Available online at www.sciencedirect.com

ScienceDirect

IFAC Papers Online
CONFERENCE PAPER ARCHIVE

IFAC-PapersOnLine 49-5 (2016) 230–235

A simplified control scheme for the Depth of Anesthesia

Juliana Almeida * **Teresa Mendonça** ** **Paula Rocha** *

* *Faculdade de Engenharia da Universidade do Porto, Rua Dr. Roberto Frias s/n, 4200-465 Porto, Portugal*
Research Center for Systems and Technologies (SYSTEC), Rua Dr. Roberto Frias s/n, 4200-465 Porto, Portugal.
(e-mail: almeidajfc@gmail.com, mprocha@fe.up.pt)
** *Faculdade de Ciências da Universidade do Porto, Rua do Campo Alegre s/n, 4169-007 Porto, Portugal.*
Research Center for Systems and Technologies (SYSTEC), Rua Dr. Roberto Frias s/n, 4200-465 Porto, Portugal,
(e-mail: tmendo@fc.up.pt)

Abstract: In this paper a new simplified control scheme for the depth of anesthesia that only requires the knowledge of the half of the model parameters is proposed. Two control laws are designed in parallel to control the amount of the hypnotic dose and the amount of the analgesic dose. Furthermore, an identification procedure to obtain the necessary model parameters is implemented. The results were validated by simulations based on real data collected during surgeries.

Keywords: Control design, identification method, depth of anesthesia.

1. INTRODUCTION

The recent technological advances in the monitoring devices for biomedical systems justify the increasing focus on the research of dedicated automatic control systems. In this context, the automatic control of drug administration during general anesthesia is one application of particular interest. During general anesthesia, several drugs are administered to induce and maintain areflexia, hypnosis and analgesia. In this paper we focus on these two last components. Hypnosis is defined as the absence of consciousness and the inability of the patient to recall intra operative events. This is achieved by the administration of hypnotics, e.g., propofol, and is measured by the electroencephalographic activity. The Bispectral Index (BIS), T. J. Gan (1997), is the most widely used index to infer the hypnosis of a patient. It is related to the responsiveness level and the probability of recalling intra operative events, and ranges from 97.7 (fully awake and alert state) to 0 (total absence of brain activity). During a standard general anesthesia, the BIS level should vary between 40 and 60. Analgesia is obtained by the administration of analgesics, e.g., remifentanil, and it allows the loss of the pain. The level of analgesia cannot be measured directly and must be estimated based on autonomic reactions, such as changes in blood pressure and heart rate, sweating, pupil reactivity and the presence of tears, Guignard (2006). It turns out that hypnotics and analgesics interact in such way that their effect is enhanced when administered together. In this way, both types of drugs contribute to the depth of anesthesia (DoA). It is commonly accepted that the DoA is also well described by the BIS level, T. J. Gan (1997).

In order to describe the drug absorption, distribution and biotransformation in the patients body, Pharmacokinetic/Pharmacodynamic (PK/PD) models are the most commonly used, Haddad (2010). These models have a Wiener structure: a linear part, usually represented as compartmental models, in series with a nonlinear static function for the drug effect. The compartmental models are positive linear models composed by a finite number of interconnected homogeneous, well-mixed subsystems called compartments.

Due to the large number of patient dependent parameters present in the PK/PD models, in this paper a simplified compartmental MISO Wiener model will be used to describe the relation between the hypnotic and analgesic doses with the BIS level. This model was proposed by M. M. Silva (2014) and uses only four parameters to characterize the patient while keeping a good modeling accuracy, M. M. Silva (2013).

Based on this, here a positive control law is designed to control the BIS level in line with the work presented in F. N. Nogueira (2014). However, whereas in F. N. Nogueira (2014) all the four model parameters are used to design the controller, here a new simplified control law that only requires the knowledge of two of the four model param-

⋆ This work was financially supported by: Project POCI-01-0145-FEDER-006933 - SYSTEC - Research Center for Systems and Technologies - funded by FEDER funds through COMPETE2020 - Programa Operacional Competitividade e Internacionalizao (POCI) and by national funds through FCT – Fundação para a Ciência e Tecnologia; The author Juliana Almeida acknowledge the support from FCT – Fundação para a Ciência e Tecnologia – under the doctoral grant SFRH/BD/87128/2012.

