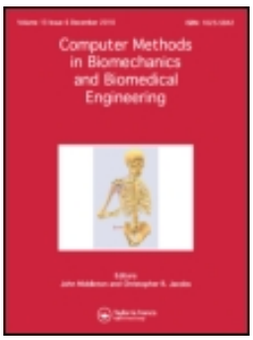

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Adaptive computer control of anesthesia in humans

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This paper presents an efficient computer control technique for regulation of anesthesia in humans. The anesthetic used is propofol and the objective is to control the degree of hypnosis of the patient. The paper describes the basic hardware/software setup of the system and the closed-loop methodologies. The bispectral index (BIS) is considered as the feedback signal. The control methods proposed here are based in the use of proportional integral controllers with dead-time compensation to avoid undesirable oscillations in the BIS signal during the process. The compensation is based on the Smith predictor. To guarantee the applicability of the method to different patients, an adaptive module to tune the compensator is developed. Some real and simulated results are presented in this work to attest the efficiency of the methods used.

Keywords: anesthesia control; computer control; propofol; proportional plus integral control; adaptive control

1. Introduction

The interest of anesthesia control has grown notably in recent years (Hemmerling 2007). The reason for this is the availability of indicators of the patient state. These variables can be used for feedback in closed-loop control systems. In particular, the anesthestic process involves the regulation of three important physiological variables: hypnosis, analgesia and muscular relaxation. The interest of this work is focused on the hypnosis control in general anesthesia surgery. As an indicator of the depth of hypnosis in the patient, the most common variable is the bispectral index (BIS). The variable that will be taken as an indicator of the degree of hypnosis is the BIS. The BIS is an empirical parameter, without units, derived from the analysis of the electroencephalogram (EEG). It has been show that the BIS correlates well with the depth of anesthesia. Its value decreases progressively from 100 (maximum alert state) to 0 (no electrical activity).

There are two different approaches to hypnosis control: signal-based control and model-based control. This work focuses on signal based control of anesthesia. In particular, innovations in the proportional integral (PI) control of intravenous anesthesia with propofol are presented. The PI controller is an easy, simple and efficient solution for the control of almost every system. As it is well known, the setup of the PI controller involves the tuning of the proportional gain and the integral gain. An adequate choice of these parameters will produce a satisfactory performance in the closed-loop control system. In anesthesia, it is important to guarantee a smooth and stable transitory around the reference BIS. Different works present results with a stable response but an oscillatory behaviour around the set point (Absalom and Kenny 2003).

The proposal of this work is to present a computer-based control system to control the hypnosis of the patient. This tool appears as a helpful tool for the anaesthetist during the anesthetic process. Concerning the control methodologies, in the paper an innovative compensation mechanism to improve the stability margins of the process is presented. The objective is to avoid oscillations in the patient's hypnotic state. In this way, the global performance of the system is improved. These experiments have been proposed in simulation and the results have been compared to the controller without compensator. To make the strategy applicable to different patients an adaptive scheme has been designed so that the controller adapts the algorithm to the dynamics of the specific patient.

The organisation of the paper is as follows: it begins with a revision of the basic concepts in anesthesia control. Then the results of the PI controller are presented. In the next section, a dead-time compensator is designed and simulation results are shown and compared with the PI control. In Section 5, a detailed description of an adaptive scheme for the compensator is presented together with comparisons with the manually adjusted controller.

2. Anesthesia basics

The main variables that describe the anesthetic process are depicted in Figure 1. In this figure, an input–output

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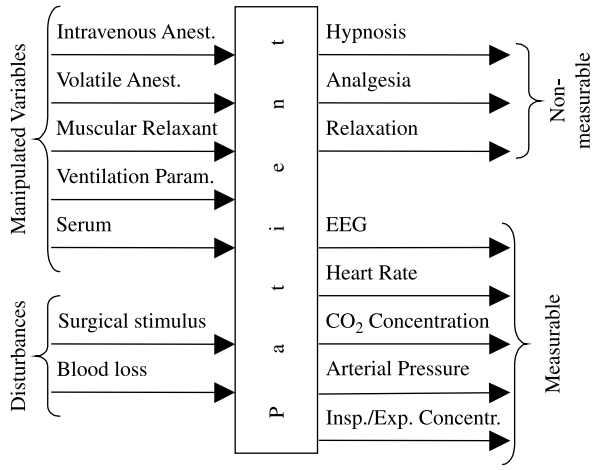

Figure 1. Input–output description of the anesthetic process.

