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A modified PID-based control scheme for depth-of-hypnosis control: Design and experimental results

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ABSTRACT

Background and Objective: Many methodologies have been proposed for the control of total intravenous anesthesia in general surgery, as this yields a reduced stress for the anesthesiologist and an increased safety for the patient. The objective of this work is to design a PID-based control system for the regulation of the depth of hypnosis by propofol and remifentanil coadministration that takes into account the clinical practice. *Methods:* With respect to a standard PID control system, additional functionalities have been implemented in order to consider specific requirements related to the clinical practice. In particular, suitable boluses are determined and used in the induction phase and a nonzero baseline infusion is used in the maintenance phase when the predicted effect-site concentration drops below a safety threshold. *Results:* The modified controller has been experimentally assessed on a group of 10 patients receiving general anesthesia for elective plastic surgery. The control system has been able to induce and maintain adequate anesthesia without any manual intervention from the anesthesiologist. *Conclusions:* Results confirm the effectiveness of the overall design approach and, in particular, highlight that the new version of the control system, with respect to a standard PID controller, provides significant advantages from a clinical standpoint.

1. Introduction

Hypnosis, analgesia, and paralysis are the three main effects of general anesthesia, and three different drugs are used in total intravenous anesthesia (TIVA) to achieve these effects. Propofol and remifentanil are commonly employed as hypnotic and analgesic agents, respectively. Neuromuscular blocking drugs are used to achieve paralysis (NMBAs). In general anesthesia, hypnosis and analgesia are always required. Propofol and remifentanil administration must be properly balanced in order to achieve a patient state suitable for surgery, by considering that these drugs show a synergistic effect [1]. Paralysis can be required only to facilitate endotracheal intubation and to improve the surgical conditions in specific types of surgery. Moreover, NMBAs have no significant interaction on hypnosis or analgesia.

Induction, maintenance, and emergence are the three distinct temporal phases of general anesthesia. In typical clinical practice, during the induction phase, the patient is given appropriate boluses of propofol and remifentanil to produce an anesthetic state sufficient to begin the surgical procedure. During the maintenance phase, the anesthesiologist monitors the patient's anesthesia state and changes the drug infusion accordingly. During both induction and maintenance, the anesthesiologist titrates the anesthetics relying on recommended dosages and infusion patterns, which are then further modified based on the patient's actual needs. The delivery of anesthetics is stopped during the emergence period, and the patient regains consciousness.

Evaluating the patient's anesthesia state is a crucial task for the anesthesiologist. Indeed, because direct measures of hypnosis and analgesia are not available, indirect markers such as hemodynamic variables, brain electrical activity, and other qualitative clinical indicators must be used. Since drug dosing relies on subjective eval-

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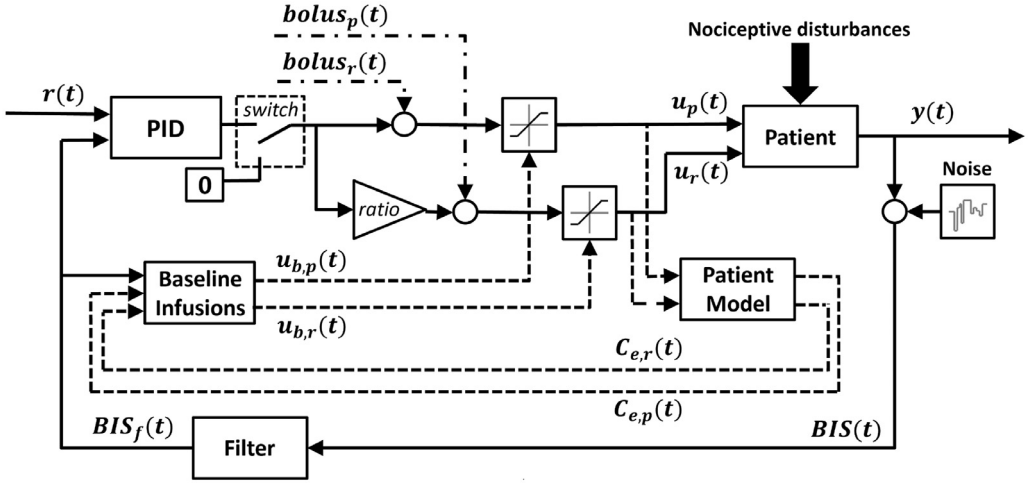

Fig. 1. Block diagram of the modified control architecture.

Table 1
Demographics of the patients enrolled in the study.

Patient	Age	Height [cm]	Weight [kg]	Gender
1	80	170	75	M
2	43	174	114	F
3	69	162	75	F
4	58	167	63	F
5	28	160	50	F
6	60	188	120	M
7	44	170	90	M
8	37	163	55	F
9	54	164	59	F
10	68	156	70	F

uation of the anesthetic state, it is highly dependent on anesthesiologist's experience, and this could affect the outcome of anesthesia in terms of patient's well-being. In fact, drug underdosing can cause intra-operative awareness that can lead to the onset of post-traumatic stress disorder in the post-operative phase [2]. Conversely, anesthetic drugs overdosing can cause severe arterial hypotension and can affect the quality of the post-operative phase [3].

In order to support the anesthesiologist in the drug dosing task, target-controlled infusion (TCI) devices have been introduced [4]. These systems provide both the induction boluses and the maintenance rates by calculating an appropriate infusion profile based on a pharmacokinetic model of the drug to be administered. However, TCIs are model-based systems that work in an open loop fashion. Hence the anesthesiologist needs to adjust the target concentration on the basis of the observed clinical response to compensate for the unavoidable mismatch between the dynamics of the patient and the TCI model.

Closed-loop control of general anesthesia has increasingly attracted research interest in the past decades with a significant expansion during the last five years [5,6]. Many randomized controlled trials comparing closed-loop control to conventional manual control in a variety of clinical settings have been conducted. These studies have shown the advantage of automatic control in terms of ability to maintain physical variables of interest inside clinical recommended ranges, reduction of drug dosage and recovery time [7,8].

In order to design a closed-loop system, a quantitative feedback variable is required. In the mid-90s the introduction of the Bispectral Index Scale (BIS, Aspect Medical Systems, Norwood, USA) as a quantitative measure of depth of hypnosis (DoH) has allowed the development of single-input-single-output (SISO) control systems for the automatic regulation of propofol infusion. For example, solutions based on robust PID control [9–11], optimized PID control [12] and event-based control [13] have been proposed in the literature. The effectiveness of SISO control systems has been demonstrated in experiments with a variety of control architectures, including PID control [14,15], model-based control [16], model predictive control [17,18] and fuzzy control [19]. However, clinical investigations have also highlighted the need of controlling remifentanil infusion to obtain a completely automated anesthesia control systems [20].

Multiple-input-multiple-output (MIMO) control scheme that also takes analgesia into account have therefore been developed and tested, obtaining promising results in clinical trials [21–23]. However, the indicators of analgesia that are used to titrate remifentanil in these systems are not commonly accepted in the clinical practice. Indeed, despite promising results (see e.g., [24,25]); the development of a reliable measure of analgesia is still an open problem.

As an alternative to MIMO systems, multiple-input-single-ouput (MISO) control schemes that exclusively rely on a measure of DoH have been developed. Since a single output (the DoH) is controlled by two inputs (the infusion rates of propofol and remifentanil) the system is overactuated. In other words, the same DoH level can be obtained with different opioid-hypnotic balances, which leaves a degree of freedom to be constrained by using considerations deriving from the clinical practice. In this context, in [26] a rule-based PID-like controller, which considers the different metabolization times of propofol and remifentanil, has been proposed. The resulting opioid-hypnotic balance is embedded in the defined set of rules. The control system performs automatically both induction and maintenance of anesthesia and has been clinically evaluated on a population of 83 patients.

Conversely, in [27] a habituating control framework, where the opioid-hypnotic balance is decided by the anesthesiologist by imposing a baseline effect-site concentration of remifentanil, has been proposed. In this control system wavelet-based anesthetic value for central nervous system (WAV_{CNS}) is used instead of BIS as feedback signal for DoH. The control system performs automatically both induction and maintenance of anesthesia and has been clinically evaluated on 80 patients.

A different approach has been developed in [28], where the opioid-hypnotic balance can be selected by the anesthesiologist by imposing the ratio between the infusion rates of propofol and remifentanil. The controller is a PID whose tuning parame-