10.1016/j.ifacol.2016.07.118

eters is proposed. Moreover, an identification procedure to obtain the two necessary parameters is implemented. Our results are illustrated by simulations based on data collected during general anesthesia in one surgery.

This paper is organized as follows. Section 2 presents the model used to design the control scheme, the proof of the parameter independence in the mass convergence and the identification procedure. The obtained results are shown in Section 3 and the conclusions are drawn in Section 4.

2. PARAMETER INDEPENDENCE IN THE MASS CONVERGENCE

This section presents our new positive control law for the BIS level that uses a compartmental description of the system. The BIS model used in this paper is first introduced.

2.1 MISO Wiener model

The BIS model proposed in M. M. Silva (2014) for the description of the joint effect of hypnotics and analgesics in the human body consists of two linear parts: one for the relationship between the hypnotic dose and its effect concentration and another for the effect concentration of the analgesic. These linear sub-models are connected in parallel and then followed by a nonlinear static equation that describes the drug interaction and corresponding effect.

The hypnotic linear dynamics is hence modelled by

$$C_e^P(s) = \frac{k_1\, k_2\, k_3 \alpha^3}{(s\, +\, k_1\alpha)\,(s\, +\, k_2\alpha)\,(s\, +\, k_3\alpha)}\, U^P(s) \qquad (1)$$

and the linear model for the effect concentration of the analgesic is similarly given by

$$C_e^R(s) = \frac{l_1\, l_2\, l_3 \eta^3}{(s\, +\, l_1\eta)\,(s\, +\, l_2\eta)\,(s\, +\, l_3\eta)}\, U^R(s) \qquad (2)$$

where $C_e^P(s)$ and $C_e^R(s)$ are the Laplace transforms of the effect concentration of the hypnotic and the analgesic, $c_e^P(t)$ and $c_e^R(t)$, respectively; $U^P(s)$ and $U^R(s)$ are the Laplace transforms of the input doses of the hypnotic (propofol) and the analgesic (remifentanil) $u^P(t)$ and $u^R(t)$, respectively. $k = [k1\ k2\ k3]$ and $l = [l1\ l2\ l3]$ are parameters that have been suitably determined in M. M. Silva (2014), and α and η are patientdependent parameters. The state-space representation of the linear part for the hypnotic model is

$$\begin{cases} \dot{x}^P(t) = \alpha A^P x^P(t) \,+\, \alpha B^P u^P(t) \\ c_e^P(t) = [0\ 0\ 1]\, x^P(t) \end{cases} \qquad (3)$$

where the matrix A^P and the vector B^P are defined as

$$A^P = \begin{bmatrix} -k_3 & 0 & 0 \\ k_2 & -k_2 & 0 \\ 0 & k_1 & -k_1 \end{bmatrix},\ B^P = \begin{bmatrix} k_3 \\ 0 \\ 0 \end{bmatrix}$$

Similarly, the statespace representation of the linear part for the analgesic model is

$$\begin{cases} \dot{x}^R(t) = \eta A^R x^R(t) \,+\, \eta B^R u^R(t) \\ c_e^R(t) = [0\ 0\ 1]\, x^R(t) \end{cases} \qquad (4)$$

where the matrix A^R and the vector B^R are defined as

$$A^R = \begin{bmatrix} -l_3 & 0 & 0 \\ l_2 & -l_2 & 0 \\ 0 & l_1 & -l_1 \end{bmatrix},\ B^R = \begin{bmatrix} l_3 \\ 0 \\ 0 \end{bmatrix}$$

The nonlinear static equation proposed in M. M. Silva (2014) to describe the drug interaction and the relation between the effect concentration and the actual drug effect is given by

$$y(t) = \frac{y_0}{1 + z(t)^\gamma}, \qquad (5)$$

$z(t) = m\, U^P(t) \,+\, U^R(t)$, $U^P = \frac{c_e^P}{C_{50}^P}$ and $U^R = \frac{c_e^R}{C_{50}^R}$; m and γ are patient-dependent parameters and C_{50}^P and C_{50}^R have fixed values for all patients, this can be viewed as a simplified Hill equation; $y(t)$ is the level of BIS. The vector θ is the parameter array, $\theta = [\alpha\ \eta\ m\ \gamma]$.

