$CumArea_{10}$	12.1 (0.045)	16.6 (0.059)	18.6 (0.032)	16.1 (0.041)
$PartArea_2$	1.65 (0.004)	2.06 (0.005)	2.12 (0.013)	2.01 (0.004)
$PDecay_5$	1.96 (0.005)	1.42 (0.007)	1.17 (0.003)	1.48 (0.005)

SE, standard error

TABLE III
STATISTICAL SIGNIFICANT LEVEL: ONE-SECOND SEGMENT

p-value	Awk vs.Sdt	Sdt vs.Ansth	Ansth vs.BS
$CumArea_{10}$	<0.0005	<0.0005	<0.0005
$PartArea_2$	<0.0005	0.001	<0.0005
$PDecay_5$	<0.0005	0.002	<0.0005

TABLE IV
STATISTICAL SIGNIFICANT LEVEL: TEN-SECOND SEGMENT

p-value	Awk vs.Sdt	Sdt vs.Ansth	Ansth vs.BS
$CumArea_{10}$	<0.0005	0.01	<0.0005
$PartArea_2$	<0.0005	0.015	<0.0005
$PDecay_5$	<0.0005	0.006	<0.0005

Analyzing Tables I and II some information about the complexity of the signal can be extracted. In fact, for lower values of $CumArea_{10}$ and $PartArea_2$, the AMIF presents higher decay ($PDecay_5$) and thus the signal presents higher complexity [14]. It can be noticed that:

$$PDecay_5(Awk) > PDecay_5(BS) > PDecay_5(Sdt) > PDecay_5(Ansth)$$

$$CumArea_{10}(Awk) < CumArea_{10}(BS) < CumArea_{10}(Sdt) < CumArea_{10}(Ansth)$$

$$PartArea_2(Awk) < PartArea_2(BS) < PartArea_2(Sdt) < PartArea_2(Ansth)$$

That denotes a major complexity of the EEG if the patient is awake and a major regularity if the patient is in anesthetized state. The EEG loses its complexity when it goes from awake to sedated and sedated to anesthetized states. Instead, during burst suppression state the signal complexity increases to values almost similar to sedated state. This can be due to the patterns of higher amplitude, in the EEG, that characterize the burst suppression state.

Considering the discriminant analysis, windows of 1 s gave better results than windows of 10 s, since this length of segment was not able to characterize all DOA states. Table V shows percentages of well classified one-second segments calculated by applying the discriminant function using $CumArea_{10}$, $PartArea_2$, $PDecay_5$ considering adjacent states of DOA.

TABLE V
% OF WELL CLASSIFIED SEGMENTS: ONE-SECOND SEGMENT

	Awk(%) Sdt(%)	Sdt(%) Ansth(%)	Ansth(%) BS(%)
$CumArea_{10}$	88.9 %	72.2 %	82.4 %
	88.9 %	76.5 %	77.8 %
$PartArea_2$	88.9 %	72.2 %	94.1 %
	88.9 %	76.5 %	77.8 %
$PDecay_5$	88.9 %	72.2 %	82.4 %
	88.9 %	76.5 %	77.8 %

Table VI presents the P_k values and the standard errors (SE) achieved for $CumArea_{10}$, $PartArea_2$, $PDecay_5$, AAI and CePropo when using the DOA states and CePropo as references, respectively. For this analysis, the burst-suppression state has been discarded due to the different trend shown by the proposed variables in that state. The cells of the table for which the P_k value would be 1 due to the direct relationship between variable studied and reference have been left blank. The three proposed indexes achieve a P_k value of 0.79 when the DOA states are used as references. This implies a rather good correlation with the DOA states, even if it is lower than the value of P_k= 0.91(SE=0.01) of CePropo. When CePropo is the reference, the P_k value for the proposed variables decreases, P_k = 0.71(SE=0.01) and it is below the value achieved for the AAI, P_k = 0.85(SE=0.01).

TABLE VI
PREDICTION PROBABILITY: ONE-SECOND SEGMENTS

Reference	$CumArea_{10}$ P_k (SE)	$PartArea_2$ P_k (SE)	$PDecay_5$ P_k (SE)	*AAI* P_k (SE)	*CePropo* P_k (SE)
State	0.79 (0.01)	0.79 (0.01)	0.79 (0.01)		0.91 (0.01)
CePropo	0.71 (0.01)	0.71 (0.01)	0.71 (0.01)	0.85(0.01)	

P_k (SE): P_k prediction probability; SE, standard error

Higher percentages of well classified one-second segments were obtained combining two AMIF variables. By adding more variables to the discriminant function it was not possible to increase the percentages of well classified segments. In Table VII, it is shown the best combinations of variables that give quite high percentages of well classified one-second segment for all the adjacent states.

TABLE VII
% OF WELL CLASSIFIED SEGMENTS: ONE-SECOND SEGMENT

Variable	Awk(%) Sdt(%)	Sdt(%) Ansth(%)	Ansth(%) BS(%)
$PDecay_5$+$CumArea_{10}$	88.9 %	61.1 %	94.1%
	100 %	94.1 %	77.8%
$PartArea_2$+$PartArea_5$	88.9 %	72.2 %	82.4%
	94.4 %	82.4 %	77.8%
$PartArea_2$+$CumArea_{10}$	88.9 %	66.7 %	82.4 %
	100 %	82.4 %	77.8%

IV. CONCLUSIONS

Auto-mutual information function (AMIF) was applied to one-second and ten-second windows of EEG recorded during surgery in order to characterize the depth of anesthesia (DOA). Several variables were defined from the AMIF in order to explore the complexity involved in DOA process. It was found that EEG signal presents a decreasing level of complexity from awake to anesthetized state. The regularity is lost when the burst suppression episode appears.

The results show that the single and combined AMIF parameters were able to correctly classify the states up to 94.1% and up to 100%, respectively. Globally, the best percentages were obtained combining two AMIF variables and using segments of the EEG of 1 s. Performance would increase whether each state were characterized by a particular variable, although in this work each selected variables were able to describe all DOA states.

The AMIF seems to be a good method of classifying different conditions of the patient under anesthesia. However, this work represents a preliminary study about the advantages taken from the application of mutual information function on the discrimination between adjacent states of DOA. Additional tests will be made in order to validate the results using more data taken from other patients. Other studies have been developed [5, 6, 15] using the same database but with different algorithms for DOA characterization. It could be noticed that combining two variables of AMIF quite comparable percentages of well classification of DOA states are achieved. A future study would be combining the best variables obtained from the different proposed algorithms, in order to improve the results for a future online implementation.

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