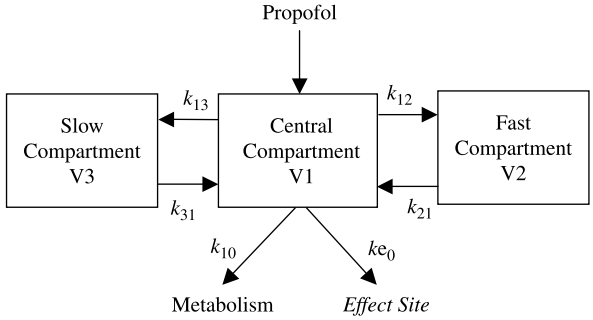

Figure 2. Compartmental model.

description of the system is shown. As can be observed, manipulated variables are anesthetics, relaxants or serums. Perturbations in the system are signals that can occur at any time (surgical stimulation, blood loss, ...). The output variables can be measurable and not measurable. The main interest in anesthesia is focused on non measurable variables: hypnosis, analgesia and muscular relaxation. Although these variables are not directly measurable, there are methods to estimate them that are used in clinical practice. These methods are based on the use of alternative variables whose behaviour allows the estimation of the non-measurable ones.

This work deals with hypnosis control in humans. Hypnosis is a general term indicating loss of consciousness and absence of the memory of the intervention after awake. Currently, the techniques that have been considered more efficient for this are based in the processing of the patient EEG (Kazama et al. 1999; Struys et al. 2000).

The description of the BIS dynamics has been done mainly with physiological based models. These models consist of a pharmacokinetic part (PK) to describe the drug distribution in the internal organs and a farmacodynamic part (PD) to describe the drug effect on the physiological variables of interest.

The drug distribution in the body depends on transport and metabolic processes which in many cases are not clearly understood. However, dynamical models based on conservation laws that capture the exchange of material between coupled macroscopic subsystems or compartments, are widely used to model these processes.

Figure 2 shows a model based in three compartments: central, fast and slow. The central compartment is the volume in which initial mixing of the drug occurs, and thus can be thought to include the vascular system (blood volume) and for some drugs the interstitial fluid. The fast peripheral compartment represents a compartment of the body that absorbs the drug rapidly from the central compartment, and thus can be thought of as comprising tissues of the body that are well-perfused (such as muscles and vital organs). Finally the slow peripheral compartment is used to mathematically represent a compartment into which re-distribution occurs more slowly, and thus can be thought of as including tissues with a poor blood supply (such as adipose tissue).

The drug is infused in the central compartment and then distributed to the slow and fast compartment and eliminated trough metabolism. Defining the drug concentration variable of the ith compartment as C_i, the propofol distribution can be described as:

$$V_1 \frac{\partial C_1}{\partial t} = V_2 C_2(t) k_{21} + V_3 C_3(t) k_{31} - V_1 C_1(t)(k_{10} + k_{12} + k_{13}) + u(t), \tag{1}$$

$$V_2 \frac{\partial C_2}{\partial t} = V_1 C_1(t) k_{12} - V_2 C_2(t) k_{21}, \tag{2}$$

$$V_3 \frac{\partial C_3}{\partial t} = V_1 C_1(t) k_{13} - V_3 C_3(t) k_{31}, \tag{3}$$

$$\frac{\partial C_e}{\partial t} = C_1(t) k_{e0} - C_e(t) k_{e0}, \tag{4}$$

where $u(t)$ represents the drug infusion rate in the central compartment and V_i is the volume of the ith compartment. The dynamics of the compartmental model are defined by the following diffusion constants: k_{10} (rate constant for drug metabolism), k_{12} (rate constant for re-distribution of drug from central to fast peripheral compartment), k_{21} (rate constant for re-distribution of drug from fast to central compartment), k_{13} (rate constant for redistribution of drug from central to slow compartment) and k_{31} (rate constant for redistribution of drug from slow to central compartment).

Common PK models for propofol are the Marsh model (Marsh et al. 1991) and the Schnider model (Schnider et al. 1998). Differences between both models can be seen in Table 1.

Table 1. Comparisons of Marsh and Schnider models for PK of propofol.

	Marsh model	Schnider model
V_1 (min^{-1})	0.228 L/Kg	4.27 L
k_{10} (min^{-1})	0.119	0.0443 + 0.0107*(BW-77) −0.0159*(LBM-59) + 0.0062*(HT-177)
k_{12} (min^{-1})	0.112	0.302−0.0056*(Age-53)
k_{13} (min^{-1})	0.0419	0.196
k_{21} (min^{-1})	0.005	1.29−0.024*(Age-53)
k_{31} (min^{-1})	0.0033	0.0035
k_{e0} (min^{-1})	1.21	0.456

BW, body weight; LBM, Lean Body Mass and HT, Height.

