Optimized PID Controller for Propofol and Remifentanil Coadministration: Influence of Opioid-Hypnotic Balance

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Abstract:
In the practice of total intravenous anesthesia, the regulation of the balance between opioid and hypnotic drugs is fundamental since it has a significant impact on depth of hypnosis and hemodynamics. Therefore, in the implementation of a fully automated control system for anesthesia, this aspect must be considered. In a recently devised PID-based control scheme for propofol and remifentanil coadministration, the opioid-hypnotic balance is handled by imposing a ratio between the infusion rates of these two drugs. The anesthesiologist can choose the most suitable balance during each phase of surgery by changing the ratio. The aim of this paper is to evaluate and discuss the benefits that this solution can bring in the clinical practice. In order to do so, the proposed solution has been tested in simulation by using a recently devised open source patient simulator that takes into account both anesthetic and hemodynamic variables. Simulation results show that the proposed approach automatically induces and maintains the desired depth of hypnosis and, furthermore, it gives the anesthesiologist the possibility to better manage the patient's hemodynamics by selecting the most appropriate opioid-hypnotic balance for each situation.

Keywords: Depth of hypnosis control, PID control, propofol remifentanil coadministration, optimization.

1. INTRODUCTION

In the clinical practice of general anaesthesia, hypnosis and analgesia are balanced in order to achieve a patient state suitable for surgery (Bouillon et al., 2004). Hypnosis consists of the suppression of the activity of the central nervous system that causes unconsciousness, while analgesia consists of the suppression of the physiological responses to nociceptive stimulation. In total intravenous anesthesia (TIVA) hypnosis and analgesia are obtained by means of two separate drugs, namely propofol and remifentanil. The anesthesiologist administers these drugs by following recommended infusion patterns and by adjusting them based on patient's response to painful stimulation and on the alterations of the hypnotic state. The drug dosing task is demanding for the anesthesiologist and can lead to errors due to distraction and fatigue. For this reason the introduction of closed-loop control systems for automatic anesthesia regulation is particularly appealing as they can support the anesthesiologist by reducing the workload. However, these systems need a quantitative feedback in order to be implemented. In the last decades, various depth of hypnosis (DoH) monitors have been introduced. They provide a quantitative estimate of the level of hypnosis based on the analysis of the electroencephalogram. Among these monitors, one of the most widely accepted by clinical practitioners is the bispectral index scale (BIS, Aspect Medical Systems, Norwood, USA) (Rampil, 1998). The availability of such monitoring systems has led to the development of single-input-single-output (SISO) control systems that use DoH measurement as feedback variable and the infusion rate of propofol as control variable. Different control solutions have been proposed, such as PID control (Soltesz et al., 2013; Padula et al., 2017), model predictive control (Ionescu et al., 2008), event-based control (Merigo et al., 2017) and fuzzy control (Mendez et al., 2018). However the anesthesia control problem is inherently multiple-input-multiple-output (MIMO) since analgesia plays a fundamental role in presence of nociceptive stimulation (Van Heusden et al., 2013) and anesthetic

drugs have an effect on hemodynamics (Elliott et al., 2000). Despite MIMO control systems have been proposed (Hemmerling et al., 2013; Joosten et al., 2019), their application is still limited. This is mainly due to the fact that reliable analgesia indicators are not available yet, despite encouraging results have been recently obtained (Ghita et al., 2020; Neckebroek et al., 2020). Due to the absence of a reliable measure of nociception, the multiple-input-single-output (MISO) problem has been investigated, where both propofol and remifentanil infusions are regulated solely by measuring DoH. This implies that there is a degree of freedom that must be considered in the controller design as the same DoH can be obtained with different concentrations of propofol and remifentanil. In (Merigo et al., 2019) a PID control scheme for the coadministration of propofol and remifentanil based on the measurement of BIS has been proposed. The extra degree of freedom has been managed by imposing a balance between the infusion rate of the two drugs. The anesthesiologist can select the value of the ratio in order to provide the desired opioid-hypnotic balance. The performance of this solution has been experimentally evaluated on 10 patients undergoing plastic surgery and promising results have been obtained (Schiavo et al., 2021). However, in this experimentation a fixed ratio value was considered.

In this paper the effect of the ratio on anesthesia is evaluated in simulation by exploiting a recently devised open source patient simulator that takes into account both anesthetic and hemodynamic variables (Ionescu et al., 2021).

