Variable Time-Delay Estimation for Anesthesia Control During Intensive Care

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***Abstract*—The presence of artifacts plays a crucial role in automatic sedation systems and may introduce variable time delays (TDs) in the closed-loop-control structures. This paper presents a successful procedure to estimate the varying TD of the bispectral index (BIS) monitor used in closed-loop control during intensive care. The TD estimation (TDE) is based on the cross-correlation analysis technique and the method is validated with real measured signals of propofol and BIS. Extended prediction self-adaptive control is used in combination with a Smith predictor to reduce the computational burden imposed by the variable TD. The conclusion is that an online TDE of the BIS monitor improves the performance of the closed-loop system for reference tracking, disturbance rejection, and overall stability.**

***Index Terms*—Anesthesia control, cross-correlation analysis, dead-time compensation (DTC), intensive care unit, model-based predictive control (MPC), time-delay estimation (TDE).**

I. Introduction

ACCURATE sedation using a combination of hypnotics and analgesics has become an integral part of critical care practice in minimizing patient discomfort and decreasing mortality rate [1]. Clinical experience with critically ill patients has revealed that standard dosing guidelines result often in an inappropriate under- or oversedation leading to increased morbidity and mortality due to huge interpatient pharmacological variability [2]. The benefit of automated closed-loop control is that the drug delivery is continuous, as opposed to intermittent control (i.e., standard practice). One major problem for the control algorithms is that it has to deal with erroneous feedback information, biased either by the presence of artifacts or by patient model mismatch [3]. In biological systems, such erroneous information often originates from artifacts (e.g., eye movement, leg movement, coughing, sneezing, choking, shivering), which decrease the quality of the measured signals leading to complex numerical filtering techniques. The latter require longer computation times, hence introducing artificial time delays (TDs), which vary from one time instant to another, dependent on the signal quality [4]. If not dealt-with appropriately, such varying TDs are a source of poor feedback control.

Advanced control techniques such as model-based predictive control (MPC) can successfully deal with variable TDs, nonlinearities, and input and output constraints [5]. Since MPC relies on the availability of a patient model, it is important to provide accurate information to the controller in order to maximize its performance. In the case of anesthesia, the TD varies between 40–180 s, and it is important that its value is known at all times and taken into account by the control strategy.

To estimate the TD, some authors have used the concept of group delay, which is defined as the variation of the phase with respect to the frequency [6]–[8]; but this technique can be applied only when there is a fixed TD between the input and output signals [9]. Moreover, it has been shown that a negative group delay can be obtained in simple systems as a bandpass filter, erroneously indicating that the signal output is produced before the input signal [10].

Other linear methods for TD estimation (TDE) use the Hilbert transform to link the transfer function of a minimum phase system with the logarithm of its gain [6], or the Hilbert transform in presence of noise [11], [12]. The cross-correlation analysis is the simplest and probably the most widely applied technique to estimate TD [13]. The TDs are usually not fixed, but vary in time, and different approaches have been recently proposed to tackle this problem in the field of biomedical applications [14]. Although most methods are based on parameter estimation, a parametric model that represents the relationship between the input and output signals is not always available. Hence, it is necessary to make use of nonparametric estimation methods.

The aim of this contribution is to introduce and validate a TDE method based on the correlation analysis to overcome the lack of TD information in online clinical trials for closed-loop sedation in ICU. The TDE is then used in the prediction model of the extended prediction self-adaptive control algorithm (EPSAC) [5]. The TDE method is tested with real clinical data from ICU patients showing good agreement with TD values reported in the specialized literature.

The paper is structured as follows. In Section II, the materials and the theoretical framework regarding the cross-correlation analysis and the procedures used are presented. The TDE results obtained for several patients are shown in Section III. The performance analysis for the different TDE procedures is realized in Section IV, and the conclusion is summarized in Section V.

Manuscript received March 16, 2010; revised August 6, 2010; accepted October 6, 2010. Date of publication October 18, 2010; date of current version January 21, 2011. This work was supported by the Flemish Institute for Innovation through Science and Technology, Belgium, through the IWT-TBM Project 060776. *Asterisk indicates corresponding author*.

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Digital Object Identifier 10.1109/TBME.2010.2088121

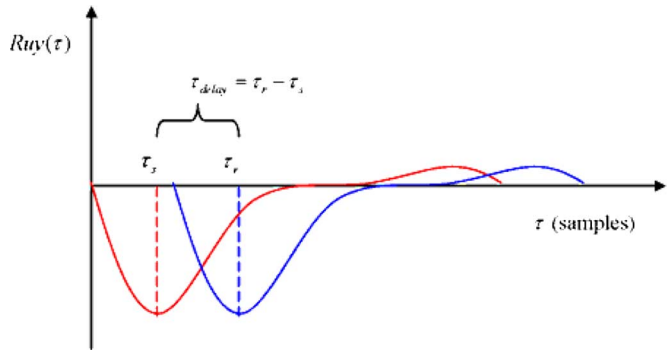


Fig. 1. Schematic representation of the TDE from correlation functions.