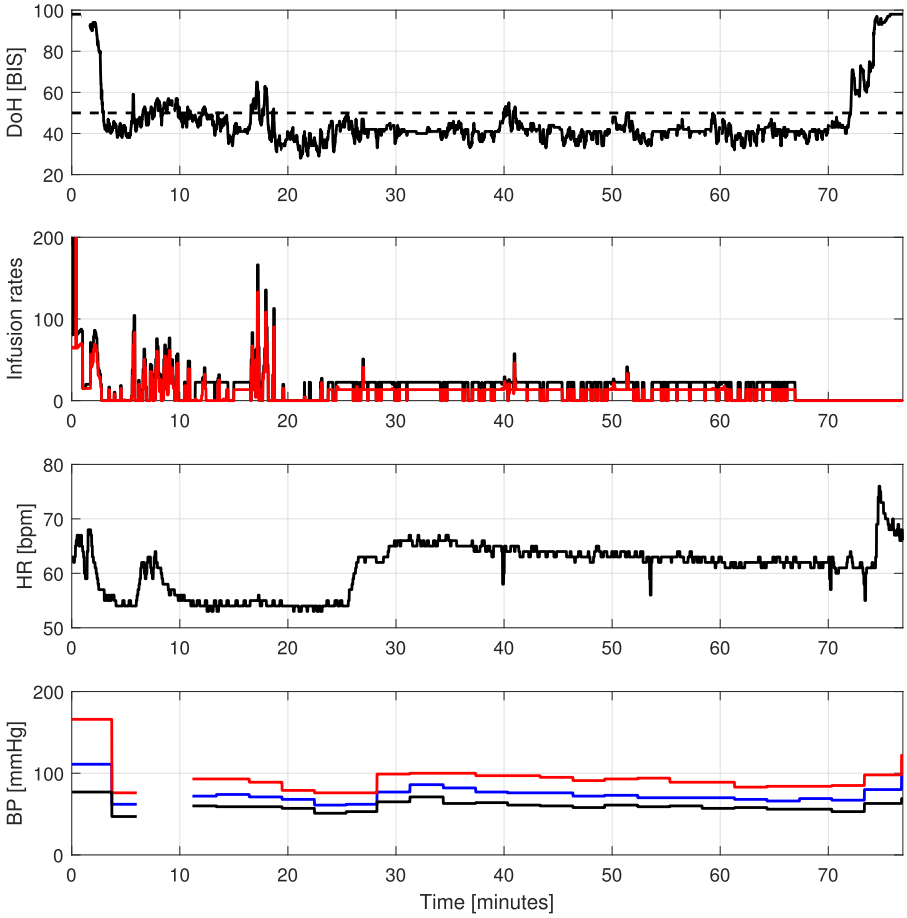

Fig. 2. Clinical variables of patient 1 (80 years old male, 170 cm high, 75 kg of weight, undergoing melanoma excision and sentinel lymph node biopsy). From top to bottom: BIS (solid line) and BIS set-point (dashed line); propofol (black) and remifentanil (red) infusion rates in ml/h; heart rate; systolic (red), diastolic (black) and mean (blue) blood pressure. Missing data are due to temporary issues with sensors reading. After the induction phase, the BIS remains steadily around the value of 40 while the controller is infusing almost only the baseline drugs infusions with the exception of a rise around minute 20 that is rapidly compensated by the controller. The sharp rise in the value of heart rate and blood pressure around minute 30 is due to the administration of the vasoactive medication ephedrine. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

ters have been selected by optimizing a performance index over a diverse dataset of 13 patients. In [29] the experimental results obtained with the aforementioned solution have been presented. The promising results confirmed the effectiveness of the PID-based control. Moreover, the comparison with the results obtained with manual control has shown that the behavior of the closed-loop system is consistent with the trends observed in the clinical practice.

In this paper we present a modified version of the control scheme proposed in [29], which has been designed in order to take into account specific requirements related to the clinical practice (which might be slightly different depending on the anesthesiologist).

In particular, in addition to the PID based continuous regulation of the infusion, the control system automatically administers propofol and remifentanil boluses at the beginning of the induction phase. This addition to the original control system has been implemented to bridge the gap between the automatic regulation and the clinical practice by delivering a faster loss of consciousness. In this way, we reduce the risk for patients to experience discomfort and anxiety due to pain on propofol injection and create better conditions for manually assisted ventilation. Indeed, even if in [29] the PID controller alone was sufficient to adequately induce anesthesia and no problems were experienced during the insertion of laryngeal mask or endotracheal tube, the anesthesiologist might prefer the use of a bolus to fully ensure a rapid induction phase. This phase is critical. Anesthesia must be induced in a short time in order to rapidly secure the patient's airway. Concurrently, overdosing must be avoided as it can provoke side-effects such as severe arterial hypotension. Taking this issues into account, control solutions specifically designed for the induction phase have been proposed in the literature. To formally guarantee overdosing prevention, an explicit reference governor control scheme has been proposed in [30] and, to minimize the induction time, an optimized feedforward control has been proposed in [31]. Despite the promising results obtained in simulation by these solutions, their effectiveness has not been clinically assessed yet. Conversely, the technique of exploiting drug boluses in closed-loop systems to induce anesthesia has been tested in clinical experimentations. In [20] a fixed volume of propofol is administered as bolus at the beginning of anesthesia to reduce the induction time. In [17] an induction sequence of an initial bolus of propofol followed by a continuous infusion is employed. The propofol dosage is calculated based on the patient's weight. Being a feedforward approach, it guarantees that the desired amount of drug is administered but it has the disadvantage of not taking into account the actual value of DoH. In [32] the derivative action of a PID controller is exploited to produce a bolus of propofol at the beginning of anesthesia induction. This is a feedback approach that takes into account the actual value of DoH but, in case of loss of the feedback signal, it does

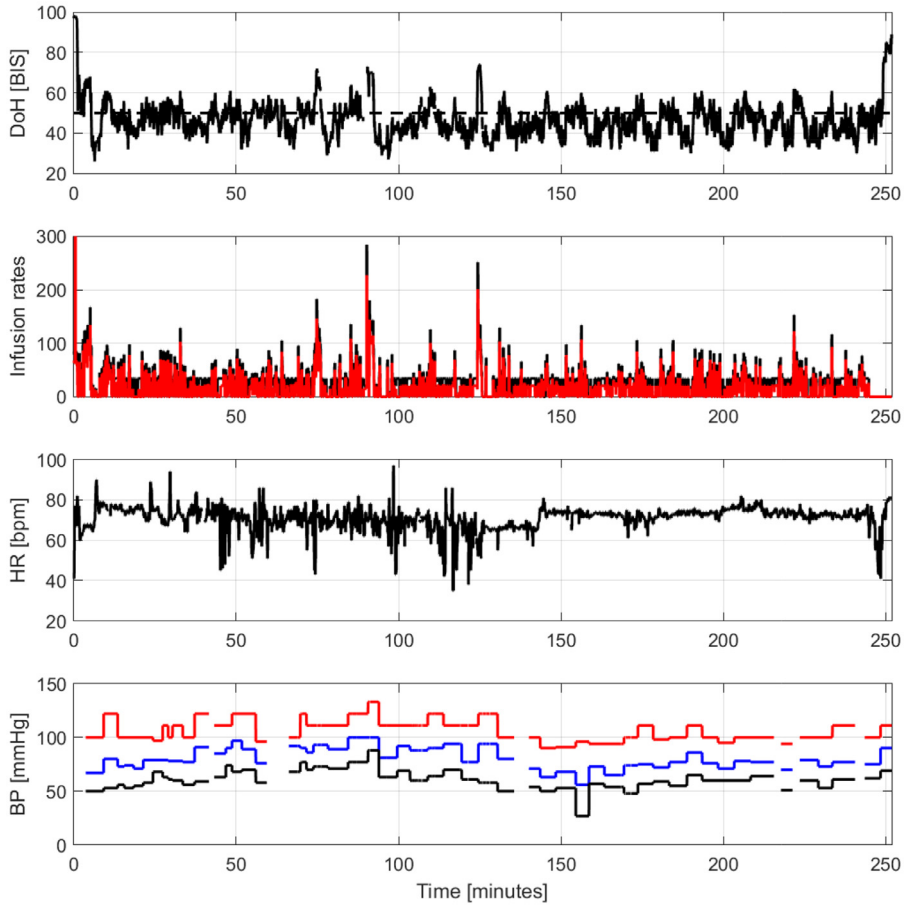

Fig. 3. Clinical variables of patient 2 (43 years old female, 174 cm high, 114 kg of weight, undergoing mastectomy). From top to bottom: BIS (solid line) and BIS set-point (dashed line); propofol (black) and remifentanil (red) infusion rates in ml/h; heart rate; systolic (red), diastolic (black) and mean (blue) blood pressure. Missing data are due to temporary issues with sensors reading. After the induction phase the BIS shows limited oscillations inside the interval from 40 to 60 with the exception of three rises around minutes 75, 20 and 125 that are rapidly compensated by the controller. The hemodynamic variables remain stable throughout the surgical procedure. The noise in the heart rate plot is due to artifacts induced by the electrocautery machine. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

not guarantee that the desired amount of drug is administered to the patient. In this paper, both boluses of propofol and remifenanil are automatically administered by the control system while control solutions proposed so far consider only propofol. Moreover, in this work a combined feedforward/feedback approach is proposed. The first phase of induction is performed by administering the drug boluses in feedforward. However, the dosage of drugs administered with the boluses is not sufficient to reach the target level of DoH. Hence, the induction phase is completed in feedback by the PID controller. This allows us to combine the advantages of both feedforward and feedback approaches.

Another improvement of the original algorithm is the administration of a nonzero baseline infusion during the maintenance phase when the predicted effect-site concentration drops below a safety threshold. These baseline infusions are inherited form the clinical practice where drug infusions are never set to zero during the maintenance phase. Conversely, this might occur when a PID controller is used and the BIS value is below the set-point value. The baseline infusions also help to avoid the oscillations in the feedback variable observed in three patients of the study [29]. This situation occurs because, during phases of low surgical stimulation, the BIS remains below the target value for long time intervals. Consequently, the infusions are zero and the drugs are metabolized. This should be avoided as, when the surgical stimulation is resumed, the drug dosage is not sufficient to compensate for it. This causes a quick surge of the BIS that is compensated by the controller resulting in a subsequent reduction of the BIS and to the possible repetition of the phenomenon. Although no negative clinical consequences were observed, it appeared that the performance could have been improved. By introducing the baseline infusions, the system always guarantees that a minimum amount of drug is administered to the patient, thus preventing an excessive increase of the BIS. To account for the different metabolization times, the baseline infusions for propofol and remifentanil are handled separately. The introduction of baseline infusions and of safety constraints on the effect-site concentrations have been already proposed and discussed in the literature. In [33,34] safety constraints on the minimum and maximum values of propofol effect-site concentration have been considered by imposing a saturation of the control action when the bounds are reached. In [26] safety bounds on the effect-site concentrations of both propofol and remifentanil are considered. In [35] a baseline infusion of remifentanil is administered in order to guarantee a desired effect-site concentration. These methodologies impose fixed bounds on the estimated effect-site concentrations of the drugs. However, due to model uncertainties and to the high variability of the response to drug administration, the imposed bounds could be inappropriate for some patients. In this case, the anesthesiologist must intervene manually to adjust those bounds. Thus, the advantage of closed-loop systems in reducing the anesthesiologist workload is partially lost. In the

