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# TIME DELAY ESTIMATION APPROACH FOR THE BIS MONITOR BASED ON CROSS-CORRELATION TECHNIQUE

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**ABSTRACT**

An alternative approach to time delay estimation for the Bispectral Index (BIS) monitor is presented in this work. The practical implementation of the cross-correlation analysis (CCA) method is presented. The time delay estimation using windows and the robustness comparison between Peaks-Shift Correlation (PSC) and CCA methods are studied. Although both estimation methods are based on the correlation analysis, the time delay obtained with each one is different because the principle of the algorithms is different as well.

**Keywords:** bispectral index monitor, cross-correlation analysis, patient, time delay.

## 1. INTRODUCTION

The evaluation of time lag has been studied in many applications, and different estimation methods have been applied. Various authors have used the concept of "group delay" to estimate the time-delay [1], [2], [3], [4]. The latter is defined as the variation of the phase concerning the frequency because typically, the value of time-delay affects only the phase spectrum of the signal. Frequency domain algorithms are available for estimating the group delay and phase delay between finite sampled signals [5].

Time-delay estimation for biological systems is investigated by Müller *et al*. [6] using a cross-correlation method and three sophisticated interpretations of the phase spectrum. One of them uses the Hilbert transform method. All three methods were used in three physiological systems, but the Hilbert transform method gave the best results. Cabot introduced the underpinning theory of this technique [7]. Due to the limitations in the measurement, biomedical signals are often noise and artifact contaminated. A new time-delay estimation algorithm and its application experiments are presented in [8]. The method from [8] is more robust than the existing time-delay estimation algorithms based on wavelet-domain correlation and higher-order spectra. Different methods for time-delay estimation as Cross-correlation, the Fast Fourier Transform, and a new method based on adaptive least-squares filtering were applied to multichannel seizure EEG of epileptic patients [9]. The adaptive least-squares filtering method used real signals in non-stationary conditions and proved to give the best results.

A new method for time-delay estimation is proposed in [10]. The approach gave good results when artificial signals were used. It was applied to the analysis of myoelectric manifestations of muscle fatigue during electrical stimulation at frequencies up to 35 Hz. In this case, the performance of the proposed technique was superior to that of spectral analysis.

For anesthesia applications, the electrical activity of the brain must be monitored continuously. One of the most common devices used for this purpose is the BIS monitor. BIS is a measure derived from the electroencephalogram (EEG) signals, and it is closely related to the level of consciousness. The BIS monitor requires some time to calculate index value, depending on the changes in the BIS level and on the presence of artifacts. Time-delays between 14 and 155 seconds can be found even when there are no artifacts [11]. A procedure that can estimate the BIS monitor's time delay is also presented in [12].

This work is organized as follows: In the first part, the theoretical framework regarding the time delay estimation method is presented; the practical implementation of the CCA method is presented for simulated and clinical cases. Finally, the time delay estimation using windows and the robustness comparison between PSC and CCA methods are performed.

## 2. MATERIALS AND METHODS

### 2.1 Patient Model

The block diagram of the patient model used in this study is presented in Figure-1.

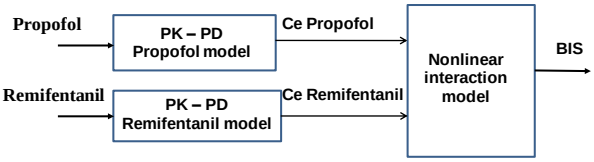


**Figure-1.** Block diagram of the patient model.

Propofol is the most common hypnotic drug used in general anesthesia, and Remifentanil is an analgesic drug. The distribution of these drugs in the body can be described by pharmacokinetic and pharmacodynamic (PK-PD) models [13], [14]. BIS is related to the effect of the two drugs by a nonlinear relation called the Hill curve [15], [16] (see Figure-2). BIS ranges between 0 and 100 [15]. Zero means that the patient does not have cerebral activity, and 100 denotes that the patient is awake and

conscious (e.g., 70 indicates that the patient is in moderate sedation).