II. Materials and Methods

A. Time-Delay Estimation

Three methods are presented for TDE: offline; semionline; and online; all based on the cross-correlation technique. The cross-correlation function between two sampled signals $u(m)$ (cause) and $y(m)$ (effect) measures the degree of correlation [15]. The cross correlation is defined by

$$R_{uy}(\tau) = E\{u(m)y(m-\tau)\} \tag{1}$$

where τ is the lag, and $E\{\bullet\}$ denotes the expected value and m is the sample. A common estimator used in practice for the cross correlation is defined by

$$R_{uy}(\tau) = \frac{1}{N}\sum_{m=0}^{N-\tau-1} u(m+\tau)y(m), \qquad 0 \le \tau \le (N-1) \tag{2}$$

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

$$\hat{R}_{uy}(\tau) = \frac{R_{uy}(\tau)}{\sqrt{\sigma_u^2\sigma_y^2}} \tag{3}$$

where σ_u^2 is the variance of the input signal $u(m)$

$$\sigma_u^2 = \frac{1}{N}\sum_{m=0}^{N-1} u(m)^2. \tag{4}$$

The variance of the output signal σ_y^2 is analogously defined. The result of the cross-correlation function is multiplied by a Blackman–Harris window to reduce leakage effects [14].

A minimum value of the cross-correlation function between the propofol input and the real bispectral index (BIS) can be found at time τ_r, as depicted schematically in Fig. 1. The value of τ_r denotes the summed effect between the measured dynamic response and the unknown TD introduced by the BIS monitor. In order to estimate the value of this TD, the propofol signal is applied to the patient model and a simulated BIS signal without TD 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 patient (no instrumentation delay). The TD introduced by the BIS device is then calculated as follows:

$$\tau_d = \tau_r - \tau_s. \tag{5}$$

The first TDE algorithm denotes an offline method, which applies the cross-correlation analysis using the entire number of samples from the propofol and BIS signals. As such, this method is only used to gather insight upon the expected value of the TD, but it cannot be used for control purposes in online computations. To detect changes in TD, one can estimate the TD by applying the cross-correlation analysis over windows of 256 samples (i.e., semionline method). For an online monitoring of the changes affecting the values of TD, it is necessary to use sliding windows; in this case, we make use of a 256 sample window, slided every sample.

B. EPSAC With Variable TDE

In a discrete time formulation, the objective of a model predictive controller is to find the future process input sequence that optimizes a cost function over a certain prediction horizon $(N_1, \ldots, N_2)$. Thus, at each sampling instant, the process model expressing the nonlinear dynamic relationship between the process output y and the manipulated process input u (i.e., $y(t) = f[y(t-1), \ldots, u(t-1), \ldots])$ is used to produce output predictions. The future control sequence is the solution of an online optimization problem, which typically consists of minimizing the summed squares of the predicted output deviations from the setpoint r

$$\min_{u(t|t),\ldots,u(t+N_u-1|t)} J = \sum_{k=N_1}^{N_2} [y(t+k|t) - r(t+k|t)]^2 \tag{6}$$

where $y(t+k|t)$ denotes the prediction of the process output at discrete time instant $t+k$ based on information available up to the discrete time instant t, and $r(t+k|t)$ is the setpoint. Commonly, only N_u components of the future control sequence are allowed to vary, inputs beyond the control horizon N_u are set to the last computed value: $u(t+j|t) = u(t+N_u-1|t)$, $j = N_u, \ldots, N_2 - 1$.

Considering a receding horizon mechanism, only the first component out of the N_u optimal control moves is applied to the process. The rest of the control sequence is discarded and the entire procedure is repeated at the next sampling instant.

Compared to the current standard MPC strategies, EPSAC considers the process output predictions as being the sum of two parts: 1) a term that is independent of the future control actions y_{base} and represents the result of past control actions u_{base}; and 2) a term that depends linearly on the future control actions as a result of the optimal control action δu [5]. This allows to obtain an analytical solution in the case of unconstrained control, or a well-known quadratic programming solution in the case of constrained control. In both cases, this leads to a quick solution of the MPC problem with low-complexity software compared to the more general optimization solvers.

