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A PID-based Structure for MISO Approach to Anaesthesia Control Problem

A. Pawłowski * **M. Schiavo** ** **A. Visioli** **

* *Department of Control Systems and Mechatronics, Wrocław University of Science and Technology, Janiszewskiego 11/17, 50-372 Wrocław, Poland, e-mail: andrzej.pawlowski@pwr.edu.pl*
** *Dipartimento di Ingegneria Meccanica e Industriale, University of Brescia, Via Branze 38, 25123 Brescia, Italy, e-mail: michele.schiavo@unibs.it, antonio.visioli@unibs.it*

Abstract: This work introduces a control architecture based on Proportional-Integral-Derivative (PID) controller addressing drugs co-administration in the total intravenous anaesthesia process. The control problem focuses on a multiple-input-single-output nonlinear process, where the infusion rates of propofol and remifentanil are the control variables and the Bispectral Index Scale (BIS) is the controlled variable. The analyzed structure exploits an external predictor of the patient state that converts the control problem to the linear case. The interaction between the used drugs is handled by a reference converter element through continuous re-computation of the setpoint. The proposed control system is evaluated by exploiting a set of virtual patients that are representative of a wide population. The scenario considers induction and maintenance phases, as both of them are important from a practical point of view. The obtained results show that the PID controller in combination with the external predictor is able to meet all the clinical requirements, which is confirmed through the analysis of process specific performance indexes.

Keywords: control of anaesthesia, multivariable process, predictor, PID control, performance evaluation

1. INTRODUCTION

To successfully achieve total intravenous anaesthesia (TIVA) process objectives, an anaesthesiologist needs to induce a desired patients state, related to depth of hypnosis (DoH), analgesia and muscular blockade, through manual adjustment of drugs infusion rates (propofol, remifentanil and curare, respectively) (Pasin et al., 2017; Ionescu et al., 2021). From a clinical perspective the control problem can be split into two separate objectives, addressing on the one hand, muscular blockade and on the other hand, DoH and analgesia. This is because the interaction between muscular blockade and the other sub-processes is weak and it can be treated as separate task. On the contrary, analgesia and DoH need to be addressed simultaneously due to the strong super-additive effect of remifentanil over propofol (Struys et al., 2003; Liu et al., 2017). From the control engineering point of view, analgesia and DoH are considered as a multivariable control problem, with possible multiple-input-multiple-output (MIMO) and multiple-input-single-output (MISO) configurations (Khodaei et al., 2020; Mahfouf et al., 2005). In the first approach, it is assumed that the effect of each infused drug can be measured through medical devices using, for example, measures like a pain index and the Bispectral Index Scale (BIS). However, this approach is rarely considered in the clinical practice due to the lack of a reliable pain monitoring technique. The MISO configuration takes into account the simultaneous infusion of propofol and remifentanil and their effect on the DoH through the BIS variable. Such a configuration is a feasible problem, both from clinical and engineering perspectives.

Due to the multivariable nature of the control problem, model based control techniques like Model Predictive Control (MPC) have been frequently proposed to handle drug co-administration (Eskandari et al., 2020; Pawlowski et al., 2022b). The main advantage of the MPC control techniques is the constraints handling mechanism that allows saturation limits and slew rates of the infusion pumps to be properly handled. Undoubtedly, these techniques are very interesting from the control engineering perspective, allowing available information of the patients to be exploited and to be used in the controller design. However, they rely on the patient model, which is affected by modelling uncertainties (Ionescu, 2018). This can have detrimental effects on the performance of a control scheme. Another group of control systems designed for the MISO approach to TIVA exploits the well known and widely used PID controller (Merigo et al., 2020; Schiavo et al., 2021). In this group, most of the designed control configurations considers the fixed ratio between two dosed drugs, being easily treatable by the PID controller. Special attention to this control problem has been paid in (Schiavo et al., 2021) where different ratio values have been tested and tuning rules for controller design have been proposed. Nevertheless, under this assumption, in the analyzed system no explicit information regarding interaction between drugs has been included in the control schemes.