The paper is organized as follows. The patient simulator is presented in Section 2. The control system considered is described in Section 3. Simulation results are presented in Section 4 and discussed in Section 5, finally, conclusions are drawn in Section 6.

2. PATIENT SIMULATOR

In this paper the open source patient simulator proposed in (Ionescu et al., 2021) has been used. It implements both anesthetic and hemodynamic variables and takes into account their interaction. It receives the propofol and remifentanil infusion rates as inputs and gives, as outputs, the BIS and the Ramsay Agitation Sedation Score (RASS) as a measure of analgesia. The simulator also gives as output the mean arterial pressure (MAP) and the cardiac output (CO) as hemodynamic variables. It can also receive as input dopamine, sodium nitroprussiade (SNP) and atracurium and can give the neuromuscular blockade (NMB) as output. However, these latter variables have not been considered in this work. In fact, we focus on the effect of propofol and remifentanil on BIS, RASS and hemodynamic variables. It is worth noting that RASS is used as a surrogate measure of analgesia since more specific measurements are not available yet. Since the simulator is open source we have made some changes. In particular we have changed the units of measures of the infusion rates of propofol and remifentanil to mg/s and μg/s respectively by scaling the input in order to better interface the simulator with our control system, in particular with the proportional gain of the PID controller. Moreover, the nonlinear model describing the interaction between propofol and remifentanil has been replaced with the one used in (Merigo et al., 2019). In this way we can perform the simulation on the same dataset of thirteen patients used in (Merigo et al., 2019), thus obtaining a fair comparison. Indeed, in (Merigo et al., 2019) only the DoH has been considered while in this paper also the hemodynamic variables are considered. In particular, the nonlinear interaction model is (Bouillon et al., 2004):

Id	Age	H [cm]	W [kg]	G	$C_{e_{50},p}$	$C_{e_{50},r}$	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. Model parameters of the patients dataset for propofol and remifentanil coadministration (H: height, W: weight, G: gender).

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

where E_0 is the baseline BIS level in the drug-free patient, E_{max} is the maximum BIS decrease and γ characterizes the receptiveness of the patient to the drug mixture. Then, U_{prop} and U_{remif} are the effect-site concentrations of propofol and remifentanil normalized with respect to half of the effect-site concentration required to reach the maximum effect:

$$U_{prop}(t) = \frac{C_{e,p}(t)}{C_{e_{50},p}}, \quad U_{remif}(t) = \frac{C_{e,r}(t)}{C_{e_{50},r}}, \tag{2}$$

ϕ is an dimensionless parameter that represents the combination power of propofol and remifentanil:

$$\phi = \frac{U_{prop}(t)}{U_{prop}(t)+U_{remif}(t)}; \tag{3}$$

$U_{50}(\phi)$ is a term required for the normalization of the drugs combined effect:

$$U_{50}(\phi) = 1 - \beta\phi + \beta\phi^2, \tag{4}$$

where β describes the synergetic effect of propofol and remifentanil. The parameters of the thirteen patients of the considered dataset are given in Table 1. Finally, the simulator includes the possibility to simulate disturbances of the hypnotic state caused by surgical stimulation. In this work the surgical stimulation profile included in the original simulator has been replaced with the double step profile proposed in (Soltesz, 2013). This simple profile has been chosen, because it allows an easier evaluation of the controller performance.

3. CONTROL SYSTEM DESCRIPTION

The control system architecture considered in this paper has been described in (Schiavo et al., 2021) and it is briefly reviewed hereafter. A schematic view of the control loop is shown in Figure 1. The control scheme is based on a PID controller. The feedback variable is the measure of the BIS, the set-point variable is the target BIS value and

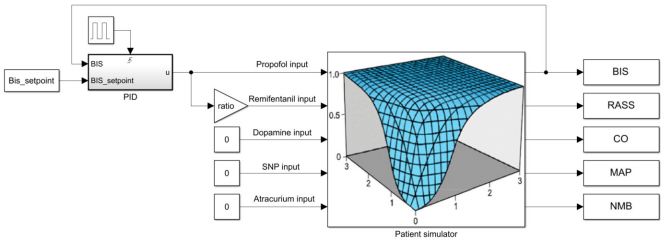

Fig. 1. Schematic representation of the control loop considered. This figure has been adapted from (Ionescu et al., 2021).

