VOL. 12, NO. 7, APRIL 2017 ISSN 1819-6608
ARPN Journal of Engineering and Applied Sciences

www.arpnjournals.com

TIME DELAY ESTIMATION FOR BIS MONITORUSED INGENERAL ANESTHESIA

Diego F. Sendoya-Losada, Faiber Robayo Betancourt and José Salgado Patrón
Department of Electronic Engineering, Faculty of Engineering, Surcolombiana University, Neiva, Huila, Colombia
E-Mail: diego.sendoya@usco.edu.co

ABSTRACT

The purpose of this work is to present a procedure which is able to estimate the time delay of the BIS monitor. To achieve this, the pharmacokinetic and pharmacodynamic models of the patients are placed in a simulation scenario with a variable and known time delay and with a reasonable amount of noise, in order to reproduce the conditions of the BIS monitor and the artifacts present in the intensive care unit. This artificial system is used to test the different procedures based on the cross-correlation analysis. Finally, the real signals recorded during clinical trials were used to estimate the time delay of the BIS monitor.

Keywords: anesthesia control, cross-correlation analysis, intensive care unit, time delay estimation.

1. INTRODUCTION

Adequate anesthesia can be defined as a reversible pharmacological state where the patient's muscle relaxation, analgesia and hypnosis are guaranteed. Anesthesiologists administer drugs and adjust several medical devices to achieve such goals and to compensate the effect of surgical manipulation while maintaining the vital functions of the patient.

One of the devices used by clinicians to assess the depth of anesthesia is the Bispectral Index monitor (or BIS monitor), which uses electroencephalographic (EEG) signals (closely related to the level of consciousness of the patient) in order to derive a monotonous measure of depth of anesthesia in a range from 0 to 100.BIS equals to 0 means that the patient does not have cerebral activity and BIS equals to 100 denotes that the patient is awake and conscious. When the patient is in Intensive Care Unit (ICU), the desired BIS target is 50 and must remain between 40 and 60.

The purpose of this work is to present a procedure which is able to estimate the time delay of the BIS monitor. This time delay will be used further in themathematical model of a predictive control algorithm. To achieve this, a set of artificial data is used initially in order to test the methods for Time Delay Estimation (TDE), andthe resampled real data recorded from clinical trials are used at the end.

In order to obtain the artificial data the pharmacokinetic (PK) and pharmacodynamic (PD) models are placed in a simulation scenario with a variable and known time delay and with a reasonable amount of noise, this allows imitating the conditions of the BIS monitor and the artifacts present in the ICU. This artificial scenario represents the real system with variable time delay.

To produce the simulated BIS, the artificial Propofol signal is applied to the PK-PD model of the patient obtaining a simulated C_{eProp} signal. This signal is applied to the Sigmoid Hill model, which uses nominal values to produce the simulated BIS signal without time delay.The artificial Propofol and BIS signals obtained are used jointly with the simulated BIS in order to test the different procedures based on the cross-correlation analysis.

Subsequently, the real Propofol and BIS signals recorded during clinical trials are used. In this case, the real BIS signal has an unknown time delay introduced by the BIS monitor as well as a reasonable amount of noise. To produce the simulated BIS, the real Propofol signal is applied to the simulator, which uses the PK-PD model of the patient to obtain a simulated C_{eProp} signal. This signal is applied to the Sigmoid Hill model, which uses nominal values to produce the simulated BIS signal without time delay. Figure-1 shows this procedure. In this case, the different procedures based on the cross-correlation analysis are also used.

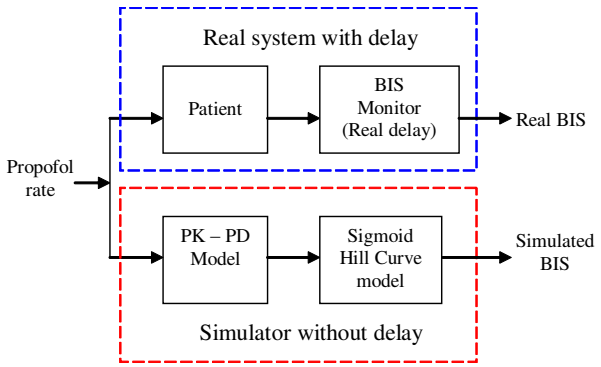

Figure-1. Block scheme for the parallel comparison of the real and simulated signals.

2. MATERIALS AND METHODS

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

$$R_{uy}(l) = E\{u(k)y(k-l)\}$$

where l is the lag and $E\{\cdot\}$ denotes the expected value. A common estimator used in the practice for the cross-correlation is:

$$R_{uy}(l) = \begin{cases} \frac{1}{N}\sum_{k=0}^{N-l-1} u(k+l)y(k), & 0 \le l \le N-1 \\ \frac{1}{N}\sum_{k=0}^{N+l-1} u(k)y(k-l), & -(N-1) \le l \le -1 \end{cases}$$

where N is the total number of measured samples. This function is often normalized and expressed as:

$$\hat{R}_{uy}(l) = \frac{R_{uy}(l)}{\sqrt{\sigma_u^2 \sigma_y^2}}$$

where σ_u^2 is the variance of the input signal $u(k)$ and it is defined by:

$$\sigma_u^2 = \frac{1}{N}\sum_{k=0}^{N-1} u(k)^2$$

The variance of the output signal $y(k)$ is defined analogously. The result of the cross-correlation function is multiplied by a Blackman-Harris window to reduce the leakage effect.