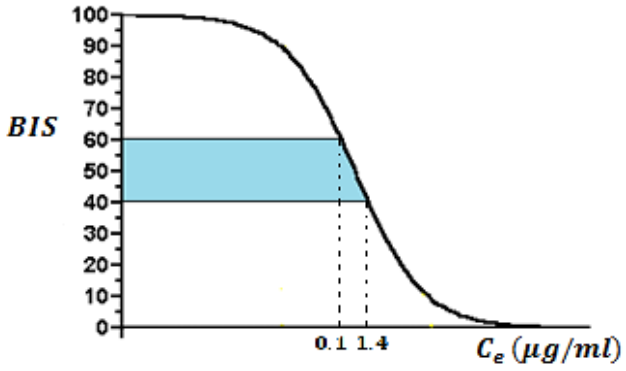


**Figure-2.** Hill Curve.

In the case of one drug (SISO case), the Hill curve is represented by the following relation:

$$BIS(t) = E_0 - E_{\max} \cdot \frac{Ce^{\gamma}(t)}{Ce^{\gamma}(t) + C_{50}^{\gamma}} \quad (1)$$

$E_0$ denotes the baseline value (awake state), and by convention, a value of 100 is assigned. $E_{\max}$ denotes the maximum effect achieved by the drug. $Ce$ is the drug effect-site concentration, $C_{50}$ is the drug concentration at half maximum effect and represents the patient sensitivity to the drug, and $\gamma$ determines the steepness of the curve.

### 2.2 Estimation Method

The method is presented first for the single-input single-output (SISO) case, and then it is extended to the multiple-input single-output (MISO) case.

After surgery, when the patient arrives at the Intensive Care Unit (ICU), the desired BIS target is 50 and must remain between 40 and 60 for a good sedation level. Around 50, BIS can be approximated by a line, using the following relation (SISO case)

$$BIS(t) = a \cdot Ce(t) + b \quad (2)$$

Where $a$ represents the slope of the linear approximation, and $b$ is a constant value. The real and simulated BIS signals were obtained based on the scheme presented in Figure-3. The Propofol infusion is applied to the patient, and the real BIS signal is recorded by the BIS monitor. As mentioned above, the monitor introduces a time-delay. The same Propofol infusion rate is used in the simulator to obtain the simulated BIS signal. The effective concentration of the drug is calculated using the PK-PD patient model. The simulated BIS signal is related to the effective concentration of the drug by the Hill curve. A delay is added to simulate the delay introduced by the real monitor.

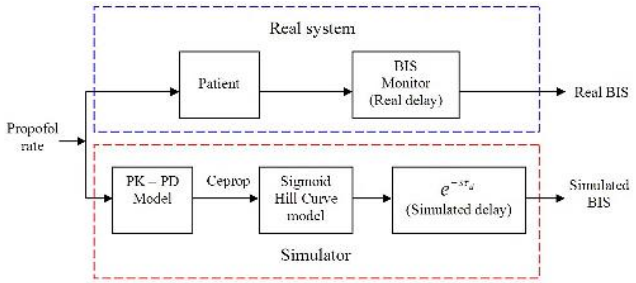


**Figure-3.** Schematic representation of the real and simulated BIS signals for SISO case.

Considering the time-delay introduced by the BIS monitor, the real BIS signal can be expressed by the following relation.

$$BIS(t) = a \cdot Ce(t - \tau) + b \quad (3)$$

The simulated BIS signal can be denoted as below, assuming no disturbances.

$$BIS(t) = a \cdot Ce(t - \hat{\tau}) + \hat{b} \quad (4)$$

Where, $a$ and $a$ are the slopes of the linear curve for real and simulated cases, respectively; $b$ and $\hat{b}$ represents the intersection of the line with the BIS axis for the real and simulated cases, respectively; $\tau$ and $\hat{\tau}$ are the time-delays in samples for real and the simulated cases, respectively. The following relation can be derived from equation (4):

$$\frac{BIS(t - (\tau - \hat{\tau})) - \hat{b}}{a} = Ce(t - \tau) \quad (5)$$

Where, $\tau - \hat{\tau} = \tilde{\tau}$ is the difference (in samples) between the time-delay of the real BIS signal and the time-delay of the simulated BIS signal. If $\tilde{\tau} \succ 0$, the real BIS signal is delayed concerning the simulated signal. In practice, $\tilde{\tau} \succ 0$ is considered because the real BIS time-delay is more significant than the simulated time-delay.