From the point of view of hypnosis control, the variable of interest is not the blood concentration but the concentration in the place where the effect on the controlled variable is produced (*effect site concentration*). Thus, when there is a simultaneous measure of the drug concentration in blood and its effect on the brain, drug latency can be observed that produces a temporal displacement between the peak of blood concentration and the drug effect. To include this dynamic in the model a fourth compartment is added. This compartment is known as the *effect site*. This compartment is assumed to be attached to the central compartment and has negligible volume. The diffusion constant of the effect site is k_{e0}.

On the other hand, the drug's pharmacodynamics, that represents the BIS in terms of the effect site concentration, is governed by:

$$\mathrm{BIS} = f(C_e). \tag{5}$$

The f function is usually taken as a EMAX model whose profile suits the described process:

$$\Delta\mathrm{BIS} = \Delta\mathrm{BIS}_{\max}\frac{C_e^{\gamma}}{C_e^{\gamma} + EC_{50}^{\gamma}}, \tag{6}$$

$$\Delta\mathrm{BIS} = \mathrm{BIS} - \mathrm{BIS}_0, \tag{7}$$

$$\Delta\mathrm{BIS}_{\max} = \mathrm{BIS}_{\max} - \mathrm{BIS}_0. \tag{8}$$

BIS_0 corresponds to the awake state, $\mathrm{BIS}_{\max}$ represents the minimum achievable BIS and EC_{50} represents the concentration in the effect site for which the effect is half the maximum value, γ represents the sensitivity of the patient to mall concentration variations in the effect site. This parameter can be seen as index that measures the degree of nonlinearity of the model. Normally, the values $\mathrm{BIS}_0 = 100$ and $\mathrm{BIS}_{\max} = 0$ are assumed.

3. Hardware/software setup

The main elements that constitute the control system are depicted in Figure 3. As can be observed there is a computer that centralises the monitoring and control task in the system.

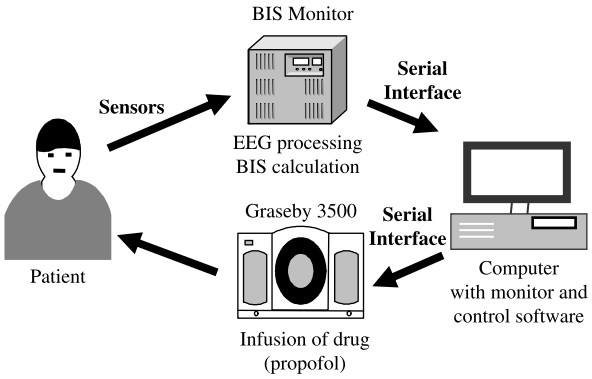

Figure 3. Main elements of the closed-loop control system.

As commented, the variable of interest in the patient is the BIS. This variable is provided by the BIS monitor. In this work, the Aspect® A-2000 monitor was used. The communication with the computer was implemented via a RS-232 serial interface.

Concerning the actuator, in this work the Graseby® infusion pump was used for drug infusion in the patient. The pump is also governed via a RS-232 serial interface. Apart from sending commands to the pump, the program in the PC reads continuously its state to detect eventual failures, syringe changes, etc.

The program in the computer has all the routines to monitor and control the system. The basic control routine is based on a PI controller (Albino et al. 2006; Reboso et al. 2007). This law establishes that the drug rate to be applied is computed using information of the error signal. The explicit formula is:

$$u(t) = Kp \times e(t) + Ki \times \int_0^t e(t)\,\mathrm{d}t, \tag{9}$$

where $u(t)$ is the propofol infusion rate (ml/h), $e(t)$ is the error at time instant t in the BIS variable, $e(t) = \textit{Desired BIS} - \textit{Current BIS}$.

Kp and Ki are the constant parameters (proportional, and integral, respectively) of the PI controller.

The main program was designed with a visual and user-friendly interface (see Figure 4). Apart from processing information, the program also manages and saves all the information of the process.

An important point in the system is the implementation of several alarms to avoid problems caused by eventual failures of any of the elements in the control loop. Thus, there are alarms to solve problems related to missing BIS signal, excessive infusion rate in the pump, etc.