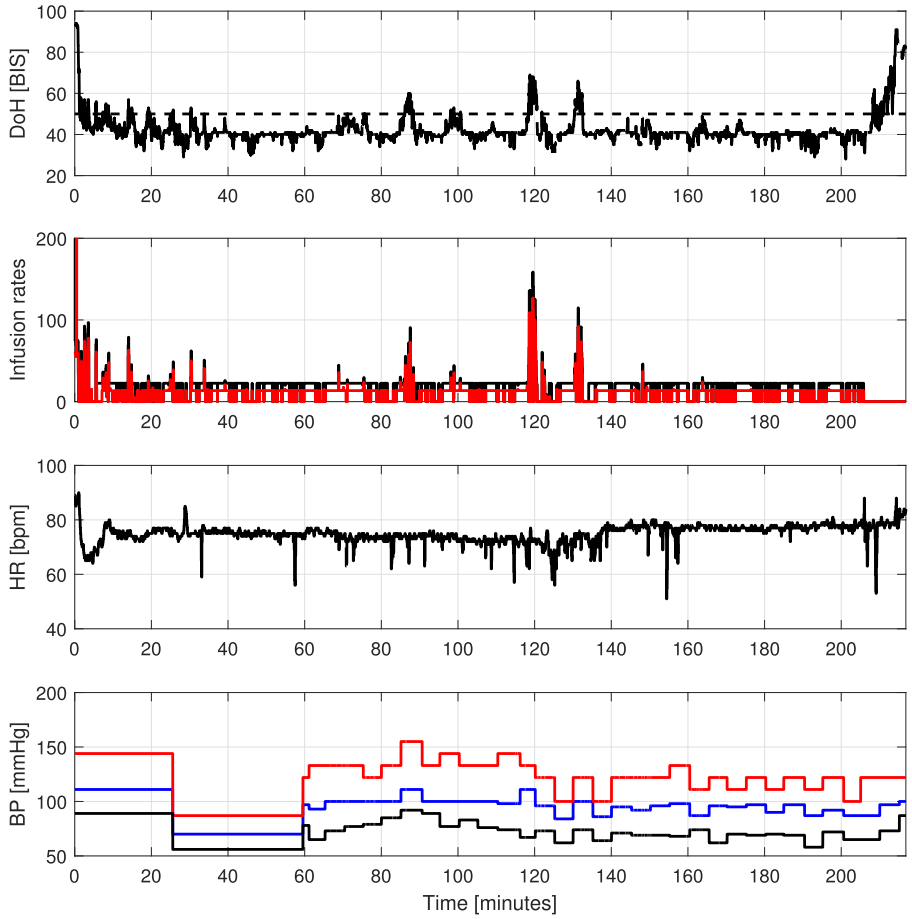

Fig. 4. Clinical variables of patient 3 (69 years old female, 162 cm high, 75 kg of weight, undergoing mastoplasty). From top to bottom: BIS (solid line) and BIS set-point (dashed line); propofol (black) and remifentanil (red) infusion rates in ml/h; heart rate; systolic (red), diastolic (black) and mean (blue) blood pressure. After the induction phase the BIS remains steadily around the value of 40 while the controller is infusing almost only the baseline drugs infusions with the exception of three rises around minutes 90, 120 and 130 that are rapidly compensated by the controller. The hemodynamic variables remain stable throughout the whole surgical procedure. The noise in the heart rate plot is due to artifacts induced by the electrocautery machine. The lack of update of the blood pressure plot during the first 60 min is due to a data recording issue. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

approach proposed in this work, the baseline infusions are activated only when the BIS is above the safety threshold of 40. By doing so, the baseline infusions are administered on the basis of the effect-site concentration estimated by the model and by the actual level of DoH of the patient. Thus, the risk of overdosing is reduced and the manual intervention of the anesthesiologist is not required.

The effectiveness of the changes described above has been experimentally assessed on a population of 10 patients undergoing general anesthesia for plastic surgery and the obtained experimental results are presented in this paper. The paper is organized as follows. The control system is described in Section 2. The results obtained with the proposed control solution are presented in Section 3 and a comparison with the PID controller proposed in [29] is given in Section 4. Results are discussed in Section 5. Finally, conclusions are drawn in Section 6.

2. Methods

The control system considered in this work is a variation of the solution presented in [28,29], where the architecture and the tuning methodology employed have been thoroughly described. In this paper we propose two major modifications of the original control system described above in order for the closed-loop system to better match the clinical needs.

A schematic representation of the modified control system is shown in Fig. 1.

The PID controller structure and its tuning have not been changed with respect to [29]. The two changes affect the induction and the maintenance phase, respectively. As regards the induction phase, the automatic induction sequence has been redesigned to administer a 1 mg/kg bolus of propofol $bolus_p(t)$ and a 1 µg/kg bolus of remifentanil $bolus_r(t)$. The boluses are given as feedforward control actions in open loop (that is, the PID controller is disconnected). The patient's weight is provided to the system and the bolus volumes of propofol and remifentanil are calculated accordingly. When the control system is started, the bolus of propofol is administered by setting the propofol infusion pump at its maximum infusion rate for the time required to administer the target volume. After a pause of 5 s the bolus of remifentanil is administered by following the same procedure with the remifentanil infusion pump. Immediately after the end of the remifentanil bolus the loop is closed and the PID controller is applied with the integral action that is reset to zero. The dosage of the bolus of propofol has been chosen according to Roberts manual infusion scheme [36], while for remifentanil it has been chosen according to the dosing guidelines reported on remifentanil data sheet. Boluses are administered sequentially and not simultaneously as this last modality would result in a high flow rate that could damage the vein as the two drugs share the same venous access. Moreover, the bolus of

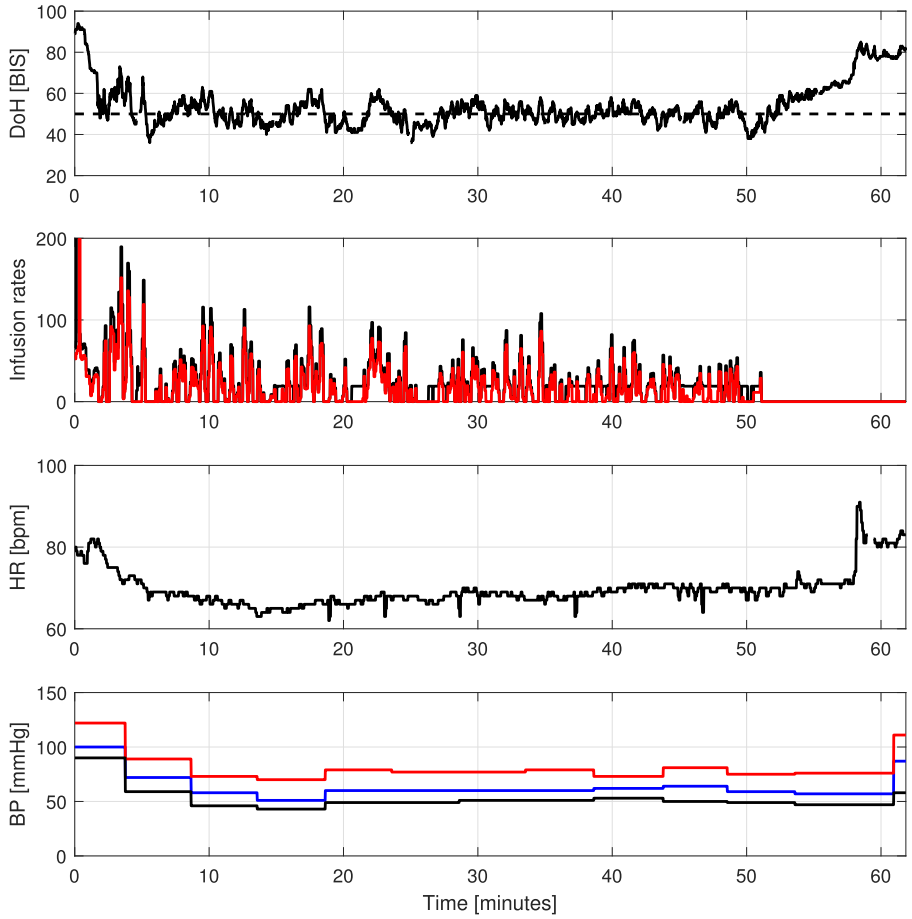

Fig. 5. Clinical variables of patient 4 (58 years old female, 167 cm high, 63 kg of weight, undergoing melanoma excision and sentinel lymph node biopsy). From top to bottom: BIS (solid line) and BIS set-point (dashed line); propofol (black) and remifentanil (red) infusion rates in ml/h; heart rate; systolic (red), diastolic (black) and mean (blue) blood pressure. After the induction phase the BIS remains steadily inside the recommended range from 40 to 60. The hemodynamic variables remain stable throughout the surgical procedure. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

propofol is given before the bolus of remifentanil to ensure that propofol-induced loss of consciousness occurs before the onset of the respiratory depressive side effect of remifentanil, as this could cause discomfort to the patient.

As regards the maintenance phase, the baseline infusion of propofol $u_{b,p}(t)$ is administered when the predicted effect-site concentration $C_{e,p}(t)$ falls below a safety threshold and the low-pass filtered BIS value $BIS_f(t)$ is above 40. The same applies for remifentanil with $u_{b,r}(t)$ and $C_{e,r}(t)$. The predicted effect-site concentrations of propofol and remifentanil are calculated by using the nominal pharmacokinetic/pharmacodynamic (PK/PD) model of Schnider [37,38] and Minto [39], respectively, which have been implemented in the *Patient Model* block shown in Fig. 1. In this study $u_{b,p}(t)$ and $u_{b,r}(t)$ have been set equal to 6 mg/kg/h and 0.15 µg/kg/min, respectively, while $C_{e,p}(t)$ and $C_{e,r}(t)$ have been set equal to 3 µg/ml and 4 ng/ml, respectively. These values has been chosen by considering standard dosages that are usually recommended in the clinical practice of TIVA. In particular, $u_{b,p}(t)$ and $C_{e,p}(t)$ have been chosen according to Roberts manual infusion scheme [36], while $u_{b,r}(t)$ and $C_{e,r}(t)$ has been chosen according to the guidelines reported in [40].

3. Experimental results

In this trial 10 patients scheduled for elective plastic surgery have been enrolled. Their demographic data are shown in Table 1 while the types of surgery and the number of patients is shown in Table 2. The duration of the surgery, the region of the body involved, and the amount of painful stimulation vary significantly. The same clinical protocol described in [29] has been used.

Table 2
Type and number of surgical procedures.