For a variable TD, however, the values of N_1 and N_2 vary with the dead-time index. In order to avoid complex matrix manipulations (varying matrix sizes every sample time), an alternative solution for controlling processes that present significant and

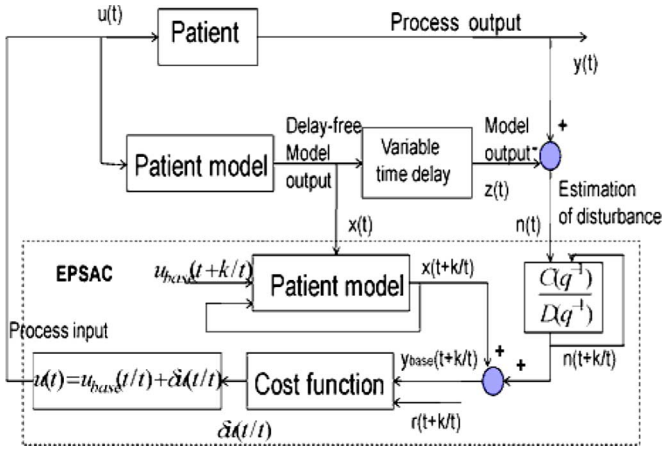


Fig. 2. Schematic representation of the TDE in the EPSAC closed-loop control. See text for nomenclature.

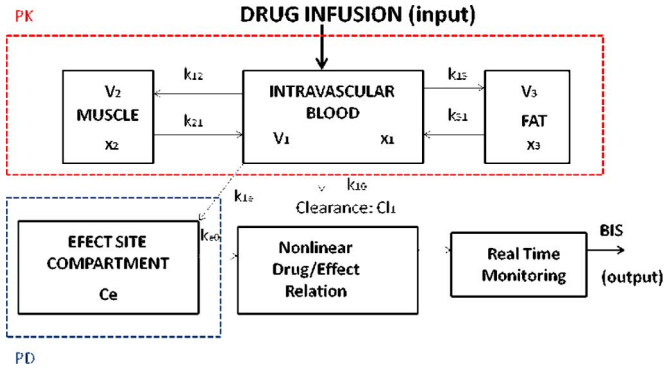


Fig. 3. PK–PD compartmental model of a patient for propofol effects on BIS.

varying dead times is to make use of a dead-time compensator (DTC). The Smith Predictor (SP) was the first control system proposed in the literature that included a DTC, and is perhaps one of the most widely used methods to compensate the variable TD problem [16]. The combination of the filtered SP with the EPSAC, namely, SP-based EPSAC (SP-EPSAC), provides a control strategy for linear processes with variable TD [17].

In this paper, we design a predictive controller with constant design parameters (N_1, N_2), as schematically depicted in Fig. 2. The patient model consists of the three compartmental model from [18]. At each sampling instant, the delay-free patient model output $x(t)$ is calculated using the stored values $[x(t-1), \ldots, u(t-1), \ldots]$. At the same sampling instant, the variable TD is computed from (5). Once the number of TD samples N_d is known, $x(t-N_d)$ can be selected out of the stored x-values, such that $z(t) = x(t-N_d)$. In such an approach, the minimum prediction horizon is no longer varying and obviously equal to one. Hence, the maximum prediction horizon remains constant.

C. Patient Model for Prediction

The MPC strategy makes use of a prediction model, hence, the patient's pharmacokinetic (PK) and pharmacodynamic (PD) models are necessary to predict the BIS output as a result of propofol infusion. The PK model describes the distribution of propofol in the patient's body, while the PD model describes the relationship between propofol concentration in the blood and its clinical effect. The generalized PK–PD model for propofol is depicted in Fig. 3. The propofol PK–PD mathematical model, the rates of drug metabolism or elimination, the rates of drug transfer between different compartments, and the volumes of distribution are taken from [18].

In this figure, x_1 denotes the amount of drug in the central compartment (blood) and its units are milligrams (mg). The peripheral compartments model the drug exchange between the blood and the other body tissues. The amount of drug in these compartments is denoted by x_2 (muscle tissue) and x_3 (fat mass), respectively. The constants k_{ij}, for i j, denote the drug transfer frequency from the jth to the ith compartment and its units are min^{-1}.

The propofol concentration in the effect-site compartment is given by C_e, and its units are micrograms per milliliter (μg/ml). C_e is directly related to the measured drug effect and to quantify this effect during real time monitoring, the BIS monitor is used. This device displays a monotonous measure of depth of anesthesia in a range from 0 to 100. The measured BIS can be related to the effect-site concentration C_e by the empirical static but time-varying nonlinear relationship, called also the *Sigmoid Hill Curve*

$$\text{BIS}(t) = E_0 - E_{\max} \cdot \frac{C_e^{\gamma}(t)}{C_e^{\gamma}(t) + C_{50}^{\gamma}}. \tag{7}$$

E_0 is the BIS value when the patient is awake; $E_{\max}$ is the maximum effect that can be achieved by the infusion of propofol; C_{50} is the propofol concentration at half maximum effect and represents the patient sensitivity to the drug; and γ determines the steepness of the curve. Since these parameters are unknown and different for each patient, some nominal values have been used for the simulations. The nominal value for C_{50} is 2.5 μg/ml and for γ is 3.01. The other two parameters of the Hill curve, $E_{\max}$ and E_o are considered equal to the value of 100 [19].

