Dead-time Compensation in Intravenous Anesthesia Control

Juan Albino Méndez, Santiago Torres, José Antonio Reboso and Héctor Reboso

***Abstract*—This paper presents preliminary results of anesthesia control experiments in humans. The drug used is propofol and the administration is intravenous. The objective is to regulate the hypnosis depth in the patient. To achieve this, the Bispectral Index is taken as the feedback signal. In this work, results of the pharmacokinetics and pharmacodynamics modelling of the patient are presented. Physiological models have been considered and simulation tools have been used for validation. Results with Proportional Integral controllers are presented. Then the algorithm is modified with a dead-time compensator to improve the transitory response of the Bispectral Index. The results are compared to check the benefits of the compensator. A further step in the algorithm is the inclusion of an adaptive scheme so that the compensator designed can be adapted to different patients.**

I. Introduction

THE advances in automatic control of anesthesia have been important in recent years [1]. The main reason for this is the availability of indicators of the hypnotic state of the patient. In fact, one of the main problems in anesthesia control is that the main variables defining the anesthetic process (hypnosis, analgesia and muscular relaxation) are not directly measurable.

The interest of this work is focused in the hypnosis control in general anesthesia surgery. The indicator considered to measure the degree of hypnosis is the Bispectral Index (BIS). The complexity of the problem grows exponentially when other specifications are taken into account like muscular relaxation or analgesia. For hypnosis control, the structure of the controllers proposed have two different approaches: signal-based control and model-based control.

This work focus on signal based control of anesthesia. In particular, innovations in the 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 parameter 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 [2].

The proposal of this work is to present a compensation mechanism to improve the stability margins of the process, so that the patient will remain in a less oscillating 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 paper begins with a revision of the basic concepts in anesthesia control. Then the results of the PI controller are presented. In section IV a dead-time compensator is designed and simulation results are shown and compared with the PI control. An adaptive scheme is described in section V and comparisons with the manually adjusted controller are performed.

II. General Concepts of Anesthesia Control

The description of the anesthetic process is generally done with the variables shown in Figure 1. In the figure an input-output 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 in non measurable variables: hypnosis, analgesia and muscular relaxation.

As commented previously, the problem of having non measurable variables is solved having alternative variables whose behaviour allows the estimation of the non-measurable ones.

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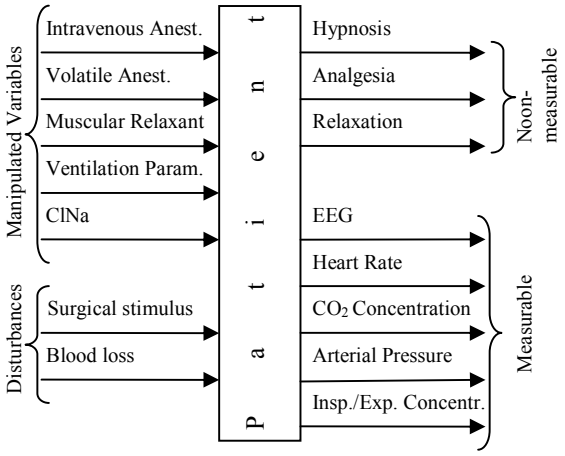

Fig 1. Input-output description of the anesthetic process.

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 electroencephalogram (EEG), [3], [4].

The variable that will be taken as an indicator of the degree of hypnosis is the Bispectral Index (BIS). The Bispectral Index is an empirical parameter, without units, derived from the analysis of the EEG. The BIS related linear and directly with the consciousness degree. Its value decreases progressively from 100 (maximum alert state) to 0 (no electrical activity). The correlation between these variables is dynamical so that there is always an optimal correlation with the hypnotic state: consciousness-unconsciousness, sedation degree, ability to remember and process information, etc.