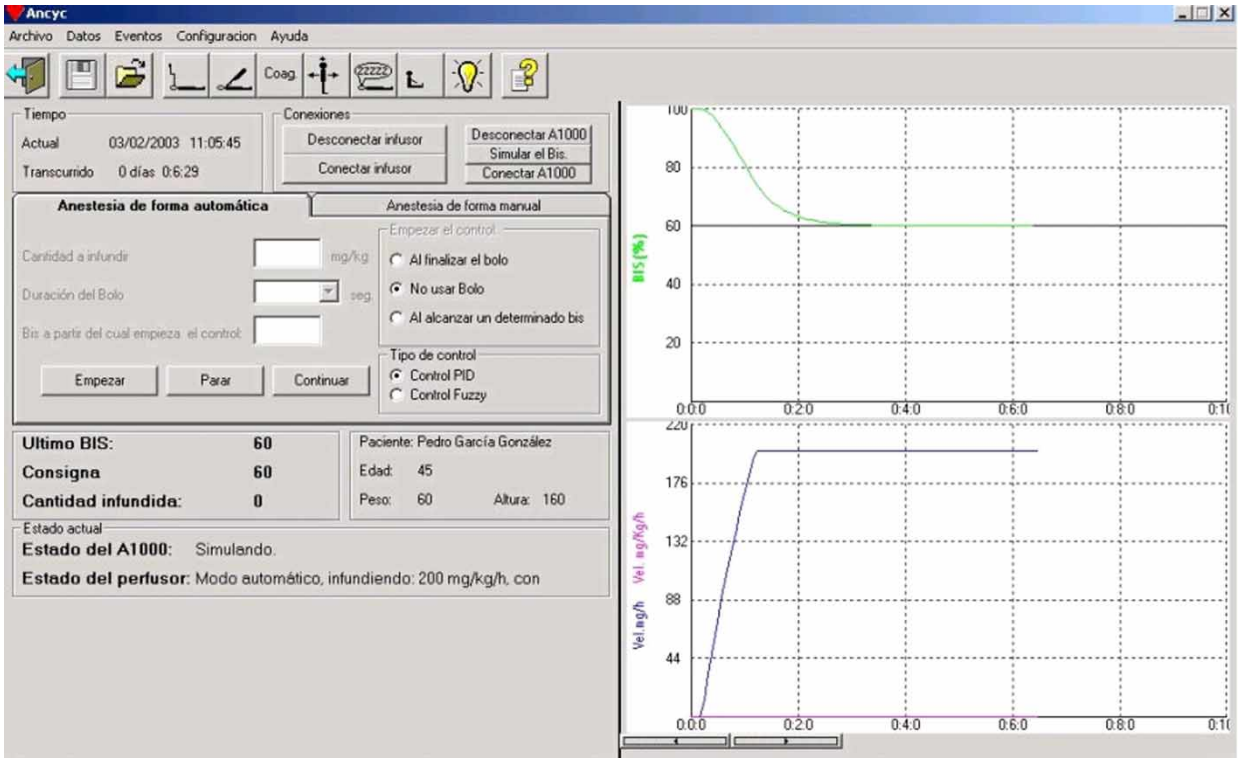

Figure 4. View of the main window of the control program.

4. PI-control results

The goal is to make a manual induction with propofol and remifentanil and maintain a BIS target during the maintenance of anesthesia. Reminfentanil infusion was adjusted manually and rocuronium was administered in bolus as needs.

The study was approved by the *Ethical and Research Committee of the Hospital Universitario de Canarias* and has written informed consent of the patients. The study was performed on a population of 15 patients of 30–60 years.

In the real proofs, a BIS target (BISr) of 50 is considered while the measurement and actuation period is 5 s. Before starting its operation, the software checks that all the security alarms are programmed.

In the operating room, the patient was connected to the BIS monitor, and the anesthesia system was started in monitor mode. After the patient had breathed 100% oxygen for 3 min, the system was switched to manual mode, and anesthesia was induced by means of a 2 mg/Kg propofol manual bolus. Once the patient achieves a BIS = 50, the system is switched to automatic and the PI controller is responsible for regulating the BIS around the objective.

The adjustment of the controller gains was made in an empirical way trying to get a smooth transitory and a stable response. This task was done following standard procedures in online process control engineering. For this, the presence of a control expert was necessary together with the anesthesiologist in the operating theatre. Thus, after several trials adequate values for PI controller where found to be $Kp = 0.67$, $Ki = 0.055$. This set of values was tested in the whole population of the study with satisfactory results. Figures 5 and 6 present the evolution of the anesthesia for two different patients. As can be

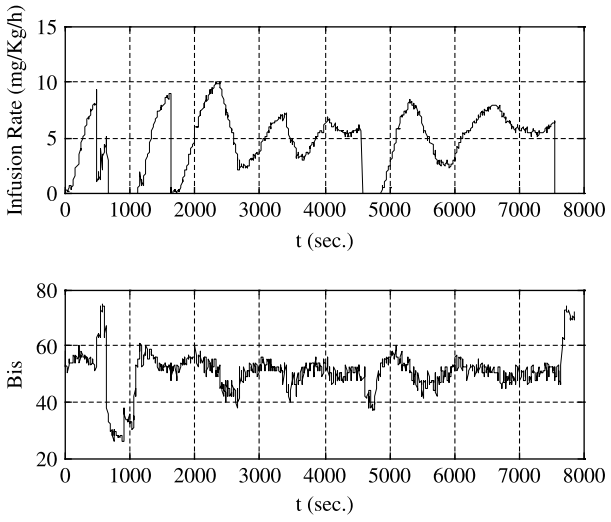

Figure 5. Results of anesthesia automatic control on patient 1.

