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Abstract. Brain-Computer Interfaces (BCIs) are devices offering alternative means of communication when conventional means are permanently, or non-permanently, impaired. The latter is commonly induced in general anesthesia and is necessary for the conduction of the surgery. However, in some cases it is possible that the patient regains consciousness during surgery, but cannot directly communicate this to the anesthetist due to the induced muscle paralysis. Therefore, a BCI-based device that monitors the spontaneous brain activity and alerts the anesthetist is an essential addition to routine surgery. In this paper the use of Permutation Entropy (PE) as a feature for 'conscious' and 'unconscious' brain state classification for a BCI-based anesthesia monitor is investigated. PE is a linear complexity measure that tracks changes in spontaneous brain activity resulting from the administration of anesthetic agents. The overall classification performance for 10 subjects, as assessed with a linear Support Vector Machine, exceeds 95%, indicating that PE is an appropriate feature for such a monitoring device.

Keywords: Permutation Entropy, anesthesia monitor, electroencephalogram, Support Vector Machine, Brain-Computer Interface

1 Introduction

Brain-Computer Interfaces (BCIs) are devices aimed primarily at providing an alternative means of communication through establishing a 'direct connection' between the brain and a device; in this way the conventional means of communication (through peripheral nerves and muscles) are bypassed [1]. Traditionally, in a BCI system the user consciously performs various mental tasks, voluntary modulation of brain activity or spontaneous event-related activity in order to issue different commands to control a device [2]. A BCI system can be useful not only when permanent loss of communication occurs, but also when non-permanent loss of communication occurs over a period of time. The latter is routinely performed, for example, as part of general anesthesia (GA) during surgery. This is achieved through the co-administration of neuromuscular blocking agents, together with the anesthetic

agents, in order to achieve patient immobility necessary for the conduction of the surgery [3]. Under normal circumstances this drug-induced immobility is desired since the patient is under anesthesia. However, in rare cases it is possible that the patient regains consciousness during surgery unbeknown to the anesthetist; this could be a direct result of a number of factors, such as insufficient amount of administered anesthetic, and equipment failure [4]. In such cases the induced immobility leaves the patient with no means of communicating this to the anesthetist. Awareness during surgery is a highly traumatic experience with long-term psychological consequences; therefore, quick detection and subsequent intervention is important. A BCI device that monitors the general state of hypnosis of the patient can provide the means of communication necessary to alert the anesthetist. The operation of such a BCI device is based on monitoring the spontaneous brain activity as obtained from an electroencephalogram (EEG), which exhibits different characteristics under consciousness, and lack of it. By monitoring the changes in the observed characteristics of the patient's spontaneous brain activity the device is, thus, able to issue an alert when a 'conscious' state is detected. In this way, the patient can still communicate (involuntarily) to the anesthetist that he/she is conscious, despite his/her inability to do so using conventional means of communication.

Currently, commercially available EEG-based monitors are being introduced for routine patient monitoring during surgery. Two of the most commonly used devices are the BIS monitor (Aspect Medical Systems, Natick, MA) [5], and the Datex-Ohmeda S/5™ Entropy Module (originally by Datex-Ohmeda Division, Instrumentation Corp., Helsinki; now with GE Healthcare) [6]. These devices usually operate by converting some combination of various EEG characteristics into a single number from 0-100 representing the level of hypnosis (100 - 'fully awake', 0 - 'isoelectricity'). At the simplest level these monitors use the loss of high frequencies and shift to low frequencies observed during anesthesia as a measure of anesthetic drug action. However, the precise algorithms utilized by some monitors are proprietary and their specifics are not known. For example, the BIS monitor integrates several disparate descriptors of the EEG, developed from a large volume of clinical data, into a single variable that correlates with behavioral assessments of sedation and hypnosis. In addition, they suffer from reliability issues, such as the inability to differentiate between an anesthetized patient or a patient who is simply asleep [7-9], unresponsiveness to specific anesthetic agents [10, 11], and being affected by the administration of other agents, such as neuromuscular blockers [12].

In addition to commercially available monitors, a number of other methods have also been utilized in order to characterize the anesthetic-induced changes observed in the EEG. The main observations concern the changes in the frequency content of the EEG after administration of anesthetic agents, thus various traditional frequency-based methods are used (see [13] for a review), as well as higher order spectral analysis [14, 15]. Other methods include various entropy-based measures [16-18] and complexity-based measures [19, 20]. Administration of anesthetic agents has also been found to affect various characteristics of auditory event-related potential activity, such as latency and amplitude [21, 22]. All these methods identify that the EEG during anesthesia becomes a more predictable signal with larger amplitude and lower frequency content. Despite the use of various measures to characterize anesthetic-induced EEG changes, only a few of them have been validated in terms of their

feasibility in the discrimination between 'conscious' and 'unconscious' states, as viewed from the perspective of a pattern recognition problem.