Taking into account the aforementioned aspects, in this work a PID-based control structure for drug co-administration in MISO scheme for the TIVA is presented and analyzed. The control structure is built exploiting the concept previously presented in (Pawlowski et al., 2022b), where the MPC strategy as a feedback controller has been applied. The system analyzed in this work consists of an external predictor and a reference converter element. The first one is used to reduce the nonlinear MISO control problem to the linear case through the inversion of the nonlinear part of the pharmacokinetic-phamacodynamic (PK-PD) model and this introduces indirect control of the BIS. The second one is used to convert the control system reference, which is provided using the BIS measure, to an intermediate variable that represents the estimated concentrations of drugs. In such a configuration, propofol and remifentanil infusion rates are the control variables and BIS is the controlled variable that represents the DoH. Moreover, to meet the clinical requirements, the parameters of the whole system, including those of the PID controller and of the external predictor, are adjusted through an optimization method. The proposed design applies also a gain scheduling technique, providing separate tuning of the system for induction and maintenance phases. The evaluation of the analyzed system is performed in simulation for a control scenario which considers both the induction and the maintenance phases. In the first phase, the objective is to reach the desired level of the DoH in a predefined time interval. During the maintenance stage, a response of the control system to the surgical stimuli, represented as unmeasurable step disturbances, is tested. Additionally, a set of performance indexes are computed to fairly evaluate the system. This analysis is performed for the set of thirteen virtual patients being representative for a wide population (Ionescu et al., 2008). The obtained results show that the proposed PID-based approach is able to handle the multivariable control problem, achieving the necessary performance.

This work is organized as follows: first drugs co-administration in general intravenous anesthesia is briefly introduced. This part includes also the description of the used patient model as well as the set of virtual patients considered during evaluation. Clinical requirements are summarized in Section 3. Next, in Section 4, the designed control architecture is introduced and described, including the tuning procedure for the system. The simulation study for a control scenario is described in Section 5, including computed process specific performance measures. Lastly, conclusions are provided in Section 6.

2. DRUG CO-ADMINISTRATION IN ANAESTHESIA PROCESS

In the analyzed approach, the control problem is focused on the multivariable system where the DoH is determined by the simultaneous co-administration of propofol and remifentanil. In this context, a patient model that captures the mutual interaction of the drugs is needed. For this, the PK/PD model is exploited providing the possibility of predicting how the infused drugs affect the BIS, which is used as a measure for the DoH level.

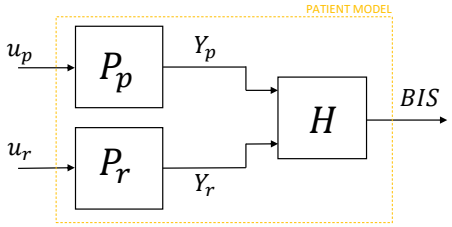

Fig. 1. Patient model with MISO structure.

2.1 Patient model

For the proposed system, a MISO model with a Wiener structure is used, and its general scheme is shown in Figure 1. This configuration is derived from the PK/PD three-compartment mammillary model (Bouillon et al., 2002), by concatenation of the resulting linear elements of the model and their connection with the nonlinear part, which is represented by a Hill function, as shown in (Pawlowski et al., 2022b). In such a case, u_p and u_r refers to the drugs infusion rates (manipulated variables), respectively for propofol and remifentanil and BIS represents the DoH level of the patient (controlled variable). Moreover, Y_p and Y_r represent the normalized effect-site concentrations as defined in (Schinder et al., 1999). Then, P_p and P_r are linear transfer functions that represent the resulting linear dynamics of the PK and PD structure of the model. Finally, the nonlinear element H is defined in the following way:

$$H = E_0 - E_{max}\left(\frac{\left(\frac{Y_p(t)+Y_r(t)}{U_{50}(\phi)}\right)^{\gamma}}{1+\left(\frac{Y_p(t)+Y_r(t)}{U_{50}(\phi)}\right)^{\gamma}}\right) \tag{1}$$

where E_0 reflects the patient state in fully awake situation (no infusion of the drugs), $E_0 - E_{max}$ defines the maximum allowable effect and γ refers to the patient responsiveness to drugs (gradient of the curve). The $U_{50}(\phi)$ parameter reflects the power of the two drugs at the ϕ co-administration ratio, associated to the half (50%) of the maximum effect. More detailed information regarding this modelling approach can be found in (Bouillon et al., 2002; Minto et al., 1997).