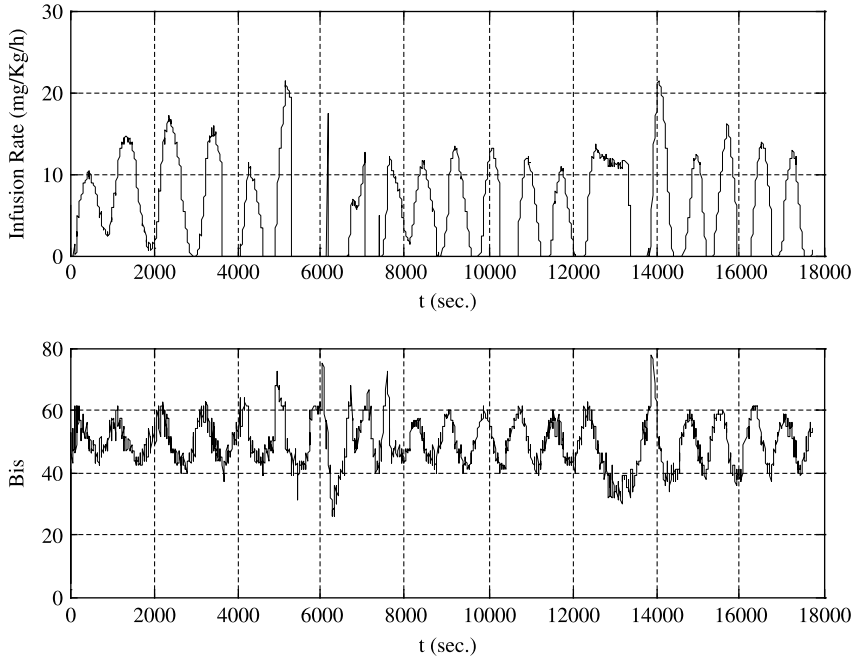

Figure 6. Results of anesthesia automatic control on patient 2.

observed, in both cases the system remains stabilised around the reference value with an oscillation of near ± 10 units in the worst case (patient 2).

The study revealed that although results are satisfactory, eventually the performance of the controller can decrease. There are two main factors that contribute to this. First of all, the variability between patients implies that the nominal PI parameters chosen are not the best choice for all the patients.

Together with this, the dead time present in the system also contributes to reduce the phase margin of the closed-loop system. For example in Figure 6, the evolution of the BIS is quite oscillatory. The next section proposes a mechanism to reduce the negative effect of this time-delay.

5. Smith predictor for dead-time compensation

As seen on previous section, the PI controller usually gives a response with oscillations around the BIS reference value. In this section, the control algorithm is modified in order to compensate these oscillations and get a better transitory. The results shown in this paper are obtained in simulation. The patient model for use in simulation is adjusted previously using real data.

To make the simulations experiments of the proposed algorithm, a physiologic model of the patient dynamics was designed. The results shown in this section are obtained for patient 2. As mentioned, the model has two parts: pharmacokinetics and pharmacodynamics. The parameters defining each submodel were obtained in simulation.

After converging to a satisfactory model for the patient, the values obtained for the pharmacokinetics model were $k_{10} = 0.006$, $k_{12} = 11.0$; $k_{21} = 14.04$, $k_{13} = 10.02$, $k_{31} = 283.50$ and $k_{e0} = 0.0063$. The values for the pharmacodynamics model were EC50 $= 610.0$, $\gamma = 1.5$, $\mathrm{BIS}_0 = 100$ and $\mathrm{BIS}_{\max} = 0$. The procedure to obtain these parameters was to adjust the parameters in simulation in order to reproduce the behaviour of the patient real data.

The validation of the model in this patient can be seen in Figure 8(a). The modelled BIS (dashed lines) fits to the real BIS (continuous line).

It is important to note that this model is used only for simulation purposes. The reason to develop an *ad hoc* model for this patient is to have a more accurate model to test the controller in this patient. The controller designed in this work is not based on this model. This means that for real application in the operating theatre this model is not used at all so the strategy proposed can be used in any patient.

