33rd Annual International Conference of the IEEE EMBS
Boston, Massachusetts USA, August 30 - September 3, 2011

Entropy Measures for Discrimination of 'awake' Vs 'anaesthetized' State in Recovery from General Anesthesia

N. Nicolaou, *Member, IEEE/EMBS,* S. Houris, P. Alexandrou, and J. Georgiou, *Senior Member, IEEE*

***Abstract*—Approximate Entropy (ApEn) and Permutation Entropy (PE) have been recently introduced for assessment of anesthetic depth. Both measures have previously been shown to track changes in the electrical brain activity related to the administration of anesthetic agents. In this paper ApEn and PE are compared for the automatic classification of 'awake' and 'anesthetized' state using a Support Vector Machine to assess their robustness for potential use in a device for monitoring awareness during general anesthesia. It was found that both measures provide linearly separable features and we are able to discriminate between the two states with accuracy greater than 96% using either of the two entropy measures.**

I. Introduction

General anesthesia is a chemically-induced reversible state of unconsciousness and depression of reflexes to afferent stimuli. Modern anesthesia involves the administration of different drugs to achieve the desired components of unconsciousness, amnesia, analgesia and immobility. Awareness during general anesthesia, even though considered a rare event, has severe psychological consequences for those who experience it. The incidence of awareness ranges from 0.1-0.8% [1] and is affected by a number of factors, such as patient characteristics and the type of surgery [2]. Devices that monitor the depth of anesthesia are now commercially available; such devices could provide a valuable means of identifying awareness during surgery, particularly since the patient himself cannot communicate this to the anesthetist due to the induced immobility. These devices function by monitoring specific changes in the electrical brain activity (EEG), as obtained through 2 electrodes placed on the patient's forehead, and usually converting them to a number corresponding to the level of hypnosis (0-100; no activity – fully awake respectively). Available monitors are based on changes in the spectral content of the EEG, which are non-unique to anaesthesia.

Recently entropy measures have been applied to study the changes in the EEG activity induced by administration of anesthetic agents. More specifically: (1) Permutation Entropy (PE) is a linear measure of complexity based on mapping a time series on a symbolic sequence to describe the relationships between present and past samples [3]. Its previous application on EEG data obtained from anaesthesia has shown that PE tracks the level of hypnosis, as its values decrease with an increasing level of hypnosis [4-5]. The simplicity and fast speed of estimation constitute PE a good candidate for real-time and online applications. (2) Approximate Entropy (ApEn) is a measure of signal irregularity based on nonlinear dynamics [6]. It has recently been applied to study changes in the EEG regularity as a result of anesthetic agent administration [7-8].

In this paper we utilize a Support Vector Machine (SVM) to classify EEG segments, obtained from 10 patients recovering from surgery under general anaesthesia, into one of the two states 'Awake' and 'Anesthetized' using PE and ApEn as features.

II. Methods

A. Dataset

The data used in this study were collected from 10 male patients of age 39.8±21.3 undergoing general and urological surgery at Nicosia General Hospital, Cyprus. The 24-channel configuration of the TruScan32 (Deymed Diagnostic) was used 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 and data was sampled at 256Hz. Data recording usually commenced while patients were still awake prior to administration of the anesthetic agents (induction), continued throughout the entire surgery, and until patients regained consciousness (ROC) at the end of surgery some time after the intravenous administration of anesthetics was switched off. The average duration of the EEG records is approximately 70mins (min: 40mins, max: 90mins). ROC was defined as the point at which the patient regained consciousness started responding to verbal commands or tactile stimuli by the anesthetist at the end of surgery. 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 propofol bolus. During induction some patients also received boluses of neuromuscular blocking agents and analgesic drugs. Maintenance of GA was achieved with an intravenous

Manuscript received April 11, 2011. This work falls under the Cyprus Research Promotion Foundation's Program for Research, Technological Development and Innovation 2008 (DESMI 2008). DESMI 2008 is co-funded by the Republic of Cyprus and the European Regional Development Fund (Grant: DIDAKTOR/DISEK/0308/20).