Type of surgery	Number of patients
Melanoma excision and sentinel lymph node biopsy	4
Mastoplasty	4
Mastectomy	1
Escharotomy and microsurgical flap	1

The recorded BIS, heart rate, mean blood pressure, drugs infusion rates are shown, for each patient, in Figs. 2–11. The level of BIS recorded during the procedure and the BIS set-point are shown in black solid line and black dashed line, respectively, in the top plot of each figure. In the second plot, propofol and remifentanil infusion rates, in ml/h, are represented by black and red lines, respectively. The third and fourth plots are heart rate and blood pressure, and in particular, the systolic, diastolic, and mean blood pressures are represented with a red, a black, and a blue solid line in the bottom plot. In the plots there are some missing data that are due to temporary issues with sensors reading. From the individual values of time courses it is possible to observe that the variables remain within clinically acceptable limits through the entire proce-

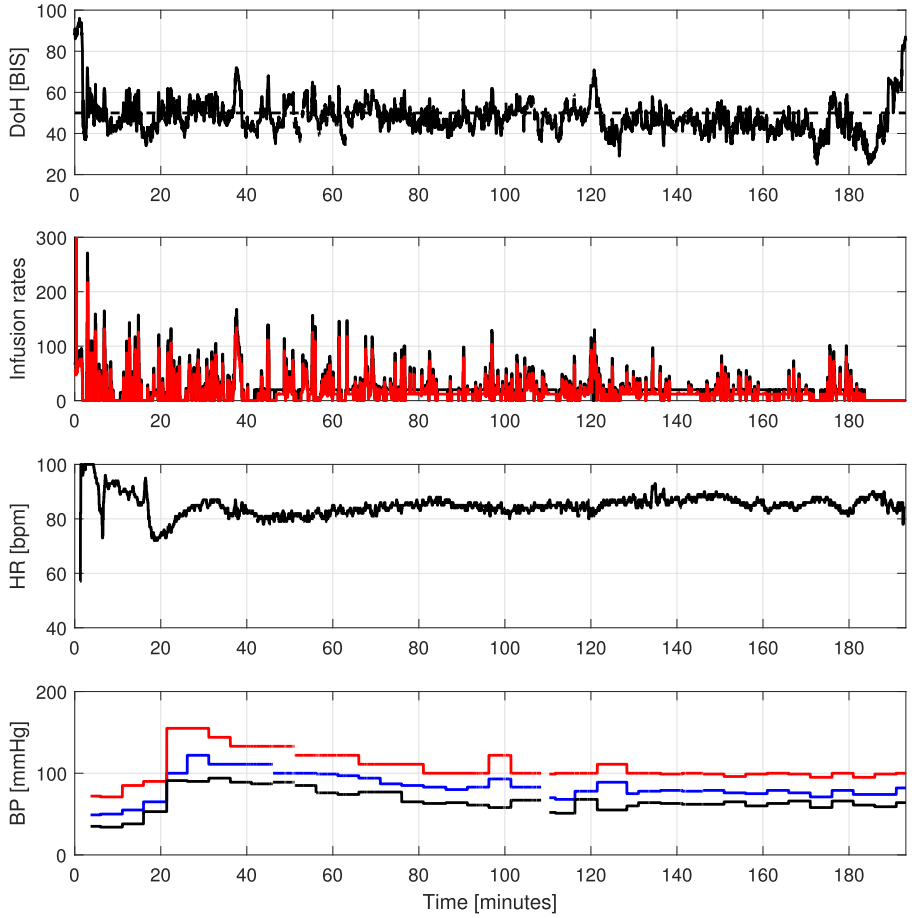

Fig. 6. Clinical variables of patient 5 (28 years old female, 160 cm high, 50 kg of weight, undergoing mastoplasty). From top to bottom: BIS (solid line) and BIS set-point (dashed line); propofol (black) and remifentanil (red) infusion rates in ml/h; heart rate; systolic (red), diastolic (black) and mean (blue) blood pressure. Missing data are due to temporary issues with sensors reading. The BIS shows limited oscillations inside the interval from 40 to 60 with the exception of two rises around minutes 40 and 120 that are rapidly compensated by the controller. The sharp rise in the value of heart rate and blood pressure around minute 20 is due to the administration of the vasoactive medication ephedrine. Afterwards, the hemodynamic variables remain stable throughout the surgical procedure. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 3
Performance indexes for the induction phase.

Patient	*Induction time* [min]	*Lowest BIS*	*Propofol dose* [mg/kg]	*Remifentanil dose* [µg/kg]
1	2.73	40	1.59	2.21
2	1.65	49	1.09	1.38
3	1.18	45	1.23	1.25
4	1.7	47	1.55	1.68
5	1.87	37	2.07	2.83
6	1.55	43	1.25	1.57
7	2.05	42	1.31	1.71
8	2.7	51	2.17	2.48
9	4.68	51	2.77	4.45
10	1.07	36	1.50	1.36
Average	2.12	44	1.65	2.09

dure and for all patients. Propofol and remifentanil infusion rates always assumed sensible values, common for the clinical practice.

The closed-loop system autonomously induced and maintained anesthesia for all the patients enrolled, without the need for the anesthesiologist to intervene.

Table 3 shows the results achieved during the induction phase. The induction time is defined as the time interval between the beginning of infusions and the time when the BIS enters the range [40, 60] and stays there for the next 30 s. The lowest BIS is the minimum observed value of the BIS in the 60 s following the induction time. Propofol dose and remifentanil dose are the amounts of drugs administered during the induction time expressed in mg/s and µg/s, respectively. From the induction times in Table 3, we observe that anesthesia was rapidly induced in all patients. In particular, anesthesia was induced, on average, in 2.12 min. The longest induction time of 4.68 min was observed in patient 9 and was caused by the temporary loss of the BIS signal during the induction phase. This was in turn caused by the artifacts introduced by anesthesiologist's movements during intubation. These results meet the target induction time, which, in our clinical context, i.e., elective plastic surgery, was of 3 min with the possibility to tolerate an induction time up to 5 min and no problems were reported by

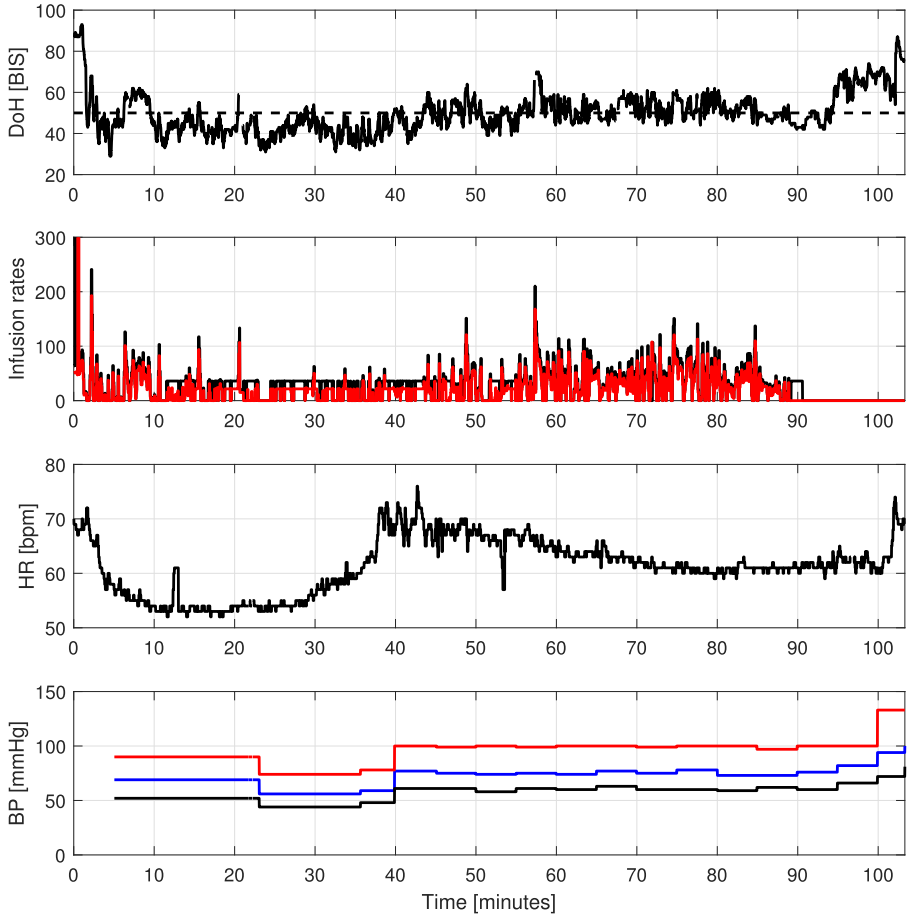

Fig. 7. Clinical variables of patient 6 (60 years old male, 188 cm high, 120 kg of weight, undergoing escharotomy and microsurgical flap). From top to bottom: BIS (solid line) and BIS set-point (dashed line); propofol (black) and remifentanil (red) infusion rates in ml/h; heart rate; systolic (red), diastolic (black) and mean (blue) blood pressure. Missing data are due to temporary issues with sensors reading. It is possible to notice a phase of low surgical stimulation followed by a phase of strong surgical stimulation which begins around minute 40. During the first phase the BIS remains steadily around the value of 40 while the controller is infusing almost only the baseline drugs infusions. During the second phase the infusions are increased by the controller. The effect of surgical stimulation is also visible on the hemodynamic variable that increase around minute 40. However, the values remains within clinical acceptable limits and the patient does not show tachycardia or hypertension. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

the anesthesiologist. For all the patients enrolled, the insertion of the endotracheal tube or the laryngeal mask was performed without difficulties or clinically relevant reactions, thus indicating an appropriate anesthetic coverage. The fast induction was achieved without causing an excessive BIS undershoot as it is possible to notice by observing the lowest BIS. In particular, the lowest average value of BIS after induction is 44. Two patients out of ten show an undershoot of the BIS below the recommended value of 40, namely patient 5 and patient 10. They have a lowest BIS of 37 and 36 respectively. However, as it is shown in Figs. 6 and 11, the undershoot is short-lasting and there are no signs of hypotension or bradycardia. Moreover, none of the patients shows the onset of burst-suppression of the electroencephalogram which is a phenomenon that is correlated with an excessive level of DoH. The propofol and remifentanil induction dosages are compatible with the clinical practice. In particular, on average, anesthesia is induced with 1.65 mg/kg of propofol and 2.09 μg/kg of remifentanil.