For artificial data, $u(k)$ corresponds to the artificial Propofol signal and $y(k)$ is the artificial BIS level. On the other hand, $u(k)$ corresponds to the real Propofol signal and $y(k)$ is the real BIS level when the database obtained from ICU is used. Three methods are used for TDE: offline TDE, semi-online TDE and online TDE.

2.1 Offline TDE

The first algorithm used to estimate the time delay applies the cross-correlation analysis using the complete Propofol and BIS signals.

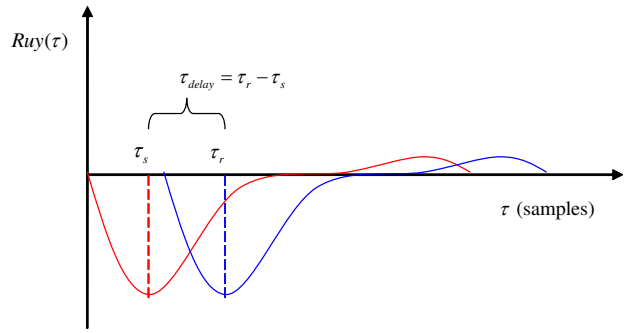

Figure-2. Schematic representation of the TDE from correlation functions.

As it is seen in Figure-2, a minimum value of the cross-correlation function can be found at time τ_r because when the Propofol increases, the BIS level decreases. This τ_r is the sum between the response due to the dynamic characteristics of the patient and the time delay introduced by the BIS monitor. In order to estimate the value of this time delay, the Propofol signal is applied to the simulator and a simulated BIS signal without time delay is obtained. Performing the cross-correlation analysis between these two signals a minimum value of the cross-correlation function can be found at time τ_s. This τ_s is related only to the dynamic response of the system. The difference between τ_r and τ_s represents the estimated time delay (τ_d) introduced by the BIS monitor.

2.2 Semi-Online TDE

While the patient is in ICU, its dynamics is continuously changing (intra-patient variability). Furthermore, the patient response is corrupted by artifacts (disturbances). When these artifacts occur, the instrumentation delay increases (the BIS monitor needs more time to calculate a BIS value and takes EEG values from previous time instants to find useful information). As a result, the time delay during disturbances is higher than in the moments without disturbances.

To detect those changes the second algorithm to estimate the time delay applies the cross-correlation analysis dividing the complete signals in small parts of fixed length. In this case the signals are divided in windows of 256 samples. Thus, the cross-correlation analysis is used in order to estimate the time delay on each window. In this way, it can be seen more easily when a change takes place in the time delay.

2.3 Online TDE

In order to control the BIS level in ICU using an adaptive control strategy, the prediction model used by the model-based controller has to be updated at each sampling time and the time delay estimation must be performed continuously. To detect the changes in the time delay of the BIS monitor the third algorithm estimates the delay by means of the cross-correlation analysis, sliding a window of 256 samples along the signal in order to process the current sample and the 255 previous data. This means that in each sampling time the algorithm uses the information present in the current measurement and past information in order to observe more easily when a change takes place in the time delay due to the change in the patient dynamics and disturbances.

3. RESULTS AND DISCUSSIONS

3.1 Artificial data

In order to test the effectiveness of the algorithms used for time delay estimation, a set of artificial signals is used initially. To generate these signals, the PK-PD model of the patient with a time delay between 10 and 200 seconds is used to represent the patient and the delay introduced by the BIS monitor (see Figure-3).

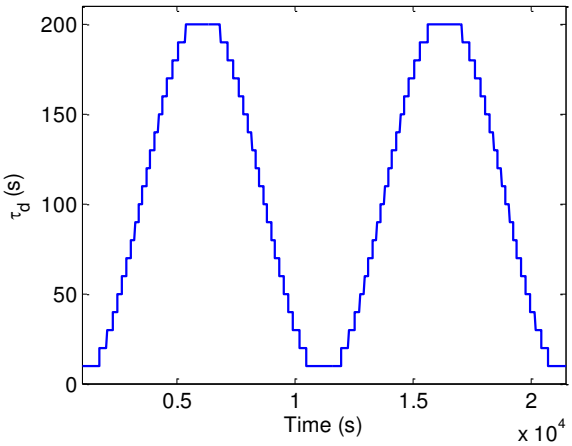

Figure-3. Variable time delay for artificial signals.

Additionally, a pseudo random (colored) noise is included to the system output in order to represent the disturbances recorded in the BIS monitor. The noise level added makes the artificial BIS signal to vary with ± 3 units around the set-point. In this case, the BIS target is a sinusoid signal, which varies between 40 and 60.

The artificial Propofol signal is applied to the simulator in order to obtain the simulated BIS without time delay. The comparison between the artificial BIS with variable and known time delay and the simulated BIS without time delay can be observed in Figure-4.

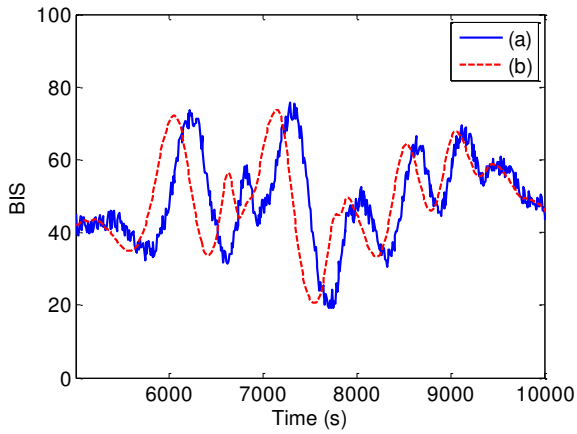

Figure-4. (a) Artificial and (b) Simulated BIS.