N. Nicolaou is with the KIOS Research Centre and Holistic Electronics Research Lab, Dept. of Electrical and Computer Engineering, University of Cyprus, Kallipoleos 75, 1678 Nicosia, Cyprus (phone: +357-22893801; fax: +357-22893815; e-mail: nicoletta.n@ucy.ac.cy).

J. Georgiou is with the Dept. of Electrical and Computer Engineering, University of Cyprus, Kallipoleos 75, 1678 Nicosia, Cyprus.

S. Houris and P. Alexandrou are with the Nicosia General Hospital, Old Nicosia-Limassol Road, Nicosia, Cyprus.

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).

B. Permutation Entropy

PE is a linear complexity measure for time series [3]. 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) at a distance τ between them, and which overlap by $(m-1)$ samples. For a given embedding dimension there will be $m!$ possible permutations (motifs). If each permutation is considered as a symbol, the embedded time vectors 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 is defined as:

$$H_p(m) = -\frac{1}{\ln(m!)}\sum_{j=1}^{J} p_j \ln p_j \qquad (1)$$

J is the distinct number of symbols for a given embedding dimension $(J \le m!)$. 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 PE, the more regular the time series.

C. Approximate Entropy

Approximate Entropy (ApEn) is a measure originating from nonlinear dynamics, which quantifies the unpredictability or randomness of a signal [6]. It is also estimated by, first, splitting the time series of length N into n-dimensional segments, $\mathbf{x}_i$, such that the predictability of current samples can be estimated based on the knowledge of the previous n samples. The number of pairs of n-dimensional segments that are in close proximity, $count$, is estimated based on a distance function such that $count =$ number of $\mathbf{x}_j$ for which $d[\mathbf{x}_i, \mathbf{x}_j] \le r$. $d[...]$ is the maximum absolute difference of the corresponding scalar components of each segment, and r is a variable specifying the tolerance in the 'closeness' of the vectors (a good choice is usually $r = k\sigma$, where $k \in [0.1, 0.25]$ and σ is the standard deviation of the signal [9]). The vector proximity is then used to define $C_i^n(r) = count/(N-m+1)$. ApEn is then estimated as:

$$AE = \Phi^n(r) - \Phi^{n+1}(r) \qquad (3)$$

$$\text{where } \Phi^n(r) = \frac{1}{N-n+1}\sum_{i=1}^{N-n+1} \ln C_i^n(r) \qquad (4)$$

ApEn reflects the dissimilarity in the occurrence of patterns of length n and more complex patterns of length $n+1$. In other words, the more regular the time series, the bigger the similarity between $n-$ and $(n+1)$ –dimensional segments. Thus, a perfectly regular time series has an ApEn value of 0. As the irregularity of the time series increases, so does the ApEn.

D. Support Vector Machine

SVMs belong to the family of kernel-based classifiers [9]. 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.

E. Data Analysis

The main function of a DOA monitor is to alert the anesthetist when a subject becomes aware during surgery. Therefore, a minimal requirement for a DOA monitor is the ability to distinguish between the two states 'Awake' and 'Anesthetized' (class 'A' and 'B' respectively). This was assessed through the following analysis:

(1) Segments corresponding to the two classes were extracted from the continuous EEG recordings of 10 subjects around the ROC marker (132s pre- and 66s post-ROC).

(2) Five brain areas were defined as the average activity of specified electrode grids: 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). Visual inspection of the acquired data identified electrodes with bad quality signals from bad contact or no contact, which were subsequently excluded from estimation of the averages.