5.1 Predictor design

The proposal exposed in this work is to improve the performance of the closed-loop system by means of a compensation of the time-delay present in the system.

The origin of this time-delay is the period of time from the start of infusion pump until the drug is distributed along the central compartment. The majority of the works in the literature do not explicitly consider the presence of this time-delay in the proposed models. In Section 2, time-delay is not considered in the system model. But in real proofs, some delays (t_d) between 1 and 2 min have to be considered to have a realistic model of the dynamics. Under this hypothesis, a time-delay compensator based on the Smith predictor theory has been proposed to be added to the PI controller (Smith 1972; Normey-Rico and Camacho 2007). It has to be noted also that there is an initial time delay to get the first BIS measure of about 60 s. However, this cannot be considered as a time delay as its effect appears only in the initial sample. Before starting the practice the software checks that a valid BIS signal is present.

The basis of the Smith predictor is to consider the feedback of the controlled variable (BIS(t)) without delay. As this is variable is not available, the predictor estimates this value (BIS(t)) and uses this estimation as the feedback signal. To correct the deviations between this estimation and the real value, a correction term, resulting from the error between the estimation and the measured BIS, is added to the feedback signal.

As it is well known, the basics of this compensation algorithm consider the formulation of the Smith predictor for linear systems. To apply the Smith predictor to the nonlinear model of the patient, a first-order plus a time-delay approximation of the patient model is considered. Thus, the configuration employed in this work can be seen in Figure 7. A delay between 90 and 120 s is considered in the simulations. In Figure 8(b), the obtained results with patient 2 are shown. The evolution of the BIS signal with the Smith predictor (in solid line) is much better than with the PI controller (in dotted line), and does not show oscillations around the reference BIS value.

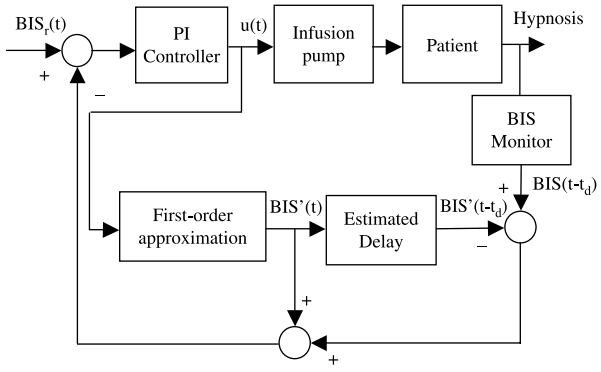

Figure 7. PI Controller with Smith predictor for patient hypnosis control.

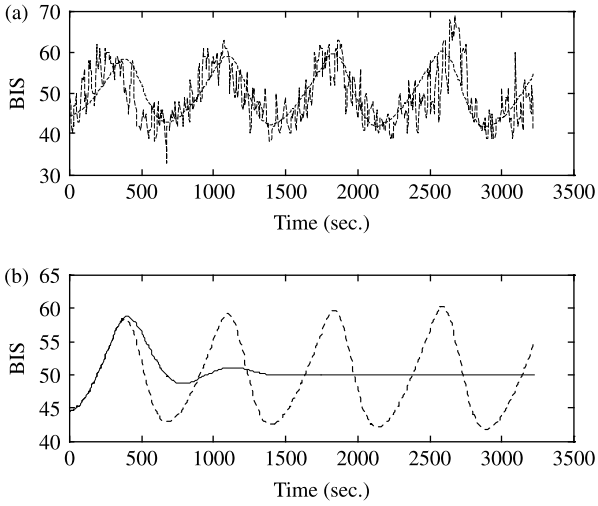

Figure 8. (a) Simulated BIS output (dotted) and real patient BIS output (solid) obtained under the action of a PI controller. (b) PI controlled output (dotted) and PI with delay-time compensation output (solid).

6. Adaptive Smith predictor

As it can be viewed in the previous section, the main advantage of the time-delay compensation for the PI controller is a better performance in the transitory of the BIS signal. This advantage is conditioned to obtain a good first-order approximation of the system.

In the results of Figure 8, a first order model of the patient was adequately tuned in order to obtain a satisfactory result. However, this model has to be changed in at least two situations. First, when the operation point changes due to a change in the BIS reference for the same patient. Second, when the controller is applied in a different patient, whose physiologic model has to be estimated.

The aim of the algorithm proposed here is to make the time-delay compensator independent of the model assumed for the patient. In order to obtain a simple adaptive algorithm which guarantees the closed-loop stability, the model reference adaptive controller (MRAC) is used.

