Preprints of the 21st IFAC World Congress (Virtual)
Berlin, Germany, July 12-17, 2020

First experiments of anesthesia control with optimized PID tuning

Michele Schiavo * **Fabrizio Padula** ** **Nicola Latronico** ***
Luca Merigo * **Massimiliano Paltenghi** **** **Antonio Visioli** †

* *Dipartimento di Ingegneria dell'Informazione, University of Brescia, Brescia, Italy, (e-mail: m.schiavo003@unibs.it)*
** *Department of Mathematics and Statistics, Curtin University, Perth, Australia, (e-mail: fabrizio.padula@curtin.edu.au)*
*** *Department of Medical and Surgical Specialties, Radiological Sciences and Public Health, University of Brescia, Brescia, Italy, (e-mail: nicola.latronico@unibs.it)*
**** *Department of Anesthesiology, Critical Care and Emergency, Spedali Civili, Brescia, Italy, (e-mail: maxpaltenghi@gmail.com)*
† *Dipartimento di Ingegneria Meccanica e Industriale, University of Brescia, Brescia, Italy (e-mail: antonio.visioli@unibs.it)*

Abstract: In this paper we present and discuss the first experimental results obtained with a recently devised PID control scheme for the propofol and remifentanil coadministration in general anesthesia. In particular, the depth of hypnosis is controlled by considering only the bispectral index scale as the process variable and the extra degree of freedom in the controller is handled by selecting an appropriate ratio between the infusion rates of the two drugs. The parameters of the PID controllers are selected by using a tuning rule obtained through an optimization procedure that exploits the PK/PD model of a set of patients. A gain scheduling approach is used to switch between two sets of tuning parameters, one for the induction phase and the other for the maintenance phase. The experimental results confirm the effectiveness of the overall design approach.

Keywords: Total intravenous anesthesia, Depth-of-Hypnosis, PID control, Coadministration.

1. INTRODUCTION

Closed-loop control of anesthesia during surgery has attracted considerable research effort in the last decades (Bailey and Haddad, 2005; Linkens, 1992). In fact, compared to manual control, it provides significant benefits such as the reduction of the anesthesiologist workload (even if he/she has to be present in any case for supervision and intervention in case of emergency), the avoidance of problems due to distraction or fatigue, an increase of the patient safety thanks to the continuous monitoring and, finally, the potential lower administration of drugs with a faster post-operative recovery and the reduction of side effects.

In the clinical practice of total intravenous anesthesia (TIVA), the infusion of different drugs is regulated to achieve a patient state suitable for the surgery. Specific administered drugs induce unconsciousness, with a desired level of depth of hypnosis (DoH) of the patient, suppress the physiological responses to nociceptive stimulation and, in specific cases, block the neuromuscular activity. The most common hypnotic drug is propofol, while the analgesic one is remifentanil. The coadministration of these two drugs has a synergic effect on the DoH.

Many control systems have been developed (mainly based on a simple proportional-integral-derivative (PID) controllers, but also on other paradigms) considering the bispectral index scale (BIS) signal as feedback and only propofol infusion as control variable, and experimental results have shown the effectiveness of this approach (Struys et al., 2001; Absalom and Kenny, 2003; Absalom et al., 2002; Puri et al., 2007; Reboso et al., 2019; Neckebroek et al., 2019). However, it is recognized that it is also relevant to handle nociceptive stimulations by properly controlling the infusion rate of remifentanil (van Heusden et al., 2014). In principle, a multiple-input-multiple-output (MIMO) control system should be used by considering, in addition to the BIS signal, a measure of the analgesic coverage (Ionescu et al., 2014; Padmanabhana et al., 2019). Relevant experimental results in this context have been presented in (Hemmerling et al., 2013), where an empirical algorithm is used. However, analgesia monitors are still not generally accepted in clinical practice, and for this reason control structures for a multiple-input-single-output (MISO) process for the coadministration of propofol and remifentanil have been developed. The aforementioned solutions only exploit the BIS measure as feedback signal, which implies that there is a degree of freedom in the controller design that has been handled by implementing empirical rules in (Liu et al., 2011, 2012) and by setting suitable weights in a model predictive control framework in (Ionescu et al., 2011). Alternatively, a mid-ranging controller has been devised in (Soltesz et al., 2012), where the