2.2 Patients data set

The tuning and the evaluation of the proposed control system are performed by using a set of virtual patients that has been previously used in the literature (Ionescu et al., 2008; Nascu et al., 2015). The set consists of twelve individuals plus one additional patient whose data is obtained as an algebraic mean of those of the previous twelve patients. This data set is widely used for tests and performance assessment of controllers designed for the anaesthesia process.

3. REQUIREMENTS AND CONSTRAINTS

The main clinical goal is to keep the DoH level at the desired setpoint $r_{BIS}(t) = 50$, by using the BIS signal as the feedback variable. Moreover, as in the clinical practice, there is a fixed ratio K between the infusion rates of

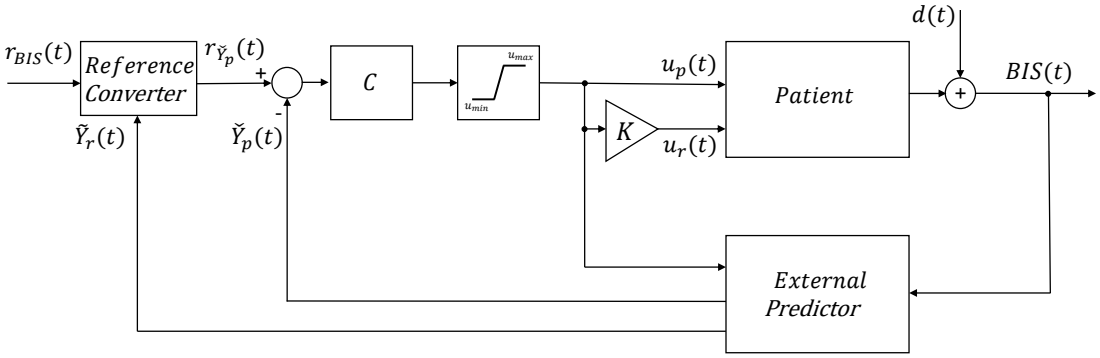

Fig. 2. The proposed PID-based control system architecture.

propofol and remifentanil (expressed in $[mg/s]$ and $[\mu g/s]$, respectively). For the performed analysis, this ratio has been set to $K = 2$, being the most common value for the considered clinical scenario. Then, the infusion rate of propofol $u_p(t)$ (expressed in $[mg/s]$) is limited by the saturation block between $u_{min} = 0$ and $u_{max} = 6.67$ $[mg/s]$. Consequently, remifentanil infusion rate $u_r(t)$, taking into account the fixed ratio K, is saturated between 0 and 13.34 $[\mu g/s]$. To properly reflect the phases of the surgical intervention, the whole procedure is split into two stages, the induction and the maintenance phases. In the first one, the goal is to quickly achieve the desires value of the DoH (setpoint value) without excessive undershoot. In particular, a BIS lower than 60 should be obtained in less than 3 minutes while avoiding BIS values below 40. Finally, in the maintenance phase the main controller task is to keep the BIS inside the recommended range 40-60 and to compensate as soon as possible the surgical stimuli that are modelled as output step disturbances.