3.1.1. Results for offline TDE

The normalized Cross-Correlation Functions (CCF) obtained with the offline algorithm can be observed in Figure-5.

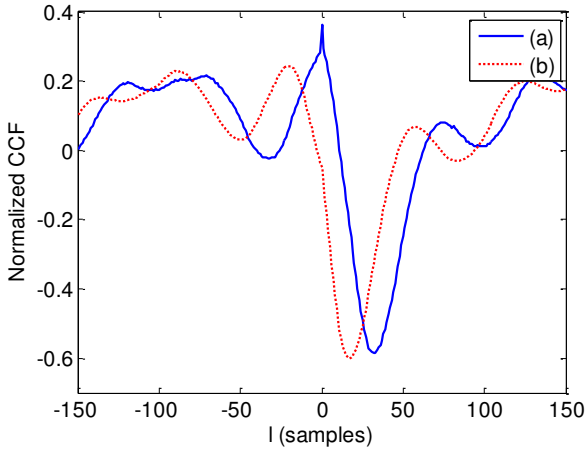

Figure-5. (a) CCF between artificial Propofol and BIS signals; (b) CCF between artificial Propofol and simulated BIS signals.

It can be observed that the difference between the minimum values of each CCF is 15 samples (150 seconds). This value corresponds to an average value for the time delay. The offline TDE was performed for each patient using artificial data and the results are presented en Table-1.When the cross-correlation analysis is applied to the artificial signals using the total measurements, the average estimated time delay has a value of 143.33 seconds with a standard deviation of ±9.85 seconds. In order to validate the delay obtained with the first algorithm, the estimated time delay is added to the simulator and the artificial Propofol signal is used as input. The error between the artificial BIS signal with variable time delay and the simulated BIS signal with fixed time delay estimated by the offline algorithm is calculated with the following formula:

$$MSE = \frac{1}{N}\sum_{k=1}^{N}|y(k) - \hat{y}(k)|^2$$

where $y(k)$ is the artificial BIS signal used to estimate the time delay and $\hat{y}(k)$ is the simulated BIS signal when the estimated time delay is added. The Mean Squared Error (MSE) obtained in this case is 69.45. The results obtained for each patient are summarized in Table-1.

Table-1. TDE and MSE for each patient when the Offline method is applied to the artificial signals.

Patient	TDE (s)	MSE
1	140	71.36
2	160	70.21
3	130	68.48
4	130	65.07
5	150	70.72
6	150	70.07
7	130	67.32
8	150	72.48
9	140	74.85
10	140	73.09
11	150	69.45
12	150	70.42

Taking into account that the time delay applied to the artificial data varies between 10 and 200 seconds, the estimated value for time delay presents a very high error. In this case, the MSE has an average value of 70.29 with a standard deviation of ±2.61, which corresponds to a very high value. If the estimated time delay is increased or decreased a known amount of samples ($\pm\Delta\tau_d$) and that value is used for simulation then the new MSE value calculated can be higher or lower than the initial one (see Figure-6).

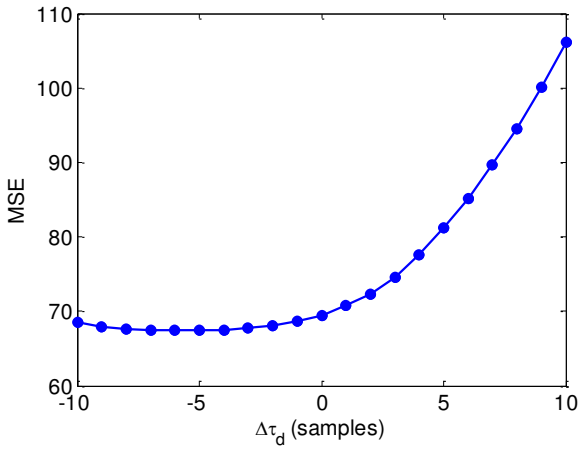

Figure-6. MSE variations when the estimated time delay is higher or lower than the value found by the offline algorithm.

This means that the initially calculated MSE value does not guarantee the minimum error between the artificial BIS signal and the simulated BIS signal when the estimated time delay is added. The MSE obtained in this case is 69.45, but it can be observed above that the MSE is a minimum when the time delay value is 4 samples below the value calculated with this algorithm, i.e. if the estimated time delay is 110 seconds instead of 150 seconds, then the MSE is decreased to 67.44.

3.1.2. Results for Semi-Online TDE

When the semi-online algorithm is used on the artificial data, different delays are obtained for each window (W_1 – W_8): 20 s for the first window, 110 s for the second window, 150 s for the third window, 70 s for the fourth window, 10 s for the fifth window, 160 s for the sixth window, 160 s for the seventh window and 80 s for the last window (see Figure-7).

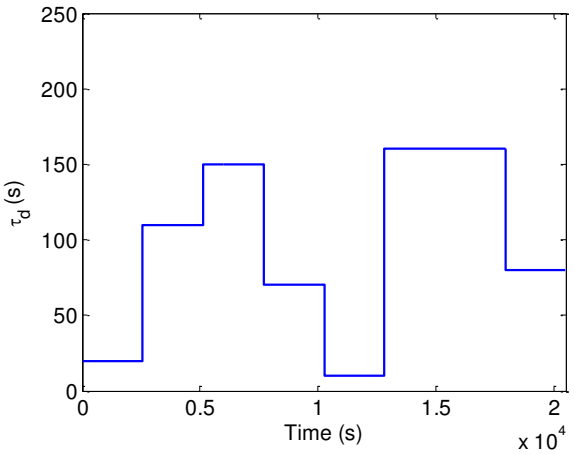

Figure-7. Semi-Online TDE using artificial signals.