different metabolization times of the two drugs has been exploited. In (van Heusden et al., 2017), the additional degree of freedom is handled by the user, who determines the the opioid-hypnotic balance by selecting the desired effect-site concentration of remifentanil. A different explicit approach has been proposed in (Merigo et al., 2019). In particular, the degree of freedom in the controller with one input and two outputs allows the anesthesiologist to select a desired ratio between the remifentanil and the propofol infusion rates, depending on the nature of surgery. A PID controller is then used to determine the value of the control variables, and its tuning has been performed by exploiting an evolutionary algorithm that considers a dataset of pharmacokinetic/parmacodynamic (PK/PD) models that are representative of a wide population of patients. The robustness with respect to inter- and intra-patient variability is verified through a Monte Carlo simulation. The peculiarity of our control systems is that both induction and maintenance are dealt in closed-loop through a gain scheduling approach. First, a set a tuning parameter is selected for the induction phase, then, we switch to a different tuning, specifically developed for the maintenance phase (Padula et al., 2017). In this paper, we present the first experimental results obtained by applying the method proposed in (Merigo et al., 2019) (note that there is only a small number of clinical trials where the DoH is entirely controlled in closed-loop (i.e., induction and maintenance) and both infusions of propofol and remifentanil are fully automated). In particular, the control system is applied to four patients undergoing plastic surgery. The patients have different demographics and, although the number of them is not large enough to draw definitive conclusions, the preliminary results suggest that the approach developed in (Merigo et al., 2019) is sound. In fact, the aim of the paper is twofold: (i) to demonstrate the practical effectiveness of the devised control structure; (ii) to demonstrate the viability of the tuning approach that is based on the classical PK/PD model available in the literature (Minto and Schnider, 2008). The paper is organized as follows. The control system is briefly reviewed in Section 2. The clinical protocol and the instrumentation are described in Section 3. The experimental results are presented and discussed in Section 4 and, finally, conclusions are drawn in Section 5.

2. CONTROL SYSTEM

2.1 Problem formulation

The coadministration of propofol and remifentanil should be performed in such a way that the BIS level is driven from its initial value (close to 100) to the set-point one equal to 50 (which implies a level of hypnosis between moderate and deep) in a short time (less than 4 min) and avoiding an excessive undershoot. In particular, a value of the BIS lower than 40 should be avoided as it might yield a dangerous hypotension (Lindholm et al., 2009). Then, during the whole surgery procedure, the BIS value should be kept in the safe range between 40 and 60 despite the presence of disturbances (which are usually modelled as additive signals to the system output) due to noxious stimuli.

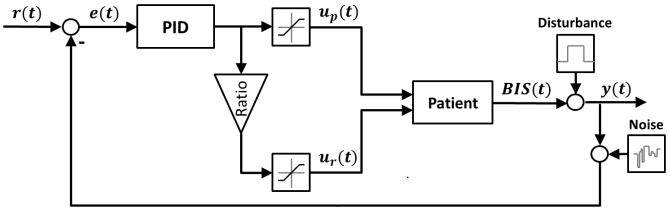

Fig. 1. The control scheme for propofol and remifentanil coadministration.

2.2 Control scheme

The control system is briefly reviewed in this section for the sake of clarity. More details can be found in (Merigo et al., 2019). The control scheme is shown in Figure 1, where $r(t)$ is the reference value set to 50, $BIS(t)$ is the actual BIS value, $y(t)$ is the output of the BIS monitor, which is corrupted by measurement noise, and $e(t)$ is the control error. Then, $u_p(t)$ is the propofol infusion rate (in mg/min) and $u_r(t)$ is the remifentanil infusion rate (in μg/min). The saturation blocks on the control action represent the maximum and the minimum infusion rates achievable with the syringe pumps (see Section 3) with a minimum value of 0 mg/s and a maximum value of 6.67 mg/s for propofol (Propofol 20 mg/ml) and a minimum value of 0 μg/s and a maximum value of 16.67 μg/s for remifentanil (Ultiva 50 μg/ml).

A key role of the control architecture is played by the ratio block, which allows the anesthesiologist to select a desired balance between opioid and hypnotic. Depending on the kind of surgery, by expressing the remifentanil infusion in μg/s and the propofol infusion in mg/s, the remifentanil-propofol ratio can range from 0.5 to 15, but its typical value is equal to 2 (Vuyk et al., 1997). This latter value is the one used in the clinical trials presented hereafter.

