State Change Detection Using Multivariate Synchronization Measure from Physiological Signals

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Abstract

The cardiovascular system can be macromodelled as a collection of coupled oscillators [1]. Recently, the use of mutual couplings of these oscillators to characterize the state of the system during anaesthesia has been proposed. Assuming that the synchronization status between three systems, namely, the cardiac, respiratory and cortical oscillators, changes with respect to the depth of anaesthesia, we analyzed the synchronization between these three oscillators using a measure of synchronization, the S-estimator. Furthermore, we applied a statistical assessment to detect precisely the deep-light change of anaesthesia.

1. Introduction

The incidence of awareness among patients undergoing surgery is nonzero (Table 1). In other words, there are still a large number of patients who remain conscious during surgery due to lack of anaesthetic and who are unable to give any voluntary indication of awareness because of the muscle relaxant effect. This problem is particularly severe since, for clinical reasons, the anaesthesia should be kept as light as possible.

The idea of the depth of anaesthesia was first proposed by Dr. John Snow in 1845. Since then, many techniques have been introduced to measure this evaluation quantity. A well-publicized approach to assessing the depth of anaesthesia is the bispectral index technique known as BIS [2]. Regrettably, the use of this method is controversial and not 100% reliable. Similarly, all the other available methods have not yielded promising results [3].

Recently, one new approach has been proposed to improve this situation. According to Stefanovska and Bračič [1], the cardiovascular system can be perceived as a noisy dynamical system whose coupling coefficients depend on the depth of anaesthesia. The use of mutual couplings of these oscillators has been implemented to characterize the state of the system. This idea was tested on the physiological indicators (activity of heart (ECG) and respiration) of anaesthetized rats using synchronization indices and synchrograms. The results showed that the synchronization state could be used to characterize the depth of anaesthesia [6]. Despite the cardiac and respiratory rhythms in rats being approximately four times faster than those in humans, the dynamics of the cardiovascular - respiratory system in rats and humans is very similar; therefore, it seems plausible that similar results may also be applied to humans. However, applying this analysis to humans may not be reliable, since, in contrast to anaesthetized rats whose respiration does not need to be assisted, human respiration is often controlled by forced ventilation during surgery. Therefore, a third system, the brain system, has been added to the study[7]. An analysis based on the wavelet transform has shown that the frequency contents of the brain waves also vary over time [8]. Presently, assuming that the coupling directions between the three systems change when anaesthesia lightens, research on coupling directions using pairs of instantaneous frequencies in each case is in progress [9]. Meanwhile, other methods of analyzing the synchronization between these systems to find some other indices to define the depth of anaesthesia are being investigated in order to create a reliable measure by combining several such indices.

In this study, we place the emphasis on synchronization. We calculate a measure of synchronization called the ”S-estimator” [10] from the results of experiments along an experimental time series, and examine how synchronization changes according to the anaesthetic effect. The advantage of this method is its ability to directly examine the multivariate time series, since we must analyze data recorded simultaneously from three systems. Moreover, we introduce a Wilcoxon rank sum test [11] as a statistical assessment in order to detect more precisely the time of the anaesthesia state change.

Table 1: Incidence of awareness during surgery (after Pomfrett [4] and Myles et al. [5])

Author	Date	Sample	Awareness %
Hutchinson	1960	656	1.2
Harris	1971	120	1.6
McKenna	1973	200	1.5
Wilson	1975	490	0.8
Liu et al.	1990	1000	0.2

2. Method

In this section, we shall introduce the concept of synchronization and then, we will explain how this concept is used with the synchronization analysis method, which calculates a measure of synchronization called the ”S-estimator”.

2.1. Definition of synchronization

We define synchronization as a process whereby two (or more) dynamical subsystems adjust some of their time-varying properties to a common behavior as a result of coupling or a common external force.