In both real and simulated cases, $Ce$ is obtained using the same PK-PD model; therefore, the following equation is derived from (5) and (3):

$$BIS(t) = a \cdot BIS(t - \tilde{\tau}) + \tilde{b} \quad (6)$$

With $a = \frac{a}{a}$, $\tilde{b} = b - \frac{\hat{b}}{a}a$, and $\tilde{\tau} = \tau - \hat{\tau}$.

Nominally $a = 1$, $\tilde{b} = 0$, and $\tilde{\tau} = 0$ in case that the two signals are not influenced by noise or disturbances. The slope of the real linear BIS from equation (3) is equal to the linear simulated BIS slope equation (4). If $\tilde{\tau} = 0$

indicates there is no time-delay between the real and simulated signals.

The linear relation between real BIS and simulated BIS is obtained from equation (6) and can be written as:

$$y(t) = a \cdot u(t - \tilde{\tau}) + \tilde{b} \tag{7}$$

Where $y(t)$ is the real BIS signal and $u(t)$ is the simulated BIS signal.

### 2.2.1 Cross-Correlation

The cross-correlation function measures the degree of correlation between two signals (cause-effect). The cross-correlation between two sampled signals $u(t)$ and $y(t)$ is described by:

$$R_{uy}(l) = E\{u(t)y(t+l)\} \tag{8}$$

$$R_{uy}(l) = \lim_{N\to\infty} \frac{1}{N} \sum_{t=0}^{N-1} u(t)y(t+l) \tag{9}$$

With $N$ the total number of measured samples.

The correlation is applied to the equation (7):

$$y(t+l) = a \cdot u(t - \tilde{\tau} + l) + \tilde{b} \tag{10}$$

The following relations can be derived:

$$E\{u(t)y(t+l)\} = E\left\{u(t) \cdot \left[a \cdot u(t - \tilde{\tau} + l) + \tilde{b}\right]\right\} \tag{11}$$

$$R_{uy}(l) = a \cdot R_{uu}(l - \tilde{\tau}) + \tilde{b}\mu_u \tag{12}$$

Equation (12) is used to find the minimum cost function in order to obtain $a$ and $\tilde{\tau}$ parameters. By definition, $\mu_u$ is the mean value of the signal. The exact estimation of the $\tilde{b}$ parameter is not essential since a wrong evaluation will result in a steady-state error that will be removed by the controller.

### 2.2.2 Extension to the MISO case

During the clinical trials, two drugs were used: Propofol and Remifentanil. Therefore, the method presented above was extended to the MISO case.

The concentration-response linear relation of the two drugs can be described as:

$$BIS(t) = a \cdot Cu(t) + b \tag{13}$$

where,

$$Cu(t) = \frac{C_{e\Pr op}(t)}{C_{50,\Pr op}} + \frac{C_{e\mathrm{Re}m}(t)}{C_{50,\mathrm{Re}m}} \tag{14}$$

The relation between the two inputs of drugs and $BIS$ is described using the response surface methodology [15]. The simulated BIS signal can be expressed by:

$$BIS(t) = a \cdot Cu(t - \hat{\tau}) + \hat{b} \tag{15}$$

The input $Cu(t)$ is, in this case, a surface, and $a$ represents the slope of the surface [15]. Analogously, the real BIS signal can be represented like:

$$BIS(t) = a \cdot Cu(t - \tau) + b \tag{16}$$

The algorithm is implemented in the same way as for the SISO case, having this time as input $Cu(t)$.

## 3. RESULTS AND DISCUSSIONS

### 3.1 Simulation Study

The real BIS recorded in the ICU is the combined effect of a manifold of drugs, not only Propofol and Remifentanil. It is also affected by artifacts (head movement, coughing).

The BIS signals obtained for patients controlled in open-loop were analyzed to select those signals which vary significantly when the two drugs are applied.

The simulated BIS signal and the test signal used to validate the method are illustrated in Figure-4.