In this paper we utilize a Support Vector Machine (SVM) to classify EEG segments into one of the two states 'Conscious' and 'Unconscious' using Permutation Entropy (PE) as a feature obtained from the EEG of 10 patients undergoing general anesthesia surgery. PE is a complexity measure based on mapping a time series on a symbolic sequence to describe the relationships between present and past samples [23]. Its previous application on EEG data obtained from anesthesia has shown that PE tracks the level of hypnosis, as its values decrease with an increasing level of hypnosis [24, 25]. The simplicity and fast speed of estimation constitute PE a good candidate for real-time and online applications. Therefore, such a feature could potentially be utilized in an anesthesia-monitoring BCI device.

2 Methods

2.1 Dataset

The data used in this study were collected from 10 male patients undergoing general and urological surgery at Nicosia General Hospital, Cyprus. The 24-channel configuration of the TruScan32 (Deymed Diagnostic) was used with sampling rate at 256Hz, and electrodes placed at positions Fp1, Fp2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1 and O2, according to the International 10/20 system, with an FCz reference. No filtering was performed during or after data collection. Data recording usually commenced while patients were still awake prior to administration of the anesthetic agents (anesthetic induction - AI), continued throughout the entire surgery, and until patients regained consciousness (ROC) after the surgery. The point at which the patients stopped responding verbally to commands by the anesthetist occurred less than a minute after administration of the anesthetic bolus, depending on patient characteristics. ROC was defined as the point at which the patient started responding to verbal commands or tactile stimuli by the anesthetist. GA was induced by the on duty anesthetist using the regular procedures of the hospital. Standard patient monitoring was used and all patients were preoxygenated via a face mask prior to anesthesia induction with a Diprivan bolus (propofol 1%, 10 mg/ml, induction dose 2-4 mg/kg depending on patient characteristics). During induction some patients also received boluses of neuromuscular blocking agents (cisatracurium, rocuronium, or atracurium) and analgesic drugs. Maintenance of GA was achieved with an intravenous administration of propofol at concentrations ranging between 20-50 ml/h (200-500 mg/h) depending on patient characteristics and surgery requirements. In most patients remifentanil hydrochloride (Ultiva®; 2 mg, dissolved in 40ml) was also administered intravenously throughout surgery at a rate ranging between 2-15 ml/h (0.1-0.75 mg/h).

2.2 Permutation Entropy

PE is a linear complexity measure for time series [23]. The relationship between present values and a fixed number of equidistant values at a given past time is captured through a symbolic mapping of the continuous time series. This mapping is achieved by splitting the time series into segments containing m samples (where m is called the embedding dimension), and which overlap by $(m-1)$ samples. The distance between each sample is defined by a time-lag, τ. Thus, each segment is defined as:

$$X(t) = \left[x(t), x(t+\tau), ..., x(t+m\tau)\right] . \quad (\mathbf{1})$$

For a given embedding dimension there will be $m!$ possible permutations (motifs). If each permutation is considered as a symbol, the embedded time vectors $X(t)$ can be represented by a symbol sequence, j, each having probability distribution p_j. Thus, based on the Shannon entropy definition the normalized PE, H_p, of a given time series, $x(t)$, is defined as:

$$H_p(m) = -\frac{1}{\ln(m!)} \sum_{j=1}^{J} p_j \ln(p_j) . \quad (\mathbf{2})$$

where J is the distinct number of symbols for a given embedding dimension $\left(J \le m!\right)$. The factor $\frac{1}{\ln(m!)}$ is a normalization factor such that $0 \le H_p / \ln(m!) \le 1$. PE measures the departure of a time series from a complete random one: the smaller the value of the PE, the more regular the time series. The upper bound, $H_p = \ln(m!)$, is attained when all of the possible $m!$ permutations appear in the time series with the same probability, something which is more likely to be observed when the EEG signal is dominated by high frequencies. This implies that H_p increases with the irregulatiry of the time series. At slower frequencies the permutations corresponding to peaks and troughs are observed less frequently, i.e. the EEG is more regular, hence the permutations appear with different probabilities, which decreases the PE of the signal. With regards to the embedding dimension, m, if this is too large then it becomes difficult to detect changes in the time series. However, if this is too small, then there are very few distinct states (symbols) and the scheme will not work. For EEG signals values of $m = 3,...,7$ have been recommended [23]. For the time lag, it is adequate to use a value of $\tau = 1$ to extract most of the information in the EEG [24, 25], hence this value is commonly chosen for EEG analysis.