Consider a large stationary, deterministic, finite-dimensional dynamical system, which can be divided into *n*-and *m*-dimensional subsystems, respectively.

$$\begin{cases} \frac{d\mathbf{x}}{dt} = \mathbf{f_1}(\mathbf{x}, \mathbf{y}; t) \\ \frac{d\mathbf{y}}{dt} = \mathbf{f_2}(\mathbf{x}, \mathbf{y}; t) \end{cases} \qquad \mathbf{x} \in \mathbb{R}^n, \mathbf{y} \in \mathbb{R}^m \tag{1}$$

We say that two subtrajectories $\mathbf{x}(t)$ and $\mathbf{y}(t)$ of the whole system are synchronized with respect to the properties (time-dependent measures) $\mathbf{g_x}$ and $\mathbf{g_y}$

$$\begin{cases} \mathbf{g_x} : \mathbb{R}^n \bigotimes \mathbb{R} \to \mathbb{R}^k \\ \mathbf{g_y} : \mathbb{R}^m \bigotimes \mathbb{R} \to \mathbb{R}^k \end{cases} \qquad k \leq min(m, n) \tag{2}$$

if there is a time-independent mapping $\mathbf{h} : \mathbb{R}^k \bigotimes \mathbb{R}^k \to \mathbb{R}^k$ such that

$$\| \mathbf{h}[\mathbf{g_x}(\mathbf{x}), \mathbf{g_y}(\mathbf{y})] \| = 0 \tag{3}$$

where $\| \cdot \|$ is any norm in $\mathbb{R}^k$. This unifying definition covers most phenomena usually considered to be synchronization [12]. Condition (3) requires a property $(\mathbf{g_x})$ of the trajectory $\mathbf{x}(t)$ to be in a fixed relation $(\mathbf{h})$ with another property $(\mathbf{g_y})$ of the trajectory $\mathbf{y}(t)$, and it implies that synchronized subtrajectories lie on an r-dimensional manifold, where r depends on $\mathbf{h}$ and is $1 \leq r \leq k$. Consequently, the dimensionality of synchronized dynamics $(n + m - r)$ becomes smaller than that of generic asynchronous dynamics $(n + m)$ in the whole system [12], [13].

2.2. S-estimator

By exploiting the above concepts, we quantify the amount of synchronization within a multivariate time series, recorded from each system, by comparing the actual dimensionality of the set of samples of the trajectory with the expected full dimensionality of an asynchronous trajectory. We perform this comparison by considering an embedding technique based on principal components analysis (PCA) [14] because it is a multivariate method. PCA explains the variance-covariance structure of multivariate data through a few linear combinations of the original variables. A given multivariate time series with k components can be transformed into the population principal components (PC) by a linear transformation projecting the original time series into the eigenbase of the covariance matrix (correlation matrix, if the data have been power normalized) of the time series itself [15]. In this coordinate system, the relative importance of each principal component in justifying the variance of the original time series is given by the normalized eigenvalue associated with its corresponding eigenvector. The application of this method to the delay-embedded (DE) coordinates is indeed possible since a given univariate time series $y(t)$ can be transformed into a multivariate time series through the delay embedding

$$y(t) \to \Theta(t) = [y(t)y(t-\tau) \cdots y(t-K\tau)] \tag{4}$$

where the time delay τ and the window size K may be computed through autocorrelation or self-mutual information [14].

The S-estimator is a measure of the amount of synchronization using an information-theory-inspired measure defined as the complement of the entropy of the normalized eigenvalues of the corresponding correlation matrix. The more disperse the eigenspectrum is, the more numerous the significant PCA components are (which means a higher embedding dimension), and the higher the entropy of the eigenspectrum is. On the contrary, the more concentrated the eigenspectrum, the fewer the significant PCA components (which means a lower embedding dimension), and the lower the entropy of the eigenspectrum.

For the sake of simplicity, let us consider a K-variate non-delay-embedded time series. All measurement vectors $\mathbf{u_i}$ are written as a matrix $\mathbf{U}$ such that

$$\mathbf{U} = \begin{bmatrix} \mathbf{u_0} \\ \mathbf{u_1} \\ \vdots \\ \mathbf{u_{N-1}} \end{bmatrix} \mathbf{u_i} \in \mathbb{R}^K \tag{5}$$

where K is the number of time series and N is the index of the time series. The corresponding $K \times K$ correlation matrix is given by

$$\mathbf{C} = \frac{1}{N}\mathbf{U}^T\mathbf{U} \tag{6}$$

If $\lambda_1, \ldots, \lambda_K$ are its eigenvalues and

$$\lambda'_i = \frac{\lambda_i}{\sum_{j=1}^{K} \lambda_j} = \frac{\lambda_i}{tr(\mathbf{C})} \tag{7}$$

are the corresponding normalized eigenvalues, the quantity

$$S = 1 + \frac{\sum_{i=1}^{K} \lambda'_i log(\lambda'_i)}{log(K)} \tag{8}$$

is a measure inversely proportional to the embedding dimension of the observed dynamical phenomenon; thus, it is proportional to the amount of synchronization.