The algorithm is performed for each patient and the results are summarized in Table-2.When the cross-correlation analysis is applied to the artificial signals by means of the second method, the algorithm calculates an average time delay for each window. The mean value and the standard deviation for the estimated delays in each window are displayed at the bottom of the Table-2.

In order to validate de results, the MSE is calculated. In this case, $y(k)$is the artificial BIS signal used to estimate the time delay using the semi-online algorithm and $\hat{y}(k)$ is the simulated BIS signal when the estimated time delay is added. The MSE obtained in this case is 8.79. The results obtained for each patient are summarized in Table-2.

When the semi-online TDE algorithm is used, it is observed that the average MSE value decreases to 7.93 with a standard deviation of ±1.87. Moreover, when the estimated time delay for each window is increased or decreased in order to validate the result, this new MSE value can be higher or lower. In this case, the MSE value calculated initially does not assurance the minimum error between the artificial BIS signal and the simulated BIS signal when the estimated delay with the semi-online TDE algorithm is added. For instance, the time delay needed to obtain a minimum value for MSE is 2 samples above the calculated value using this algorithm (see Figure-8).

Table-2. TDE and MSE for each patient when the Semi-Online method is applied to the artificial signals.

Patient	TDE (s)								MSE
	W_1	W_2	W_3	W_4	W_5	W_6	W_7	W_8	
1	110	140	140	50	10	210	170	90	9.62
2	10	160	150	70	70	170	160	30	6.25
3	30	130	140	60	20	150	160	60	9.83
4	50	160	150	60	50	110	170	50	6.62
5	20	200	150	30	20	210	160	90	7.47
6	120	110	170	70	30	80	180	70	7.67
7	40	150	150	60	40	210	150	90	6.60
8	30	210	170	70	50	240	200	30	6.07
9	60	200	160	70	10	110	150	50	13.01
10	60	180	150	60	30	200	170	70	7.71
11	20	110	150	70	10	160	160	80	8.79
12	50	220	150	70	10	160	160	50	7.14
Mean	48.57	158.57	152.14	64.29	26.43	168.57	164.29	64.29	7.93
Std	±32.78	±39.00	±9.75	±13.42	±19.46	±45.21	±13.42	±20.65	±1.87

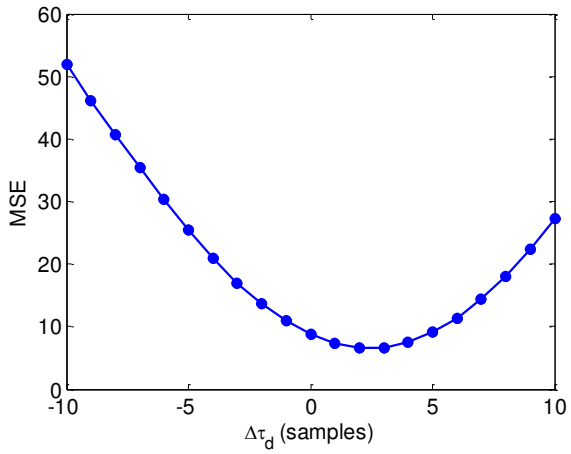

Figure-8. MSE variations when the estimated time delay is higher or lower than the value found by the semi-online algorithm.

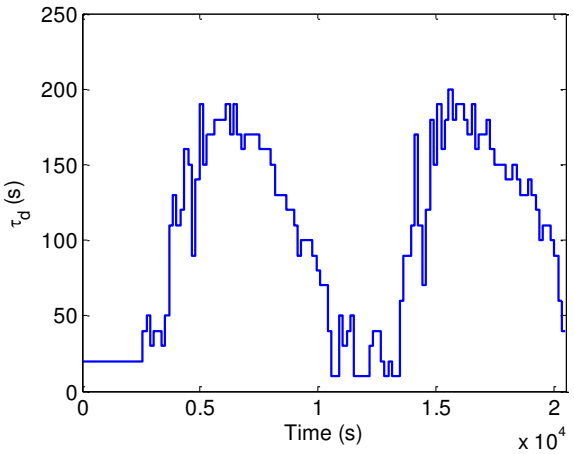

Figure-9. Online TDE using artificial signals.

3.1.3. Results for online TDE

The online TDE algorithm uses the cross-correlation analysis by means of a sliding window of 256 samples along the artificial signals. Smaller differences between the artificial time delay and the estimated time delay can be observed in case of the online algorithm (Figure-9). When the cross-correlation analysis is applied to the artificial signals by means of the third method, the algorithm uses some stored measurements and the measurement in the current time instant to estimate the time delay.

The MSE is calculated again in order to validate de results. Here $y(k)$ is the artificial BIS signal used to estimate the time delay using the online algorithm and $\hat{y}(k)$ is the simulated BIS signal when the estimated time delay is added. The MSE obtained in this case is 7.05. The results obtained for each patient are summarized in Table-3.

Table-3. MSE for each patient when the online method is applied to the artificial signals.