The PID controller transfer function is

$$C(s) = K_p \left(1 + \frac{1}{T_i s} + \frac{T_d s}{\frac{T_d}{N} s + 1} \right) \tag{1}$$

where K_p is the proportional gain, T_i is the integral time constant, T_d is the derivative time constant and $N = 5$ determines a low-pass filtering of the derivative action, avoiding the amplification of the measurement noise. A discretized version of the PID controller has been implemented in the system (see Section 3). In addition to the use of a low-pass filter on the derivative action, the measurement noise has been further filtered by implementing a simple moving average filter that considers the last eight samples of the BIS signal. The filter uses the same weight for the last 8 samples of the BIS signal. This choice is the result of a trial and error process on signals acquire during surgery, where a number different options have been considered.

2.3 PID controller tuning

The PID controller has been tuned by considering a set of PK/PD models of 13 patients that are representative of the general population (Struys et al., 2004). The classical PK/PD model of propofol and remifentanil coadministration (Minto and Schnider, 2008) has been considered

for the purpose of simulating the patients in the tuning procedure. The model comprises two linear systems in parallel whose outputs are coupled through a static nonlinear Hill function. In particular, the linear part of the propofol (resp. remifentanil) model relates the propofol (resp. remifentanil) infusion rate $u_p(t)$ (resp. $u_r(t)$) with the effect-site concentration $C_{e,p}(t)$ (resp. $C_{e,r}(t)$). The parameters of the linear part of the model depend on age, weight, height and gender of the patient. Then, the nonlinear Hill function relates the effect-site concentrations to the BIS value as follows:

$$BIS(t) = E_0 - E_{max}\left(\frac{\left(\frac{U_{prop}(t)+U_{remif}(t)}{U_{50}(\phi)}\right)^{\gamma}}{1+\left(\frac{U_{prop}(t)+U_{remif}(t)}{U_{50}(\phi)}\right)^{\gamma}}\right), \tag{2}$$

where E_0 is the baseline value (close to 100) representing the initial drug-free output of the patient, $E_0 - E_{max}$ is the maximum reachable effect, γ determines the maximum slope of the curve (which is a measure of the patient sensitivity), and $C_{e_{50},p}$ and $C_{e_{50},r}$ are the concentrations of propofol and remifentanil necessary to reach half of the maximal effect. Then, β determines the synergetic effect of propofol and remifentanil in DoH through the functions $U_{prop}(t)$, $U_{remif}(t)$ and $U_{50}(\phi)$, which are expressed as:

$$U_{prop}(t) = \frac{C_{e,p}(t)}{C_{e_{50},p}}, \quad U_{remif}(t) = \frac{C_{e,r}(t)}{C_{e_{50},r}} \tag{3}$$

$$\phi = \frac{U_{prop}(t)}{U_{prop}(t)+U_{remif}(t)}, \quad U_{50}(\phi) = 1 - \beta\phi + \beta\phi^2. \tag{4}$$

The parameters for the models of the 13 patients used to determine the PID parameters have been presented in (Merigo et al., 2019) but are also shown in Table 1 for the reader's convenience.

For each remifentanil-propofol ratio, a particle swarm optimization (PSO) algorithm (Kennedy, 2011) has been employed to find the optimal PID parameters that minimize the worst-case integrated absolute error over the whole dataset of models. Formally, defining the integrated absolute error as

$$IAE = \int_0^{\infty} |r(t) - BIS(t)|dt, \tag{5}$$

the following optimization problem has been solved:

$$\min_{K_p,T_i,T_d} \max_{k\in\{1,\dots,13\}} \mathrm{IAE}_k(K_p,T_i,T_d), \tag{6}$$

In this context, the induction and the maintenance phases have been considered separately, and both phases are automatically handled by the PID controller. Indeed, an optimal set of PID parameters has been determined by considering the response of a set-point step signal from the value 100 to the value 50 and another set of parameters has been determined by considering the response of an additive disturbance signal that consists of a step of amplitude 10 that acts on the systems output for 10 minutes. A gain scheduling approach is employed so that a set of PID parameters is used in the induction phase until the BIS value of the patient settles in a range from 40 to 60 and then another set is used to compensate for disturbances due to noxious stimuli until the end of the surgery procedure. Note that we adopt in this paper a population-based robust tuning, so that the same parameters guarantees stability and satisfaction of clinical constraints for all patients.