When all time series are completely synchronized, the correlation matrix $\mathbf{C}$ has $\lambda'_1 = 1$ and $\lambda'_i = 0 (i \neq 1)$, hence the S-estimator gives $S = 1$. On the contrary, when there is no synchronization, $\mathbf{C}$ is diagonal and $\lambda'_i = 1/K$, hence $S = 0$.

For the same reason as mentioned before, this computation can be applied in a similar fashion to delay-embedded data.

3. Data Analysis

In this section, we will explain how experiments were performed and how we analyzed the obtained data using the S-estimator. Moreover, we describe the statistical assessment that was used to detect the state change from the obtained results.

3.1. Experiments

The experiments were performed on 10 adult, male Wistar rats. The depth of anaesthesia was assessed at 5 min intervals by the skin-pinch test. EEG, ECG and respiration were recorded simultaneously. The experiment started with a negative response, i.e., when the rat stopped responding to a reflex withdrawal of the limb, and terminated with the reappearance of a positive response. The three signals were digitized at a 1 kHz sampling rate with 16-bit resolution.

3.2. Analysis

In order to evaluate the temporal change of synchronization among the three measured systems, we computed the S-estimator for the data obtained in the experiments by a sliding window technique. The window length is set to 1s. (1000 data points) and the overlap length is set to 0.8s. (800 points). Fig. 1 shows the results for rat #9. As we can see from Fig. 1, the value of S seems to increase slightly at the beginning, but suddenly begins to decrease at about 38min. We can also note that the value of S is not very high. This is interesting, because it allows us to consider these three physiological systems as a set of weakly coupled oscillators.

Previously, another analysis had been carried out on the same recorded signals, i.e., the data from rat #9. From those results, the respiration frequency was found to increase and become erratic at 38min, and simultaneously, the cardiac frequency increased. Using the wavelet method it was calculated that the δ-wave in the EEG slightly increased in frequency during the initial deep phase of anaesthesia and underwent a marked decrease in amplitude at 38±5min. The θ-and γ_2-oscillations also undergo changes at 37.5min with an appreciable increase in the amplitude after transition. Furthermore, from the synchrograms computed for the cardiorespiratory systems, it was found that synchronization ends at 43±3min.

Our detected point of change exactly coincides with the above results. Consequently, it seems appropriate to designate this point as the point of deep-light change in anaesthesia. However, as it can be seen from Fig. 1, the S-estimator is noisy and it is not easy to detect the exact point of change from the figure.

3.3. Statistical assessment

In order to detect, statistically more precisely, the state-change point of anaesthesia, we calculated the statistical assessment value p using a Wilcoxon rank sum test. This is a two-sided rank sum test of the hypothesis that two independent samples come from distributions with equal medians, and yields the p-value. p is the probability of observing the given result. In the extreme case, when the null hypothesis is true, i.e., the medians are equal, $p = 1$. Hence, the closer the p-value is to zero, the more confident we are in rejecting the null hypothesis.

We performed the test on two sets of samples of 30s. length (150 samples) that were separated by 8min intervals (2400 samples) and moved along the time axis. In this way, it is possible to detect the first pair, because the second set statistically differs from the first set, which is 8min in the past. Fig. 2 shows that there is abundant evidence of a highly significant change at 40min.

To evaluate the robustness of the statistical detection, we changed the parameters, i.e., the window length and the interval length, and calculated the p-value. As can be seen from Fig. 3 and Fig. 4, small lengths do not give good results; nevertheless, there remains a wide range of suitable parameters.

All the experimental results for the other rats also show a decrease in the S-estimator at the point of deep-light change of anaesthesia, and the p-value allows us to locate the change accurately in time.

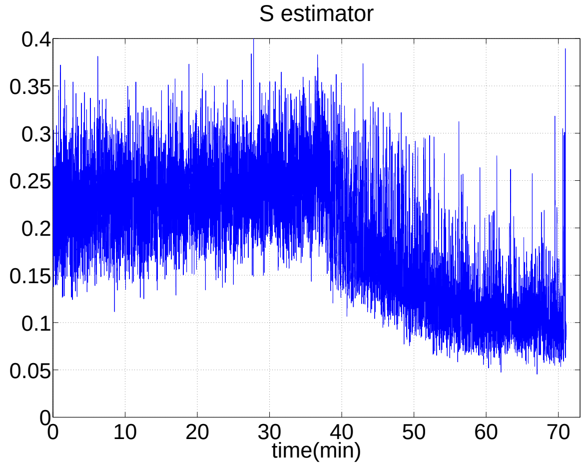

Figure 1: Synchronization measure obtained by clustering three oscillators (ECG, Respiration and EEG) together for rat #9