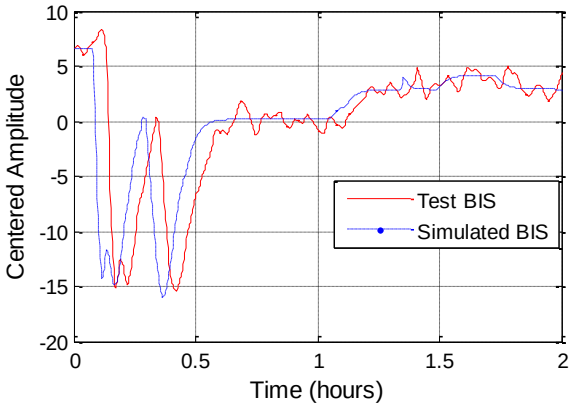


**Figure-4.** Simulated BIS signal and test signal with 10% noise and time-delay of 20 samples added.

For validation purposes, a representation of the real BIS signal called "test signal" was built. A time-delay was added to the simulator to represent the delay introduced by the BIS monitor. Additionally, a pseudo-random (colored) noise was included in the simulator output to describe the BIS monitor's noise, as shown in Figure-5.

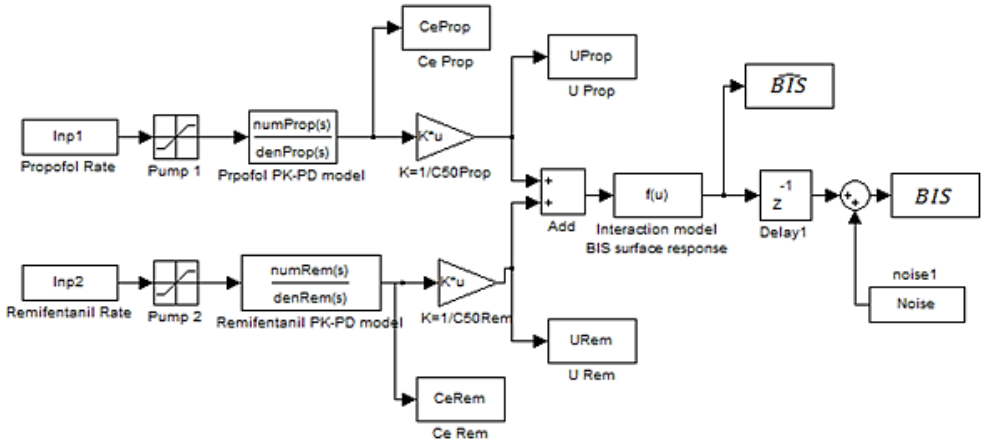


**Figure-5.** Simulated BIS signal with noise and time delay added - MISO case.

Two hours (from the 2nd hour until the 4th hour) from the total measurement of the signals were taken into account. In this part, it is possible to observe the changes in the real BIS signal, and both drugs are administered. The mean value of the considered signals was removed, and then the signals are centered to zero. The cross-correlation method was used with $y(t)$ being the test signal and $u(t)$ the simulated BIS signal. The cost function was obtained to identify the required parameters. The time-delay for the simulated signal and the test signal was set to $\hat{\tau}=1$ and $\tau=1$, respectively to test the method. The method works appropriately if $\tilde{\tau}=\tau-\hat{\tau}=0$ and $a=1$. The obtained cost function is represented in Figure-6.

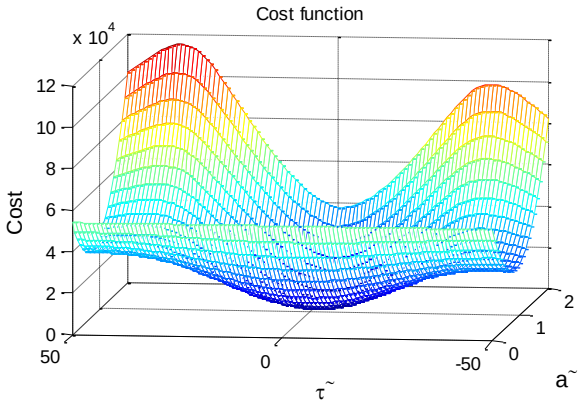


**Figure-6.** Cost function using the simulated BIS and the test signal.

The cost function curve shows the curve convergence to a specific point marked by a minimum $\tilde{\tau}$ and $a$. This point was obtained for $a=1$ and $\tilde{\tau}=0$. For $a=1$ (the slope of the simulated signal is equal to the slope of the test signal) and $\tilde{\tau}=0$ (the delay between the two signals, in samples), we can conclude that the method works correctly.