2.3 Support Vector Machines

SVMs belong to the family of kernel-based classifiers [26]. The main idea behind SVMs is to use kernel functions to perform operations in the "data" space, corresponding to an implicit mapping of the data in a higher dimensional "feature" space where a hyperplane (decision boundary) that can separate the classes can be found. The simplest case is a linear SVM trained to classify linearly separable data. The constructed constraints define two parallel hyperplanes whose distance from the estimated decision boundary is maximal. The points lying on the two hyperplanes are called the support vectors. Estimating the decision boundary subject to the set of given constraints is a constrained optimization problem that can be solved in the Lagrange optimization framework.

2.4 Data Analysis

The main function of an anesthesia monitor is to alert the anesthetist when a subject becomes aware during surgery. Therefore, the minimal requirement is the ability to distinguish between the two states 'Conscious' and 'Unconscious' (class 'A' and 'B' respectively). To assess this, the following was performed:

(1) Segments of a few minutes duration corresponding to the two classes were extracted from the continuous EEG recordings at AI and ROC based on markers in the EEG record of each patient indicating AI and ROC. Data from 10 subjects were available for analysis (S1-S10).

(2) The average activity over the left frontal (LF: electrodes Fp1, F7, F3, T3, C3), right frontal (RF: Fp2, F8, F4, C4, T4), left posterior (LP: T5, P3, O1), right posterior (RP: T6, P4, O2), and midline (Z: Fz, Cz, Pz) brain areas was estimated. Visual inspection of the acquired data identified electrodes with bad quality signals from bad contact or no contact; these electrodes were subsequently excluded from estimation of the average activity. For subject S4, all electrodes in the right posterior area were excluded from the analysis due to bad electrode contact. Since no artifact removal was performed this averaging removed some of the effects of artifacts.

(3) PE ($m = 3$, $\tau = 1$) was estimated over 2-second non-overlapping windows of the EEG segments from each of the five brain areas. Non-overlapping windows were used such that, at each 2-s segment, the current value of PE was estimated from new data and was not based on previous data – this is an important consideration for future online application of the method. Feature vectors consisted of the following 5-dimensional values:

$$X_C^i = \left[H_{p(LF)}^i(m) \quad H_{p(RF)}^i(m) \quad H_{p(LP)}^i(m) \quad H_{p(RP)}^i(m) \quad H_{p(Z)}^i(m) \right]. \qquad (3)$$

where $C \in \{A, B\}$ corresponds to one of the two classes, and $i = 1,...N_C$ denotes the ith 2-s segment from all the available segments of each class (N_C). Since no pre-processing or artifact removal was performed, the estimated PE values were smoothed (moving average filter, $n = 10$ samples).

(4) Performance was evaluated for each subject separately over B=50 bootstrap repetitions. In each repetition, 70% of the available data for a subject was used for training, while the remaining 30% was used for testing. Classification was performed using a linear SVM. Performance was assessed as the sensitivity (4), specificity (5) and average accuracy (6):

$$Sensitivity = SE = \frac{TN}{TN_n} \ . \tag{4}$$

$$Specificity = SP = \frac{TP}{TP_n} \ . \tag{5}$$

$$Accuracy = AC = \frac{1}{2}\left(\frac{1}{B}\sum_{b=1}^{B} SE_b + \frac{1}{B}\sum_{b=1}^{B} SP_b \right) . \tag{6}$$

where TP (TN) is the number of true positives (negatives), and TN_p (TN_n) is the total number of positive (negative) examples respectively. In the following investigations, examples of class 'A' (conscious) were considered as positive, while class 'B' (unconscious) as negative.

3 Results

Induction of anesthesia causes a decrease in the estimated PE values, with return to baseline values when consciousness is recovered at the end of anesthesia. This can be seen in the grand average PE obtained over all subjects over the five pre-defined brain areas (figure 1; the right posterior area was unavailable for subject S4, hence S4 was excluded from the grand average PE estimation). This decrease in the PE is a direct result of the fact that during anesthesia the fast brain rhythms are substituted by slower brain rhythms; hence, the PE tracks this shift from faster to slower frequencies. In addition, the EEG segments representing ROC are extracted after the intravenous administration of propofol is switched off. As the blood-level concentration of anesthetic agent decreases the PE shows a more gradual return to baseline level (figure 1, thin line), compared to the PE at AI (figure 1, thick line) where a bolus of anesthetic agent is administered. It can also be seen that it is possible to separate the two classes using a linear decision boundary; hence, a linear SVM is utilized here.