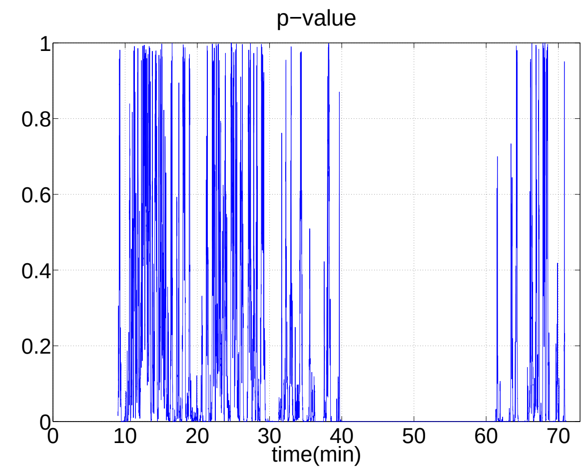

Figure 2: Statistical assessment of S-estimator obtained for rat #9

4. Discussion

Despite the excellent results we have obtained, we still do not know what makes the value of the S-estimator decrease when the anaesthesia lightens. It may be simply because the interactions between the three systems decline according to the effect of the anaesthesia, but this seems to be too simplistic. It is natural to consider that the complexity of each system changes according to the level of anaesthesia and thus, influences the S-estimator. Furthermore, because we reconstructed the state space of each system using the delay-embedding method, the actual S-estimator contains the information of correlation among the state variables of each system that should be normalized.

To avoid this problem, we need a new version of the S-estimator which takes the complexity inside each system into account and removes it from the synchronization analysis. The investigation of this method and its analysis will be a future topic of study.

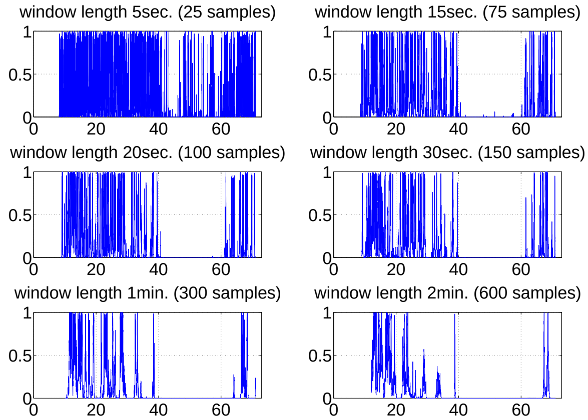

Figure 3: p-value obtained with several window lengths (x-axis is time (min).)

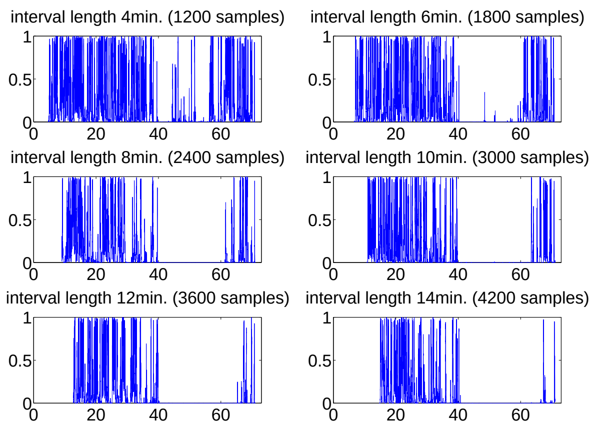

Figure 4: p-value obtained with several interval length (x-axis is time (min).)

5. Conclusions

We applied the use of a synchronization measure, the S-estimator, to physiological signals, namely, the cardiac, respiratory and cortical signals, obtained from experiments on rats. From the results, we found that the synchronization status changes with respect to the depth of anaesthesia. Due to the impossibility of determining the precise point where the state changes during anaesthesia, we introduced a statistical assessment, the Wilcoxon rank sum test, to detect a statistical change. This allowed us to determine the moment of change accurately.

This research is just in the beginning stage and there still remain many open questions. However, we are convinced that our index of the depth of anaesthesia will be useful and will contribute to reducing the number of patients that awake during surgery. We hope that one day the number of patients undergoing surgery who remain awake reaches zero.

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