D. Synthetic and Clinical Data

To validate the accuracy of the TDE algorithm, the PK and PD patient models are used in a simulation scenario with a variable TD τ_d shown in Fig. 4 in order to reproduce the conditions of the BIS monitor and the artifacts present in the ICU. Hence, the synthetic BIS signal had a known TD between 10 and 200 s. Additionally, a random (colored) 10% noise is included to the system output in order to represent the disturbances recorded in the BIS monitor. The additional noise level makes the synthetic BIS signal to vary with ± 3 units around the setpoint, as shown in Fig. 4.

Once the accuracy of the TDE has been proven, one can obtain the TDs from clinical ICU trials. The biometric values of the 11 patients selected for this study are given in Table I. All these patients have undergone cardiac surgery prior to ICU, in the Ghent University Hospital, and the data have been recorded for 6–7 h. The BIS reference has been modified by the ICU nurse whenever necessary and oscillated between 40–55 BIS values. Effects

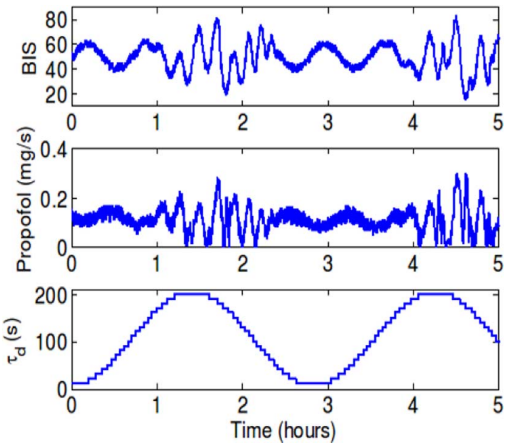


Fig. 4. Synthetic propofol, BIS, and TD signals used to test the accuracy of the TDE procedures.

TABLE I
BIOMETRIC VALUES OF THE PATIENTS SELECTED FOR THIS STUDY; ALL THE PATIENTS WERE MALE, EXCEPT PATIENTS 6 AND 8

Patient	Age(years)	Length(cm)	Weight (Kg)
1	74	164	88
2	67	161	69
3	75	176	101
4	45	171	64
5	57	182	80
6	74	155	55
7	72	192	73
8	69	168	84
9	60	190	92
10	61	177	81
11	54	173	86
Mean ± Std	**64.36 ± 9.76**	**173.55 ± 11.54**	**79.36 ± 13.22**

from other drug administered prior to ICU (from surgery) and during ICU period have not been taken into account. From a closed-loop control point of view, they are regarded as disturbances. All effects on BIS, which are not coming from propofol directly are viewed as model mismatch.

EPSAC strategy was used to control the level of sedation, namely the BIS. The EPSAC prediction model used the PK–PD model with a nominal Hill curve and an initialized TD = 10 s. The parameters of the PK-PD model were calculated for each patient, based on the biometric values previously presented. Consequently, the real signals of propofol and BIS used for the estimation of the TD were obtained. As an example, Fig. 5 shows the propofol and BIS signals administered in closed loop to patient 9 during ICU. The MPC–EPSAC closed-loop control is applied with a prediction horizon of $N_2 = 10$ samples, a control receding horizon of $N_u = 1$ and $N_1 = 1$ samples, and a sampling period of 10 s.

E. Evaluation Criteria

For each TDE method, the corresponding error is calculated with the following formula:

$$\text{MSE} = \frac{1}{N}\sum_{k=1}^{N} |y(k) - \hat{y}(k)|^2 \tag{8}$$

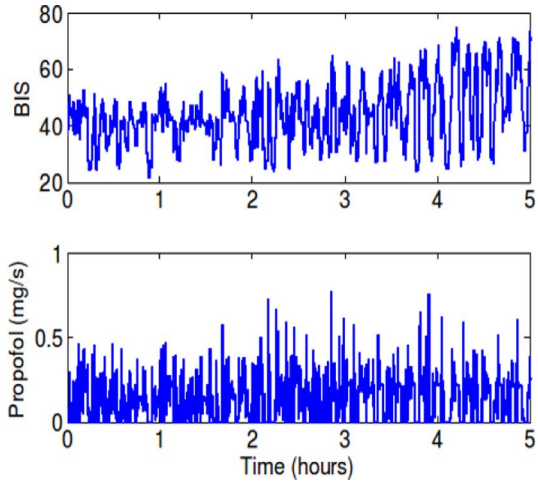


Fig. 5. Real propofol and BIS signals recorded in ICU.