Following this control scheme, the controller parameters are adjusted by an adaptation law which depends on the error between the system output (BIS) and the model reference output defined for this closed-loop. Minimising a certain cost-function involving this error, an adaptation law of the adjustable controller parameters is obtained. The configuration of this controller can be seen in Figure 9. In this case, the adjustable parameters are the static gain and the time constant of the approximated first-order model used in the Smith predictor.

Let $G(s)$ be the estimated first-order model for the compensator, where the static gain K_{DC} and the time

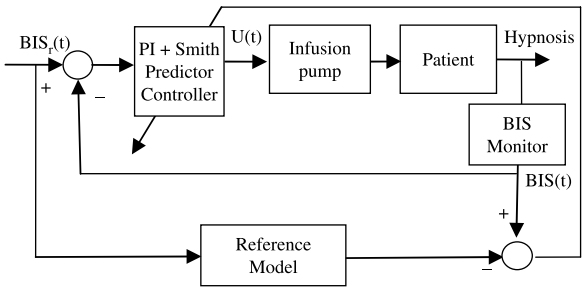

Figure 9. PI with Smith predictor controller inserted in the adaptive control scheme MRAC. The error between the system output and the model reference output is used to update the parameters of the PI with Smith predictor controller.

constant τ are the parameters to be updated by the adaptive scheme:

$$G(s) = \frac{K_{\mathrm{DC}}}{\tau s + 1}. \tag{10}$$

Once a quadratic cost function in the error between the system output and the model reference output, e_{m}, is chosen, the updating of the controller parameters is made by applying the MIT rule:

$$\dot{\theta} = \gamma_1 e_{\mathrm{m}} \frac{\partial \mathrm{BIS}}{\partial \theta}, \tag{11}$$

where θ is the parameter to update and γ_1 is a constant called *learning rate*. After making some computation, the final expression for BIS signal in closed-loop is

$$\mathrm{BIS} = \frac{\mathrm{BIS}_0 - \mathrm{TF}(s)}{1 - \mathrm{LF}(s)} \tag{12}$$

being

$$F(s) = \frac{(K_{\mathrm{p}} s + K_i)(\tau s + 1)}{s(\tau s + 1) - (K_{\mathrm{p}} s + K_i)(\mathrm{e}^{-st_{\mathrm{d}}} - 1)K_{\mathrm{DC}}} \tag{13}$$

$$T = \frac{(\mathrm{BIS}_0 - \mathrm{BIS}_{\max})B_4 \mathrm{BIS}_{\mathrm{r}}}{\mathrm{EC}_{50}} \tag{14}$$

$$L = \frac{T}{\mathrm{BIS}_{\mathrm{r}}} \tag{15}$$

and supposing a near-linear performance of the system, after assuming $EC_{50} \gg x_4$ and γ in the order of the unity, so the approximation for the open-loop system is:

$$\mathrm{BIS} = \mathrm{BIS}_0 - \frac{\mathrm{BIS}_0 - \mathrm{BIS}_{\max}}{\mathrm{EC}_{50}} B_4 u, \tag{16}$$

where $x_4 = B_4 u$, being B_4 the fourth component of the input matrix in the state-space representation of the system.

With the definition of the BIS signal in closed-loop, the following expressions are obtained:

$$\frac{\partial \mathrm{BIS}}{\partial \theta} = \frac{\mathrm{BIS}_0 L - T}{(1 - \mathrm{LF}(s))^2} \frac{\partial F(s)}{\partial \theta}. \tag{17}$$

Finally, the partial derivatives in the above expression are given by:

$$\frac{\partial F(s)}{\partial K_{\mathrm{DC}}} = \frac{(K_{\mathrm{p}} s + K_i)(\mathrm{e}^{-st_{\mathrm{d}}} - 1)}{s(\tau s + 1) - (K_{\mathrm{p}} s + K_i)(\mathrm{e}^{-st_{\mathrm{d}}} - 1)K_{\mathrm{DC}}} F(s), \tag{18}$$

$$\frac{\partial F(s)}{\partial \tau} = \frac{-sK_{\mathrm{DC}}}{(\tau s + 1)} \frac{\partial F(s)}{\partial K_{\mathrm{DC}}}. \tag{19}$$

The final expressions for the updating laws of the parameters are minimised by supposing that, in the stationary, the dynamics of the closed-loop converge to the model reference dynamics.

Several simulation experiments have been made for the patient of the Figure 7, choosing as the reference model a second-order model with poles, expressed in the z-plane discrete formulation, in $z = 0.98$ and -0.75. The results are shown in Figure 10(a), where the evolution of the BIS under the self-adaptive compensator algorithm is drawn in solid line and compared with the results obtained in Figure 8(b) $-$PI and PI $+$ compensator controllers.