3. CLINICAL PROTOCOL

The control algorithm has been implemented on a standard PC and a suitable graphic user interface (GUI) has been developed in order for the anesthesiologists to easily use and supervise the system. The PC is connected to a Dräger Infinity Delta monitor (Drägerwerk, Lübeck, DE) and to two syringe pumps Graseby 3400 (Smiths Medical, London, UK) through three USB - RS232 converter cables. These devices have been chosen because they are already present and commonly used in the plastic operating room of Spedali Civili di Brescia (Brescia hospital), where the trial is conducted. The monitor sends a packet of data every 1 s with a set of information of the patient that comprises BIS, Signal Quality Index (SQI), heart rate (HR), burst suppression ratio (BSR), oxygen saturation (SpO_2), and systolic, diastolic and medium blood pressures (BP_s, BP_d, BP_m). As mentioned above, a simple moving average filter with 8 samples is applied to the BIS signal. Then, even if the PID controller is discretized with a sampling period of 1 s and its output is calculated with that sampling rate, a new value of the control variable is sent to the two syringe pumps (as a message from the RS-232 port) every 5 s. The reason for this choice is that a controller inside the pump elaborates the received command and properly actuates the syringe with drug in order to achieve the desired infusion rate and we observed experimentally that the pump is only able to satisfactory track infusion rates that changes every 5 s. The PID control law is determined in any case each 1 s in order to calculate the integral and derivative actions more precisely.

In the operating room the patient is connected to the devices after the anesthesiologist has administered 0.5 μg/kg of fentanest and 1-2 mg of midazolam as premedication in order to improve the comfort of the patient. Then, the closed-loop control is started. When (typically, after 3-4 min) the patient loses consciousness the anesthesiologist inserts the laryngeal mask or the orotracheal tube and the patient is connected to the controlled mechanical ventilation (CMV). At discretion of the anesthesiologists, bolus of curare are administered in this phase to facilitate intubation, usually 0.8 mg/kg of rocuronium.
When the patient achieves a stable level of BIS in the required range from 40 to 60, the anesthesiologist switches the system into maintenance mode and checks if the level of anesthesia is clinically adequate during the surgical procedures by monitoring the infusions rates, the presence of patient movements, the haemodynamics of the patient, the BIS level, blood loss and somatic events, like grimacing and eye opening.
The automatic infusion is finally stopped at completion of the surgical procedures, that is, when the surgeon finishes the skin sutures. Patients remain in the operating room until they regain consciousness, the laryngeal mask is removed and they can correctly state their date of birth. The patients are then taken to a recovery room for a few minutes where they are monitored and then they are visited on the first and on the second postoperative day.

The clinical trial has been approved by the ethics committee of Brescia (number NP2861).

Id	Age	Height [cm]	Weight [kg]	Gender	$C_{e50,p}$	$C_{e50,r}$	γ	β	E_0	E_{max}
1	40	163	54	F	6.33	12.5	2.24	2.00	98.8	94.10
2	36	163	50	F	6.76	12.7	4.29	1.50	98.6	86.00
3	28	164	52	F	8.44	7.1	4.10	1.00	91.2	80.70
4	50	163	83	F	6.44	11.1	2.18	1.30	95.9	102.00
5	28	164	60	M	4.93	12.5	2.46	1.20	94.7	85.30
6	43	163	59	F	12.00	12.7	2.42	1.30	90.2	147.00
7	37	187	75	M	8.02	10.5	2.10	0.80	92.0	104.00
8	38	174	80	F	6.56	9.9	4.12	1.00	95.5	76.40
9	41	170	70	F	6.15	11.6	6.89	1.70	89.2	63.80
10	37	167	58	F	13.70	16.7	3.65	1.90	83.1	151.00
12	42	179	78	M	4.82	14.0	1.85	1.20	91.8	77.90
12	34	172	58	F	4.95	8.8	1.84	0.90	96.2	90.80
13	38	169	65	F	7.42	10.5	3.00	1.00	93.1	96.58

Table 1. Parameters of the models of the 13 patients used for the optimization-based tuning procedure.

4. EXPERIMENTAL RESULTS

The results related to four patients are presented in this section. Their demographics data are shown in Table 2. They are two males and two females and they cover a large range of weights and ages. Furthermore, they were undergoing various surgical procedures. The results are shown for each patient from Figure 2 to Figure 5. For all patients the control system was capable to control the coadministration for the duration of the whole surgical procedure and the anesthesiologist never changed the infusion rates determined by the controller.