Table 4 shows the results achieved during the maintenance phase. The interval between the induction time and the instant when the automatic control is turned off at the end of surgery is referred to as maintenance duration. The percentage of BIS inside the recommended range ($BIS\ 40-60$) and the percentage of BIS below the recommended range ($BIS < 40$) are expressed as percentages with respect to the duration of maintenance. *Propofol* and *Remifentanil* are the average infusion rates during the maintenance phase. The *T awakening* is the time-to-extubation. It is defined as the time that elapses between the end of automatic control and the removal of the endotracheal tube or the laryngeal mask. It has been chosen as an indicator of anesthesia emergence since it is the time that the patient takes to regain the ability to breathe autonomously and to understand the verbal command to open the mouth. From Table 4 it appears that the BIS was maintained inside the recommended range for most of the maintenance time. In particular, on average, the BIS was kept inside the recommended range for the 83.17% of the maintenance time, with a minimum of 73.25% for patient 1. The system was also able to effectively reject surgical disturbances without causing excessive undershoot of the BIS. Indeed, the BIS has fallen under the recommended range, on average, for the 12.97% of maintenance time, and it has risen over 60, on average, for the 3.86% of maintenance time. These indexes show that, when the BIS is not in the recommended range, it is, for the most part, below 40 and not over 60. This is a sensible behavior because it prevents the risk of intra-operative awareness. The minimum value of $BIS\ 40-60$ in this study is 73.25% and it has been obtained for patient 1, who also has the highest $BIS < 40$ value of 25.21%. Hence, we can consider this patient as the one with the higher risk of overdosing. However, by checking the propofol and remifentanil maintenance dosages, it is possible

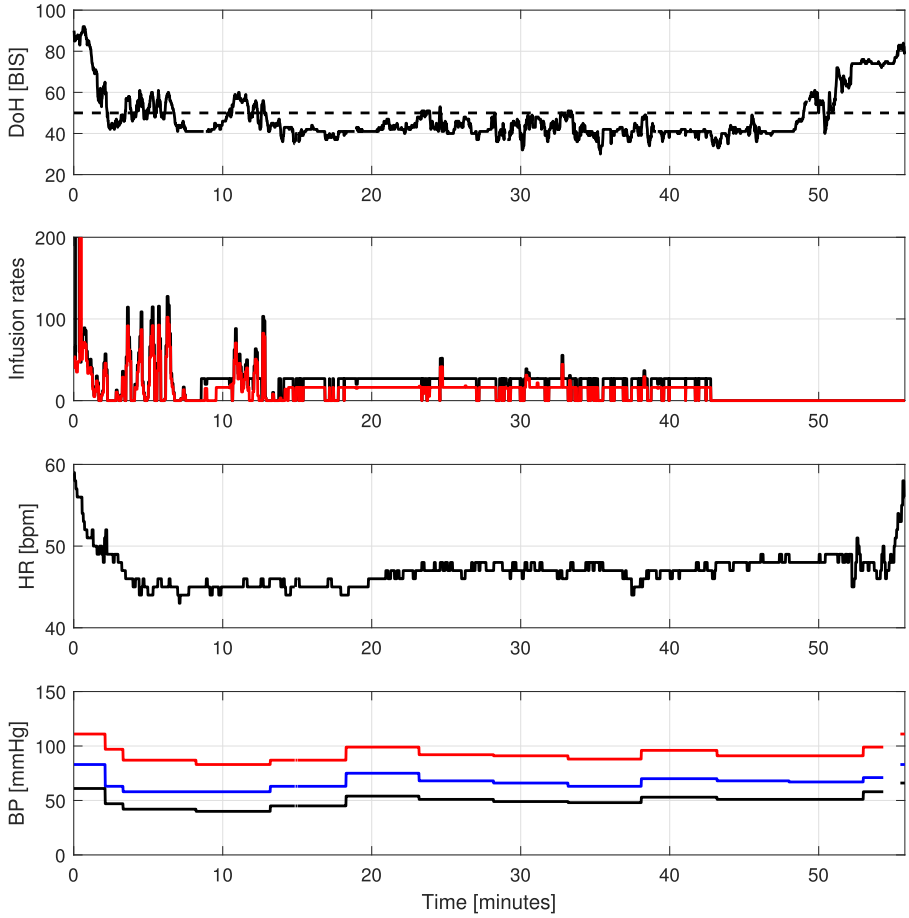

Fig. 8. Clinical variables of patient 7 (44 years old male, 170 cm high, 90 kg of weight, undergoing melanoma excision and sentinel lymph node biopsy). From top to bottom: BIS (solid line) and BIS set-point (dashed line); propofol (black) and remifentanil (red) infusion rates in ml/h; heart rate; systolic (red), diastolic (black) and mean (blue) blood pressure. After the induction phase the BIS remains steadily around the value of 40 while the controller is infusing almost only the baseline drugs infusions. The hemodynamic variables remain stable throughout the rest of the surgical procedure. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 4
Performance indexes for the maintenance phase.

Patient	*Duration*	*BIS* 40 − 60	*BIS* < 40	*BIS* > 60	*Propofol*	*Remifentanil*	*T awakening*
	[min]	[%]	[%]	[%]	[mg/kg/h]	[µg/kg/min]	[min]
1	64.18	73.25	25.21	1.54	4.55	0.12	7.57
2	243.17	73.97	20.40	5.63	5.38	0.12	10.13
3	204.67	75.15	22.00	2.85	4.78	0.12	8.4
4	49.40	93.83	1.55	4.62	8.16	0.23	7.12
5	181.77	86.59	8.00	5.41	9.82	0.30	8.48
6	89.03	84.14	11.77	4.09	5.48	0.16	11.25
7	40.70	87.06	11.43	1.51	5.28	0.14	12.30
8	62.50	89.73	7.15	3.12	9.29	0.26	6.73
9	178.15	81.77	11.19	7.04	9.17	0.27	5.08
10	176.93	86.25	10.97	2.78	7.04	0.17	4.00
Average	129.05	83.17	12.97	3.86	6.90	0.19	8.11

to note that they are below the average of the considered population and they are also below the recommended values used in the clinical practice of 6 mg/kg/h of propofol and 0.15 µg/kg/min of remifentanil. Moreover, the patient does not show the onset of burst-suppression. In addition, the patient does not exhibit clinical signs of hypotension or bradycardia, see Fig. 2. The sharp rise in the value of heart rate and blood pressure recorded around minute 30 is due to the administration of the vasoactive medication ephedrine that was requested to the anesthesiologist by the surgeons in order to facilitate the hemostasis procedure. On the other hand, the patient with the highest risk of underdosing is patient 9, who has the highest *BIS* > 60 value of 7.04%. However, this patient has also the highest values of propofol and remifentanil maintenance dosages, which are above the recommended values. Moreover, hemodynamics remains stable throughout the whole surgical procedure, with no episodes of hypertension and tachycardia and no patient's movements have been reported by the anesthesiologist. The average propofol and remifentanil infusion rates are compatible with the clinical practice. In particular, on average, anesthesia was maintained with 6.90 mg/kh/h of propofol and

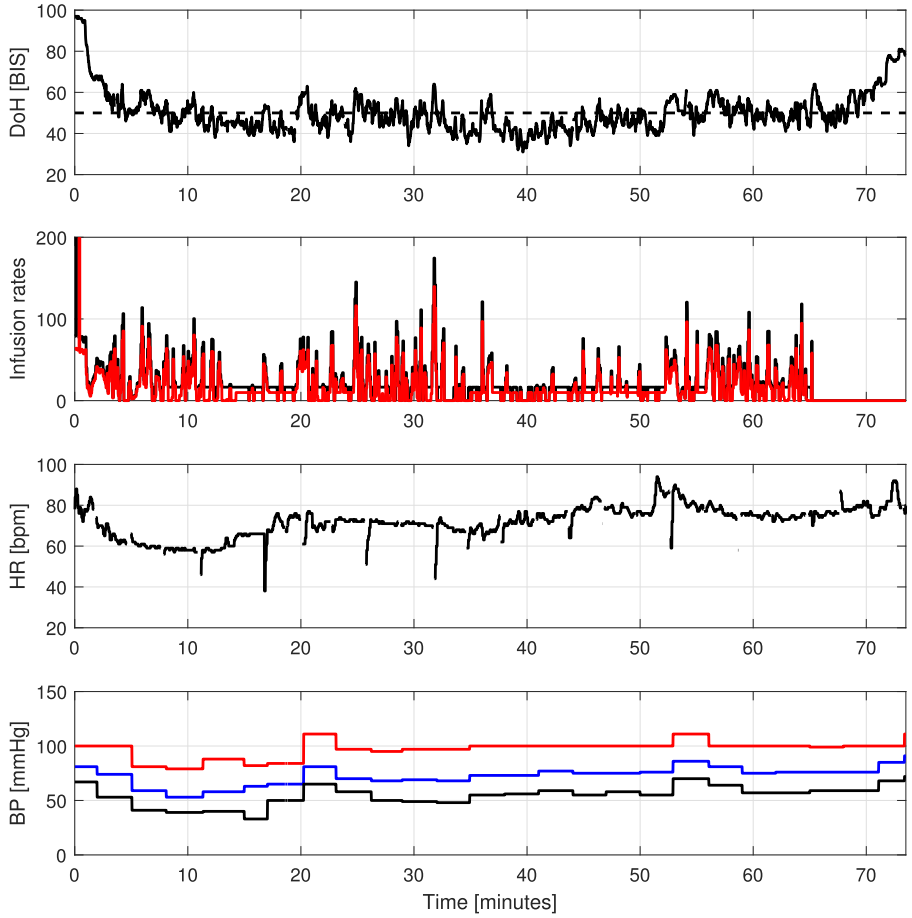

Fig. 9. Clinical variables of patient 8 (37 years old female, 163 cm high, 55 kg of weight, undergoing melanoma excision and sentinel lymph node biopsy). From top to bottom: BIS (solid line) and BIS set-point (dashed line); propofol (black) and remifentanil (red) infusion rates in ml/h; heart rate; systolic (red), diastolic (black) and mean (blue) blood pressure. After the induction phase the BIS shows limited oscillations inside the interval from 40 to 60 and the hemodynamic variables remain stable throughout the surgical procedure. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

0.19 μg/kg/min of remifentanil. Finally, the average T awakening of 8.11 min is fully compatible with the clinical practice.