In Figure 10(b), the evolution of the static gain under this self-adaptive scheme is shown. As it can be observed, some extra oscillations are produced with respect to the previous algorithm, which corresponds to the period of time in that the parameter is adapting.

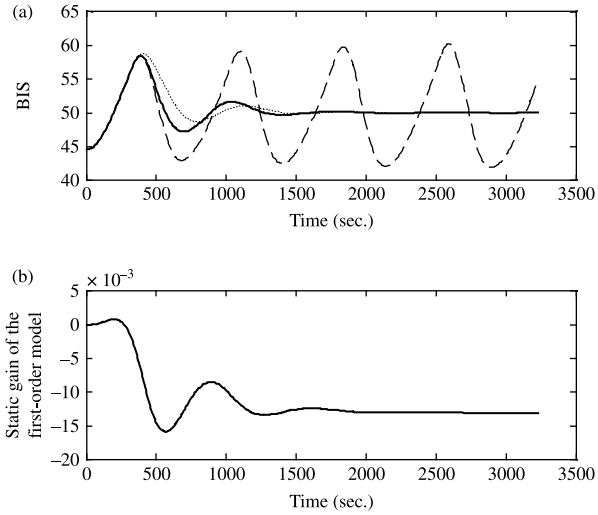

Figure 10. (a) PI controlled system output (dotted), PI with Smith predictor controlled output (dashed), and self-adaptive time-delay compensation controlled output (solid) compared for the same patient. (b) Evolution of the static gain of the first-order approximation model of the time-delay compensation.

Once the optimal values for the parameters are reached, the performance of the system is very similar to the previous controller. In that case, the static gain took a value of -0.037. In this case, the stabilising value for this parameter is near the half. However, the performance is also satisfactory. Moreover, no assumptions over the system had to been made, which is the main advantage of this new algorithm.

7. Conclusion

This work presents an automatic control system for intravenous anesthesia. The hardware and software was designed to provide the anaesthesiologist a robust and user friendly tool to assist him during the anesthetic process.

The control algorithms are based on the PI controller and have been improved with dead-time compensation modules that notably improve the performance of the overall patient response.

To guarantee the applicability of the algorithms to different patients, an adaptive control based on a MRAC configuration was designed to adjust the main parameter of the compensator according to each patient's dynamics. Simulation results attest to the efficiency of the methods.

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Note

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References

Absalom AR, Kenny NC. 2003. Closed-loop control of propofol anaesthesia using biespectral indexTM: performance assessment in patients receiving computercontrolled propofol and manually controlled remifentanil infusions for minor surgery. Br J Anaesth. 90(6):737–741.

Albino J, Reboso MH, Torres S, Acosta L. 2006. Modelado y control de la infusión de anestesia intravenosa mediante el índice biespectral. XXVII Jornadas de Automática, Almeria, Spain, p. 293–298.

Hemmerling TM. 2007. Automated anesthesia. Adv Anesth. 25: 17–39.

Kazama T, Ikeda K, Morita K, Kikura M, Doi M, Ikeda T, Kurita T, Nakajima Y. 1999. Comparison of the effect-site keO s of propofol for blood pressure and EEG bispectral index in elderly and younger patients. Anesthesiology. 90(6): 1517–1527.

Marsh B, White M, Morton N, Kenny GNC. 1991. Pharmacokinetic model driven infusion of propofol in children. Br J Anaesth. 67:41–48.

Normey-Rico JE, Camacho EF. 2007. Control of dead-time processes. Birkhauser: Series: Advanced Textbooks in Control and Signal Processing, London.

Reboso JA, Méndez JA, Esteban JL, Torres S, Acosta L. 2007. Felipe Gonzalez-Miranda design of a closed loop controller for intravenous anesthesia with propofol. First World Congress of Total Intravenous Anesthesia-TCI, Venecia, Italia, Septiembre.

Schnider TW, C F, Minto PL, Gambus C, Anderson DB, Goodale SL, Shafer J. 1998. Youngs: the influence of method of administration and covariates on the pharmacokinetics of propofol in adult volunteer. Anesthesiology. 88:1170–1182.

Smith C. 1972. Digital computer process control. Scranton, PA: Intext Education Publishers.

Struys MM, De Smet T, Depoorter B, Versichelen LF, Mortier EP, Dumortier FJ, Shafer SL, Rolly G. 2000. Comparison of plasma compartment versus two methods for effect compartment-controlled targetcontrolled infusion for ropofol. Anesthesiology. 92(2):399–406.