Patient	MSE
1	9.06
2	7.01
3	10.20
4	7.67
5	7.87
6	7.90
7	7.64
8	8.83
9	10.30
10	8.42
11	7.05
12	7.52

When the online TDE algorithm is applied, the average MSE value is increased to 8.32, but with a lower standard deviation of ±1.08. Furthermore, when the estimated time delay for each time instant is increased or decreased and the MSE is calculated once more, then these new MSE values are always higher than the initial one.

This means that the initially calculated MSE value assurances the minimum error between the artificial BIS signal and the BIS signal when the estimated delay with the online TDE algorithm is added. The MSE variations using the online TDE algorithm are shown in Figure-10.

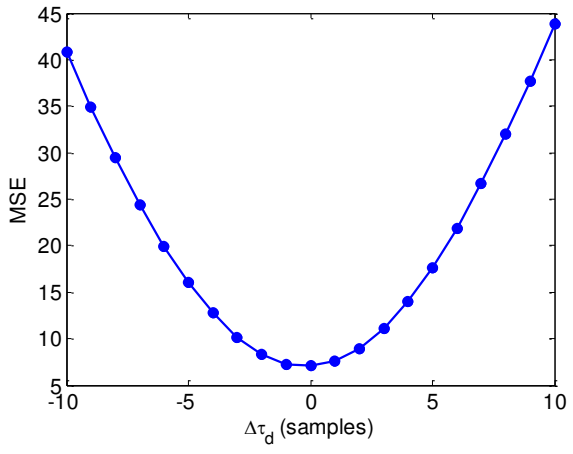

Figure-10. MSE variations when the estimated time delay is higher or lower than the value found by the online algorithm.

3.2 Real data

The database of the real signals employed in this section was recorded during clinical trials on patients in ICU. The parameters of the PK-PD model were calculated for each patient, based on the biometric values. As result of this scenario, the Propofol and BIS signals were obtained. These signals were resampled with a sampling time of 10 seconds ($f_s = 0.1\ Hz$). The real Propofol signal is applied to the simulator to obtain the simulated BIS without time delay. The comparison between the real BIS with variable and unknown time delay and the simulated BIS without time delay can be observed in Figure-11.

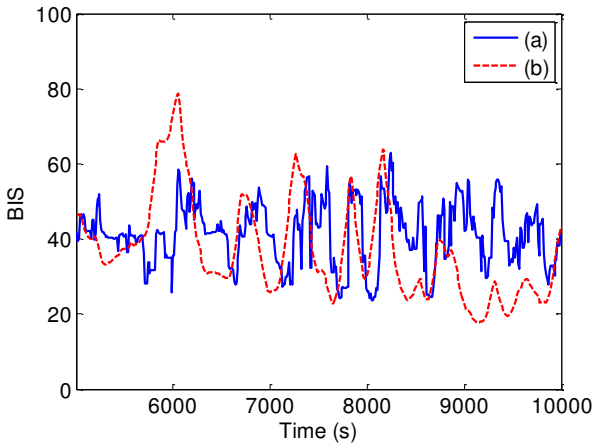

Figure-11. (a) Real and (b) Simulated BIS.

3.2.1. Results for offline TDE

Figure-12 shows the offline method results obtained for one patient. The difference between the minimum values of each CCF is 6 samples (60 seconds).In this case, the cross-correlation functions have visibly more than one negative peak, which shows that the difference between the two signals does not consist of a pure delay. The offline TDE was performed for each patient using real data and the results are presented in Table-4.

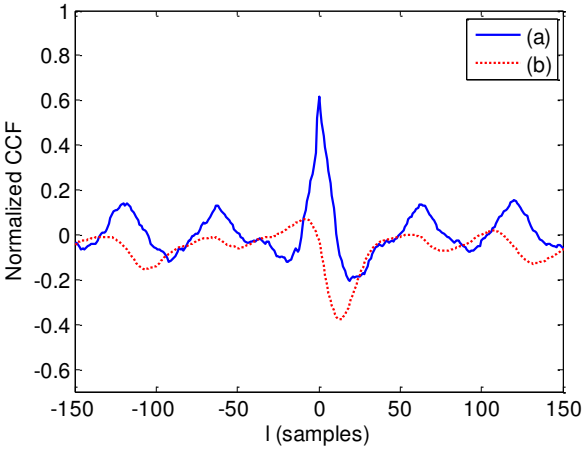

Figure-12. (a) CCF between real Propofol and BIS signals; (b) CCF between real Propofol and simulated BIS signals.

Table-4. TDE and MSE for each patient when the Offline method is applied to the real signals.

Patient	TDE (s)	MSE
1	350	653.6
2	140	465.6
3	150	446.8
4	480	805.5
5	230	473.9
6	210	254.7
7	170	688.0
8	160	363.8
9	90	384.7
10	60	432.8
11	310	379.9
12	120	865.9

When the cross-correlation analysis is applied to the real signals using the total measurements, the average estimated time delay has a value of 190.71 seconds with a standard deviation of ±119.13 seconds.

The estimated time delay is added to the simulator and the real Propofol signal is used as input in order to evaluate the delay obtained with the first algorithm. The MSE between the real BIS signal with variable time delay and the simulated BIS signal with fixed time delay estimated by the offline algorithm is calculated. In this case, $y(k)$ is the real BIS signal used to estimate the time delay and $\hat{y}(k)$ is the simulated BIS signal when the estimated time delay is added. The (MSE) obtained in this case is 432.8. The results obtained for each patient are summarized in Table-4.