(3) The entropy measures were estimated over 2-second non-overlapping windows of the EEG segments from each of the five brain areas. The use of segments with such short duration ensures the stationarity of the EEG segments analyzed. Thus, the PE and ApEn feature vectors consisted of the following 5-dimensional values respectively:

$$PE_C^i = \left[H^i_{p(LF)}(m) \quad H^i_{p(RF)}(m) \quad H^i_{p(LP)}(m) \quad H^i_{p(RP)}(m) \quad H^i_{p(Z)}(m)\right] \qquad (5)$$

$$ApEn_C^i = \left[AE_{LF}^i(r,n) \quad AE_{RF}^i(r,n) \quad AE_{RF}^i(r,n) \quad AE_{RF}^i(r,n) \quad AE_{RF}^i(r,n) \right] \tag{6}$$

$C \in \{A, B\}$ corresponds to one of the two classes, and $i = 1,..., N_C$ denotes the i[th] 2-s segment from all the available segments of each class (N_C). After following guidelines in the literature the parameters for estimating the entropy measures were set as: $m = 3$ for PE [3], and $r = 0.1, n = 2$ for ApEn [10]. Since no pre-processing or artifact removal was performed, the entropy values were smoothed (moving average filter, $n = 10$ samples).

(4) Performance was evaluated over $B = 50$ bootstrap repetitions. In each repetition, 70% of the available data was used for training, while the remaining 30% was used for testing. Linear and non-linear (Radial Basis Function, radius 1) SVM was investigated. Performance was assessed as the sensitivity (7), specificity (8) and average accuracy (9):

$$SE = \frac{TN}{TN_n} \quad (7), \qquad SP = \frac{TP}{TN_p} \tag{8}$$

$$AC = \frac{1}{2}\left(\frac{1}{B}\sum_{b=1}^{B} \frac{TP}{TN_p} + \frac{1}{B}\sum_{b=1}^{B} \frac{TN}{TN_n} \right) \tag{9}$$

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

III. Results

Previous studies indicate that the administration of anesthetics has the effect of decreasing the estimated PE values. This effect can be seen in figure 1 (left column), which shows the estimated subject-average PE over the five defined brain areas. During anesthesia a shift from higher to lower frequencies is observed and the brain activity becomes more regular, with posterior predominance. This effect is captured both by PE and ApEn, which display lower and higher values respectively over posterior regions (fig.1 (e)-(h)) compared to frontal regions (fig.1 (a)-(d)) during anesthesia. At the point of ROC the PE is seen to increase, as the brain activity changes from lower to higher frequency rhythms. A corresponding increase in the ApEn values, indicating the return to more irregular activity, is only observed over posterior regions. Over frontal regions, the ApEn values display a decrease, followed by a slow increase. This is not unexpected as ApEn depends on the concentration of anesthetic agent. Here, intravenous anesthetic administration was switched off some minutes earlier. Hence, it is possible that ApEn has already increased following the metabolism of the anesthetic agents by the body and here we are observing smaller fluctuations (see also fig.2 in [8] for this effect). This requires further investigation over the entire duration of the surgery.

TABLE I
SINGLE-SUBJECT MAXIMUM AND MINIMUM LINEAR CLASSIFICATION

Feature	Maximum			Minimum		
	SP	SE	AC[a]	SP	SE	AC
PE	1.00	0.99	0.99	0.84	0.79	0.81
ApEn	1.00	0.99	0.99	0.92	0.96	0.95

[a]SP: Specificity; SE: Sensitivity; AC: Accuracy

TABLE II
SINGLE-SUBJECT MAXIMUM AND MINIMUM NONLINEAR CLASSIFICATION

Feature	Maximum			Minimum		
	SP	SE	AC[a]	SP	SE	AC
PE	1.00	0.99	0.99	0.98	0.93	0.96
ApEn	0.99	1.00	0.99	0.94	0.96	0.95

[a]SP: Specificity; SE: Sensitivity; AC: Accuracy

Figure 2 shows the estimated SP, SE and AC, averaged over all subjects and bootstrap repetitions. The mean accuracy (± standard deviation) obtained is (a) linear SVM: 0.96±0.05 and 0.97±0.01; and (b) nonlinear SVM: 0.98±0.01 and 0.98±0.01 for PE and ApEn respectively. The subject-wise maximum and minimum classification results obtained for PE and ApEn are shown in tables I (linear SVM) and II (nonlinear SVM).