The description of the BIS dynamics has been done mainly with physiological models. These models consists 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 more used PK model is the Marsh model that has been widely studied and represents the patient as a set of compartments: central, fast and slow (see Figure 2) [5]. The central compartment corresponds to the apparent blood volume of the patient (the place where the drug is infused). .

The fast and show compartments represent fat and bone tissue. The Marsh model is defined according to the following diffusion constants: k10 (metabolic clearance), k12 (clearance from fast compartment to central), k21 (clearance from central to fast), k13 (clearance from central to slow compartment) and k31 (clearance from slow to central compartment).

From the point of view of hypnosis control the variable of interest is not the blood concentration but the concentration

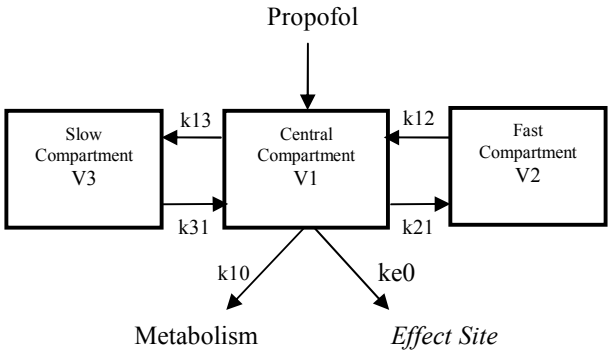

Fig. 2. Compartment model.

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 dynamics in the model a fourth compartment is added. This compartment is known as *effect site*. This model is assumed to be attached to the central compartment and has negligible volume. The diffusion constant of the effect site is *k*e0.

Defining the variable that represents the *i*-th compartment as C_i, the propofol distribution can be obtained as:

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

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

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

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

where u(t) represents the drug infusion rate in the central compartment. This expression defines the pharmacokinetics of the drug. On the other hand, the drug's pharmacodynamics, that represents the BIS in terms of the effect site concentration, is governed by:

$$BIS = f(C_e) \quad (5)$$

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

$$\Delta BIS = \Delta BIS_{\max} \frac{C_e^{\gamma}}{C_e^{\gamma} + EC_{50}^{\gamma}}, \quad (6)$$

$$\Delta BIS = BIS - BIS_0, \quad (7)$$

$$\Delta BIS_{\max} = BIS_{\max} - BIS_0. \quad (8)$$

BIS_0 corresponds to the awake state, 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 $BIS_0 = 100$ and $BIS_{max} = 0$ are assumed.

III. PI CONTROL BY BIS FEEDBACK

The control strategy used in this work is based on a PI controller that uses the BIS as feedback signal [6], [7]. A scheme of the control system can be viewed in figure 3. The elements of the closed-loop control are:

- BIS monitor: in this case, the ASPECT A-2000 monitor is used. This device is serial-connected to the PC to transmit the BIS data obtained from the patient.
- Monitoring and control program: this program runs in a laptop and contains all the implemented control routines. The interface with the rest of devices is through the serial port.
- Infusion pump: this is de actuator device and is governed from the laptop.

The procedure to start the controller is divided in two steps. First, a manual bolus is applied on the patient to carry him to the BIS target value. Then, the automatic mode of the procedure, based on a PI controller, starts.

In the real proofs, a BIS reference (BIS_r) of 50 is considered while the measurement and actuation period is 5 seconds. The adjustment of the controller gains was made in an empirical way trying to gate a smooth transitory and a stable response. Once all the security alarms are programmed, real control proofs on patients in operating room were made.

The obtained results were satisfactory due to the hypnosis level of the patient was stabilised around the BIS reference. In figure 4 the results of one of the experiment is shown. As can be viewed, the system remains stabilised around the reference value with an oscillation of near ±10 units.

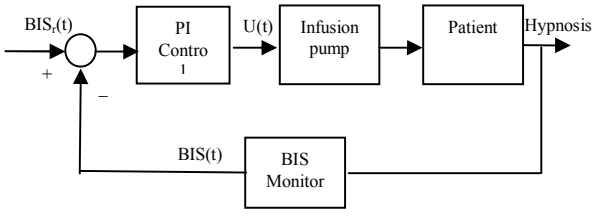

Fig. 3. Hypnosis control scheme using a PI controller.