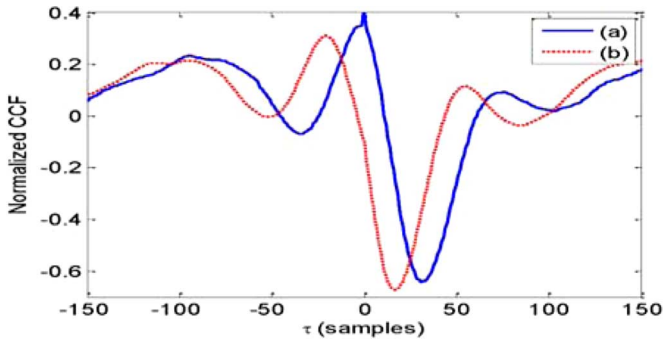


Fig. 6. Illustrative example: (a) CCF between synthetic propofol and BIS signals with known TD of 15 samples; and (b) CCF between synthetic propofol and BIS signals without TD.

where $y(k)$ is the synthetic, respectively, the measured BIS signal from patient, and $\hat{y}(k)$ is the predicted output with estimated TD.

III. RESULTS

A. From Synthetic Data

As an illustrative example that the concept described in Section II-A works, Fig. 6 shows the normalized cross-correlation functions (CCFs) obtained with the offline algorithm, using the biometric values of patient 9. The difference between the minimum values of each CCF is 15 samples (i.e., 150 s), validated by the artificial (i.e., known) TD introduced in the simulator.

Different delays are obtained for each window when the semionline TDE algorithms is applied to detect the (known) TD from Fig. 4. For instance, for patient 9, we obtain: 50 s for the first window, 140 s for the second window, 170 s for the third window, 70 s for the fourth and fifth windows, 180 s for the sixth window, 170 s for the seventh window, and 80 s for the last window.

Finally, the online TDE algorithm uses the cross-correlation analysis by means of a sliding window of 256 samples along the synthetic signals. This algorithm is performed for each patient

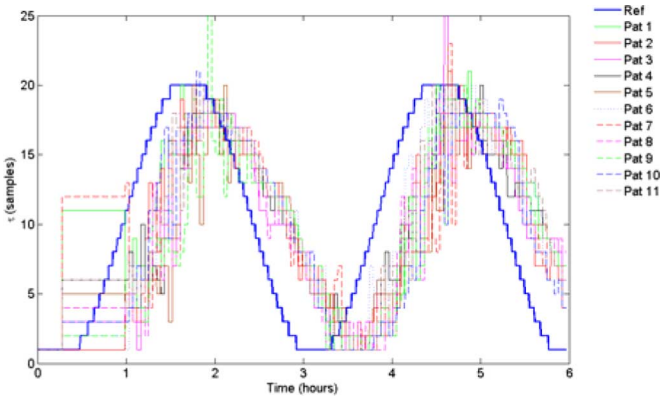


Fig. 7. TDE for each patient using the online TDE algorithm.

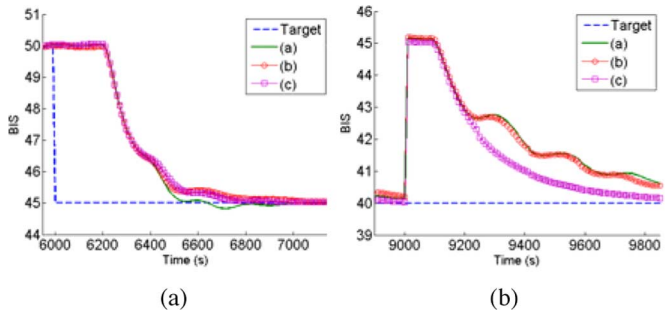


Fig. 8. (a) Detailed presentation for tracking and (b) disturbance rejection: (a) offline; (b) semionline; and (c) online TDEs.

and the results are depicted in Fig. 7. Smaller differences between the synthetic TD and the estimated TD can be observed in case of the online algorithm.

The variation in performance by means of the mean squared error (MSE) were 70.03 ± 2.26 for the offline method, 7.39 ± 1.68 for the semionline method, and 7.84 ± 1.29 for the online method.

B. EPSAC With Adapted TD

The final objective is to improve the control performance by using the estimated TD to update the prediction model of the EPSAC algorithm. The performance of the closed-loop system with the TD information for tracking reference BIS values is evaluated. Furthermore, the disturbance rejection is analyzed when some step disturbances are applied to the output of the closed-loop system. The overall performance of the simulated closed-loop system obtained with the three methods in case of patient 9, for both reference tracking and disturbance rejection, is presented in detail in Fig. 8.

In order to validate the performance of the TDE in the closed-loop system, the MSE was evaluated with (8). In this case, $y(k)$ is the reference BIS signal and $\hat{y}(k)$ is the predicted output of the closed-loop system. Table II presents the MSE obtained for each patient.