the control actions are propofol and remifentanil infusions. The other inputs of the simulator are not considered in this control scheme and are set to zero. The PID controller is implemented in standard ideal form, its transfer function is:

$$PID(s) = K_p \left(1 + \frac{1}{T_i s} + \frac{T_d s}{\frac{T_d}{N} s + 1} \right), \tag{5}$$

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 the time constant of the low-pass filter of the derivative action. The measurement noise has been additionally filtered by implementing a moving average filter on the BIS measurement. The infusion rate of propofol and remifentanil are bounded between 0 mg/s and 6.67 mg/s and 0 μg/s and 16.67 μg/s respectively. An anti-windup strategy has been implemented by using the conditional integration technique (Visioli, 2006). The derivative action has been applied to the feedback signal only, and not on the control error in order to avoid the derivative-kick phenomenon. The PID controller has been implemented in discrete time by considering a sampling period of 1 s according to the maximum update frequency provided by the BIS monitor but the control signal is down-sampled to 5 s in order to cope with the update rate of commercial infusion pumps (Graseby 3400, Smiths Medical, London, UK). The key aspect of this control architecture is represented by the ratio between propofol and remifentanil infusions since it allows the anesthesiologist to select a desired opioid-hypnotic balance. The ratio is expressed by dividing the remifentanil infusion rate in μg/s by the propofol infusion rate in mg/s. In the proposed control system the ratio value can be selected in the range from 0.5 to 15. This range has been selected based on clinical considerations described in (Merigo et al., 2019). The same effect on BIS can be obtained with different concentrations of propofol and remifentanil. By selecting a lower ratio, the BIS target is obtained with a higher propofol concentration and a lower remifentanil concentration, hence the hypnotic component of anesthesia is predominant. This situation is desirable in case of little painful stimulation or in case of concomitant use of loco-regional analgesics as this allows the reduction of the infused dose of remifentanil, thus reducing opioid-induced side-effects. On the contrary, by selecting a higher ratio, the BIS target is obtained with a lower propofol concentration and a higher remifentanil concentration, hence the analgesic component is predominant. This configuration is indicated for surgical phases that involve strong painful stimulation but increases the risk of opioid-induced side-effects. In the clinical practice an advisable opioid-hypnotic balance is generally obtained with a ratio equal to 2 (Vuyk et al., 1997).

Parameter	Set-point	Disturbance
K_p	$0.015 \cdot (ratio)^{-0.43} - 0.0019$	$0.045 \cdot (ratio)^{-0.36} - 0.011$
T_i	280.09	171.83
T_d	33.25	19.01

Table 2. Tuning rules for the induction and maintenance phases.

3.1 PID controller tuning

Since the static gain introduced by (1) changes according to the propofol and remifentanil concentrations, the gain of the controlled system changes according to the desired opioid-hypnotic balance. Hence, the tuning parameters of the PID controller should be selected according to the selected ratio value. Moreover, the PID controller should be able to handle both induction and maintenance of anesthesia. The optimization-based tuning procedure has been thoroughly described in (Merigo et al., 2019, 2020). It relies on solving a min-max optimization problem where the optimal PID parameters are obtained by minimizing the worst-case integral absolute error (IAE) by simulating the response of the dataset of patients given in Table 1:

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

where k is the number of the patient in the dataset and

$$IAE = \int_0^\infty |BIS_{setpoint}(t) - BIS(t)| dt \tag{7}$$

The optimization problem has been solved by using a particle swarm algorithm (Kennedy and Eberhart, 1995) for 16 values of the ratio in the range 0.5-15. Then the optimal PID tuning parameters have been fitted in order to obtain a tuning rule that relates the PID parameters to the ratio value. The induction and the maintenance problems have been addressed separately, hence two different tuning rules have been obtained and they are given in Table 2. Since two different sets of parameters are obtained, a gain scheduling approach is necessary. In order to properly handle the transition between the two sets of parameters, a bumpless switching mechanism has also been implemented.