4. Performance comparison

In order to better evaluate the effectiveness of the additional functionalities implemented in the modified control system, a performance comparison with the previous version of the control system proposed in [29] is performed. For the sake of clarity, in the rest of the paper we will indicate as **(a)** the control system proposed in [29] and as **(b)** the new control system proposed in this paper. Continuous data are analysed using a Mann-Whitney U test and categorical data are analyzed using a Fisher's Exact test. Significance level is set at 5%. Data are presented with median and interquartile range (IQR).

In both groups ten patients have been enrolled. Patients demographics for both groups are compared in Table 5. There are no statistically significant differences between the two groups.

To highlight the effect of the propofol and remifentanil induction boluses, the induction performance indexes of the two control systems are compared in Table 6. We observe that **(b)** provides a statistically significant ($P < 0.05$) reduction of the induction time and of the remifentanil induction dose, while there are no statistically significant differences ($P > 0.05$) between **(a)** and **(b)** regarding the lowest BIS and the propofol induction dose. The boxplots of the induction performance indexes are shown in Fig. 12 where the differences between the two groups in the induction time and in the remifentanil induction dose are clearly visible. The outlier is due to patient 9, as explained in Section 3. Regarding the propofol induction dose, the boxplots show that the results of the two groups are very similar. As regards the lowest BIS, although there

Table 5
Comparison of patients demographics. Data are presented as median (IQR), gender is expressed as male/female ratio. There are no statistically significant difference between the two groups ($P > 0.05$).

	(a)	(b)	P value
Age [years]	52.5 (9)	56.0 (25)	1.00
Height [cm]	172.0 (9)	165.5 (8)	0.17
Weight [kg]	81.5 (10)	72.5 (31)	0.34
Gender [M/F]	5/5	3/7	0.65

Table 6
Comparison of performance indexes for induction. Data are presented as median (IQR). Statistically significant differences between groups are marked with an asterisk ($P < 0.05$).

	(a)	(b)	P value
Induction time [min]	3.80 (1.28)	1.78 (0.96)	0.0028*
LowestBIS	42 (9)	44 (8)	0.3066
Propofol dose [mg/kg]	1.64 (0.81)	1.53 (0.69)	0.7337
Remifentanil dose [μg/kg]	3.14 (1.63)	1.69 (0.98)	0.0140*

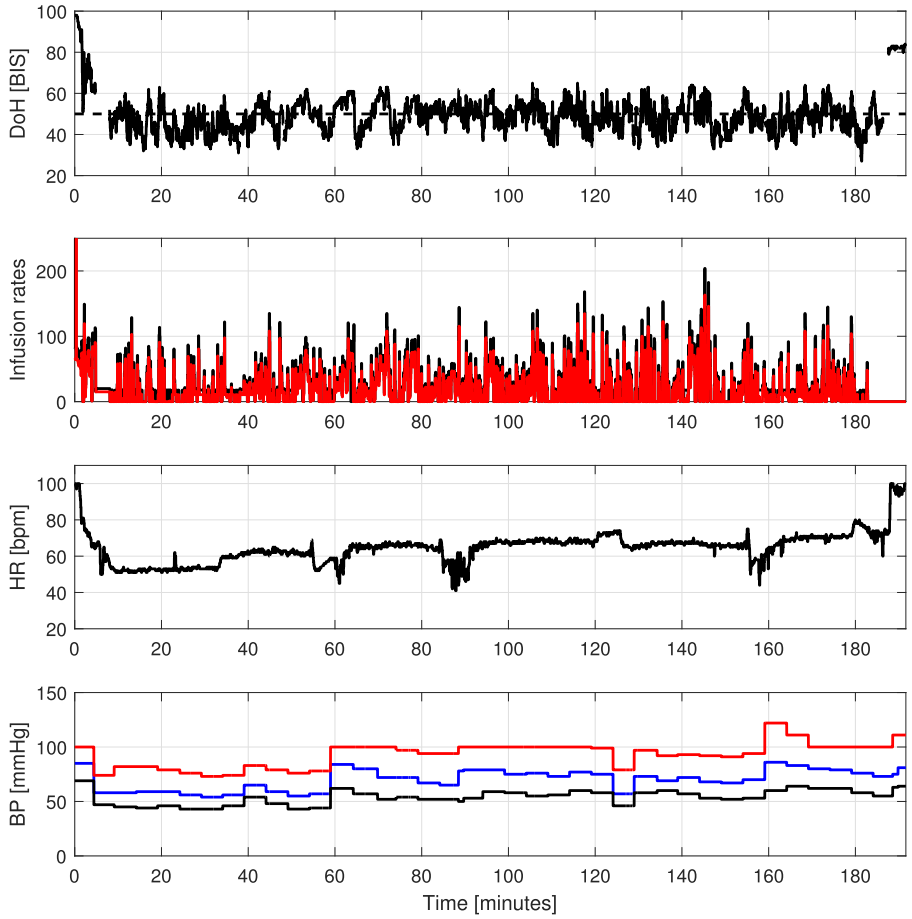

Fig. 10. Clinical variables of patient 9 (54 years old female, 164 cm high, 59 kg of weight, undergoing mastoplasty). From top to bottom: BIS (solid line) and BIS set-point (dashed line); propofol (black) and remifentanil (red) infusion rates in ml/h; heart rate; systolic (red), diastolic (black) and mean (blue) blood pressure. Missing data are due to temporary issues with sensors reading. After the induction phase the BIS shows limited oscillations inside the interval from 40 to 60 and the hemodynamic variables remain stable throughout the surgical procedure. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 7
Comparison of performance indexes for maintenance. Data are presented as median (IQR). There are no statistically significant difference between the two groups ($P > 0.05$).

	(a)	(b)	P value
BIS 40–60	79.79 (22.54)	85.20 (10.13)	0.3075
BIS<40	17.47 (23.15)	11.31 (9.50)	0.3447
BIS>60	2.97 (3.29)	3.60 (2.42)	0.5708
Propofol [mg/kg/h]	5.85 (1.14)	6.26 (3.61)	0.4274
Remifentanil [µg/kg/min]	0.20 (0.04)	0.17 (0.13)	0.7337
MDPE [%]	-9 (6.5)	-7 (10)	0.6189
MDAPE [%]	11 (6.5)	10 (5)	0.7198
WOBBLE [%]	9.2 (3.5)	7.2 (4.5)	0.5403
T awakening [min]	6.46 (4.10)	7.51 (2.92)	0.8501

are no statistically significant differences, **(b)** shows a reduced BIS undershoot with a smaller dispersion of values. The performance indexes of the two control systems in the maintenance phase are compared in Table 7 and the corresponding boxplots are shown in Fig. 13. In addition to the performance indexes presented in Section 3, also the additional performance indexes considered in [29] have been considered, namely the median performance error (MDPE), the median absolute performance error (MDAPE) and WOBBLE.

There are no statistically significant differences between the two groups ($P > 0.05$) for any of the considered performance indexes. However, interesting information can be obtained by observing the boxplots of Fig. 13. The values of BIS 40–60 and BIS<40 in **(b)** show a lower dispersion with respect to those in **(a)**. On the contrary, the values of average propofol and remifentanil infusion rates show a higher dispersion in **(b)** than in **(a)**. All the other performance indexes do not show relevant differences between the two groups.

5. Discussion

Despite the low number of patients enrolled with both control systems, interesting information can be obtained by the performance comparison in order to assess the effects of the changes made to the original control scheme. The introduction of a bolus in the induction phase has provided a reduction of the induction time. This reduces the risk for patients to experience discomfort and anxiety due to pain for the propofol injection and provides better conditions for manually assisted ventilation. The shorter induction time obtained with **(b)** has been obtained without increasing the propofol dose and reducing the administered remifentanil dose. This reduces the risk of opioid-induced side effects such as bradycardia and hypotension. Although not statistically significant, a reduced BIS undershoot with a lower variability is observed in **(b)**. This can suggest a more reliable induction of anesthesia with a reduced risk of undershoot with respect to **(a)**. In the maintenance phase there are no statistically significant differences between the