There is no difference between linear and nonlinear classification. This implies that both PE and ApEn features are linearly separable and, thus, there is no need for a complex nonlinear classifier to be utilized. Based on this finding, it may even be possible to apply a simple adaptive threshold classifier, which would be more appropriate for an online and real time anesthesia monitor. PE and ApEn show similar high performance, hence both can be utilized for discriminating between 'awake' and 'anesthetized' states. With ApEn a similar level of SP and SE is achieved, hence neither is sacrificed for the other, which is important. However, ApEn is more computationally complex and its estimation takes longer than PE. In addition, something which must be taken into consideration, both PE and ApEn essentially track the changes in the signal regularity as the brain activity shifts from higher to lower frequency after administration of the anesthetic agents. This change is not unique to anesthetic-induced unconsciousness, e.g. a similar shift in frequencies is observed during sleep. Hence, neither measure is a direct reflection of awareness, but utilizes the EEG activity as a proxy for awareness.

IV. Conclusion

We investigated the use of Permutation Entropy (PE) and Approximate Entropy (ApEn) as a means of classifying between 'awake' and 'anesthetized' state from the EEG of patients recovering from general anesthesia. Both measures provide linearly separable features and a mean classification accuracy greater than 96% is obtained. Hence, both could be potentially utilized in an anesthesia monitor to track the level of hypnosis of the patient.

ACKNOWLEDGMENT

The authors would like to thank the hospital staff and the anonymous volunteers who participated in this study.

REFERENCES

[1] S. Ranta, "Awareness with recall during general anesthesia," in *Dept of Anaesthesia and Intensive Care Medicine* Helsinki: University of Helsinki, Finland, 2002, p. 101.

[2] J. Bruhn, P. S. Myles, R. Sneyd, and M. M. R. F. Struys, "Depth of anaesthesia monitoring: what's available, what's validated and what's next?," *Brit J Anaesth,* vol. 97, pp. 85-94, 2006.

[3] C. Bandt, and B. Pompe, "Permutation Entropy - a natural complexity measure for time series," *Phys Rev Lett,* vol. 88, p. 174102, 2002.

[4] X. Li, S. Cuy, and L. J. Voss, "Using Permutation Entropy to measure the Electroencephalographic effects of Sevoflurane," *Anesthesiology,* vol. 109, pp. 448-456, 2008.

[5] E. Olofsen, J. W. Sleigh, and A. Dahan, "Permutation entropy of the electroencephalogram: a measure of anaesthetic drug effect," *Brit J Anaesth,* vol. 101, pp. 810-821, 2008.

[6] S. M. Pincus, I. M. Gladstone, and R. A. Ehrenkranz, "A regularity statistic for medical data analysis," *J Clin Monit,* vol. 7, pp. 335-345, 1991.

[7] J. Bruhn, H. Röpcke, and A. Hoeft, "Approximate Entropy as an Electroencephalographic measure of Anesthetic Drug Effect during Desflurane Anesthesia," *Anesthesiology,* vol. 92, pp. 715-726, 2000.

[8] G.-J. Noh, et al., "Electroencephalographic Approximate Entropy changes in healthy volunteers during Remifentanil infusion," *Anesthesiology,* vol. 104, pp. 921-932, 2006.

[9] C. J. C. Burges, "A tutorial on Support Vector Machines for Pattern Recognition," in *Data Mining and Knowledge Discovery*, U. Fayyad, Ed. Boston: Kluwer Academic Publishers, 1998, pp. 121-167.

