Individualized control of the depth of anesthesia based on online identification and retuning

Jorge Silva * **Teresa Mendonça** ** **Paula Rocha** ***

* *Faculdade de Engenharia da Universidade do Porto (FEUP) and Research Center for Systems and Technologies (SYSTEC), Porto, Portugal, (e-mail: jmpps@fe.up.pt).*
** *Faculdade de Ciências da Universidade do Porto (FCUP) and Research Center for Systems and Technologies (SYSTEC), Porto, Portugal, (e-mail: tmendo@fc.up.pt).*
*** *Faculdade de Engenharia da Universidade do Porto (FEUP) and Research Center for Systems and Technologies (SYSTEC), Porto, Portugal, (e-mail: mprocha@fe.up.pt).*

Abstract: In this paper a control scheme based on a simplified model for the joint action of propofol and remifentanil on the depth of anesthesia, measured by the BIS level, is proposed. The simplified model contains four patient dependent parameters, two of which can be easily estimated from the patient's BIS response to an initial bolus of propofol. Instead of estimating the remaining necessary parameters, initial guesses are assumed for these parameters in order to compute the drug dosages corresponding to a desired reference BIS level by steady-state model inversion.
The dosages are updated by means of a successive retuning procedure that ensures that the patient's BIS response achieves and maintains the desired reference level. This successive retuning scheme yields betters results than a single retuning procedure by decreasing the settling time at the target BIS value.

Keywords: Depth of anesthesia, automatic control, retuning scheme, online parameter identification, drug delivery.

1. INTRODUCTION

Automation in anesthesia has been deserving the attention of a large research community, due to the importance of developing tools that facilitate the task of anesthesiologists, (Macleod et al. (1989), O'Hara et al. (1991), Merigo et al. (2018), Mendonça and Lago (1998), Silva et al. (2012), Dumont (2012), Ionescu et al. (2008), Nogueira et al. (2015)).

One of the important issues in this field is setting up procedures for personalized administration of anesthetics.

In this paper we consider this question for the case of the depth of anesthesia (DoA). This results from the levels of hypnosis and of analgesia to which a patient is brought and is often measured by the bispectral index (BIS) – a parameter that can be obtained from an EEG.

The drugs considered here in order to induce a desired BIS level are the hypnotic propofol and the analgesic remifentanil, but our procedures also apply to other drugs.

In order to model the combined effect of propofol and remifentanil on the BIS level, we consider the model proposed in Silva et al. (2020), which is an adaptation of the proposed in Silva et al. (2010).

According to this model, the effect of concentrations of propofol and remifentanil are each of them given by a third order transfer function with one patient dependent parameter, whereas the combined drug effect is obtained from a generalized Hill equation (a static nonlinearity) with two patient dependent parameters.

Our online identification and control algorithm takes into account the usual clinical procedures that consists in the administration of a bolus of propofol followed by administration both propofol and remifentanil by continuous infusion.

More concretely, we identify the parameter of the transfer function corresponding to the effect concentration of propofol together with one of the parameters of the generalized Hill equation from the patient's response to the initial propofol bolus. The remaining parameters (i.e. the one of the transfer function corresponding to the effect concentration of remifentanil and the second parameter of the generalized Hill equation) are taken to be equal to initial guesses that coincide with average population parameters computed from a database of representative real patients for which parameter estimation was carried out offline, (Silva et al. (2020), Almeida et al. (2016)).

This allows tuning the initial continuous infusion dosages for propofol and remifentanil. These dosages are then

adjusted by means of a fully automated algorithm based on successive retuning.

The obtained results are illustrated by means of simulations.

2. MODELLING AND PARTIAL PARAMETER IDENTIFICATION

According to Silva et al. (2010), the effect concentrations of propofol and remifentanil are, respectivelly, given by the following transfer functions:

$$G_p(s) = \frac{C_e^p(s)}{U^p(s)} = \frac{90\alpha^3}{(s+\alpha)(s+9\alpha)(s+10\alpha)} \tag{1}$$

and

$$G_r(s) = \frac{C_e^r(s)}{U^r(s)} = \frac{6\eta^3}{(s+\eta)(s+2\eta)(s+3\eta)}, \tag{2}$$

where $C_e^p(s)$, $C_e^r(s)$, $U^p(s)$ and $U^r(s)$ are the Laplace transforms of the effect concentrations $c_e^p(t)$ (of propofol), $c_e^r(t)$ (of remifentanil), measured in $\mu g/ml/kg$ and of the drug doses $u^p(t)$ (of propofol) and $u^r(t)$ (of remifentanil), measured in ug/kg/min. The parameters α and η are patient dependent parameters.