4. CONTROL ARCHITECTURE

The control system architecture (shown in Figure 2) is designed by taking into account the nonlinear multivariable process. In fact, the nonlinearity of the system is compensated thorough the external predictor. Moreover, drugs interaction is taken into account through the continuous re-computation of the reference signal that reflects the influence of remifentanil over propofol. The compensation of the nonlinear behaviour of the controlled process is obtained by computing the inverse of the Hill function defined in equation (1) and using an indirect control variable (action performed at external predictor block). Moreover, the use of the inverse function and of a fixed ratio between the drugs enables the possibility to calculate the impact of remifentanil over propofol and their influence over the DoH of the patient. Such a feature is used to perform the continuous re-computation of the control system reference, which reflects the super-additive effect of both drugs (performed by the reference converter element). This approach was originally proposed for the MPC technique, where it was possible to exploit the estimated concentration for the internal computation of control law (Pawlowski et al., 2022b). In this way it was possible to apply a linear MPC controller and to improve the performance by taking into account the synergistic effect of the infused drugs.

Unlike the MPC, the control system based on a classic controller like the PID cannot exploit directly the mutual interaction due to its working principle and needs to use additional external elements. The detailed description of the external predictor as well as reference converter blocks is provided in the following subsections.

4.1 External Predictor

The main role of the external predictor (shown in Figure 3) is to translate the control problem to the linear case by exploiting the PK-PD patient model (see Section 2.1). This is obtained by computing the inverse of the nonlinear element of the patient model. In this way, an intermediate variable Y_p is introduced and used for indirect control of the BIS value. The actual feedback from the process is determined by using the following formula:

$$\hat{Y}_p(t) = H^{-1}(BIS(t), \tilde{Y}_r) \tag{2}$$

where, $BIS(t)$ is the measured value and $\tilde{Y}_r$ is the estimated concentration of remifentanil obtained using a linear element of the model $\tilde{P}_r$, related to the metabolism of remifentanil. In the next step, $\hat{Y}_p(t)$ and $\tilde{Y}_p$ are subtracted, providing the difference between the concentration estimated from the process and that estimated from the model (represented by the $\tilde{P}_p$ block). Subsequently, the difference is filtered using a first-order filter F_d (with a time constant T_f), introduced to improve the robustness of the system. Finally, the filtered difference is added to the model-based estimated value of $\tilde{Y}_p$, determining the feedback data $\check{Y}_p$ for the controller. Note that the external predictor is built assuming the modelling uncertainties that are represented through the ˜ symbol. Moreover, $\tilde{H}$ represents the average value for the patients population, since the parameters of the Hill function can not be easily obtained for each individual. The detailed working principle and implementation aspects can be found in (Pawlowski et al., 2022b).

4.2 Reference converter

Following the working principle of the proposed control structure, it is necessary to convert the BIS reference signal $r_{BIS}(t)$ to the reference of the intermediate variable $\hat{Y}_p(t)$ that is denoted as $r_{\hat{Y}_p}(t)$. This is obtained using the following expression:

$$r_{\hat{Y}_p}(t) = H^{-1}(r_{BIS}(t), \tilde{Y}_r(t)) \tag{3}$$

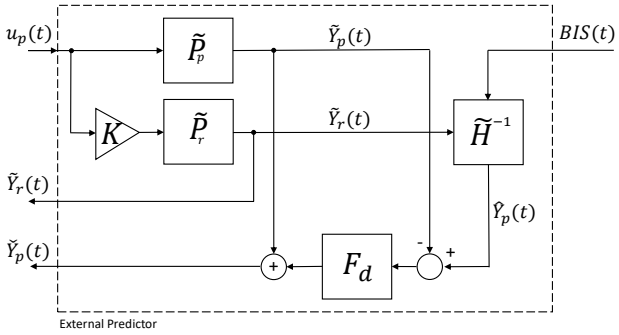

Fig. 3. Structure of the external predictor originated from (Pawlowski et al., 2022b).

In this way it is possible to reflect the variable concentration of remifentanil on the propofol effect such as it can be used by the controller. The approach forthe reference conversion technique followed in this work has been derived from the methodology introduced in (Pawlowski et al., 2022b, 2023).