4. SIMULATION RESULTS

The simulation has been performed by setting a target BIS value of 50 since it is recommended to keep the BIS inside the range from 40 to 60 for most kind of surgeries (Rosow and Manberg, 2001). The baseline values before drug administration for MAP and CO have been set to 90 mmHg and 5 l/min respectively. Generally, it is recommended to keep the MAP inside the range 65-110 mmHg and the CO inside the range 4-8 l/min. A desirable value for RASS is at least -5 since it means that the patient is unresponsive to surgical stimulation. The simulation results for anesthesia induction performed on the patient dataset of Table 1 are shown in Figure 2 where an opioid-hypnotic ratio equal to 2 has been selected. The PID controller rapidly drives the BIS to the target value of 50 without causing undershoot below the value of 40 for all thirteen patients of the dataset. As regards

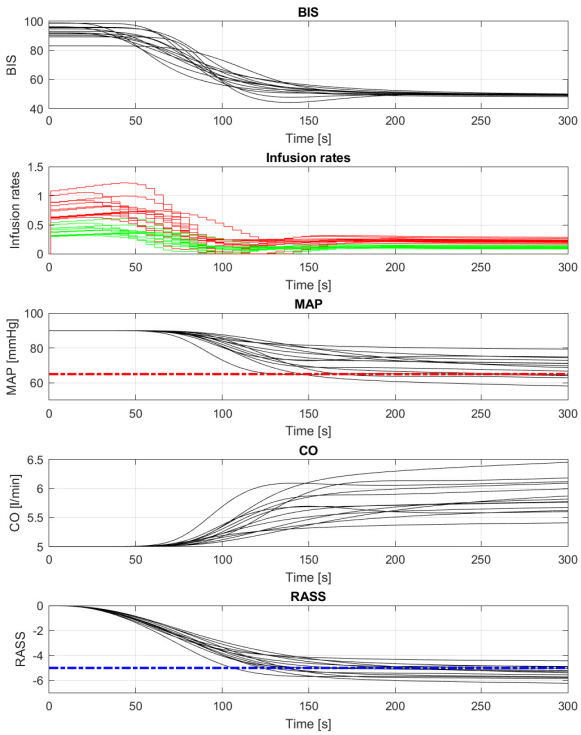

Fig. 2. Setpoint response for the thirteen patients of the dataset considered with ratio=2. Infusion rates are expressed in mg/kg/min for propofol (green solid line) and μg/kg/min for remifentanil (red solid line). The red horizontal dash-dotted line represents the MAP lower safety bound of 65 mmHg. The blue horizontal dash-dotted line represents the RASS target of -5.

the hemodynamic variables, the CO remains inside the recommended bounds for all the patients while the MAP drops below the lower bound of 65 mmHg in two out of thirteen patients, namely patients 8 and 10. The RASS varies between -4 in patient 1 and -6 in patient 8, thus indicating a slight underdosing and overdosing of analgesic respectively. Although potentially problematic MAP and RASS situations only occur in 2 out of 13 patients, they must be appropriately managed by the control system. The proposed control solution manages this issue by means of the ratio value. In Figure 3 the setpoint response for patient 1 and patient 8 is shown. These two patients show different behaviours, indeed, patient 8 appears to be more sensitive to remifentanil since it shows a RASS value below the target and shows hypotension. Conversely, patient 1 appears to be less sensitive to remifentanil since it shows a RASS value above the target and a reduce lowering of MAP with respect to baseline. Hence, is appropriate to decrease the ratio for patient 8 and increase it for patient 1 in order to reach the same BIS target with less or more remifentanil, respectively. Figure 4 shows the setpoint response for patient 1 and patient 8 obtained by setting the ratio to 2.5 and 1.3, respectively. By doing so, both patients reach the RASS target without showing hypotensive behaviours.