Table 1 shows the single-subject and subject-average sensitivity (SE), specificity (SP) and classification accuracy (AC). Overall, SE, SP and AC greater than 0.93 (93%) are obtained. The decreased performance for subject S4 could be a result of the fact that only 4 brain areas were available for analysis, resulting in 4-dimensional PE features. Data from segments extracted at the beginning and end of surgery were classified separately. A patient awaking from surgery does not regain full alertness until sometime afterwards; this time frame is very much dependent on the rate at which each person is able to metabolize the administered drugs. Therefore, the

awareness state of a patient at ROC is much more similar to the awareness state the patient will be in if awareness is experienced during surgery.

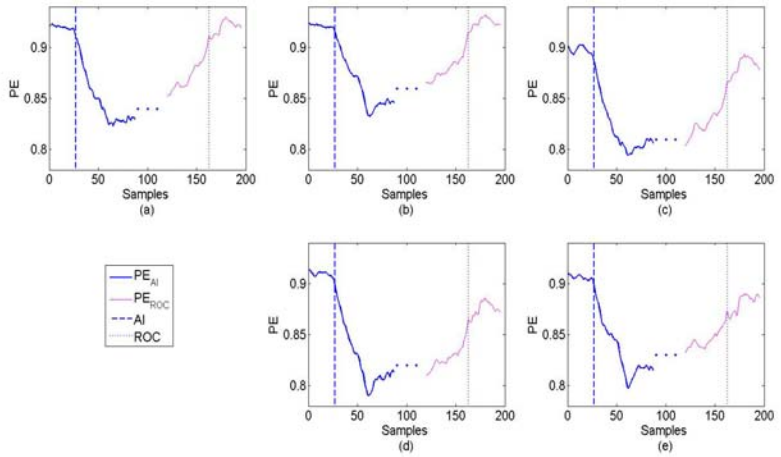

Fig. 1. Average Permutation Entropy over all patients for (a) left frontal, (b) right frontal, (c) left posterior, (d) right posterior, and (e) midline brain areas. Thick line: PE at induction (AI); thin line: PE at recovery of consciousness (ROC). Vertical lines denote the induction and recovery of consciousness (dashed and dotted lines respectively). X-axis in arbitrary samples.

Subject	**AI**			**ROC**		
	SP	***SE***	***AC***	***SP***	***SE***	***AC***
S1	1.00	0.99	0.995	1.00	0.97	0.985
S2	1.00	0.95	0.975	1.00	0.97	0.985
S3	1.00	0.94	0.970	1.00	0.75	0.875
S4	1.00	0.90	0.950	0.73	0.84	0.785
S5	1.00	0.95	0.975	1.00	0.94	0.970
S6	1.00	1.00	1.000	1.00	0.98	0.990
S7	1.00	0.90	0.950	1.00	0.98	0.990
S8	0.99	0.96	0.975	1.00	1.00	1.000
S9	1.00	0.93	0.965	1.00	0.96	0.980
S10	1.00	0.92	0.960	0.99	0.93	0.960
TOTAL	**1.00**	**0.95**	**0.975**	**0.97**	**0.93**	**0.950**

Table 1. Single-subject and average sensitivity (SE), specificity (SP) and classification accuracy (AC) with 5-dimensional PE features estimated over 5 brain areas. Classification performed with linear SVM.

Ideally, a BCI for alerting the anesthetist in case of impending awareness should display 100% SE and SP; ideal SE means that all events of awareness are captured, an alarm is raised and appropriate action is taken, while ideal SP implies that the monitor

reflects the lack of consciousness at an appropriate level of anesthesia. However, it is very difficult to have an ideal monitor and in the majority of cases a compromise between SE and SP must be made. In case of low SE, false alarms would indicate that the patient is awake, prompting the anesthetist to take action with potential disastrous consequences. In case of low SP, the alarm would not be raised in cases of awareness, no action would be taken and the patient would continue being in a conscious state, with dramatic consequences. It can be seen that in the case of an anesthesia monitor, both SE and SP are equally as important and no sacrifice of one should be made for the other. Using PE as a feature, even though SE and SP are not ideal, both are at a similarly high level. Thus, neither is sacrificed for the other.

5 Conclusion

We propose the use of Permutation Entropy as a feature in a BCI-based medical device that monitors the patients' state of hypnosis during surgery under general anesthesia in order to alert the anesthetist in cases when the patient regains awareness, but cannot voluntarily communicate this to the anesthetist. The high performance obtained encourages further investigations of PE-based classification of 'conscious' and 'unconscious' state. However, one must also bear in mind that other physiological processes, such as sleep, exhibit patterns of decreasing PE [27]. Thus, it is necessary to study both processes simultaneously in order to establish existing differences. Nonetheless, a depth of anesthesia monitor based on PE is still more advantageous than existing monitors.

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