TABLE II
MSE VALUES CALCULATED TO VALIDATE THE OVERALL PERFORMANCE OF THE CLOSED-LOOP SYSTEM FOR TRACKING AND DISTURBANCE REJECTION FOR EACH PATIENT

Patient	MSE for Offline TDE	MSE for Semi-Online TDE	MSE for Online TDE
1	32.26	18.24	18.00
2	29.08	18.33	18.10
3	32.94	18.27	17.82
4	31.55	18.15	17.75
5	32.8	18.01	17.64
6	28.22	18.45	18.11
7	31.32	18.59	17.85
8	35.13	17.84	17.52
9	33.40	17.94	17.71
10	31.28	18.20	17.63
11	30.43	18.26	17.88
Mean ± Std	**31.67 ± 1.97**	**18.21 ± 0.22**	**17.82 ± 0.19**

TDE denotes: time delay estimation

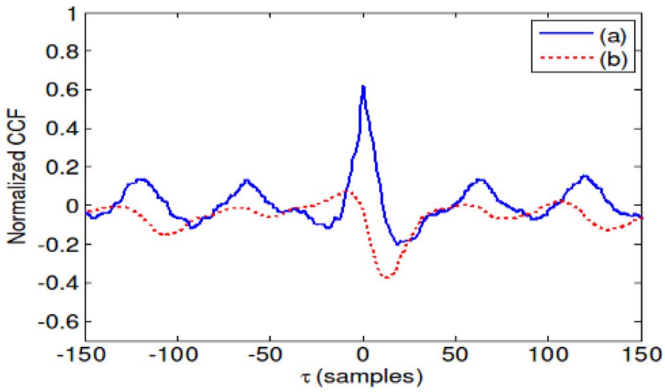


Fig. 9. Illustrative example for TDE on real signals from patient 9: (a) CCF between real propofol and BIS signals with unknown TD; and (b) CCF between real propofol and simulated BIS signals with nominal TD (1 sample).

C. Validation of the TDE on Real Clinical Signals

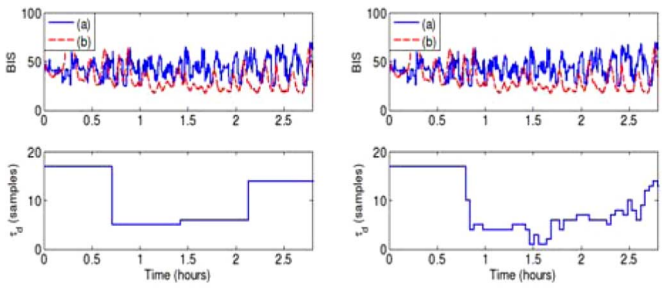
The same TDE methods are now applied using the real propofol and BIS signals. Fig. 9 shows an illustrative example for the cross-correlation (CCF) method in case of the offline method for patient 9. The difference between the minimum values of each CCF is 6 samples (60 s). It can be observed that in the case of real clinical signals, the CCFs visibly have more than one negative peak, suggesting that the difference between the two signals does not consist of a pure TD.

The semionline algorithm used to estimate the TD applies the cross-correlation analysis using small parts of the real propofol and BIS signals. The estimated TD obtained for four windows are given in Fig. 10(a).

The offline TDE had an average and standard deviation of 511 ± 186.5 for the MSE, respectively, and 207.3 ± 125.5 for the TD, when tested on data from all patients. The semionline TDE results are presented in Table III.

IV. DISCUSSION

For both synthetic and real signal validations, it is clear that the online TDE provides the best performance in terms of both clinical and control engineering benefits.



(a) (b)

Fig. 10. (a) Semionline TDE using (a) real BIS and (b) simulated BIS; and (b) results of the online TDE using (a) real BIS and (b) simulated BIS, both applied on the real signals recorded from patient 9.

TABLE III
MEAN SQUARED ERRROR (MSE) AND TIME DELAY ESTIMATION (TDE) FOR EACH PATIENT WHEN THE CROSS-CORRELATION ANALYSIS IS APPLIED TO THE REAL SIGNALS

-	MSE				TDE (s)			
-	W_1	W_2	W_3	W_4	W_1	W_2	W_3	W_4
1	482.9	258.7	546.3	354.8	200	150	240	130
2	139.4	90.8	55.7	80.6	250	120	50	50
3	192.6	136.3	430.2	537.3	290	170	200	200
4	52.6	248.2	44.5	119.9	90	400	280	270
5	203.8	297.6	97.4	182.3	170	250	60	290
6	29.0	87.0	353.5	21.3	110	40	140	70
7	47.0	126.0	154.4	172.8	140	160	180	80
8	355.4	403.0	79.7	234.9	70	110	80	90
9	112.0	105.1	74.1	103.8	170	50	60	140
10	201.8	125.6	221.6	119.9	30	100	360	310
11	858.8	170.3	527.5	405.7	150	10	170	140
Mean	**243.2**	**186.2**	**235.0**	**212.1**	**151.8**	**141.8**	**165.5**	**160.9**
Std	**245.6**	**102.0**	**194.6**	**157.8**	**76.8**	**109.1**	**100.7**	**92.9**

W_1–W_4 denote the windows; Std denotes standard deviation.