The ratio can also be changed by the anesthesiologist

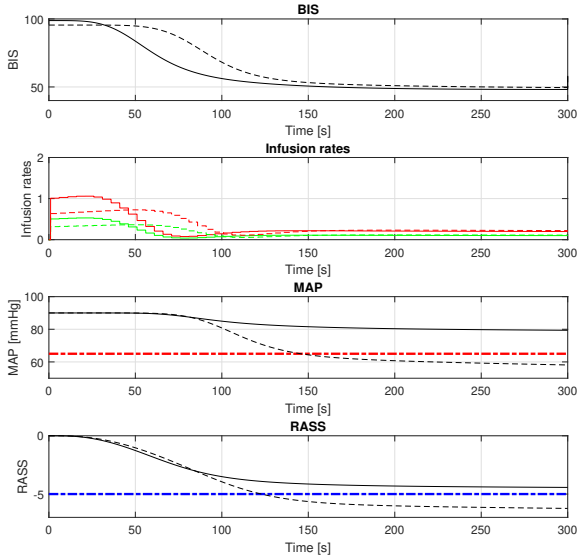

Fig. 3. Setpoint response for patient 1 (solid line) and patient 8 (dashed line) of the dataset obtained with ratio=2. Infusion rates are expressed in mg/kg/min for propofol (green solid line) and μg/kg/min for remifentanil (red solid line). The red horizontal dash-dotted line represents the MAP lower safety bound of 65 mmHg. The blue horizontal dash-dotted line represents the RASS target of -5.

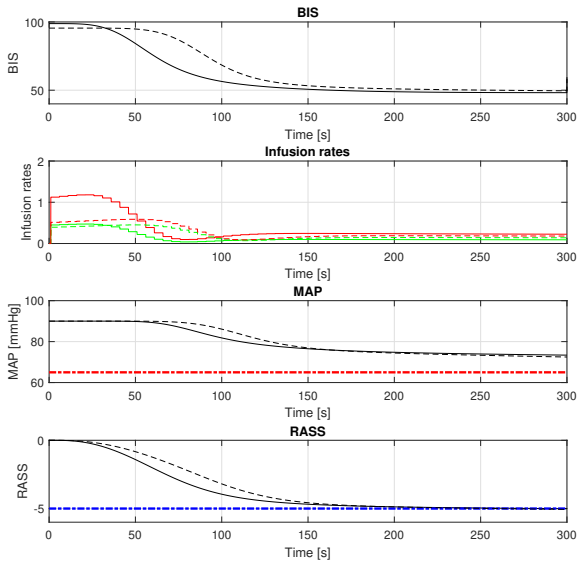

Fig. 4. Setpoint response for patient 1 (solid line) and patient 8 (dashed line) of the dataset obtained with ratio=2.5 and ratio=1.3 respectively. Infusion rates are expressed in mg/kg/min for propofol (green solid line) and μg/kg/min for remifentanil (red solid line). The red horizontal dash-dotted line represents the MAP lower safety bound of 65 mmHg. The blue horizontal dash-dotted line represents the RASS target of -5.

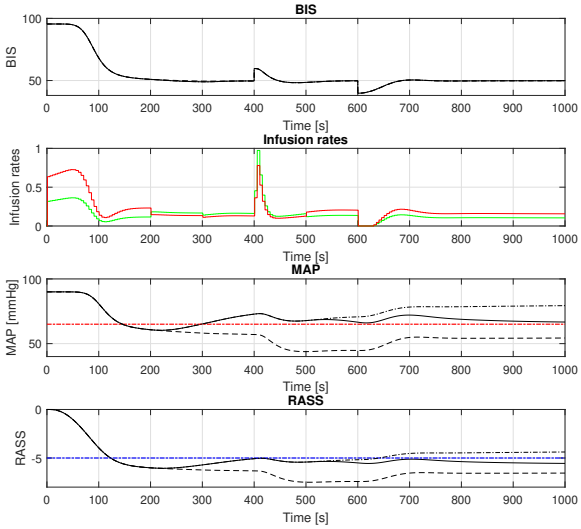

Fig. 5. Setpoint response and disturbance rejection response for patient 8. At time 200 s the ratio is switched from 2 to 0.8 and at time 500 s the ratio is switched from 0.8 to 1.5. Infusion rates are expressed in mg/kg/min for propofol (green solid line) and μg/kg/min for remifentanil (red solid line). The red horizontal dash-dotted line represents the MAP lower safety bound of 65 mmHg. The blue horizontal dash-dotted line represents the RASS target of -5. For BIS, MAP and RASS the black solid line represents the response obtained by switching the ratio, the black dashed line represents the response obtained with ratio=2 and the dash-dotted line represents the response obtained without switching the ratio from 0.8 to 1.5 at time 500 s.