Patient	Age	Height [cm]	Weight [kg]	Gender
1	41	165	58	F
2	88	174	84	F
3	60	174	78	M
4	39	170	85	M

Table 2. Demographics of the patients under closed-loop anesthesia control.

In the top plot of each figure, the BIS level is represented by a black solid line, the SQI by a red solid line and the BIS reference by a black dashed line. The drugs infusions rates are plotted in the second plot: propofol infusion (in mg/kg/min) is represented by a black line and the remifentanil infusion (in μg/kg/min) by a red line. A black dashed line marks the time instant when the gain-scheduling strategy has been applied by the anesthesiologist thorough the GUI. Hemodynamic parameters of the patient are shown in the last four plots of each figure. Indeed, we show the HR (in bpm), the $Sp0_2$ (in %) and BP (in mmHg). In particular, the BP_s is plotted by a red line, the BP_d is plotted by a black line and the BP_m is plotted by blue line (note that the acquisition is interrupted after the induction phase for patient 4). In addition, we also plot the BSR.

The devised control system provides a satisfactory performance for all four patients in both the induction and the maintenance phase providing stable hemodynamic parameters of the patient (also during long surgical procedures, see Figure 5). In general, the BIS level attains the set-point reference without excessive undershoot and with an acceptable settling time during the induction phase. Moreover, the BIS level is maintained in the range [40, 60] for most of the time during the maintenance phase. Indeed, the closed-loop control system provides satisfactorily disturbance rejection with limited undershoots and overshoots.

The infusion rates in the second plots of each figure are also satisfactory from a clinical point of view. They do not achieve excessively high or low values, which may involve the risk of overdosing or underdosing the patient. We stress that our approach does not rely on the use boluses, so the pumps always work in the standard infusion mode. Due to the feedback, the control signal is affected by residual noise, but the infusion rates during the pikes never attain the high values used in "bolus" mode. Finally, for all the patients, hemodynamic parameters are stable throughout the anesthesia. In fact, for all the patients, HR is stable at a level between 40 and 90, $Sp0_2$ is always greater than 95% and BP values are in an acceptable range during the whole surgical procedure. Further, the BSR is close to 0, with the exception of some time intervals for patient 2, which might be because of her old age, and for patient 3, which can be associated to the BIS undershooting during the induction phase. The duration of the emergence phase is also in accordance with the clinical practice, where awaking time is approximately 10 min.

The results confirm the effectiveness of the control architecture and of the tuning procedure. In particular, the analysis of the performance of the controller with these four patients suggests that the choice of selecting a suitable value for the ratio of the remifentanil-propofol infusion rates is effective in practice. Then, the tuning methodology for the PID controller proposed in (Merigo et al., 2019) has been also validated. In particular, it can be deduced that the set of 13 patients that has been used in the optimization procedure is appropriate to describe a wide population and that their PK/PD models are sufficiently accurate for the obtained PID parameters to be employed in the clinical practice.

5. CONCLUSIONS

In this paper we have presented preliminary experimental results of the application of a recently proposed control architecture for the propofol-remifentanil coadministration in general anesthesia. Our approach satisfactorily handles both induction and maintenance in closed-loop, and automatically controls the infusion of both propofol and

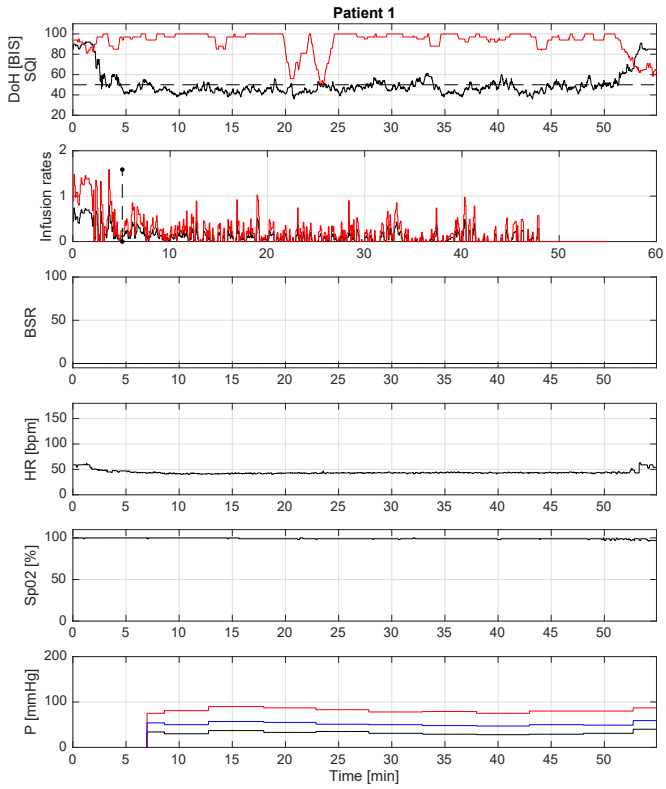

Fig. 2. Clinical data of patient 1.