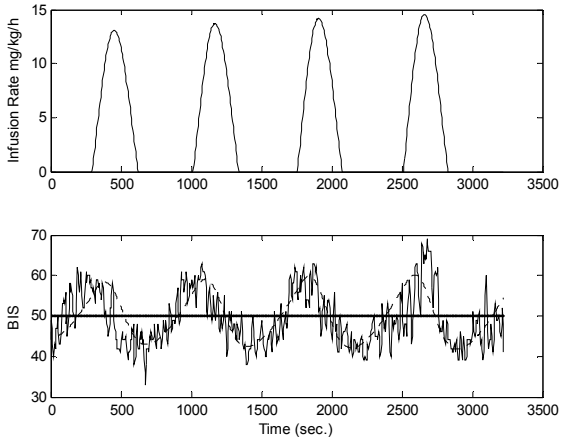

Fig. 4. Hypnosis under anaesthesia automatic control results from a real experiment with a patient using a PI controller.

IV. TIME-DELAY COMPENSATION

In previous section it can be viewed that 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 in simulation after having adjusted the patient dynamical model.

A. Model adjustment

In order to make the simulations proofs of the proposed algorithm, a physiology model of the patient dynamics was designed. As it was told, the model has two parts: pharmacokinetics and pharmacodynamics. The parameters adjustment was made in simulation.

After obtaining a satisfactory adjustment, the values for the pharmacokinetics model are k10=0.006, k12=11.0; k21=14.04, k13=10.02, k31=283.50 and ke0=0.0063. The values for the pharmacodynamics model are EC50=610.0, γ=1.5, BIS_0 =100 and BIS_{max}=0.

To validate the model the simulated response is compared with the real one. The obtained results, shown in figure 6a), prove the goodness of the model.

B. Smith Predictor

The proposal of this work is to improve the performance of the closed-loop system by means of a compensation of the system time-delay. The origin of this time-delay is the period of time between from the infusion pump starts 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 fact, in section 2, time-delay is not considered in the system model. But in real proofs, some delays between 1 and 2 minutes 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 [8].

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 5. A delay between 90 and 120 seconds is considered in the simulations. In figure 6b) the obtained results with the patient of the figure 4 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.

V. Self-adaptive Smith Predictor

The advantage of the time-delay compensation for the PI controller is conditioned to obtain a good fist-order approximation of the system. However, this model has to be changed in at least two situations: when the operation point changes, in this case the change in the BIS reference for the same patient, or where the controller is applied in a different patient, whose physiology model has to be estimated.

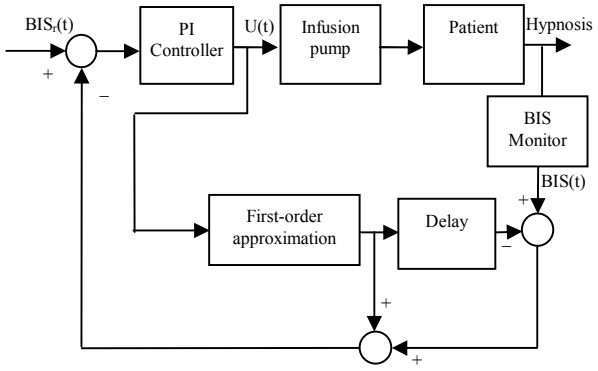

Fig 5. PI Controller with Smith Predictor for patient hypnosis control.