The combined effect of propofol and remifentanil on the BIS level, $z(t)$, can be computed from the generalized Hill equation (Silva et al. (2020))

$$z(t) = \frac{97.7}{1 + (0.1c_e^p(t) + 100mc_e^r(t))^\gamma}, \tag{3}$$

where the parameters m and γ are patient dependent.

The overall model is depicted in Figure 1.

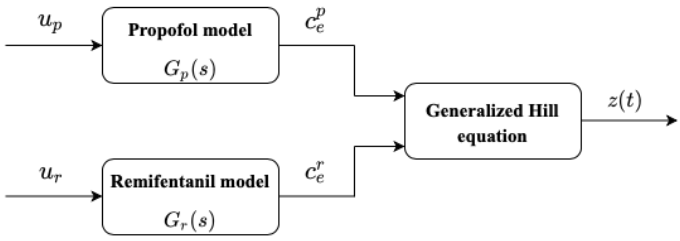

Fig. 1. General model for action of propofol and remifentanil on the BIS level.

In Almeida et al. (2016), a database of values for the parameters α, η, γ and m of the model proposed in Silva et al. (2010) was presented. This model only differs from the one to be considered here in what regards the generalized Hill equation, which is given by:

$$z(t) = \frac{97.7}{1 + (0.1mc_e^p(t) + 100c_e^r(t))^\gamma}, \tag{4}$$

i.e., the parameter m affects $c_e^p(t)$ instead of $c_e^r(t)$.

The database values were obtained based on the BIS responses of 18 real patients subject to general anesthesia and are gathered in Table 1 (see Appendix A). Note that such parameters do not coincide with the parameters α, η, γ and m of the model proposed in Silva et al. (2020), for which the generalized Hill equation has a different structure. Nevertheless, here, the parameters in Table 1 are used to simulate real patients and test the performance of our procedures.

A first approach to control the BIS level could be to consider average parameters to calibrate the drug doses. However, as shown in Figure 2, these leads to non-satisfactory results with great variability of the steady-state responses.

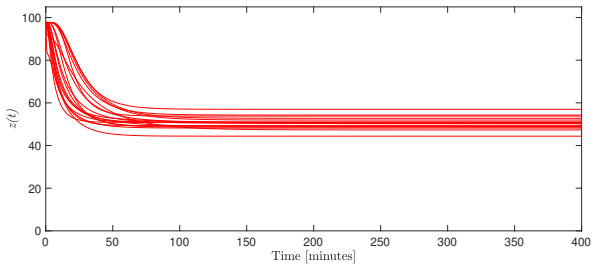

Fig. 2. Response of the BIS level of the patients of Table 1 to the doses of propofol and remifentanil computed by steady-state model inversion using the average parameters ($\overline{\alpha} = 0.0759, \overline{\eta} = 0.5825, \overline{m} = 1.7919, \overline{\gamma} = 1.8835$).

In order to obtain better results, we propose a new dose calibration procedure where partial parameter identification is combined with dosage retuning.

When an initial bolus of propofol, with a typical value of $500\mu g/kg$, is administrated, the corresponding BIS response is given by:

$$z(t) = \frac{97.7}{1 + (0.1c_e^p(t))^\gamma}, \tag{5}$$

where

$$c_e^p(t) = 625\alpha e^{-\alpha t} - 5625\alpha e^{-9\alpha t} + \\ +5000\alpha e^{-10\alpha t}, \qquad t \geq 0 \tag{6}$$

Equations (5) and (9) allow to retrieve the values of the parameters α and γ as follows. Let T be the time instant where the BIS level attains half of its maximum value (97.7), i.e., where

$$z(T) = \frac{97.7}{2} = 48.85. \tag{7}$$

It easily follows from (5) that, at this time instant, the value of c_e^p must be equal to 10, i.e.:

$$c_e^p(T) = 10. \tag{8}$$

Note that the value of T can be obtained by simple inspection of the BIS response $z(t)$. Thus, combining (8) and (9), one obtains the equation:

$$c_e^p(t) = 625\alpha e^{-\alpha t} - 5625\alpha e^{-9\alpha t} + \\ +5000\alpha e^{-10\alpha t} = 10, \tag{9}$$

where the only unknown is the parameter α. Solving this equation by numerical methods yields an approximate value, $\hat{\alpha}$, of α.