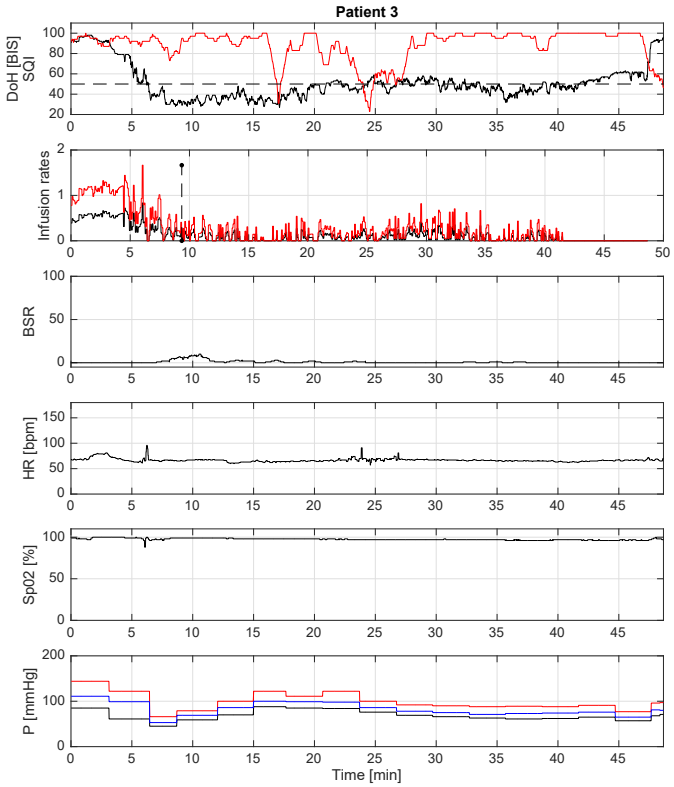

Fig. 4. Clinical data of patient 3.

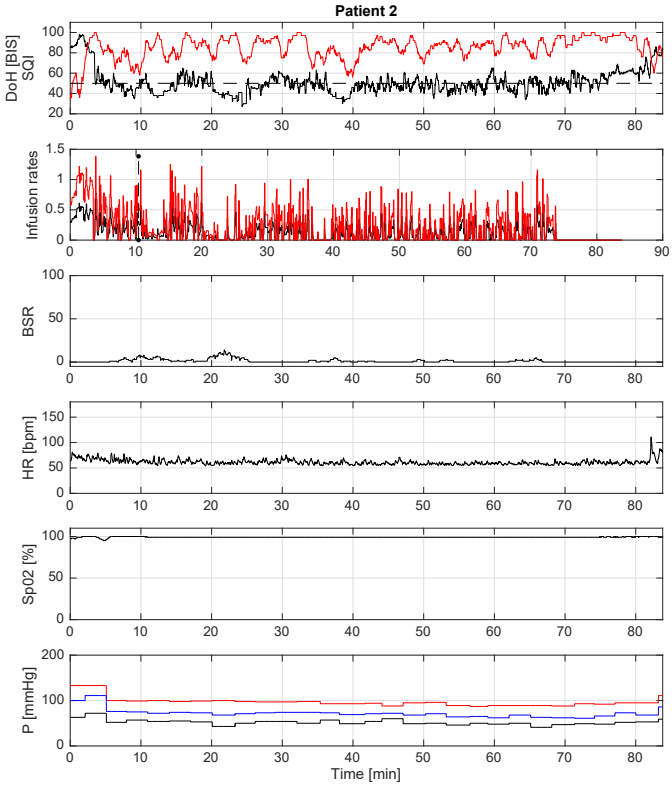

Fig. 3. Clinical data of patient 2.