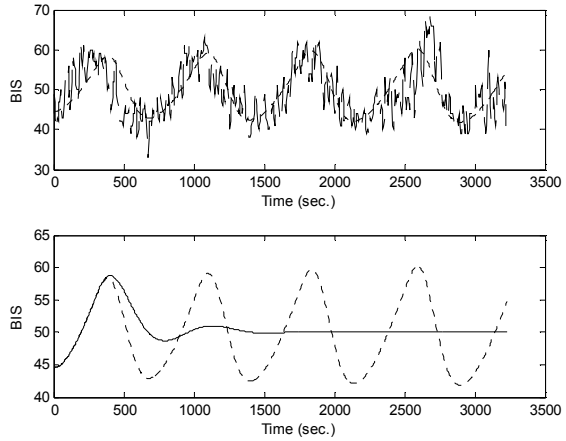

Fig. 6. a) Simulated BIS output (dotted) and real patient BIS output (solid) obtained under the action of a PI controller. b) PI controlled output (dotted) and PI with delay-time compensation output (solid).

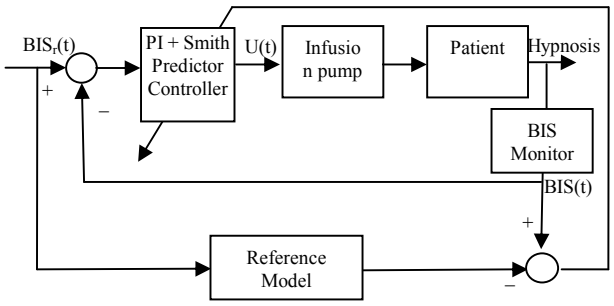

Fig. 7. PI with Smith Predictor controller inserted in the adaptive control scheme MRAC. The error between the system output and the model reference output is used to update the parameters of the PI with Smith Predictor controller.

The adjustment of the approximated first-order model of the system, in order to adapt to the changes produced by any of the mentioned situations, is made with respect to its two parameters: the static gain and the time constant of the model. To obtain a simple adaptive algorithm which guarantees the closed-loop stability, the model reference adaptive controller (MRAC) [9] 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 ion figure 7. 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.

Several simulation experiments has been made for the patient of the figure 4, choosing as the reference model a second-order model with poles, expressed in the z-plane discrete formulation, in z=0.98 and z=-0.75. The results are shown in figure 8a), 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 6b) –PI and PI+compensator controllers-. In figure 8b) 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. 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.

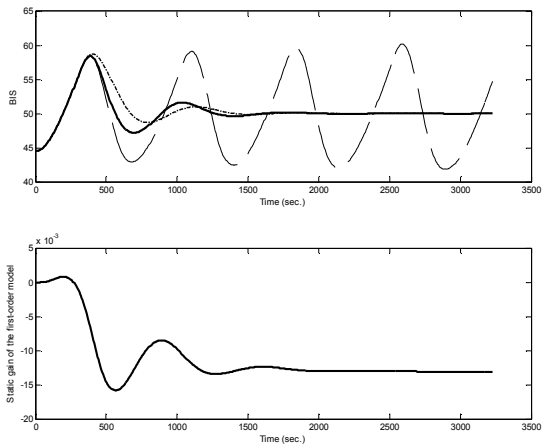

Fig. 8. a) PI controlled system output (dotted), PI with Smith Predictor controlled output (dashed), and self-adaptive time-delay compensation controlled output (solid) compared for the same patient. b) Evolution of the static gain of the first-order approximation model of the time-delay compensation.

VI. CONCLUSION

This work presents some advances in the control of intravenous anaesthesia using the biespectral index as the feedback signal of the control scheme. The obtained results show that it is possible to correct the oscillations usually present when PI controller are used for the hypnosis in general anaesthesia. The methodology proposed in this work is to compensate the effects of the transport time-delays present in the system. Moreover, an improvement of this compensation technique, based on a self-adaptive algorithm, is also proposed in order to avoid the adjustment of the patient approximation model used by the Smith Predictor. The simulated results allow auguring a satisfactory controller performance in the real clinic practise.

VII. ACKNOWLEDGMENT

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