2.2 Control law for the BIS level

The positive control law introduced in this paper is inspired on the control law for the BIS level in F. N. Nogueira (2014). This is obtained by considering two controllers in parallel: one to control the administration of the hypnotic and another to control the administration of the analgesic. The main difference is that, here, the controllers are independent of parameters α and η, respectively, which constitutes a simplification with respect to the approach in F. N. Nogueira (2014). Our aim of tracking a desired BIS level is achieved by reaching and maintaining appropriate masses of propofol and remifentanil in the patient's body (or system).

More concretely, for the hypnotic and for the analgesic, the proposed control laws obtained are, respectively,

$$\begin{cases} u^P(t) = \max\left(0, \tilde{u}^P(t)\right) \\ \tilde{u}^P(t) = -\left(\sum_{i=1}^{3} b_i^P\right)^{-1} [[1\ 1\ 1]\, A^P x^P(t) \\ \qquad\qquad + \lambda\left(M(x^P) - M^{*P}\right)\Big] \end{cases} \qquad (6)$$

$$\begin{cases} u^R(t) = \max\left(0, \tilde{u}^R(t)\right) \\ \tilde{u}^R(t) = -\left(\sum_{i=1}^{3} b_i^R\right)^{-1} [[1\ 1\ 1]\, A^R x^R(t) \\ \qquad\qquad + \lambda\left(M(x^R) - M^{*R}\right)\Big] \end{cases} \qquad (7)$$

where $M(x) = \sum_{i=1}^{3} x_i(t)$ is the actual total system mass; M^* is the desired system mass and the b_i^P and b_i^R are elements of the matrices B^P and B^R, respectively.

In the same line of what was done in F. N. Nogueira (2014), and for each drug model we can conclude that the total

system mass converges to the desired system mass M^*. Without going into details, just to give an idea of what happens, let us see the effect of the simplified control law, for the hypnotic case, assuming that $u^P(t) > 0 \, \forall t$:

$$\begin{aligned}\dot{\overbrace{M(x)}} &= [1\ 1\ 1]\,\alpha A^P x^P \\ &+ \alpha\,[1\ 1\ 1]\,B^P \left(-\left(\sum_{i=1}^{3} b_i^P\right)^{-1} [1\ 1\ 1]\,A^P x^P \right. \\ &\left. - \left(\sum_{i=1}^{3} b_i^P\right)^{-1} \lambda \left(M(x^P) - M^{*P}\right)\right) \\ &= -\alpha\lambda \left(M(x^P) - M^{*P}\right)\end{aligned} \tag{8}$$

Thus, the patient parameter α may indeed be left out of the control law for the propofol mass. Although α influences the in the speed of convergence, this can be compensated by the design parameter λ. The same happens with the parameter associated to the analgesic model, η. As can be seen in (8) the controller actions just depend on a suitable choice of the values for the desired masses, M^{*P} and M^{*R}. To compute these values, the equilibrium points of the closed–loop system, when $M(x) = M^*$ were determined and the steady-state effect concentrations c_e^P and c_e^R were shown to be equal to $M^{*P}/3$ and $M^{*R}/3$, respectively, as in F. N. Nogueira (2014). This enables to determine the value of M^{*P} and M^{*R} by the inversion of the Hill equation (5) for a desired steady-state value y^* for the BIS level.