during the course of anesthesia according to the observed response. In order to better clarify this aspect, a simulation that comprises the setpoint response and the disturbance rejection response for patient 8 has been performed and the results are shown in Figure 5. In this example, anesthesia is induced with a ratio equal to 2. Then at time 200 s the anesthesiologist observes that MAP is below the recommended value of 65 mmHg and RASS is below the target value of -5. Hence, he/she decides to lower the ratio from 2 to 0.8 in order to reduce the opioid-induced side-effects on MAP. At time 300 s the BIS settles at the setpoint value. Thus, the anesthesiologist decides to perform the gain-scheduling. By doing so the tuning parameters for disturbance rejection are selected. At time 400 s there is a disturbance on the BIS due to surgical stimulation that is compensated by the controller. At time 500 s the anesthesiologist decides to increase the ratio from 0.8 to 1.5 in order to keep a suitable analgesic coverage. The black dashed line represents the response that would have been obtained without changing the ratio from 2 to 0.8 at time 200 s. Notice that this would have caused hypotension and an excessively low RASS value. The black dash-dotted line represents the response that would have been obtained without changing the ratio from 0.8 to 1.5 at time 500 s, which would have caused a rise of the RASS above the target value. It is worth noting that the changes in the ratio value do not affect the BIS value.

5. DISCUSSION

The effectiveness of the proposed solution for propofol and remifentanil coadministration in the BIS regulation has been extensively tested in simulation in (Merigo et al., 2019) and clinically tested on a group of 10 patients in (Schiavo et al., 2021). However, the effect of the proposed control solution on hemodynamics and analgesia had not yet been investigated. The introduction of the open source patient simulator presented in (Ionescu et al., 2021) allows the analysis of the performance also with respect to these important aspects. The simulation performed on all the thirteen patients of the considered dataset, with the recommended opioid-hypnotic ratio of 2, shows that the system achieves the target BIS without violating the lower bound of MAP in eleven out of thirteen patients. In the two remaining patients the MAP falls slightly below the lower bound of 65 mmHg, thus indicating a generally good behaviour with respect to hemodynamics. The RASS is slightly above the desired target in only one out of thirteen patients, thus indicating a good analgesic coverage. These results have also been confirmed experimentally in (Schiavo et al., 2021) where none of the ten patients enrolled show clinical signs of inadequate analgesia or hemodynamic instability. However, in the simulation performed on the considered dataset, two patients, namely patient 1 and patient 8, show opposite behaviours in response to remifentanil administration. The simulations performed on these two patients by changing the ratio value have shown the importance of a control system that offers the possibility to modify this parameter to adapt to the characteristics of each patient. The simulation performed on patient 8 for both anesthesia induction and disturbance rejection has also shown the usefulness of giving to the anesthesiologist the possibility to regulate the ratio during anesthesia depending on the different situations that may occur.

Despite the good results obtained in simulation, it is important to underline that the situations considered can be simplistic compared to those that can occur in clinical practice. Indeed, there are other aspects to consider for the regulation of the opioid-hypnotic balance, such as the phase of anesthesia, the type of surgical procedure and the physiological response to stimulation. There may also be situations in which the patient shows hemodynamic instability even in the presence of reduced doses of drugs or for particular surgical procedures that affect the cardiovascular system. In these cases the use of drugs active on hemodynamics, such as vasopressors, is essential. In this sense the possibility to select the opioid-hypnotic ratio can help the anesthesiologist to manage patient's hemodynamics but it might not be sufficient to ensure hemodynamic stability. In this simulation, analgesia is represented by the RASS since other more specific measurements are not available yet. Moreover, the blunting effect of remifentanil on surgical stimulation affecting the DoH is not considered since the disturbance profile employed acts on the BIS with the same magnitude regardless of the remifentanil concentration. Since the simulator is open source, the modeling of these effects can be implemented in a future version when more sophisticated models will become available.

6. CONCLUSIONS

In this paper an optimized PID controller for propofol and remifentanil coadministration has been tested in simulation. To this end, a recently devised open source patient simulator that implements the interactions between anesthetic drugs, hemodynamics and analgesic coverage has been employed. In the proposed solution, the opioid-hypnotic balance can be manually adjusted by the anesthesiologist during the time course of anesthesia. Simulation results have shown the importance of this parameter that allows the anesthesiologist to select the most appropriate opioid-hypnotic ratio depending on the patient and on the specific phase of anesthesia. Hence, the possibility to select the ratio can help the anesthesiologist to better manage the combination of patient's DoH, analgesia and hemodynamics. Future work will include the clinical experimentation of the proposed control solution in order to validate the results obtained in this work.

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