The value of γ can be estimated by considering, at a time instant $T^* > T$, the value of the BIS response $z(t)$ corresponding to the estimated effect concentration $\widehat{c_e^p}(t)$, whose expression as a function of time is similar to (9), but with α replaced by $\hat{\alpha}$. More concretely:

$$\hat{\gamma} = \frac{\log(\frac{97.7}{z(T^*)} - 1)}{\log(0.1\widehat{c_e^p}(T^*))}, \tag{10}$$

where

$$\widehat{c_e^p}(T^*) = 625\hat{\alpha} e^{-\hat{\alpha}T^*} - 5625\hat{\alpha} e^{-9\hat{\alpha}T^*} + \\ +5000\hat{\alpha} e^{-10\hat{\alpha}T^*}, \tag{11}$$

and $z(T^*)$ is obtained by inspection of the BIS response to the initial bolus of propofol.

Now, rather than estimating the remaining parameters η and m (as is done in Silva et al. (2020)), we consider these parameters to be unknown and use a dose retuning scheme. This scheme is based on the model from Silva et al. (2020) as well as on the analysis of the patient's BIS response to pre-specified doses of propofol and remifentanil.

So, the model to be considered in the sequel is:

$$z(t) = \frac{97.7}{1 + (0.1\widehat{c_e^p}(t) + 100mc_e^r(t))^{\hat{\gamma}}}, \tag{12}$$

where $\widehat{C_e^p}(s) = \hat{G}_p(s)U_p(s)$, $C_e^r(s) = G_r(s)U_r(s)$, as in (2), and the transfer function $\hat{G}_p(s)$ is given by:

$$\hat{G}_p(s) = \frac{90\hat{\alpha}^3}{(s+\hat{\alpha})(s+9\hat{\alpha})(s+10\hat{\alpha})}. \tag{13}$$

3. BIS REFERENCE TRACKING: A SUCCESSIVE RETUNING APPROACH

During general anesthesia it is usually required to bring and maintain the value of the BIS level between 40 and 60. Here we consider the problem of tracking a BIS reference level $z^* = 50$, by administration of (piecewise) constant doses of propofol and remifentanil via continuous infusion. In order to achieve this goal, we first note that, if the parameters α, η, γ and m were accurately known, the constant doses of propofol, u_p^*, and of remifentanil, u_r^*, to be administered would be such that:

$$z^* = \frac{97.7}{1 + (0.1u_p^* + 100mu_r^*)^{\gamma}}, \tag{14}$$

since the steady-state gains of $G_p(s)$ and $G_r(s)$ are equal to 1.

However, equation (14) does not allow to uniquely determine the unknowns u_p^* and u_r^*. This problem can be overcome by imposing a fixed ratio ρ between the values of $u_p(t)$ and $u_r(t)$, and consequently, between the values of u_p^* and u_r^*. This corresponds to the scheme depicted in Figure 3.

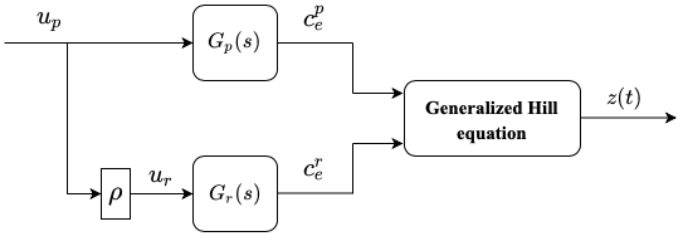

Fig. 3. New administration scheme for propofol and remifentanil with $u_r = \rho\, u_p$.