4.3 Controller

The PID controller used as feedback controller is in ideal form and it is expressed as:

$$C(s) = K_p \left(1 + \frac{1}{sT_i} + sT_d\right) \tag{4}$$

where K_p, T_i and T_d are the tuning parameters, namely, the proportional gain, and the integral and derivative time constants, respectively. These parameters need be adjusted to meet the requirements defined in the clinical specifications (see Section 3). Additionally, to ensure the proper controller structure, the derivative term includes a first-order filtering action with a time constants equal to T_d/N where $N = 10$ (Åström and Hägglund, 2006). Moreover, due to the presence of physical limitations of the actuator, the controller includes an anti-windup technique (Pawlowski et al., 2018).

4.4 Tuning of the control system

To achieve the desired control performance, the overall control system needs to be tuned, requiring the adjustment of the PID controller parameters (K_p, T_i, T_d) and of the F_d filter time constant T_f. This has been done by means of a genetic algorithm. In particular, the optimization procedure has been performed for the dataset of the virtual patients (see Section 2.2) using a cost function that minimizes the worst-case value of the Integrated Absolute Error (IAE), defined as $IAE = \int |r_{BIS}(t) - BIS(t)|dt$ (see (Padula et al., 2017; Merigo et al., 2018; Pawlowski et al., 2022a) for details). The procedure was applied for the induction and maintenance phases separately, obtaining two sets of parameters. It needs to be highlighted, that during this step the nonlinear part of the used model (represented as $\tilde{H}$) was build considering the average values parameters from the patient dataset. In this way, the modelling uncertainty has been considered. Results are summarized in Table 1. Following a gain scheduling methodology, the commutation between the two sets is performed once the induction phase is concluded (according to the clinical conditions).

Table 1. Tuning parameters for proposed architecture

	K_p	T_i	T_d	T_f
Induction	1.81	299.08	17.48	48.45
Maintenance	5.90	1517.4	19.40	74.60

5. SIMULATION STUDY AND RESULTS

The performance of the proposed PID-based structure is evaluated by means of a simulation study that comprises both anesthesia induction and maintenance. The simulation has an overall duration of 20 minutes. Anesthesia induction begins at minute 0 when a step signal from the BIS initial value to 50 is applied to $r_{BIS}(t)$. In this phase, the performance of the controller in terms of its set-point following capabilities are assessed. To quantify the performance of the controller a set of indexes proposed in the literature is used (Ionescu et al., 2008; Padula et al., 2017), They are: time-to-target (TT), which is the time required to achieve a BIS of 45, the minimum value reached by the BIS (BIS-NADIR), which quantifies undershoot, settling time at 10% (ST10) and at 20% (ST20), which are the time intervals required to obtain a BIS steadily inside the range 45-55 and 40-50, respectively. Once the BIS reaches its target value, anesthesia maintenance begins. In this phase, the performance of the controller in terms of its disturbance rejection capabilities are assessed. In the clinical practice, disturbances are caused by the presence of surgical stimulation. This is simulated by applying to the d signal a positive step signal of amplitude 10 followed

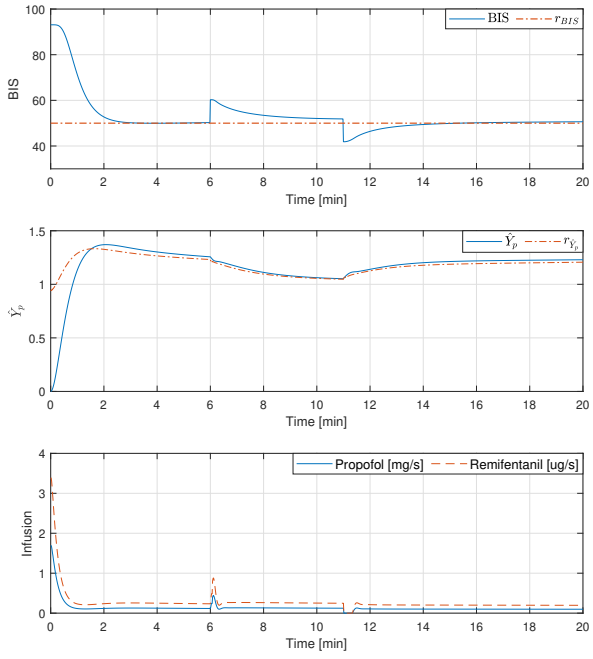

Fig. 4. Control system performance for the average patient for both phases. In the middle plot the intermediate variable $\hat{Y}_p$ and corresponding reference are shown.