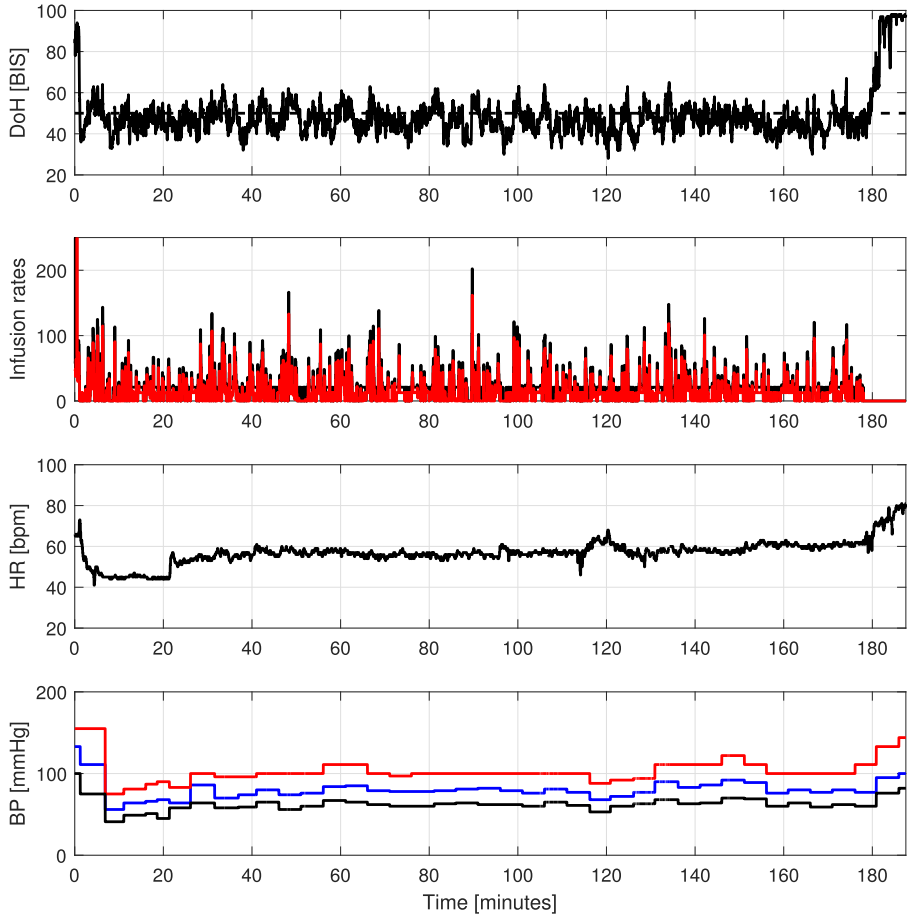

Fig. 11. Clinical variables of patient 10 (68 years old female, 156 cm high, 70 kg of weight, undergoing mastoplasty). From top to bottom: BIS (solid line) and BIS set-point (dashed line); propofol (black) and remifentanil (red) infusion rates in ml/h; heart rate; systolic (red), diastolic (black) and mean (blue) blood pressure. After the induction phase the BIS shows limited oscillations inside the interval from 40 to 60 and the hemodynamic variables remain stable throughout the surgical procedure. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

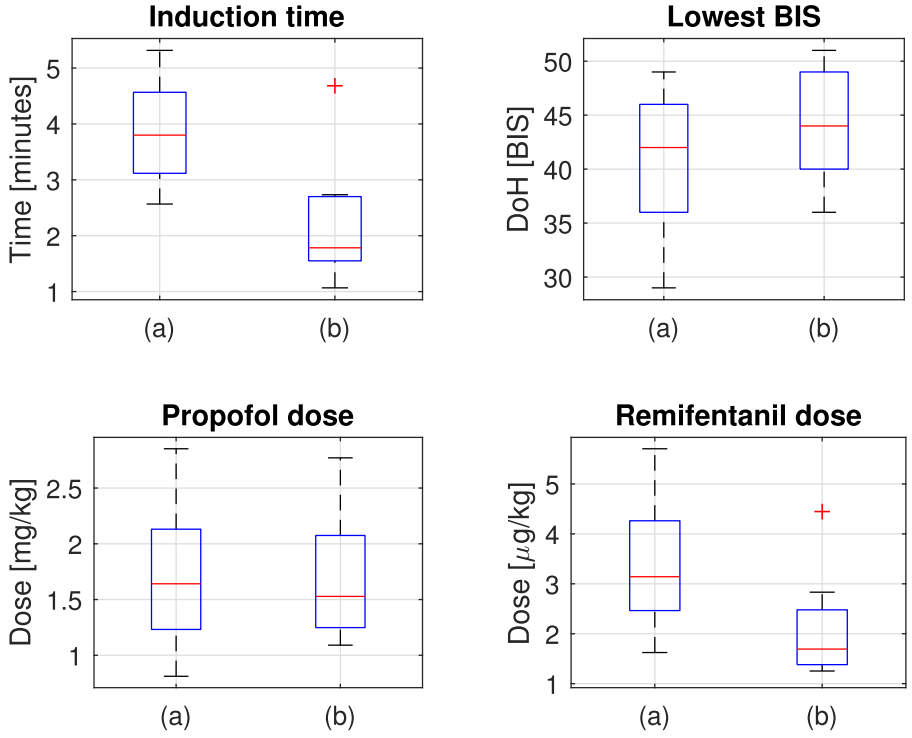

Fig. 12. Boxplots of induction performance indexes obtained with **(a)** and with **(b)**. The red horizontal line indicates the median. The bottom and the top edges of the blue box indicate the 25th and the 75th percentiles, respectively. The whiskers indicate the maximum and minimum considered values. Outliers are plotted individually with a red cross. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

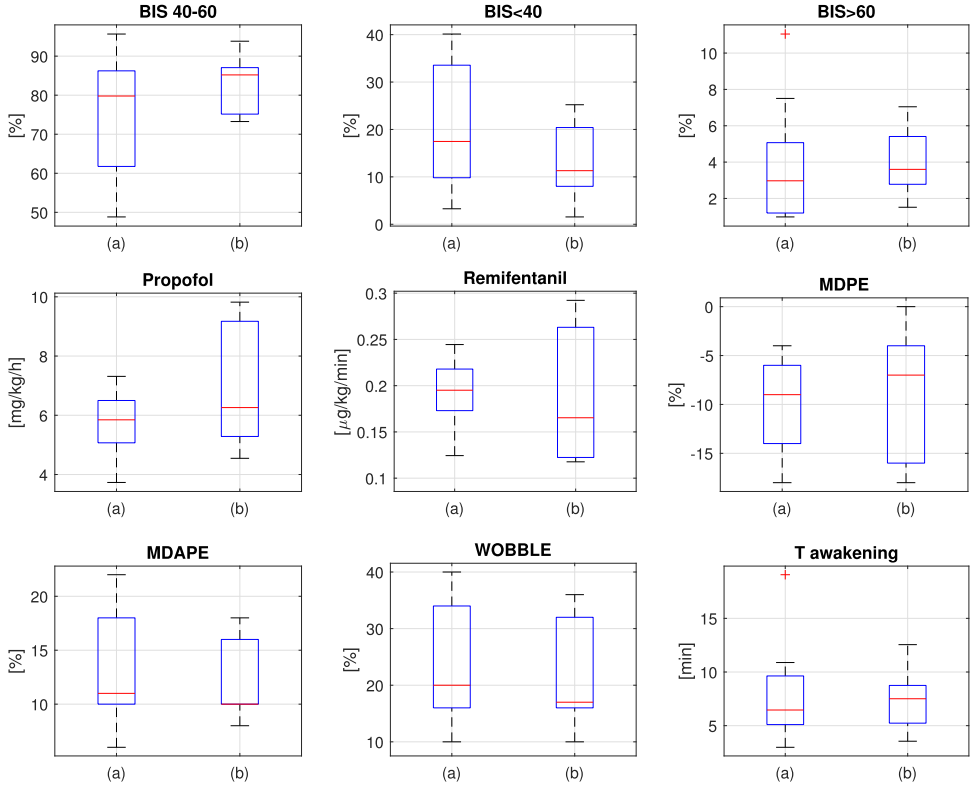

Fig. 13. Boxplots of maintenance performance indexes obtained with **(a)** and with **(b)**. The red horizontal line indicates the median. The bottom and the top edges of the blue box indicate the 25th and the 75th percentiles, respectively. The whiskers indicate the maximum and minimum considered values. Outliers are marked individually with a red cross. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

two groups for the performance indexes considered. However, in **(b)**, with respect to **(a)**, there is an increase in the median value of BIS 40–60 and a reduction in the median value of BIS<40. There is also a reduction in the variability for both indexes as indicated by the IQR. This denotes a more reliable control performance. In **(b)** it is also possible to observe a greater variability of propofol and remifentanil average infusion rates. This is due to the presence of baseline infusions that are calculated based on patient's demographic data so that the modified controller provides a patient-individualized drug administration.

Both controllers **(a)** and **(b)** provided results that are fully compatible with the clinical practice for all the patients enrolled. It is worth nothing that, despite the experimentation has been carried out in the context of plastic surgery, the types of surgical procedures differs significantly in duration and level of surgical stimulation, as shown in Table 2. Indeed, surgical interventions such as melanoma excision and sentinel lymph node biopsy have a short duration and a relatively low level of painful stimulation. Escharotomy has a short duration but a high level of painful stimulation. Finally, mastectomy and mastoplasty are surgical interventions that last for several hours and alternate phases of strong and moderate surgical stimulation. The fact that the controller has provided a performance that is fully compatible with the clinical practice for all the types of intervention gives reason to believe that it can be also applied to different types of surgery. However, a definitive answer can only be obtained through experimentation in other operating scenarios.

6. Conclusions

In this paper we have presented a modified version of a PID-based control system for propofol and remifentanil coadministration for the control of DoH by using the BIS as process variable. The changes to the original control scheme have been made to satisfy specific clinical requirements that are relevant for the anesthesiologists. We have experimentally assessed the effectiveness of the modified control on a population of 10 patients undergoing elective plastic surgery. The enrolled patients had a wide range of physical characteristics and were scheduled for procedures that greatly varied in length, body location, and level of painful stimulation. The control system was able to induce and maintain adequate anesthesia without the need for manual intervention from the anesthesiologist for all patients enrolled, thus confirming the effectiveness of the overall design approach. The results obtained suggest that the proposed changes are a significant step toward the integration of the system into the clinical practice and provide measurable clinical advantages for the patients. Encouraged by the positive results, in future studies we will seek to enroll a higher number of patients to further investigate correlation between permanence indexes and patient demographics increase the statistical relevance of the conclusions.

Declaration of Competing Interest

The authors declare that there are no conflicts of interests.

References

[1] J.P. van den Berg, A.R. Absalom, A.M. Venema, A.F. Kalmar, K.V. Amsterdam, L.N. Hannivoort, J.H. Proost, S. Meier, T.W.L. Scheeren, M.M.R.F. Struys, H.E.M. Vereecke, Comparison of haemodynamic-and electroencephalographic–monitored effects evoked by four combinations of effect-site concentrations of propofol and remifentanil, yielding a predicted tolerance to laryngoscopy of 90%, J. Clin. Monit. Comput. 35 (2021) 815–825.
[2] S.R. Tasbihgou, M.F. Vogels, A.R. Absalom, Accidental awareness during general anaesthesia - a narrative review, Anaesthesia 73 (1) (2018) 112–122.
[3] E.M. Wesselink, T.H. Kappen, H.M. Torn, A.J.C. Slooter, W.A.V. Klei, Intraoperative hypotension and the risk of postoperative adverse outcomes: a systematic review, Br. J. Anaesth. 121 (4) (2018) 706–721.