In this way, equation (14) becomes:

$$z^* = \frac{97.7}{1 + [(0.1 + 100m\rho)u_p^*]^{\gamma}}, \tag{15}$$

yielding

$$u_p^* = ke^{1/\gamma}, \tag{16}$$

where

$$k = \frac{1}{0.1 + 100m\rho}; \quad e = \frac{97.7}{z^*} - 1. \tag{17}$$

The corresponding dose u_r^* is computed as

$$u_r^* = \rho u_p^*. \tag{18}$$

Applying the same procedure with the estimated value, $\hat{\gamma}$, of γ together with an initial guess, $\widetilde{m}$, of m yields the doses $\widetilde{k}$:

$$\widetilde{u}_p^* = \widetilde{k}\; e^{1/\hat{\gamma}} \tag{19}$$

for propofol and

$$\widetilde{u}_r^* = \rho\; \widetilde{k}\; e^{1/\hat{\gamma}} \tag{20}$$

for remifentanil, where

$$\widetilde{k} = \frac{1}{0.1 + 100\widetilde{m}\rho}. \tag{21}$$

Clearly, the administration of the drug doses $\widetilde{u}_p^*$ and $\widetilde{u}_r^*$ will not bring the patient's BIS level to the desired value $z^* = 50$, but rather to a different steady-state value $\widetilde{z}^*$ that can be obtained by inspection of the BIS response. This allows retuning the dose u_p^* to a new value u_p^{ret} as described next.

First, a bolus of $500\mu g/kg$ of propofol is administered to the patient, and the parameters α and γ are estimated online as described in Section 2. At time $t = T^*$ the

estimation is complete, and the doses $\widetilde{u}_p^*$ and $\widetilde{u}_r^*$ are computed from (19) and (20). When the patient starts recovering from the initial bolus, i.e., when the BIS level starts increasing after having attained its minimum value, propofol and remifentanil are administered by continuous infusion with constant dosages $\widetilde{u}_p^*$ and $\widetilde{u}_r^*$, respectively. This leads the patient's BIS level to a steady-state value $\widetilde{z}^* \neq z^*$. The time instant, $t = \widetilde{T}^*$, when this steady-state is (approximately) reached can be automatically computed as the first instant t such that:

$$\mid z(t+\Delta) - z(t) \mid < \varepsilon, \tag{22}$$

where $\Delta > 0$ and $\varepsilon > 0$ are chosen sampling period and threshold, respectively. At this instant time, a new value u_p^{ret} for the dose of propofol is computed as follows.

Similar to (15), the relation between the steady-state value $\widetilde{z}^*$ and $\widetilde{u}_p^*$ is given by:

$$\widetilde{z}^* = \frac{97.7}{1 + \left(\frac{\widetilde{u}_p^*}{k}\right)^{\gamma}}. \tag{23}$$

Assuming that the estimate, $\hat{\gamma}$, obtained for γ is correct, i.e., that $\gamma = \hat{\gamma}$, and taking (19) into account, equation (23) is equivalent to:

$$\widetilde{z}^* = \frac{97.7}{1 + \left(\frac{\widetilde{k}}{k} e^{1/\hat{\gamma}}\right)^{\hat{\gamma}}}, \tag{24}$$

i.e.,

$$\widetilde{z}^* = \frac{97.7}{1 + \left(\frac{\widetilde{k}}{k}\right)^{\gamma} e} \tag{25}$$

Solving equation (25) for k, one obtains:

$$k = \widetilde{k} \left(\frac{e}{\widetilde{e}}\right)^{1/\hat{\gamma}}, \tag{26}$$

where

$$\widetilde{e} = \frac{97.7}{\widetilde{z}^*} - 1. \tag{27}$$

Thus, taking $\gamma = \hat{\gamma}$ and k as in (26), a new dose u_p^{ret} of propofol can be computed from (16) as:

$$u_p^{ret} = k \;\; e^{1/\hat{\gamma}}. \tag{28}$$

The administration of a constant dose u_p^{ret} of propofol and of the corresponding dose $u_r^{ret} = \rho \; u_p^{ret}$ of remifentanil from instant $t = \widetilde{T}^*$ on leads the patient's BIS level to the steady-state value:

$$z^{ret} = \frac{97.7}{1 + \left(\frac{u_p^{ret}}{k}\right)^{\gamma}} = \frac{97.7}{1 + \left(\frac{u_p^{ret}}{k}\right)^{\hat{\gamma}}} = \frac{97.7}{1+e}, \tag{29}$$

which, by (17), is equivalent to:

$$z^{ret} = \frac{97.7}{1 + \left(\frac{97.7}{z^*} - 1\right)} = z^*. \tag{30}$$

This means that the retuning process is indeed efficient and the desired reference value z^* for the patient's BIS level is successfully tracked.