Indeed, on the one hand, we have

$$z^* = \left(\frac{y_0}{y^*} - 1\right)^{1/\gamma} \tag{9}$$

and on the other hand,

$$z^* = \frac{m}{C_{50}^P}\frac{M^{*P}}{3} + \frac{1}{C_{50}^R}\frac{M^{*R}}{3} \tag{10}$$

Thus, once the patient dependent parameters α and m are known, a value of z^* is obtained from (9) that can be replaced in (10). This still leaves a degree of freedom to in the determination of M^{*P} and M^{*R} from equation (9). To eliminate this degree of freedom, we assume that $M^{*P} = \rho M^{*R}$, with $\rho \geq 0$. Using this last assumption and equation (10) we obtain the desired system masses as,

$$\begin{aligned} M^{*P} &= \frac{3\rho z^*}{\frac{1}{C_{50}^P} m\rho + \frac{1}{C_{50}^R}} \\ M^{*R} &= \frac{3 z^*}{\frac{1}{C_{50}^P} m\rho + \frac{1}{C_{50}^R}} \end{aligned} \tag{11}$$

2.3 Identification procedure

Although, the controller actions do not dependent from the parameters of the linear models, the determination of the suitable masses M^{*P} and M^{*R} depends on the parameters α and m. Therefore an identification procedure for these parameters is presented in this subsection. Note that, these two parameters appear in the Hill equation,

$$y(t) = \frac{y_0}{1 + (mU^P(t) + U^R(t))^\gamma}. \tag{12}$$

First, we identify the parameter γ and for that we assume that a constant dose (step) of the analgesic is administered as a single drug in the first t_1 minutes, after which a constant dose of the hypnotic is cumulatively administered in the next t_2 minutes.

So, for the first t_1 minutes since c_e^P is zero and, consequently, U^P is zero too, the Hill equation stays

$$y(t) = \frac{y_0}{1 + (U^R(t))^\gamma}, \tag{13}$$

and the estimation for the parameter γ is obtained by fitting the equation (14) to the patient response,

$$\hat{\gamma} = \frac{log\left(\frac{y_0}{y(t)} - 1\right)}{log\left(\frac{c_e^R}{C_{50}^R}\right)},\ 0 \leq t \leq t_1. \tag{14}$$

Between t_1 and t_2, the Hill equation is obtained by (12) with $\gamma = \hat{\gamma}$ and the estimation of the parameter m is given by fitting the equation (15) to the patient response,

$$\hat{m} = \frac{1}{U^P}\left(\left(\frac{y_0}{y(t)} - 1\right)^{1/\hat{\gamma}} - U^R\right) \tag{15}$$

3. SIMULATION RESULTS

This section presents the results obtained by the application of the control scheme proposed here to control the BIS level. The patient-dependent parameters were identified taking into account real cases that were collected using the Galeno platform. This platform was developed in the framework of the Portuguese funding agency (FCT) project Galeno, that incorporates several identification and control procedures for automation in the administration of anesthetics. Manual drug administration can be switched on by this automatic system.

Patient	α	η	m	γ
1	0.0667	0.3989	2.1502	1.7695
2	0.0874	0.0670	4.7014	0.9365
3	0.0321	0.0666	1.5265	3.3903
4	0.0489	0.1269	1.4171	1.5627
5	0.0677	0.3373	1.1444	4.1247
6	0.0737	0.2793	0.8986	0.7812
7	0.0860	0.0212	1.4203	0.9780
8	0.1041	0.1038	1.9085	1.2165
9	0.0995	0.0377	2.0485	1.3706

Table 1. Values of the patient parameters estimated by M. M. Silva (2014).