[4] A.R. Absalom, J.I.B. Glen, G.J.C. Zwart, T.W. Schnider, M.M.R.F. Struys, Target–controlled infusion: a mature technology, Anesth. Analg. 122 (1) (2016) 70–78.
[5] M. Ghita, M. Neckebroek, C. Muresan, D. Copot, Closed-loop control of anesthesia: survey on actual trends, challenges and perspectives, IEEE Access 8 (2020) 206264–206279.
[6] C. Zaouter, A. Joosten, J. Rinehart, M.M.R.F. Struys, T.M. Hemmerling, Autonomous systems in anesthesia: where do we stand in 2020? A narrative review, Anesth. Analg. 130 (5) (2020) 1120–1132.
[7] E. Brogi, S. Cyr, R. Kazan, F. Giunta, T.M. Hemmerling, Clinical performance and safety of closed-loop systems: a systematic review and meta-analysis of randomized controlled trials, Anesth. Analg. 124 (2) (2017) 446–455.
[8] L. Pasin, P. Nardelli, M. Pintaudi, M. Greco, M. Zambon, L. Cabrini, A. Zangrillo, Closed-loop delivery systems versus manually controlled administration of total iv anesthesia: a meta-analysis of randomized clinical trials, Anesth. Analg. 124 (2) (2017) 456–464.
[9] G.A. Dumont, A. Martinez, J.M. Ansermino, Robust control of depth of anesthesia, Int. J. Adapt. Control Signal Process. 23 (5) (2009) 435–454.
[10] M. Hosseinzadeh, Robust control applications in biomedical engineering: control of depth of hypnosis, in: Control Applications for Biomedical Engineering Systems, Academic Press, 2020, pp. 89–125.
[11] J.M. Gonzalez-Cava, F.B. Carlson, O. Troeng, A. Cervin, K. van Heusden, G.A. Dumont, K. Soltesz, Robust PID control of propofol anaesthesia: uncertainty limits performance, not PID structure, Comput. Methods Programs Biomed. 198 (2021) 105783.
[12] F. Padula, C. Ionescu, N. Latronico, M. Paltenghi, A. Visioli, G. Vivacqua, Optimized PID control of depth of hypnosis in anesthesia, Comput. Methods Programs Biomed. 144 (2017) 21–35.
[13] L. Merigo, M. Beschi, F. Padula, N. Latronico, M. Paltenghi, A. Visioli, Event-based control of depth of hypnosis in anesthesia, Comput. Methods Programs Biomed. 147 (2017) 63–83.
[14] N. Liu, T. Chazot, A. Genty, A. Landais, A. Restoux, K. McGee, P.A. Laloë, B. Trillat, L. Barvais, M. Fischler, Titration of propofol for anesthetic induction and maintenance guided by the bispectral index: closed-loop versus manual control: a prospective, randomized, multicenter study, J. Am. Soc.Anesthesiol. 104 (4) (2006) 686–695.
[15] G.D. Puri, B. Kumar, J. Aveek, Closed-loop anaesthesia delivery system (CLADS) using bispectral index; a performance assessment study, Anaesth. Intensive Care 35 (2007) 357–362.
[16] F.N. Nogueira, T. MendonȦa, P. Rocha, Positive state observer for the automatic control of the depth of anesthesia - clinical results, Comput. Methods Programs Biomed. 171 (2019) 99–108.
[17] Y. Sawaguchi, E. Furutani, G. Shirakami, M. Araki, K. Fukuda, A model-predictive hypnosis control system under total intravenous anesthesia, IEEE Trans. Biomed. Eng. 55 (3) (2008) 874–887.
[18] M. Neckebroek, C.M. Ionescu, K.V. Amsterdam, T.D. Smet, P.D. Baets, J. Decruyenaere, R.D. Keyser, M.M.R.F. Struys, 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, J. Clin. Monit. Comput. 33 (4) (2019) 675–686.
[19] J.A. Mendez, A. Leon, A. Marrero, J.M. Gonzalez-Cava, J.A. Reboso, J.I. Estevez, J.F. Gomez-Gonzalez, Improving the anesthetic process by a fuzzy rule based medical decision system, Artif. Intell. Med. 84 (2018) 159–170.
[20] K.V. Heusden, G.A. Dumont, K. Soltesz, C.L. Petersen, A. Umedaly, N. West, J.M. Ansermino, Design and clinical evaluation of robust PID control of propofol anesthesia in children, IEEE Trans. Control Syst. Technol. 22 (2) (2013) 491–501.
[21] T.M. Hemmerling, E. Arbeid, M. Wehbe, S. Cyr, R. Taddei, C. Zaouter, Evaluation of a novel closed-loop total intravenous anaesthesia drug delivery system: a randomized controlled trial, Br. J. Anaesth. 110 (6) (2013) 1031–1039.
[22] M. Janda, A. Schubert, J. Bajorat, R. Hofmockel, G.F.E. Noeldge-Schomburg, B.P. Lampe, O. Simanski, Design and implementation of a control system reflecting the level of analgesia during general anesthesia, Biomedizinische Technik/Biomed. Eng. 58 (1) (2013) 1–11.
[23] C.C. Peñaranda, F.D.C. Arroyave, F.J. Gómez, P.A.P. Corredor, J.M. Fernández, M.V. Botero, J.D.B. Bedoya, C.M. Toro, Technical and clinical evaluation of a closed loop TIVA system with SEDLine spectral density monitoring: multicentric prospective cohort study, Perioper. Med. 9 (1) (2020) 1–11.
[24] M. Ghita, M. Neckebroek, J. Juchem, D. Copot, C.I. Muresan, C.M. Ionescu, Bioimpedance sensor and methodology for acute pain monitoring, Sensors 20 (23) (2020) 6765.
[25] M. Neckebroek, M. Ghita, M. Ghita, D. Copot, C.M. Ionescu, Pain detection with bioimpedance methodology from 3-dimensional exploration of nociception in a postoperative observational trial, J. Clin. Med. 9 (3) (2020) 684.
[26] N. Liu, T. Chazot, S. Hamada, A. Landais, N. Boichut, C. Dussaussoy, B. Trillat, L. Beydon, E. Samain, D.I. Sessler, Closed-loop coadministration of propofol and remifentanil guided by bispectral index: a randomized multicenter study, Anesth. Analg. 112 (3) (2011) 546–557.
[27] K. van Heusden, J.M. Ansermino, G.A. Dumont, Robust MISO control of propofol-remifentanil anesthesia guided by the NeuroSENSE monitor, IEEE Trans. Control Syst. Technol. 26 (5) (2017) 1758–1770.
[28] L. Merigo, F. Padula, N. Latronico, M. Paltenghi, A. Visioli, Optimized PID control of propofol and remifentanil coadministration for general anesthesia, Commun. Nonlinear Sci. Numer. Simul. 72 (2019) 194–212.
[29] M. Schiavo, F. Padula, N. Latronico, L. Merigo, M. Paltenghi, A. Visioli, Performance evaluation of an optimized PID controller for propofol and remifentanil coadministration in general anesthesia, IFAC J. Syst. Control 15 (2021) 100121.
[30] M. Hosseinzadeh, G.A. Dumont, E. Garone, Constrained control of depth of hypnosis during induction phase, IEEE Trans. Control Syst. Technol. 28 (6) (2019) 2490–2496.
[31] M. Schiavo, L. Consolini, M. Laurini, N. Latronico, M. Paltenghi, A. Visioli, Optimized feedforward control of propofol for induction of hypnosis in general anesthesia, Biomed. Signal Process. Control 66 (2021) 102476.
[32] K. van Heusden, K. Soltesz, E. Cooke, S. Brodie, N. West, M. Görges, J.M. Ansermino, G.A. Dumont, Optimizing robust PID control of propofol anesthesia for children: design and clinical evaluation, IEEE Trans. Biomed. Eng. 66 (10) (2019) 2918–2923.
[33] K. van Heusden, N. West, A. Umedaly, J.M. Ansermino, R.N. Merchant, G.A. Dumont, Safety, constraints and anti-windup in closed-loop anesthesia, IFAC Proc. Vol. 47 (3) (2014) 6569–6574.
[34] M. Yousefi, K. van Heusden, I.M. Mitchell, J.M. Ansermino, G.A. Dumont, A formally-verified safety system for closed-loop anesthesia, IFAC-PapersOnLine 50 (1) (2017) 4424–4429.
[35] N. Eskandari, K. van Heusden, G.A. Dumont, Extended habituating model predictive control of propofol and remifentanil anesthesia, Biomed. Signal Process. Control 55 (2020) 101656.
[36] F.L. Roberts, J. Dixon, G.T.R. Lewis, R.M. Tackley, C. Prys-Roberts, Induction and maintenance of propofol anaesthesia: a manual infusion scheme, Anaesthesia 43 (1988) 14–17.
[37] T.W. Schnider, C.F. Minto, P.L. Gambus, C. Andresen, D.B. Goodale, S.L. Shafer, E.J. Youngs, The influence of method of administration and covariates on the pharmacokinetics of propofol in adult volunteers, Anesthesiology 88 (1998) 1170–1182.
[38] T.W. Schnider, C.F. Minto, S.L. Shafer, P.L. Gambus, C. Andresen, D.B. Goodale, E.J. Youngs, The influence of age on propofol pharmacodynamics, Anesthesiology 90 (6) (1999) 1502–1516.
[39] C.F. Minto, T.W. Schnider, T.D. Egan, E. Youngs, H.J. Lemmens, P.L. Gambus, V. Billard, J.F. Hoke, K.H. Moore, D.J. Hermann, K.T. Muir, Influence of age and gender on the pharmacokinetics and pharmacodynamics of remifentanil, Anesthesiology 86 (1997) 10–23.
[40] A.F. Nimmo, A.R. Absalom, O. Bagshaw, A. Biswas, T.M. Cook, A. Costello, S. Grimes, D. Mulvey, S. Shinde, T. Whitehouse, Guidelines for the safe practice of total intravenous anaesthesia (TIVA), Anaesthesia 74 (2) (2019) 211–224.