The result of the retuning procedure, for $\rho = 10^{-4}$, $\Delta = 10min$ and $\varepsilon = 0.1$, is shown in Figures 4, 5, 6 and 7.

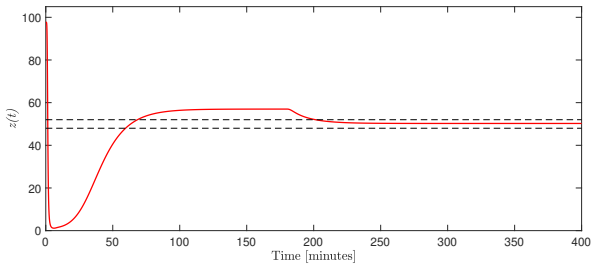

Fig. 4. BIS response of patient 6 from Table 1 to a propofol bolus of $500\mu g/kg$ followed by continuous infusion of doses of propofol and remifentanil computed as in (19) and (20) with $\widetilde{m} = 1.8$ and single dosage retuning.

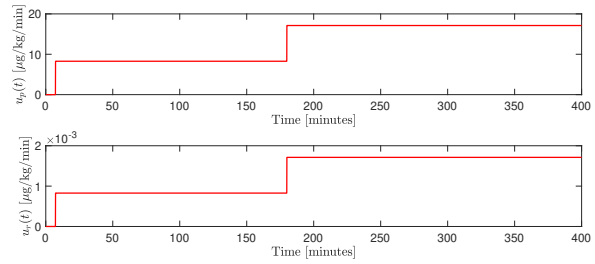

Fig. 5. Drug doses of propofol and remifentanil of patient 6 after the bolus administration.

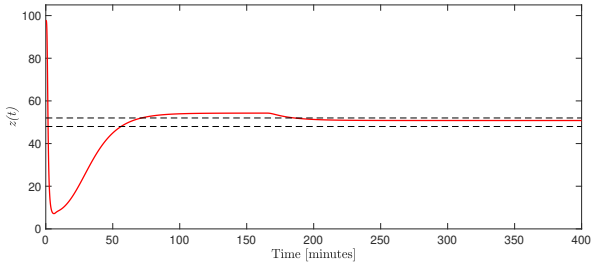

Fig. 6. BIS response of patient 3 from Table 1 to a propofol bolus of $500\mu g/kg$ followed by continuous infusion of doses of propofol and remifentanil computed as in (19) and (20) with $\widetilde{m} = 1.8$ and single dosage retuning.

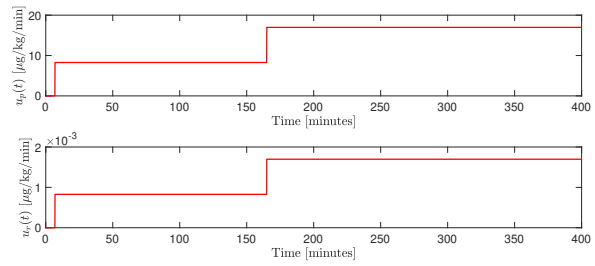

Fig. 7. Drug doses of propofol and remifentanil of patient 3 after the bolus administration.

As can be seen in figures 4 and 6, although the desired value $z^* = 50$ for BIS level is achieved, the corresponding settling time is considerably large. This is due to the fact that the retuning procedure is only applied when the BIS response to the doses $\widetilde{u}_p^*$ and $\widetilde{u}_r^*$ settles down.

In order to overcome this drawback, we propose a successive retuning procedure that starts earlier than the first settling instant $t = \widetilde{T}^*$.