The offline TDE provides biased information: an averaged value of 147.27 s with a standard deviation of ± 7.87 s for TD variations between 10–200 s. Additionally, the MSE has an average value of 70.03 with a standard deviation of ± 2.26, which again is a significantly high value compared to the MSE obtained with semionline or online TDE algorithms. Moreover, if the estimated TD is increased or decreased by a known amount of samples $(\pm \Delta\tau_d)$ and the MSE is calculated again, then this new MSE value can be higher or lower than the previous one. This suggests that the initially calculated MSE value does not guarantee the minimum error between the synthetic BIS signal (with variable and known TD) and the BIS signal when the estimated delay is inserted. The TD value corresponding to the minimum value of MSE, in case of patient 9, is five samples below the value calculated with this algorithm [see Fig. 10(a)], i.e., $\Delta\tau_d = -5$ samples.

For the semionline TDE, the averaged MSE value decreases to 7.39 with a standard deviation of ± 1.68. Also in this case, the MSE value calculated initially does not guarantee the minimum error between the synthetic BIS signal and the BIS signal when the estimated delay with the semionline TDE algorithm is added. For patient 9, the TD needed to obtain a minimum value for MSE is one sample above the calculated value using this algorithm [see Fig. 10(b)], i.e., $\Delta\tau_d = +1$ sample.

Finally, when the online TDE is applied, the averaged MSE value is similar to the semi-online TDE. However, in this case, when the estimated TD 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 original one. This means that the initially calculated MSE value guarantees the minimum error between the synthetic BIS signal and the BIS signal when the estimated delay with the online TDE algorithm is added.

Once the accuracy of the TDE algorithm has been tested, it can be applied to the real signals. These TDEs are used to update the information used in the prediction model for EPSAC. Once again, the online TDE outperforms the other methods, providing an averaged MSE value of 17.82 with a standard deviation of ± 0.19. Hence, estimating a TD closer to the real value reduces the modeling errors in the EPSAC, and therefore, the closed-loop system performance is improved (see Fig. 8). Although similar in terms of reference tracking, the online TDE outperforms the semionline TDE for disturbance rejection.

While being in ICU, the dynamic response of the patient is continuously changing (intrapatient variability). Additionally, the signals recorded from the patient are corrupted by artifacts. When these artifacts occur, the instrumentation delay increases. As a result, the TD during disturbances is higher than that in the moments without disturbances. The results obtained in this study using these TDE algorithms are similar to those discussed in [20]. When the estimation of the TD is applied on the clinical data, the influence of the window size for the semionline method defines the accuracy with which the TD variations are detected. Therefore, fixed windows of 256 samples are used and the cross-correlation analysis is applied on each window. The TD obtained is between 10 and 400 s. If windows of 64 or 128 samples are used, the method cannot find an accurate TD for some windows, in which the processed signals are merely constant. When windows of higher length are used (512 or 1024 samples), the algorithm needs more time to estimate the TD. Thus, the MSE is higher than that in the case when windows of 256 samples are used, because the TD value of larger windows 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 TD 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 can be implemented online, but the initialization of the algorithm is done using a nominal TD value.

When the cross-correlation analysis is applied using a sliding window (i.e., online TDE algorithm), the estimated TD value converges to the average values calculated using the semionline algorithm. This is due to the fact that the algorithm uses some stored measurements and the measurement in the current time instant to estimate the TD. In this way, the online TDE algorithm works properly when the TD is varying in time, even if the BIS signal is corrupted with noise, because the calculated error is acceptable from the standpoint of engineering.

As a general comment, the online TDE is a relatively simple method for detecting variations in TD during ICU, which become significant in the presence of artifacts. The semionline method may be a simplistic way to deal with inter- and intrapatient variability, but it does not guarantee unbiased estimates.

A possible drawback of the method is that the TD may vary significantly from one sample to another, if the BIS signal

quality is very poor or highly correlated to other biological effects (i.e., the correlation has an undetermined or biased minimum). Although no such cases have been encountered in our study, there are currently clinical trials with the EPSAC controller with TD adaptation on a group of ICU patients at Ghent University Hospital, Belgium. These results will then provide more insight into the accuracy of the adaptive TD EPSAC controller.

V. Conclusion

In this paper, the cross-correlation analysis has been introduced to estimate the TD originated from instrumentation (BIS monitor) during ICU anesthesia. The TDE algorithm has been tested preliminary on synthetic signals, ensuring its accuracy for online estimation purposes. Further on, the TDE algorithms have been tested on 11 patients from ICU clinical trials. The obtained results are close to similar studies reported in literature. Currently, the online TDE algorithm is introduced in an MPC strategy, and tested in clinical trials for closed-loop sedation control at Ghent University Hospital.

