Optimized Reference Signal for Induction of General Anesthesia with Propofol

Michele Schiavo [*] **Luca Consolini** [**] **Mattia Laurini** [**]
Nicola Latronico [***,****] **Massimiliano Paltenghi** [****]
Antonio Visioli [†]

[*] *Dipartimento di Ingegneria dell'Informazione, University of Brescia, Italy (e-mail: m.schiavo003@unibs.it)*
[**] *Dipartimento di Ingegneria e Architettura, University of Parma, Italy (e-mail: {luca.consolini,mattia.laurini}@unipr.it)*
[***] *Department of Medical and Surgical Specialties, Radiological Sciences and Public Health, University of Brescia, Italy (e-mail: nicola.latronico@unibs.it)*
[****] *Spedali Civili di Brescia, Brescia, Italy (e-mail: maxpaltenghi@gmail.com).*
[†] *Dipartimento di Ingegneria Meccanica e Industriale, University of Brescia, Italy (e-mail: antonio.visioli@unibs.it)*

Abstract:
In this paper we propose the use of an optimization strategy for the computation of an optimized reference (command) input to be applied to a proportional-integral-derivative (PID) based closed-loop control system for the administration of propofol during the induction phase of general anesthesia. The bispectral index scale (BIS) is the controlled variable. The proposed methodology explicitly takes into account the dynamics of the PID controller in the calculation of the reference input to minimize the induction time of anesthesia while limiting the undershoot of the BIS level. The effectiveness of the proposed methodology is assessed in simulation by means of a Monte Carlo method and the performance is compared with that of an optimally tuned PID controller and with that of a recently devised optimized feedforward control law. The effect of the PID tuning on the obtainable performance is also investigated.

Keywords: Depth of hypnosis control, feedforward control, induction, optimization.

1. INTRODUCTION

General anesthesia is a drug induced loss of consciousness during which patients are not aroused, even by painful stimulation (Blayney, 2012). It is typically used for long and invasive surgical procedures as it preserves the patient from anxiety and pain. Loss of consciousness is achieved by administering hypnotic drugs, which reduce the activity of the central nervous system. In the practice of total intravenous anesthesia (TIVA), propofol is generally used as hypnotic drug since it has a fast redistribution and metabolism (Bibian et al., 2005) and it causes relatively few side effects, if properly dosed (Tramer et al., 1997). To this end, propofol should be administered in order to induce and maintain a depth of hypnosis (DoH) suitable for surgery while avoiding excessively deep or shallow hypnotic states, which indicate propofol overdosing or underdosing, respectively. Neuro-monitoring systems are usually employed to assess DoH by analyzing the brain activity through the measurement and elaboration of the electroencephalogram (EEG). Bispectral Index Scale (BIS, Aspect Medical Systems, Norwood, USA) (Rampil, 1998) is one of the most widespread and clinically accepted DoH indicator. General anesthesia is divided into three phases: induction, maintenance and emergence. Regarding the induction phase, in TIVA, a bolus of propofol is usually administered in order to quickly bring the patient from the awaken state to a hypnotic state suitable for the start of the surgical procedure. During the maintenance phase, propofol is usually administered as a continuous infusion in order to maintain the desired hypnotic state. This is done until the emergence phase, when the propofol infusion is stopped and the patient regains consciousness. The choice of the dosage of propofol needed to induce and maintain the desired hypnotic state is not trivial due to the high variability present in the clinical response of the drug between different patients. In order to support the anesthesiologists in this task, Target Controlled Infusion (TCI) (Glen, 1998) has been introduced as a computerized infusion system that exploits a model of the patient to provide a personalized infusion profile. However, its open-loop architecture makes it subject to errors due to unavoidable model uncertainties, thus making manual adjustments necessary. Hence, automatic closed-loop control systems for propofol administration have been proposed since EEG-derived indicators of DoH such as the BIS can be employed as feedback variable. These systems are not yet used in clinical practice but encouraging experimental results have been obtained (Brogi et al., 2017; Neckebroek et al., 2019; Schiavo et al., 2021b). The design of this kind of