### 3.2 Clinical Test

The method was tested using the real BIS signal recorded in ICU. This real signal differs from the signal obtained with the simulator, since the patient received other drugs as well, not just Propofol and Remifentanil. Moreover, the real BIS is affected by some disturbances such as leg movement or coughing; these disturbances were not considered during the validation in the simulation study. Figure-7 depicts the real BIS, Propofol, and Remifentanil signals, for one selected patient.

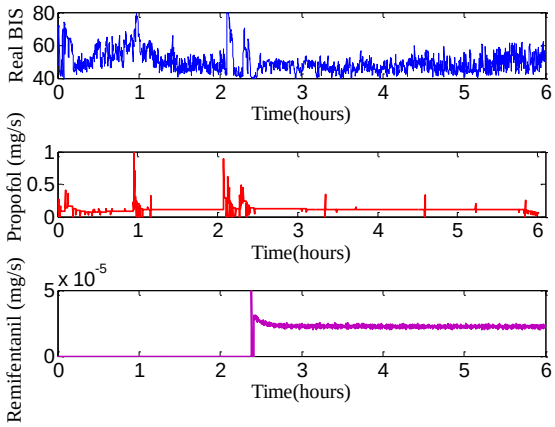


**Figure-7.** Real BIS, Propofol and Remifentanil Signals-Patient 1.

The real BIS signal was filtered with a 3rd order low-pass filter at the cut off frequency of 0.0025 Hz. When the simulator did not consider the influence of the disturbances, we expect that the estimation of the parameters was biased. Hence the disturbances were considered to obtain the simulated signal.

When a disturbance appears, BIS increases, and this is modeled in the simulated BIS by adding a step which passes through a $1^{st}$ order filter. The moment when the disturbance appears is $t_1$, and it can be determined visually from the real signal.

The simulated BIS signal is obtained with the following relation:

$$BIS(t) = a_1 C_{e\Pr op}(t-\hat{\tau}) + a_2 C_{e\mathrm{Re}m}(t-\hat{\tau}) + \hat{b} + \frac{cq^{-1}}{1-dq^{-1}}\mu(t-t_1) \quad (17)$$

where:

$$a_1 = \frac{a}{C_{50,\Pr op}} \quad (18)$$

$$a_2 = \frac{a}{C_{50,\mathrm{Re}m}} \quad (19)$$

The two signals are depicted in Figure-8.

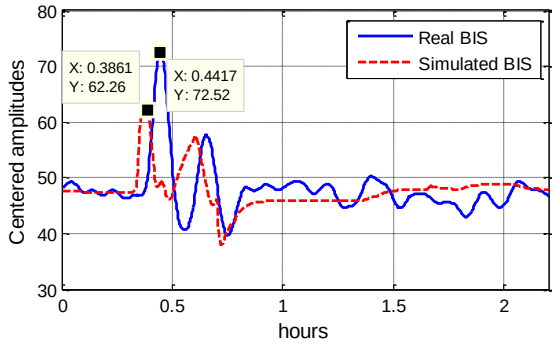


**Figure-8.** Real BIS signal and simulated BIS Signal-Patient 1

In Figure-8, it is possible to observe a time-delay of 0.058 hours, corresponding to approximately 200 seconds. By applying the proposed algorithm, the cost function from Figure-9 was obtained.

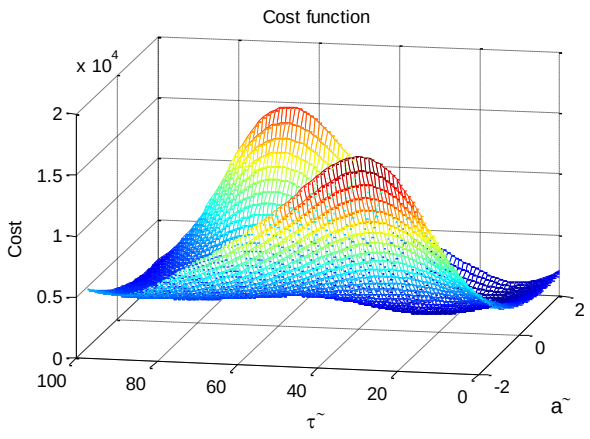


**Figure-9.** Cost function using the real BIS and the simulated BIS-Patient 1.

The minimum cost function was obtained for $\tilde{\tau} = 22$ samples and $a = 1.1$. Both parameters are closed to the expected values (20 and 1, respectively).