Let then $T_1 < \widetilde{T}^*$ be the first retuning instant, and define a sequel of retuning instants:

$$T_n = T_1 + (n-1)\Delta_{ret}, \quad n = 1, 2, 3, ... \tag{31}$$

where $\Delta_{ret} > 0$ is a pre-specified value for the time interval between two consecutive retuning instants. Adjust the doses of propofol and remifentanil as follows.
For $n = 1, 2, 3, ...$:

$$u_{p,n} = k_n \; e^{1/\hat{\gamma}}; \; u_{r,n} = \rho \; u_{p,n} \tag{32}$$

with

$$k_0 = k; \; k_n = k_{n-1} \left(\frac{e}{e_n} \right)^{1/\hat{\gamma}}, \tag{33}$$

where k is taken from (26),

$$e_n = \frac{97.7}{z(T_n)} - 1, \tag{34}$$

and e is given in (17).

The doses u_p and u_r (of propofol and remifentanil) are kept constant and equal to $u_{p,n}$ and $u_{r,n}$, respectively, in each interval $[T_n, T_{n+1})$, i.e.: $u_p(t) = u_{p,n}, u_r(t) = u_{r,n}$ $t \in [T_n, T_{n+1}), n = 1, 2, 3, ...$.

Simulation results that illustrate the described procedure are show in Figures 8, 9, 10, 11, 12 and 13.

The value of ρ was taken equal to 10^{-4}, as previously, the retuning period is $\Delta_{ret} = 5min$.

The first retuning instant T_1 was taken to be equal to the time instant t where the BIS response reaches the value $z^* - 20\%z^* = 40$, after having attained its minimum value. Experience has shown that successive retuning is not effective is started too early (since in this case, it does not lead to the desired reference level for the patient's BIS) or started too late (since, in this case, it does not improve the settling time with respect to single retuning).

In the dose plots a zoom is included to highlight the detail of the dose profile during the process of successive retuning.

As can be seen in the plots of the BIS response, the proposed successive retuning scheme considerably improves the settling time of the BIS response at the desired reference $z^* = 50$.

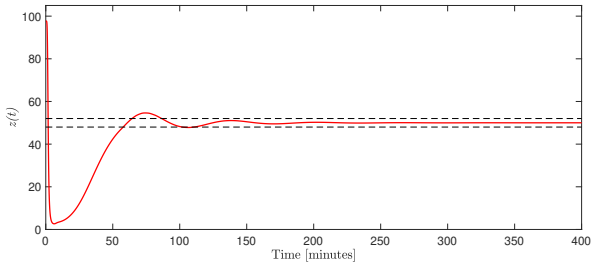

Fig. 8. BIS response of patient 6 from Table 1 to a propofol bolus of $500\mu g/kg$ followed by continuous infusion of doses of propofol and remifentanil, computed as in (19) and (20) with $\widetilde{m} = 1.8$, and successive dosage retuning.

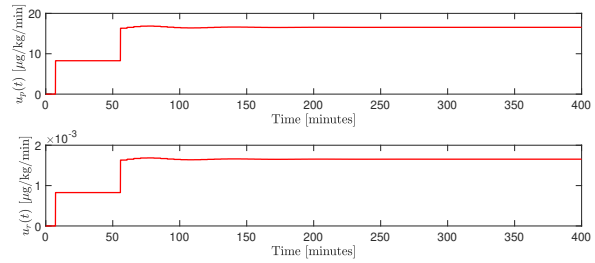

Fig. 9. Drug doses of propofol and remifentanil of patient 6 after the bolus administration.

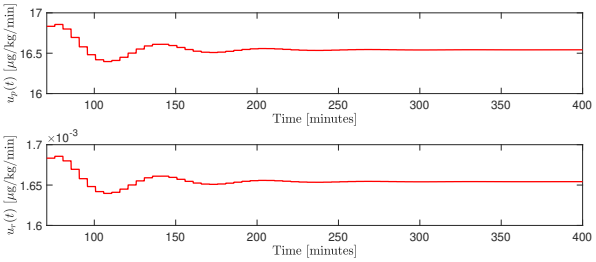

Fig. 10. Detail of the plot of the drug doses of propofol and remifentanil in Figure 9 from the initial instant of the successive retuning on.