It can be observed that the estimated value for time delay presents a very high error because the real BIS signal presents many disturbances and artifacts. In this case, the MSE has an average value of 497.79 with a standard deviation of ±182.51, which corresponds to a very high value. When the real signals are used, the estimated time delay of the BIS monitor is between 60 and 480 seconds if the offline TDE algorithm is used. The method calculates an average time delay introduced by the BIS monitor. This time delay is not reliable to be used in the patient prediction model because when some artifacts occur, the instrumentation delay changes. During the periods with disturbances the MSE value is higher; indicating that the difference between the real and the simulated BIS signal is high.

3.2.2. Results for Semi-Online TDE

The semi-online TDE algorithm applies the cross-correlation analysis using small parts of the real Propofol and BIS signals. In this case, 1024 samples of these signals (from 5010 to 15240 seconds) are taken in order to avoid some time instants where the control in closed-loop is switch off. The estimated time delays obtained for four windows (W_1 – W_4) are: 170 s, 50 s, 60 s and 140 s (see Figure-13). The algorithm is performed for each patient and the results are summarized in Table-5.

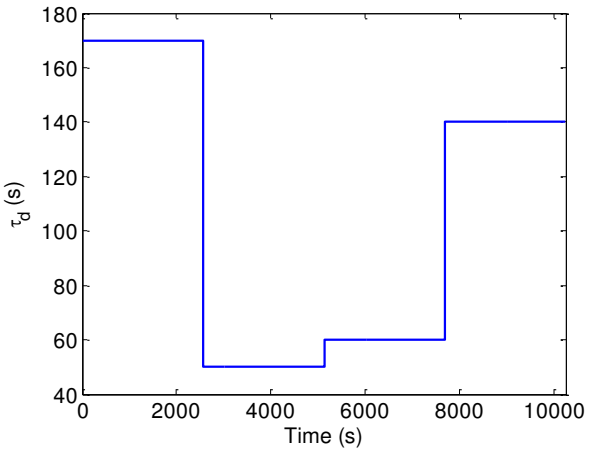

Figure-13. Semi-Online TDE using real signals.

Table-5. TDE for each patient when the Semi-Online method is applied to the real signals.

Patient	TDE (s)			
	W_1	W_2	W_3	W_4
1	200	150	240	130
2	280	120	50	40
3	330	170	160	190
4	90	40	280	270
5	170	250	60	290
6	120	30	130	50
7	170	10	60	40
8	140	150	180	80
9	70	110	90	110
10	170	50	60	140
11	30	100	360	310
12	130	10	170	140

When the cross-correlation analysis is applied to the real signals by means of the second method, the algorithm calculates an average time delay for each window.

The estimation of time delay in the first window is $\tau_d = 17$ samples. Reviewing carefully the BIS signals in this window (Figure-14), it is observed that the simulated BIS signal has a maximum value at 1710 seconds while the real one has a maximum value at 1880 seconds approximately, this indicates a time delay of 170 seconds (17 samples) between the two signals, which coincides with the estimation of time delay calculated by the algorithm.

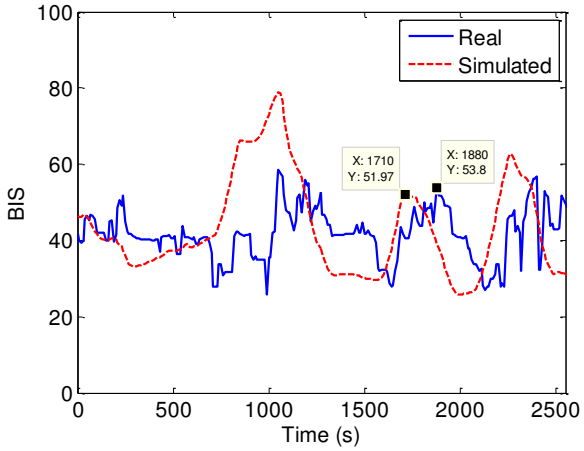

Figure-14. Semi-Online TDE for first window: $\tau_d = 17$ samples.

The estimation of time delay in the second window is $\tau_d = 5$ samples. It can be seen that in some cases the time delay between the real and simulated BIS signals is 50 seconds (5 samples), which coincides with the estimation of time delay calculated by the algorithm, for example when the simulated BIS signal has a maximum value at 4310 seconds, the real one has a maximum value at 4360 seconds (Figure-15). However, in other cases the time delay between the real and simulated BIS signals is higher or lower than 50 seconds, for example when the simulated BIS signal has a maximum value at 3170 seconds, the real one has a maximum value at 3240 seconds approximately, this is a time delay of 70 seconds (7 samples) between the two signals, which indicates that the algorithm estimates an average time delay for each window.

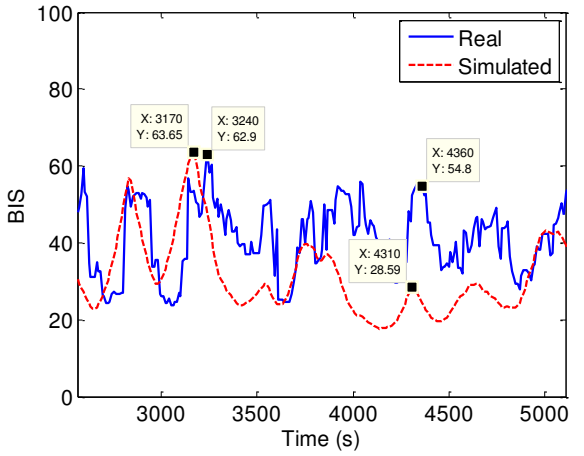

Figure-15. Semi-Online TDE for second window: $\tau_d = 5$samples.