[10] S. M. Pincus and A. L. Goldberger, "Physiological time-series analysis: what does regularity quantify?," *Am J Physiol,* vol. 266, pp. H1643-H1656, 1994.

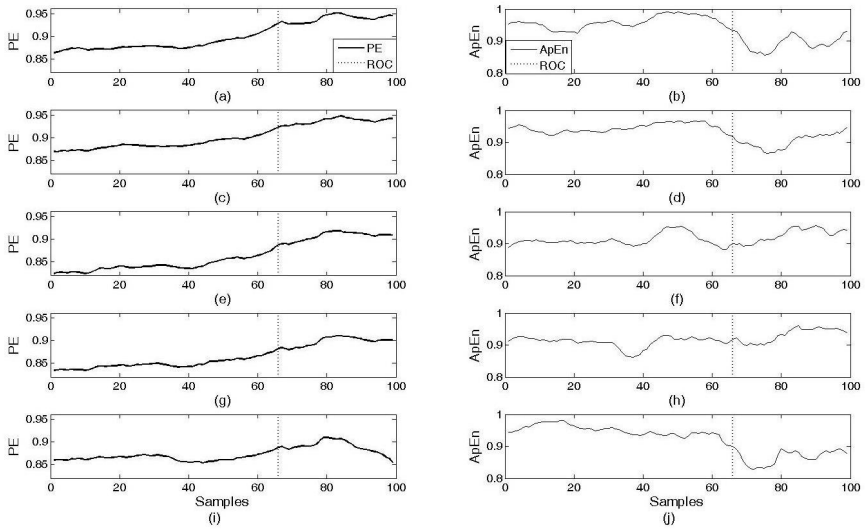

Fig.1. Average PE (left) and ApEn (right) features for the five broad brain areas: (a) and (b) – left frontal; (c) and (d) – right frontal; (e) and (f) – left posterior; (g) and (h) – right posterior; (i) and (j) – midline. Vertical dashed line: ROC marker. X-axis in arbitrary samples (every sample corresponds to a PE or ApEn value estimated over a 2-second segment).

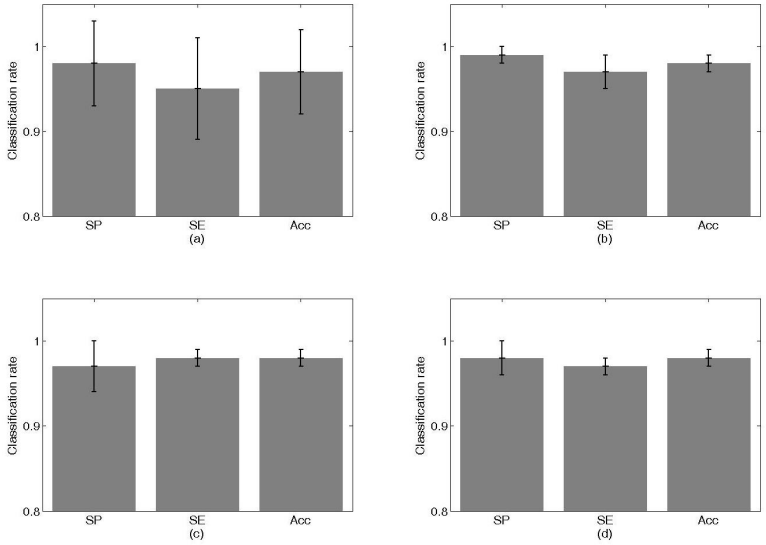

Fig. 2. Classification results averaged over 10 subjects, with error bars (mean ± standard deviation). Top row : Permutation Entropy. Bottom row : Approximate Entropy. (a) and (c) : Linear SVM. (b) and (d) : Non linear SVM (RBF). SP : Specificity (' Awake') ; SE : Sensitivity ('Anesthetized') ; AC : Accuracy $\left(\frac{SP+SE}{2}\right)$.