### 3.3 Time Delay Estimation Using Windows

An alternative approach to time delay estimation was performed, which is named Peaks-Shift Correlation, hence the total number of samples was divided into intervals of 256 samples, obtaining some windows. The CCA method is now applied in each window. In this way, it is more easily observed when a change takes place in the time delay. The patients in closed-loop were used this time because the BIS signal has significant variations in these cases.

The algorithm uses windows of 256 samples (2560 seconds or 0.7 hours). A measurement of 4.1 hours is provided for the real BIS signal, such that five windows are obtained (from 0 to 3.5 hours).

The CCA method explained previously is applied now for each window, using the real and simulated signals to obtain the time delay. Five different values of time delay are obtained. Time delay estimation for each one window is presented in Figure-10. The values obtained are shown in Table-1.

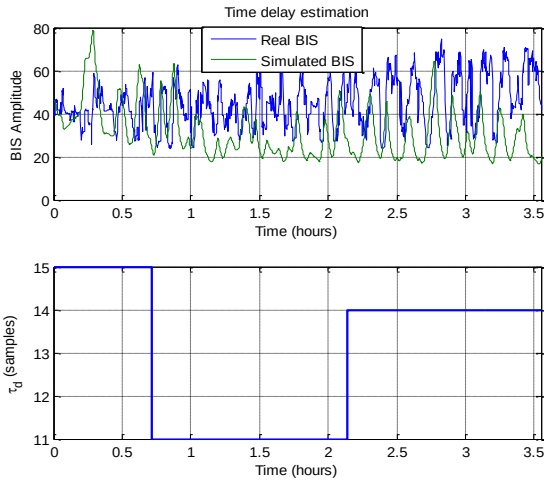


**Figure-10.** Time delay estimation using window of 256 samples.

**Table-1.** Time delay estimation for each one window.

| Window | Samples | Time (seconds) |
|---|---|---|
| 1 | 15 | 150 |
| 2 | 11 | 110 |
| 3 | 11 | 110 |
| 4 | 14 | 140 |
| 5 | 14 | 140 |

It is necessary to test the method's accuracy, so the time delay is estimated by looking at the two signals (real and simulated) in Figure-11, and the results are compared.

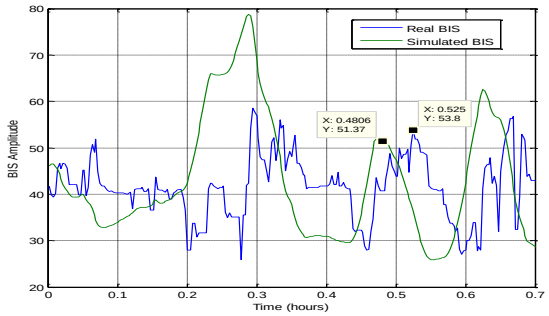


**Figure-11.** Real and simulated BIS signals - First window.

By looking at Figure-11, a time delay of 0.045 hours is obtained for the first window, and it corresponds to 16 samples. It is very close to the time delay estimated by the method. This comparison is performed for each window, and similar results between observed signal and method are obtained.

The algorithm is used for patients in a closed loop. The results show a good time delay estimation for windows in which the signals have variations in dynamic as significant oscillations. Still, the method does not have a good estimation when the signals remain without oscillations. The result obtained for another patient is presented in Figure-12.

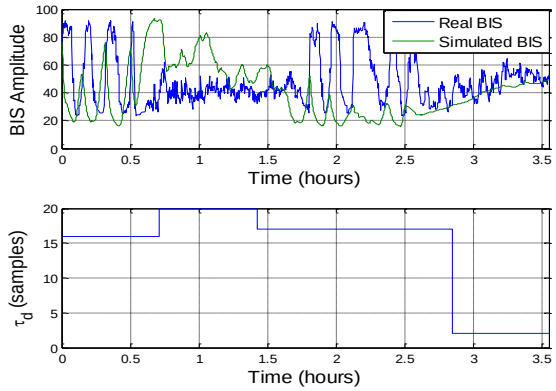


**Figure-12.** Time delay estimation using windows - another patient.

Figure-12 confirms that the method has a good estimation in the first, third and fourth windows because the signals have significant oscillations but is not a good estimation for second and fifth windows because the signals remain without important changes.