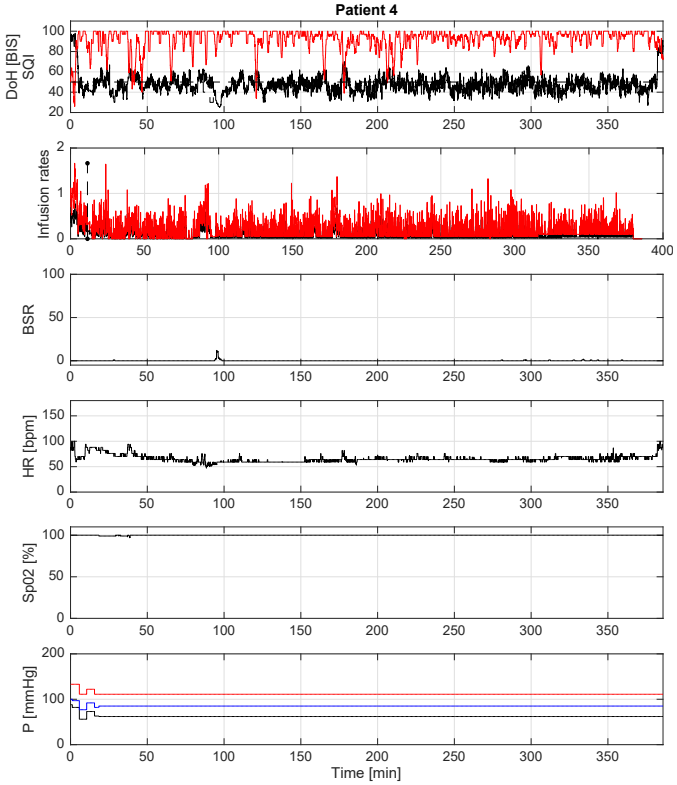

Fig. 5. Clinical data of patient 4.

remifentanil. Four patients have been considered and, for all of them, there has been no intervention of the anesthesiologists, neither in the induction nor in the maintenance phase. The whole TIVA procedure has been performed by the closed-loop system. Results are very promising, as they confirm that using a fixed ratio between the infusion rates of the two drugs is an effective way to handle the degree of freedom that results from the presence of two

actuators and one controlled variable (i.e., the BIS value). Further, the conclusions drawn in (Merigo et al., 2019) through a Monte Carlo simulation about the robustness of the optimization-based tuning procedure are confirmed. This also shows that the set of models of patients used for the optimization of the PID parameters is sufficiently rich to obtain a tuning that can be employed in a general population. Future work will include testing the controller on a large set of patients in order to obtain a complete assessment of the proposed methodology by using statistically sound sample of the population.

REFERENCES

Absalom, A.R. and Kenny, G.N. (2003). Closed-loop control of propofol anaesthesia using bispectral index: performance assessment in patients receiving computer controlled propofol and manually controlled remifentanil infusions for minor surgery. *British Journal of Anaesthesia*, 90, 737–741.

Absalom, A.R., Sutcliffe, N., and Kenny, G.N. (2002). Closed-loop control of anesthesia using bispectral index. *Anesthesiology*, 96, 67–73.

Bailey, J.M. and Haddad, W.M. (2005). Drug dosing control in clinical pharmacology. *IEEE Control Systems Magazine*, 25(2), 35–51.

Hemmerling, T.M., Arbeid, E., Wehbe, M., Cyr, S., Taddei, R., and Zaouter, C. (2013). Evaluation of a novel closed-loop total intravenous anaesthesia drug delivery system: a randomized controlled trial. *British Journal of Anesthesia*, 10, 1031–1039.

Ionescu, C.M., Keyser, R.D., and Struys, M.M.R.F. (2011). Evaluation of a propofol and remifentanil interaction model for predictive control of anesthesia induction. In *Proceedings 50th IEEE Conference on Decision and Control*, 7374–7379. Orlando, Florida.

Ionescu, C.M., Nascu, I., and Keyser, R.D. (2014). Lessons learned from closed loops in engineering: towards a multivariable approach regulating depth of anaesthesia. *Journal of Clinical Monitoring and Computing*, 28, 537546.

Kennedy, J. (2011). *Particle Swarm Optimization*. Encyclopedia of Machine Learning, Springer, Boston, MA.

Lindholm, M.L., Traff, S., Granath, F., Greenwald, S.D., Ekbom, A., Lennmarken, C., and Sandin, R.H. (2009). Mortality within 2 years after surgery in relation to low intraoperative bispectral index values and preexisting malignant disease. *Anesthesia and Analgesia*, 108(2), 508–512.