Acknowledgment

The authors would like to thank to the Ghent University Hospital team for providing the database of the real patients used in this study. The authors also acknowledge the support of D. Sendoya and F. Robayo for running simulations during their research internship at Ghent University, Belgium.

References

[1] A. M. Burns, M. Shelly, and G. Park, "The use of sedative agents in critically ill patients," *Drugs*, vol. 43, pp. 507–515, 1992.

[2] J. Kress, A. Pohlman, and J. Hall, "Sedation and analgesia in the intensive care unit," *Amer. J. Respir. Crit. Care Med.*, vol. 166, pp. 1024–1028, 2002.

[3] R. B. Northrop, *Endogenous and Exogenous Regulation and Control of Physiological Systems*. Boca Raton, FL: CRC, 2000.

[4] M. Struys, H. Vereecke, A. Moerman, and E. W. Jensen, "Ability of the bispectral index, autoregressive modelling with exogenous input-derived auditory evoked potentials, and predicted propofol concentrations to measure patient responsiveness during anesthesia with propofol and remifentanil," *Anesthesiology*, vol. 99, pp. 802–812, 2003.

[5] R. D. Keyser, "Model based predictive control," *UNESCO Encyclopaedia Life Support Syst.*, vol. 6.43.16.1, p. 30, 2003.

[6] R. C. Cabot, "A note on the application of the Hilbert transform to time delay estimation," *IEEE Trans. Acoust., Speech, Signal Process*, vol. ASSP-29, no. 3, pp. 607–609, Jun. 1981.

[7] M. L. Deaton and R. V. Foutz, "Group delay and the time-lag relationship between stochastic processes," *J. Time Ser. Anal*, vol. 1, pp. 111–118, 1980.

[8] R. A. Zakarevicius, "Group delay estimation with wideband signals," *IEEE Trans. Commun.*, vol. COM-27, no. 12, pp. 1908–1910, Dec. 1979.

[9] M. Lindemann, J. Raethjen, J. Timmer, G. Deushl, and G. Pfister, "Delay estimation or cortico-peripheral relations," *J. Neurosci. Methods*, vol. 111, pp. 127–139, 2001.

[10] M. W. Mitchell and R. Y. Chiao, "Causality and negative group delays in a simple bandpass amplifier," *Amer. J. Phys.*, vol. 66, no. 1, pp. 14–19, 1998.

[11] J. Nakano and S. Tagami, "Delay estimation by a Hilbert transform method," *Austrl. J. Statist*, vol. 30, pp. 217–227, 1998.

[12] Z. M. Hussain and B. Boashash, "Hilbert transform and time delay: Statistical comparison in the presence of Gaussian noise," *IEEE Trans. Signal Process.*, vol. 50, no. 3, pp. 501–508, Mar. 2002.

[13] C. H. Knapp and G. C. Carter, "The generalized correlation method for estimation of time delay," *IEEE Trans. Accoust., Speech, Signal Process.*, vol. 24, no. 4, pp. 320–327, Aug. 1976.

[14] T. Müller, M. Lauk, M. Reinhard, A. Hetzel, C. H. Lücking, and J. Timmer, "Estimation of delay times in biological systems," *Ann. Biomed. Eng.*, vol. 31, pp. 1423–1439, 2003.

[15] L. Ljung, *System Identification: Theory for the User*. Piscataway, NJ: IEEE, 2000.

[16] J. Normey-Rico and E. F. Camacho, *Control of Dead-Time Processes*. New York: Springer-Verlag, 2007.

[17] M. Sbarciog, R. D. Keyser, S. Cristea, and C. D. Prada, "Nonlinear predictive control of processes with variable time delay: A temperature control case study," in *Proc. IEEE Int. Conf. Control Appl. (CCA'2008)*, pp. 1001–1006.

[18] T. W. Schnider, C. F. Minto, P. L. Gambus, C. Andresen, D. B. Goodale, and E. J. Youngs, "The influence of method of administration and covariates on the pharmacokinetics of propofol in adult volunteers," *Anesthesiology*, vol. 88, no. 5, pp. 1170–1182, 1998.

[19] J. Niño, R. D. Keyser, S. Syafiie, C. Ionescu, and M. Struys, "EPSAC-controlled anesthesia with online gain adaptation," *Int. J. Adapt. Control Signal Process*, vol. 23, no. 5, pp. 455–471, 2009.

[20] S. Pilge, R. Zanner, G. Schneider, J. Blum, M. Kreuzer, and E. F. Kochs, "Time delay of index calculation: Analysis of cerebral state, bispectral, and narcotrend indices," *Anesthesiology*, vol. 104, no. 3, pp. 488–494, 2006.

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