The estimation of time delay in the third window is $\tau_d = 6$ samples. Similarly, it can be observed that in some cases the time delay between the real and simulated BIS signals is 60 seconds (6 samples), which coincides with the estimation calculated by the algorithm, for example when the simulated BIS signal has a maximum value at 6400 seconds, the real one has a maximum value at 6460 seconds approximately. However, the estimated time delay is an average time delay for this window (see Figure-16).

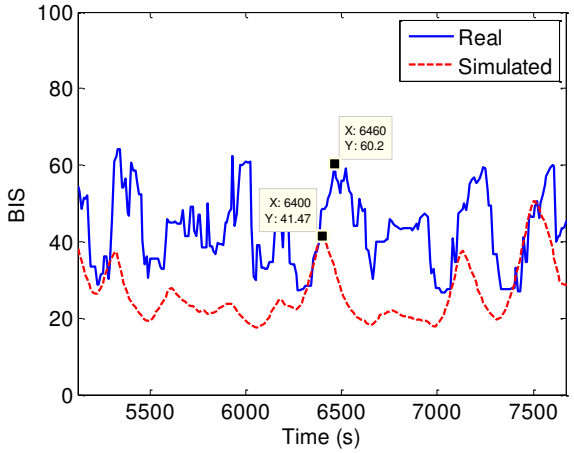

Figure-16. Semi-Online TDE for third window: $\tau_d = 6$ samples.

The estimation of time delay in the last window is $\tau_d = 14$samples. In the same way, it can be observed that in some cases the time delay between the real and simulated BIS signals is 140 seconds (14 samples), which coincides with the estimation calculated by the algorithm, for example when the simulated BIS signal has a maximum value at 9320 seconds, the real one has a maximum value at 9460 seconds (Figure-17).

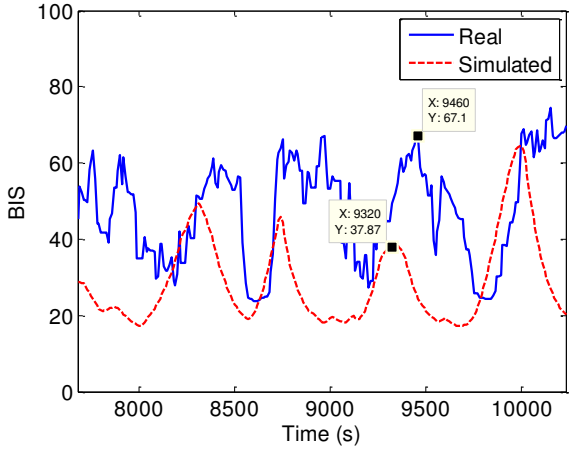

Figure-17. Semi-Online TDE for fourt window: $\tau_d = 14$samples.

When the cross-correlation analysis is applied using several windows (semi-online TDE algorithm), the changes in time delay may be observed easily. Therefore, fixed windows of 256 samples are used and the cross-correlation analysis is applied on each window. The time delay obtained is between 10 and 360 seconds for different patients. If windows of 64 or 128 samples are used, the

method cannot find an accurate time delay for some windows in which the processed signals do not have variations. When windows of higher length are used (512 or 1024 samples), the algorithm needs more time to estimate the delay, and the MSE is higher than in the case when windows of 256 samples are used, because the time delay value of each window approaches to the delay obtained using the offline algorithm. If the cross-correlation analysis is applied using windows of 256 samples the algorithm estimates more often the time delay and the accuracy is of course higher. Therefore, the cross-correlation applied on windows of 256 samples was considered the best choice for this algorithm. This algorithm cannot be implemented online because first it is necessary to store 256 samples and later to apply the cross-correlation analysis.

3.2.3. Results for online TDE

The third algorithm is used to estimate the time delay of the BIS monitor using a sliding window of 256 samples. Only 1024 samples of resampled real and simulated signals (from 5010 to 15240 seconds) are taken. Figure-18 shows the results obtained.

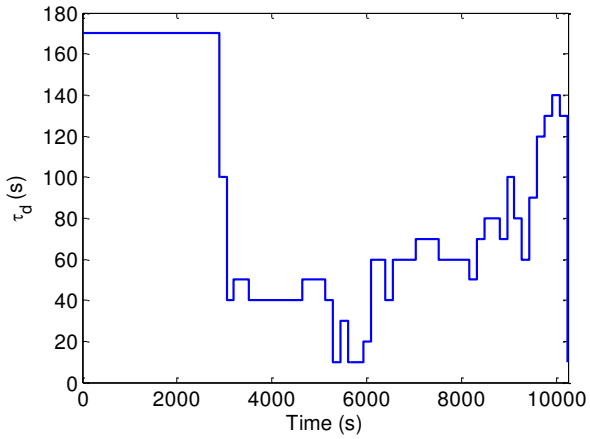

Figure-18. Online TDE using real signals.

It can be seen that using the first 256 samples the estimated time delay has an average value of 170 seconds. In the next samples, the time delay is calculated again and its value falls to a value around 10 seconds (between 5000 and 6000 seconds), and after its value rises to a value close to 140 seconds.

Comparing this result with the previous one obtained with the semi-online TDE algorithm it can be observed that the value obtained with the third algorithm converges to the average values calculated with the second algorithm (Figure-19). This is due to the fact that the third algorithm uses some stored measurements and the measurement in the current time instant to estimate the time delay. Furthermore, some peaks in the online estimated time delay can be observed because the real signal of BIS contains a lot of noise.