Table 1 shows the value for the model parameters obtained by an onine identification method, M. M. Silva (2014), for a real database with nine cases. To analyse the performance

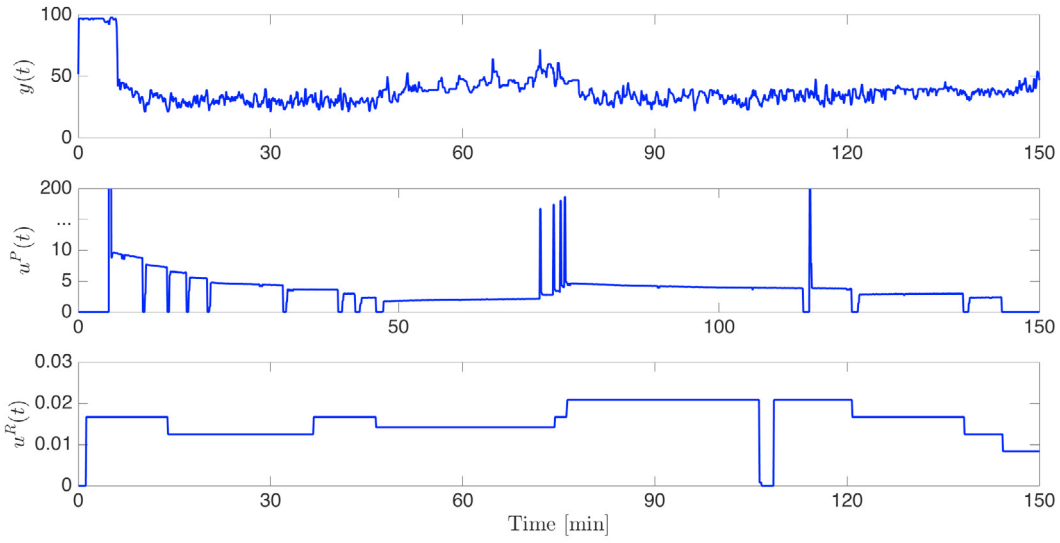

Fig. 1. Patient BIS level (upper plot) obtained with the administration of *propofol* dose, $u^P[mg/kg]$, (center plot) and *remifentanil* dose, $u^R[mg/kg]$, (bottom plot), manually controlled by clinicians.

of the proposed control scheme the second case of the Table 1 was chosen to represent the real patient.

The simulated patient was set up based on the data of the second real patient with the following characteristics: woman, with 48 years of age, a height of 158 cm, and 52Kg, subjected to general anesthesia under propofol (hypnotic) and remifentanil (analgesic) administration.

Fig. 1 shows the real BIS level and the doses of propofol and remifentanil administered during all surgery time. As it is possible to see the BIS level is a signal with a high variability due to the use of electrical devices during the surgery, *e.g.*, electric scalpel. This is the major issue of the BIS signal.

For the two cases the values of k_1, k_2, k_3, l_1, l_2 and l_3 are fixed and equal to $1, 9, 10, 1, 2$ and 3, respectively, and the values of C_{50}^P and C_{50}^R are 10 and 0.1, respectively, da Silva (2011). To apply the control laws the values for the ρ and λ were taken as 2 and 10, respectively.

Moreover the identification of the parameters of the non-linear model γ and m is performed as mentioned in equations (14) and (15), respectively. For this purpose and according with the drug profiles presented in Fig. 1, t_1 was chosen as 4 min and t_2 as 8 min. The value of the estimated parameters γ and m were 5.3073 and 1.3707. The mean values for the parameters α and η are 0.0740 and 0.1599, respectively.

Since the main contribution of this paper is the reduce of patient-dependent parameters to design the control law and the identification procedure, Fig. 2 and Fig. 3 shows the differences obtained when the BIS level is simulated according to the following scenarios:

(1) $\bar{\alpha}$, $\bar{\eta}$, $\hat{m}$, $\hat{\gamma}$ i.e., mean values for α and η and the estimation obtained by the identification procedure for γ and m;
(2) α_2, η_2, $\hat{m}$, $\hat{\gamma}$, i.e., identified values for α and η accordingly to Table 1 and the estimation obtained by the identification procedure for γ and m;
(3) α_2, η_2, m_2, γ_2, i.e., identified values for α, η, m and γ accordingly to Table 1.