Linkens, D.A. (1992). Adaptive and intelligent control in anesthesia. *IEEE Control Systems Magazine*, 12, 6–11.

Liu, N., Chazot, T., Hamada, S., Landais, A., Boichut, N., Dussaussoy, C., Trillat, B., Beydon, L., Samain, E., Sessler, D.I., and Fischler, M. (2011). Closed-loop coadministration of propofol and remifentanil guided by bispectral index: a randomized multicenter study. *Anesthesia & Analgesia*, 112, 546–557.

Liu, N., Le Guen, M., Benabbes-Lambert, F., Chazot, T., Trillat, B., Sessler, D.I., and Fischler, M. (2012). Feasibility of closed-loop titration of propofol and remifentanil guided by the spectral m-entropy monitor. *Anesthesiology*, 116, 286–295.

Merigo, L., Padula, F., Latronico, N., Paltenghi, M., and Visioli, A. (2019). Optimized pid control of propofol and remifentanil coadministration for general anesthesia. *Communications in Nonlinear Science and Numerical Simulation*, 72, 194–212.

Minto, C.F. and Schnider, T.W. (2008). Contributions of PK/PD modeling to intravenous anesthesia. *Clinical Pharmacology & Therapeutics*, 84, 27–38.

Neckebroek, M., Ionescu, C.M., van Amsterdam, K., Smet, T.D., Baets, P.D., Decruyenaere, J., Keyser, R.D., and Struys, M.M.R.F. (2019). A comparison of propofol-to-bis post-operative intensive care sedation by means of target controlled infusion, bayesian-based and predictive control methods: an observational, open-label pilot study. *Journal of Clinical Monitoring and Computing*, 33, 675686.

Padmanabhana, R., Meskina, N., Ionescu, C.M., and Haddad, W.M. (2019). A nonovershooting tracking controller for simultaneous infusion of anesthetics and analgesics. *Biomedical Signal Processing and Control*, 49, 375–387.

Padula, F., Ionescu, C., Latronico, N., Paltenghi, M., Visioli, A., and Vivacqua, G. (2017). Optimized PID control of depth of hypnosis in anesthesia. *Computer Methods and Programs in Biomedicine*, 144, 21–35.

Puri, G.D., Kumar, B., and Aveek, J. (2007). Closed-loop anaesthesia delievery system (CLADS) using bispectral index; a performance assessment study. *Anaesthesia and Intensive Care*, 35, 357–362.

Reboso, J.A., Gonzalez-Cava, J.M., Leon, A., and Mendez-Perez, J.A. (2019). Closed loop administration of propofol based on a smith predictor: a randomized controlled trial. *Minerva Anestesiologica*, 85, 585–593.

Soltesz, K., Dumont, G.A., van Heusden, K., Hägglund, T., and Ansermino, J.M. (2012). Simulated mid-ranging control of propofol and remifentanil using EEG-measured hypnotic depth of anesthesia. In *Proceedings 51st IEEE Conference on Decision and Control*, 356–361. Maui, Hawaii.

Struys, M.M., Smet, T.D., Versichelen, L.F., Velde, S.V.D., den Broecke, R.V., and Mortier, E.P. (2001). Comparison of closed-loop controlled administration of propofol using bispectral index as the controlled variable versus standard practice controlled administration. *Anesthesiology*, 95, 6–17.

Struys, M.M.R.F., De Smet, T., Greenwald, S., Absalom, A.R., Binge, S., and Mortier, E.P. (2004). Performance evaluation of two published closed-loop control systems using bispectral index monitoring: a simulation study. *Anesthesiology*, 95(1), 6–17.

van Heusden, K., Dumont, G.A., Soltesz, K., Petersen, C.L., Umedaly, A., West, N., and Ansermino, J.M. (2014). Design and clinical evaluation of robust PID control of propofol anesthesia in children. *IEEE Transactions on Control Systems Technology*, 22(2), 491–501.

van Heusden, K., J. M, A., and Dumont, G.A. (2017). Robust miso control of propofol-remifentanil anesthesia guided by the neurosense monitor. *IEEE Transactions on Control Systems Technology*, PP, 1–13.

Vuyk, J., Mertens, M.J., Olofsen, E., Burm, A.G., and Bovill, J.G. (1997). Propofol anesthesia and rational opioid selection: determination of optimal ec50-ec95 propofol-opioid concentrations that assure adequate anesthesia and a rapid return of consciousness. *Anesthesiology*, 87, 1549–1562.