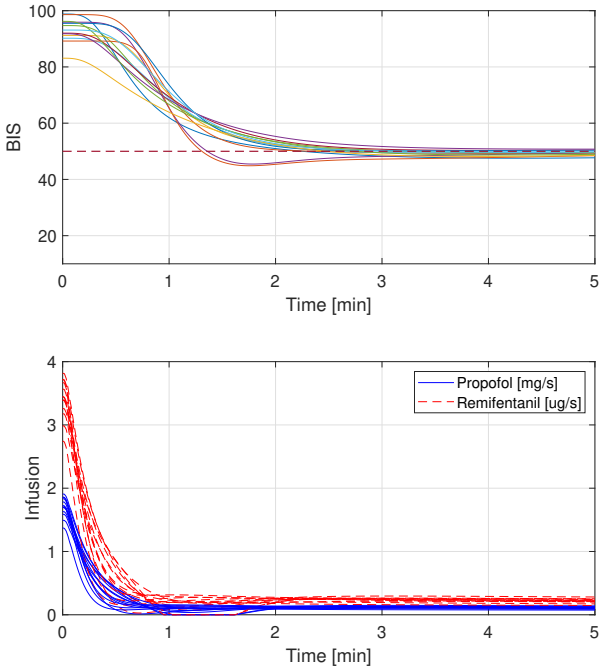

Fig. 5. The induction phase control results for the twelve patients of the considered dataset .

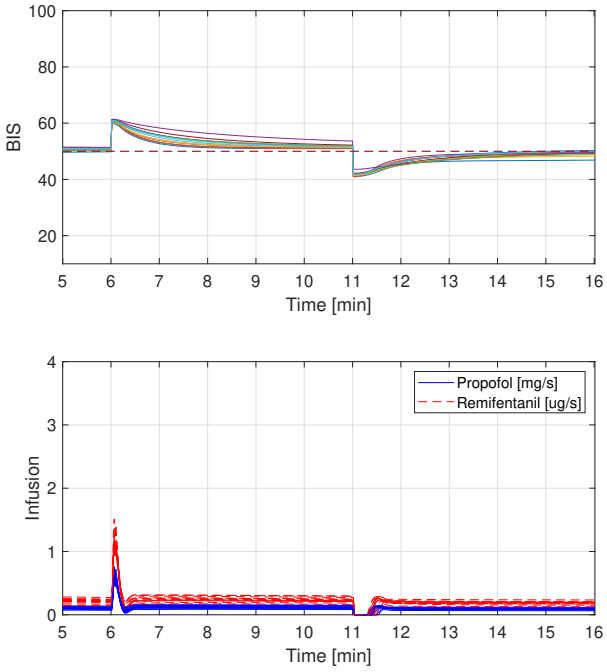

Fig. 6. The maintenance phase control results for the twelve patients of the considered dataset.

after 5 minutes by a negative step of the same amplitude. The performance is quantified with the indexes TT and BIS-NADIR, that are computed separately for the positive step and for the negative step and indicated by using the subscripts $_p$ and $_n$, respectively. As a first illustrative example, results obtained with the average patient are shown in Figure 4. From the top plot it is possible to observe that the controller satisfies all the control specifications. Indeed, in the induction phase it quickly drives the BIS to the target value without undershoot and in the maintenance phase it properly rejects the disturbance. From the bottom plot it is possible to observe that the controller delivers a smooth infusion profile that is fully compatible with those commonly used in the clinical practice. Indeed, as typical in manual control, anesthesia is induced by performing a drugs bolus, which is a large amount of drug administered in a short time. Afterwards, the controller keeps the drugs infusions at a constant value until the positive step disturbance occurs. To reject it, the controller increments the drugs infusion rates but without achieving excessively high values, which can be dangerous for the patient. When the negative step disturbance occurs, the controller decreases the drugs infusion rates to compensate it and then it resumes a constant infusion. From the middle plot it can be seen that the reference converter continuously re-computes the reference by taking into account the super-additive effect of drugs interaction.
The simulation scenario is then applied to all the patients of the data set. The results obtained for the induction and maintenance phases are shown in Figures 5 and 6,

Table 2. The performance indexes summary for the induction stage.