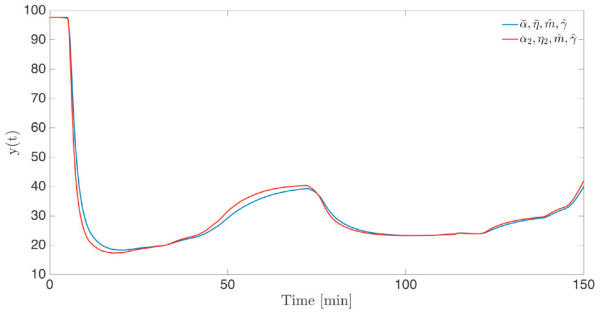

Fig. 2. BIS level evolution for the scenarios (1) and (2).

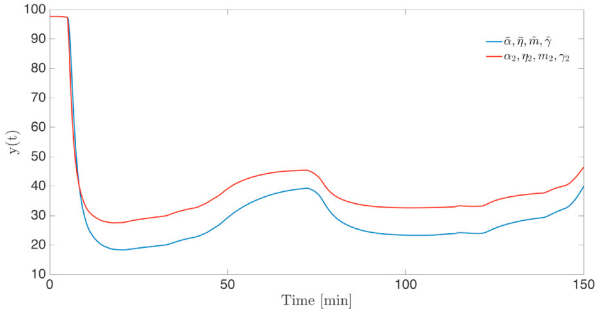

Fig. 3. BIS level evolution for the scenarios (1) and (3).

By observing the Fig. 2 we can conclude that there is no significant difference between the BIS level responses when the average of the parameters associated to the linear model is taken. Therefore we shall take the mean values of α and η in equations (3) and (4) to produce the values of $y(t)$ that are necessary in equations (14) and (15) to

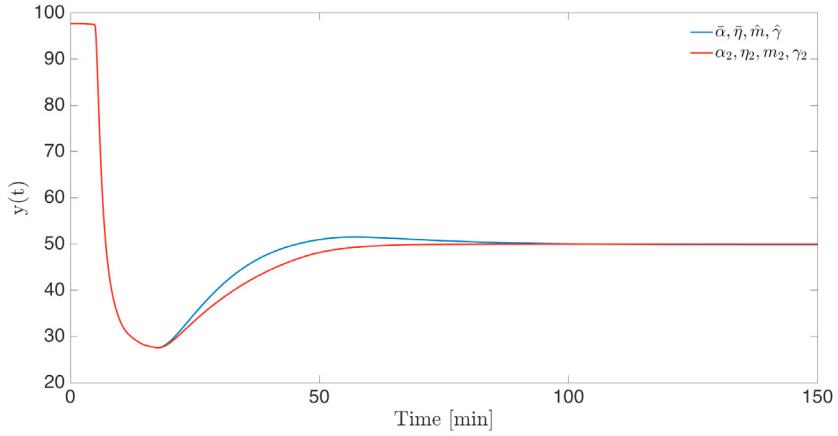

Fig. 4. Comparison between the BIS level obtained with the application of the proposed control scheme under scenario (1) (blue line) and scenario (3) (red line).

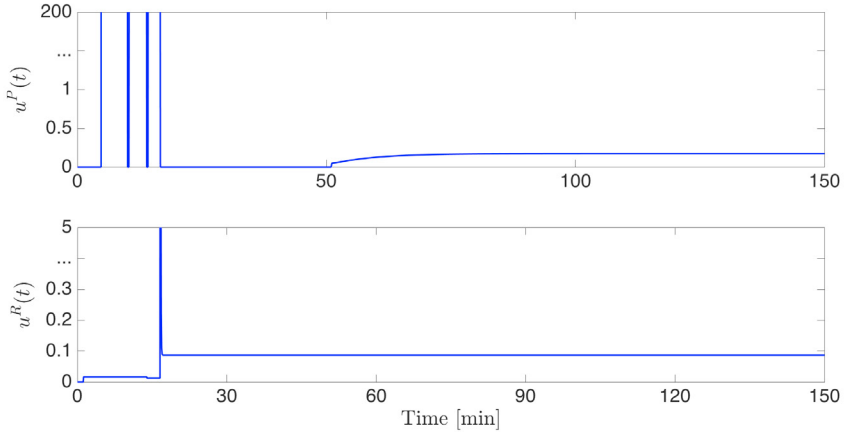

Fig. 5. Control signals obtained for scenario (1) with $0.1747mg/kg$ as the final dose for *propofol* and $0.0874mg/kg$ for the *remifentanil*.

estimate the parameters γ and m in the Hill equation. With this no significant difference we expect that the control law has a good performance when the mean of the values are used.