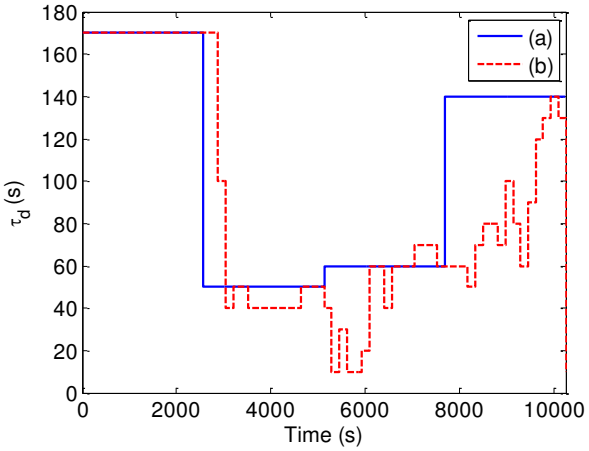

Figure-19. Comparison between (a) estimated time delay with Semi-Online algorithm and (b) estimated time delay with online algorithm.

The same online algorithm is applied to other patients. The online algorithm works properly when the time delay is varying in time even when the BIS signal is corrupted with noise because the calculated error is acceptable from the standpoint of engineering. However, if the BIS signals remain almost constant the algorithm does not possess enough information to calculate the appropriate time delay and in this case another procedure of estimation is necessary.

Recording the signals and processing them through cross-correlation analysis (of a little amount of samples) allows finding a time delay which can be used online in the prediction model used by model-based controller. However, the developed algorithm must be improved in order to allow the online estimation of time delay in a more robust manner.

The time delay has a greater influence on the simulated BIS; therefore, in the prediction model used by the model-based controller is very important to have a good estimation of the time delay because if time delay is sub-estimated, the control action is useless.

ACKNOWLEDGEMENT

This work has been funded by IWT TBM project number 060776 supported by the Flemish Institute for Innovation through Science and Technology.

REFERENCES

Bailey J. M., Haddad W. M. 2005. Drug dosing control in clinical pharmacology, IEEE Control Syst. Mag. 25: 35-51.

Chilcoat R. 1980. A review of the control of depth of anaesthesia, Transactions of the Institute of Measurement and Control. 2(1): 38-45.

Cullen D., Eger E., Stevens W., Smith N., Cromwell T., Cullen B., Gregory G., Bahlman S., Dolan W., Stoelting

R., Fourcade H. 1972. Clinical signs of anesthesia, Anesthesiology. 36(1): 21-36.

Derighetti M. 1999. Feedback Control in Anaesthesia, PhD thesis, Swiss Federal Institute of Technology (ETH), Zürich, Switzerland.

Goldmann L. 1988. Information-processing under general anesthesia: a review, Journal of the Royal Society of Medicine. 81: 224-227.

Haddad W. M., Hayakawa T., Bailey J. M. 2003. Nonlinear adaptive control for intensive care unit sedation and operating room hypnosis, American Control Conference. 2: 1808-1813.

Ionescu C., De Keyser R., Torrico B. C., De Smet T., Struys M., Normey-Rico J. E. 2008. Robust Predictive Control Strategy Applied for Propofol Dosing using BIS as a Controlled Variable during Anaesthesia, IEEE Transactions on Biomedical Engineering. 55(3): 2161-2170.

Linkens D. A., Hacisalihzade S. S. 1990. Computer control systems and pharmacological drug administration: a survey, Journal of Medical Engineering & Technology. 14(2): 41-51.

Minto C. F., Schnider T. W., Short T. G., Gregg K. M., Gentilini A., Shafer S. L. 2000. Response surface model for anesthetic drug interactions, Anesthesiology. 92(6): 1603-1616.

O'Hara D. A., Bogen D. K., Noordergral A. 1992. The use of computers for controlling the delivery of anesthesia, Anesthesiology. 77(3): 563-581.

Prys-Roberts C. 1987. Anaesthesia: a practical or impossible construct? British Journal of Anaesthesia. 59, 1341-1345.

Schnider T. W., Minto C. F., Gambus P. L., Andresen C., Goodale D. B., Youngs E. J. 1998. The influence of method of administration and covariates on the pharmacokinetics of propofol in adult volunteers, Anesthesiology. 88(5): 1170-1182.

Schwilden H., Stoeckel H. (eds). 1995, Control and Automation in Anaesthesia, Springer-Verlag, Berlin.

Sendoya-Losada D. F., Robayo Betancourt F., Salgado Patrón J. 2016. Resampling methods for signals recorded at variable sample-time intervals during general anesthesia, ARPN Journal of Engineering and Applied Sciences. 11(17): 10273-10279.

Sendoya-Losada D. F., Robayo Betancourt F., Salgado Patrón J. 2016. Validation of the mathematical model for patients used in general anesthesia, ARPN Journal of Engineering and Applied Sciences. 11(19): 11655-11662.

Shafer S. L., Longnecker D. E., Tinker J. H., Morgan G. E. 1998. Principles of pharmacokinetics and pharmacodynamics, In: Principles and Practice of Anesthesiology, McGraw-Hill (2nd ed.), New York, USA.

Viby-Mogensen J., Ostergaard D., Donati F. D. F., Hunter J., Kampmann J., Kopman A., Proost J., Rasmussen S., Skovgaard L. F. V., Wright P. 2000. Pharmacokinetic studies of neuromuscular blocking agents: good clinical research practice (GCRP), Acta Anaesthesiologica Scandmavica. 10(44): 1169-119.