Patient	**TT** [min]	**BIS NADIR**	**ST20** [min]	**ST10** [min]
1	1.42	47.54	1.1	1.41
2	1.45	49.22	1.25	1.45
3	1.63	49.48	1.31	1.63
4	1.22	45.46	1.1	1.22
5	1.8	49.46	1.36	1.8
6	1.68	49.45	1.36	1.68
7	1.88	50.32	1.45	1.88
8	1.63	50.16	1.36	1.63
9	1.18	44.87	1.08	1.88
10	1.68	48.17	1.25	1.68
11	2.05	50.76	1.5	2.05
12	1.8	48.69	1.36	1.8
13	1.73	49.97	1.4	1.73
Mean	1.62	48.74	1.30	1.68
Std. Dev.	0.25	1.81	0.13	0.22
Max.	2.05	50.76	1.5	2.05
Min.	1.18	44.86	1.08	1.22

Table 3. The performance indexes summary for the maintenance stage.

Patient	**TTp** [min]	**BIS NADIRp**	**TTn** [min]	**BIS NADIRn**
1	0.53	50.98	0.98	47.50
2	0.72	51.42	0.63	49.68
3	0.76	51.43	0.63	50.02
4	0.61	51.20	0.57	50.01
5	1.3	51.95	0.86	49.78
6	0.97	51.51	0.70	50.17
7	1.75	52.21	0.83	50.60
8	1.28	51.81	0.75	50.76
9	0.58	50.95	0.70	49.74
10	0.78	51.41	0.92	48.77
11	3.15	53.63	0.80	50.65
12	1.23	51.88	1.00	49.41
13	1.15	51.67	0.71	50.48
Mean	1.14	51.70	0.78	49.81
Std. Dev.	0.70	0.69	0.14	0.88
Max.	3.15	53.63	1.00	50.76
Min	0.53	50.95	0.57	47.50

respectively. The corresponding values of the performance indexes are shown in Tables 2 and 3. The results obtained on the whole data set confirm those of the average patient and all the control requirements are met. Indeed, as regards the induction phase, the maximum value of TT is of 2.05 minutes and the minimum value of BIS-NADIR is of 44.86. The maximum values of ST10 and ST20, respectively of 1.5 and 2.05 minutes, indicates that the controller provides a fast settling of the BIS near its target value. As regards the maintenance phase, the disturbance is quickly compensated as witnessed by the average values of TT_p and TT_n of 1.14 and 0.78 minutes, respectively. Moreover, BIS undershoots below 40 and overshoots above 60 never occurs. The maximum TT_p value of 3.15 minutes is due to the presence of a steady-state error in the BIS. This is caused by the presence of a mismatch in the model used in the external predictor with respect to the actual behavior of the patient. However, it is worth noting that this is not an issue from a clinical point of view as the steady-state error is small and all the values of BIS between 40 and 60 indicates an adequate DoH.

6. CONCLUSION

This work dealt with the design and evaluation of a drug co-administration control scheme for TIVA. This challenging multivariable nonlinear process has been approached with a control architecture where feedback control is handled by the classic PID controller in combination with a patient state predictor and a reference conversion element. Such architecture allows the super-additive effect of remifentanil over propofol to be considered. Moreover, thanks to the simultaneous tuning of the controller and of the external predictor parameters that take into account clinical limitations and recommendations, it is possible to meet control objectives. Promising results have been obtained in a simulation study performed on a representative set of virtual patients. These findings are confirmed by the process specific performance indexes.

Future work will focus on the robustness study addressing mainly the issues of inter- and intra-patient variability and impact of noise. The positive evaluation of these aspects will assure the clinical viability of the approach in the practical context.

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