### 3.4 Robustness Comparison between PSC and CCA Methods

It is proposed to compare the two methods mentioned above, a test for checking the performance when using different noise levels is performed. The signals used in both methods are the simulated BIS signal and the simulated BIS signal with noise and delay added (test signal) in the case of one patient. The noise level is increased from 10% to 40%, and the estimation of time delay is checked in each window. For both methods, the delays added in each window are 12 samples for the first window, 5 samples for the second, 6 samples for the third, and 11 samples for the fourth. This vector is referred further as "Reference $\tau_d$ ".

#### 3.4.1 Time delay estimation with PSC method

The time delay estimation using windows - PSC method for 10% of the noise is shown in Figure-13.

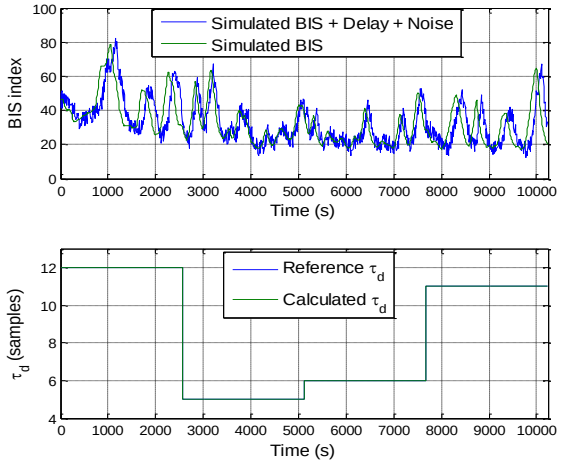


**Figure-13.** Time delay estimation using windows - PSC method for 10%.

The test shows that for 10 % and 20 % noise, the time delay is estimated correctly. When the noise is 30%, the time delay is estimated with an error of 1 sample during the second window (Figure-14). When the noise applied is 40%, the PSC method gives an error of 1 sample during the third and fourth windows.

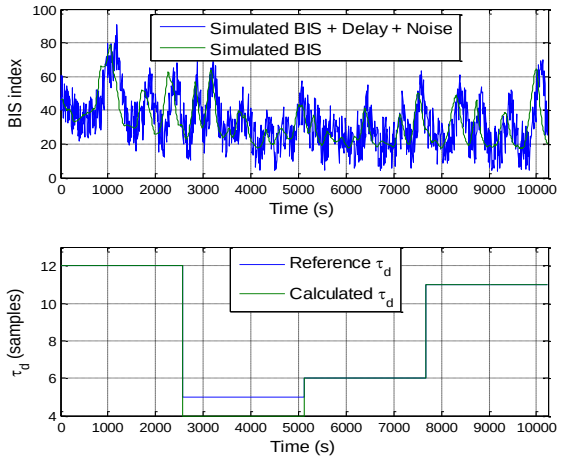


**Figure-14.** Time delay estimation using windows - PSC method for 30% of noise.

### 3.4.2 Time delay estimation with CCA method

The same robustness test was performed for the CCA method in the same patient.

The CCA method gives an error of 1 sample during the first and fourth windows when the noise added is 10% (Figure-15), and the same occurs when the noise is increased to 20%.

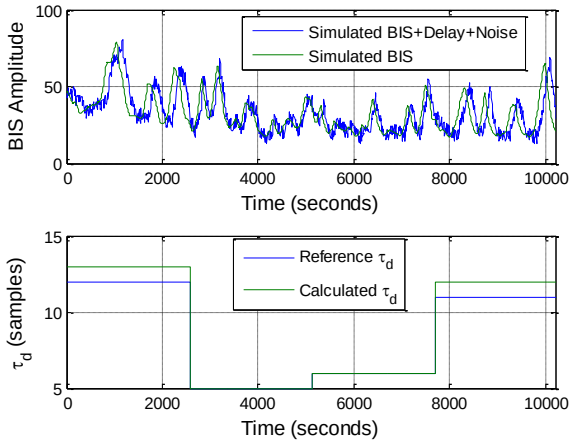


**Figure-15.** Time delay estimation using windows - CCA method for 10% of noise.

When the noise is 30%, there is an error of 1 sample for the first, second, and the third window (Figure-16). When it is 40%, the time delay is estimated with an error of 3 samples during the first window and 1 samples during the third and fourth windows.