Fig. 3 shows the difference between the BIS responses when the real values for the patient (red line) and the ones estimated by the identification procedure described in this paper (blue line) are assumed.

After the parameter estimation phase is concluded, the controller action begins in order to track a desired reference BIS level of 50. This value is accepted by the clinicians and corresponds to the average between the maximum value of 60 and minimum value of 40 commonly used during a general anesthesia. For this case the control objective is $M^{*P} = 0.5241$ and $M^{*R} = 0.2621$. Fig. 4 illustrates the BIS signal when the proposed control scheme is applied under scenario (1) (blue line) and under scenario (3) (red line). As expected, there is no significant difference between the response obtained with our control scheme (control law and identification procedure) and the control law applied with the patient parameters and the desired reference is achieved.

The corresponding control signals obtained for scenario (1) are illustrated in Fig. 5.

To validate the control scheme proposed here the BIS level using the data of the nine patients of the Table 1 was determined and as it is possible to see in Fig. 6 the desired level of 50 is achieved, as intended.

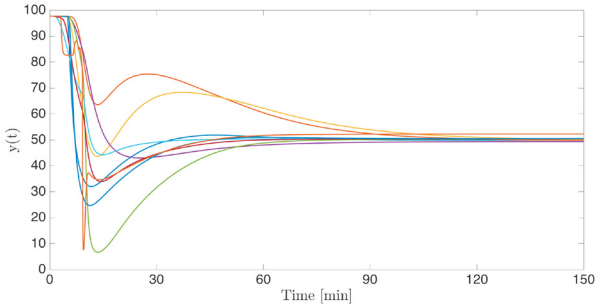

Fig. 6. BIS level evolution for the nine patients of the Table 1, under the conditions of scenario (1).

4. CONCLUSION

In this paper a new simplified control scheme for the depth of anesthesia that only requires the knowledge of two parameters of the nonlinear part of the model is proposed. This is an improvement with respect to the scheme presented in F. N. Nogueira (2014), where four parameters are needed. Two control laws are designed in parallel to control the amount of the hypnotic dose and the amount of the analgesic dose. In order to obtain the two aforementioned parameters, an identification procedure based on the patient's response was also proposed. The control scheme were was validated by simulations based on real collected data; although this is a preliminary study, the results are encouraging.

REFERENCES

da Silva, M.M. (2011). Prediction error identification of minimally parameterized wiener models in anesthesia. In *18th IFAC World Congress*, volume 18, 5615–5620.

F. N. Nogueira, T. Mendona, P.R. (2014). Controlling the depth of anesthesia by a novel positive control strategy. *Computer Methods and Programs in Biomedice*, 114(3), 87–97.

Guignard, B. (2006). Monitoring analgesia. *Best Practice and Research Clinical Anaesthesiology*, 20(1), 181–180.

Haddad, W.M. (2010). *Nonnegative and Compartmental Dynamical Systems*. Princeton University Press.

M. M. Silva, J. M. Lemos, A.C.B.A.C.T.W.T.M.c. (2013). Local identifiability and sensitivity analysis of neuromuscular blockade and depth of hypnosis models. *Computer Methods and Programs in Biomedice*, 113(1), 23–26.

M. M. Silva, T. Wigren, T.M.c. (2014). A reduced mimo wiener model for recursive identification of the depth of anesthesia. *International Journal Adaptive Control and Signal Processing*, 28(12), 1357–1371.

T. J. Gan, P. S. Glass, A.W.F.P.C.R.P.S.P.M. (1997). Bispectral index monitoring allows faster emergence and improved recovery from propofol, alfentanil, and nitrous oxide anesthesia. bis utility study group. *Anesthesiology*, 87(4), 808–815.