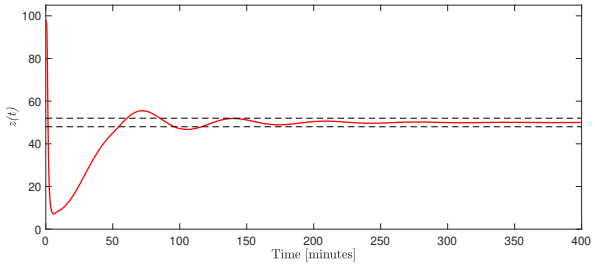

Fig. 11. BIS response of patient 3 from Table 1 to a propofol bolus of $500\mu g/kg$ followed by continuous infusion of doses of propofol and remifentanil, computed as in (19) and (20) with $\widetilde{m} = 1.8$, and successive dosage retuning.

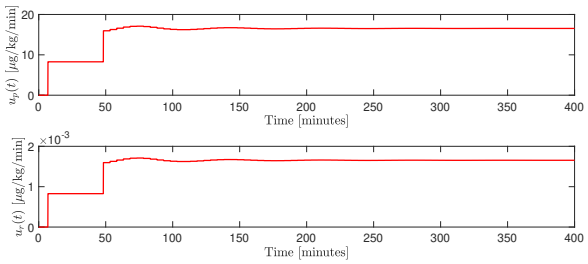

Fig. 12. Drug doses of propofol and remifentanil of patient 3 after the bolus administration.

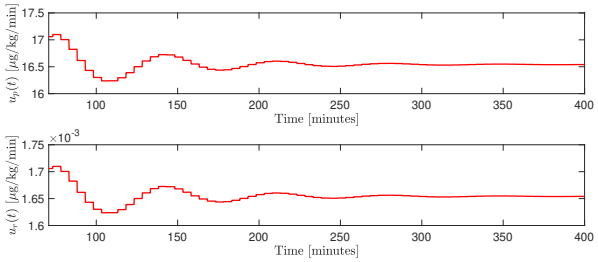

Fig. 13. Detail of the plot of the drug doses of propofol and remifentanil in Figure 12 from the initial instant of the successive retuning on.

4. CONCLUSION

An individualized automatic control scheme for the BIS level induced by the hypnotic propofol and the analgesic remifentanil was proposed.

This scheme is based on a prior online estimation of only two of the four parameters of the model that describes the action of those drugs on a patient's BIS level followed by a successive retuning scheme for the drug dosages. In this way, the goal of tracking a desired constant BIS level is achieved and the settling time of BIS response is reduced with respect to a scheme where only one retuning is performed. Moreover, it avoids the estimation of the two remaining model parameters, which involves cumbersome computations.

Although the obtained results look promising, further work is necessary to consider more realistic situations as, for instance, the presence of noise.

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Appendix A. TABLE 1

Table A.1. Parameter values for the model of Silva et al. (2010), (Almeida et al. (2016)).

Case	α	γ	η	m
Patient 1	0.0667	1.7695	0.3989	2.1502
Patient 2	0.0874	0.9365	0.0670	4.7014
Patient 3	0.0693	2.8186	0.0482	1.1700
Patient 4	0.0590	2.7594	0.0425	1.4077
Patient 5	0.0489	1.5627	0.1269	1.4171
Patient 6	0.0677	4.1247	0.3373	1.1444
Patient 7	0.0737	0.7812	0.2793	0.8986
Patient 8	0.0860	0.9780	0.0212	1.4203
Patient 9	0.0701	1.0956	0.2837	1.2164
Patient 10	0.1041	1.2165	0.1038	1.9085
Patient 11	0.0343	1.7097	3.5768	2.5451
Patient 12	0.0467	2.4877	0.1254	1.4884
Patient 13	0.0687	1.0859	4.5413	2.3951
Patient 14	0.0774	1.4038	0.0397	1.5460
Patient 15	0.0995	1.3706	0.0377	2.0485
Patient 16	0.0929	4.5194	0.1205	1.5565
Patient 17	0.0811	2.1978	0.1033	2.0338
Patient 18	0.1336	1.0846	0.2307	1.2061