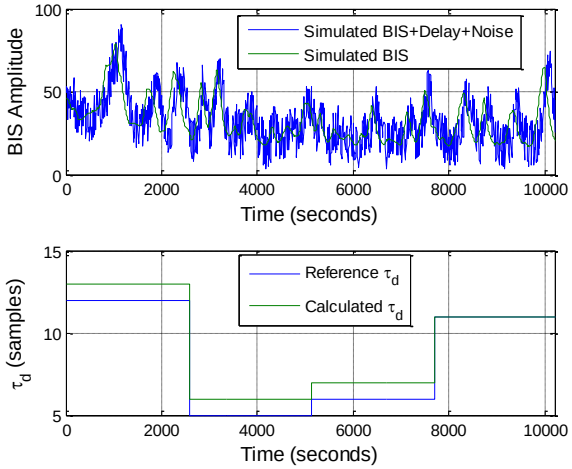


**Figure-16.** Time delay estimation using windows - CCA method for 30% of noise.

### 3.5 PSC and CCA Methods Using the Real BIS Signal

Both methods are used for time delay estimation using the real BIS signal measured for five patients. The results obtained are presented in Table-2. Fixed windows of 256 samples are used in both cases. The time delay values are given in samples for each window (W).

**Table-2.** Comparison of the two methods used for time delay estimation.

| Patient | Peaks-shift correlation method | | | | Cross Correlation method | | | |
|---|---|---|---|---|---|---|---|---|
| | W1 | W2 | W3 | W4 | W1 | W2 | W3 | W4 |
| 1 | 19 | 18 | 19 | 13 | 26 | 25 | 24 | 14 |
| 2 | 14 | 13 | 10 | 10 | 20 | 15 | 17 | 18 |
| 3 | 7 | 14 | 11 | 12 | 13 | 29 | 21 | 38 |
| 4 | 12 | 5 | 6 | 11 | 15 | 11 | 11 | 14 |
| 5 | 14 | 5 | 11 | 11 | 16 | 20 | 17 | 17 |

The Table-2 shows a difference between the time delay estimation done for each method. In the CCA method the purpose is to find adequate values for $\tilde{\tau}$ and $a$ in order to minimize the error between the cross correlation function $R_{uy}$ and the autocorrelation function $R_{uu}$. When there are high differences between the real and simulated BIS signals, it is very difficult to obtain a good accuracy in the time delay estimation.

## 4. CONCLUSIONS

In this paper, the time-delay introduced by the instrumentation (BIS monitor) during general anesthesia has been estimated using cross-correlation algorithms. Additionally, the parameters of the linear relationship between the depth of anesthesia (BIS) and the effect of the administered drugs (Hill curve) were estimated as well.

The method was presented first for the SISO case, and then it was extended to the MISO case. Initially, it was validated using simulated signals. It was proved that the method works for noise levels lower than 30% of the BIS signal. High accuracy is obtained for noise level lower than 10%.

Comparing the two methods PSC and CCA was made through a test for checking the performance when using different noise levels. The signals used in both methods are the simulated BIS signal and the simulated BIS signal with noise and delay added (test signal) in the case of one patient. The noise level is increased from 10% to 40%, and the estimation of time delay is checked in

each window. A difference between the time delay estimation done for each method was found.

Although both estimation methods are based on the correlation analysis, the time delay obtained with each one is different because the principle of the algorithms is different as well. The correlation analysis is performed in the PSC method between the *Ce* of Propofol signal with the real and simulated BIS signals. When the quantity of Propofol applied to the patient rises, then *Ce* rises also, and the BIS level is decreased. It can be observed that these signals are inversely proportional; therefore, the time delay (between the real BIS response and the simulated BIS response) is given by the difference between the minimum values of their respective cross-correlation results.

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