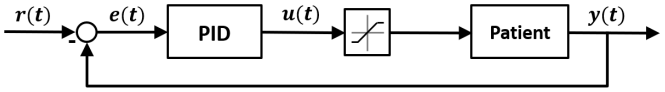

Fig. 1. Schematic representation of the control loop considered.

systems is particularly challenging especially with regard to the induction phase of anesthesia, when fast set-point tracking with a limited undershoot must be guaranteed despite the nonlinear and highly variable behaviour of the human body in response to drug administration. Different control solutions have been proposed in the literature, like PID control (Padula et al., 2017), model-based control (Merigo et al., 2018), model predictive control (Ionescu et al., 2008), input-output inversion-based control (Padula et al., 2016), event-based control (Merigo et al., 2017) and explicit reference governor (Hosseinzadeh et al., 2019). Although these solutions have provided promising results, they deviate from what is usually done in the clinical practice, where a bolus of propofol is administered in order to rapidly induce anesthesia. Thus, the induction phase with these systems might result too slow to be acceptable for some kind of patients. In order to overcome this issue, an optimized feedforward bolus strategy has been proposed in (Schiavo et al., 2021a). It aims to minimize the induction time by administering an optimized feedforward propofol bolus profile while managing the unavoidable uncertainties by using a specifically tuned PID feedback controller. This work shares the same goals of (Schiavo et al., 2021a) but here the initial bolus is obtained by applying a reference command input with the aim of taking the dynamics of the PID controller into account during the determination of the optimized feedforward control action in order to improve the robustness of the system. The paper is organized as follows. In Section 2 the control system architecture and the design methodology are described. Simulation results are presented in Section 3 and discussed in Section 4. Finally, conclusions are in Section 5.

2. CONTROL SYSTEM ARCHITECTURE AND METHODS

2.1 Control Scheme

The feedback control loop shown in Figure 1 is considered, where $y(t)$ is the measured BIS value and $u(t)$ is the control action, which represents the propofol infusion rate expressed in mg/s. This value is bounded between 0 mg/s and 6.67 mg/s by considering the maximum flow rate of 1200 ml/h of a commercial infusion pump (Graseby 3400, Smiths Medical, London, UK) and a standard propofol concentration of 20 mg/ml. The BIS reference value is denoted as $r(t)$ and $e(t)$ is the control error calculated as $e(t) = y(t) - r(t)$. The objective of the proposed design methodology is to determine $r(t)$ in order to generate a control action $u(t)$ that brings $y(t)$ to the target value by minimizing the transition time.

The control scheme of the optimized feedforward bolus proposed in (Schiavo et al., 2021a) is shown in Figure 2 for reader convenience since the proposed design methodology relies on it. Therein, $u^*(t)$ is the optimized feedforward bolus, $u_p(t)$ is the output of the PID controller, $u_s(t)$ is the control action and $y_{sp}(t)$ is the BIS set-point.

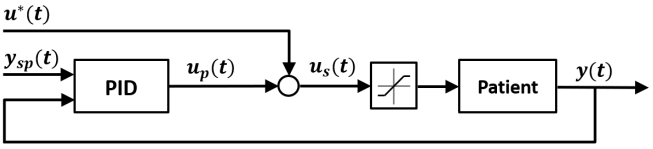

Fig. 2. Schematic representation of the optimized feedforward bolus control loop proposed in (Schiavo et al., 2021a).

2.2 Patient Model

The design of the reference signal relies on the nominal pharmocokinetic/pharmacodynamic (PK/PD) model of propofol. In this work the Schnider's model has been considered (Schnider et al., 1998, 1999). It is composed by a three-compartment PK model in series with a first-order PD model. Thus, the whole dynamics is described by a fourth-order linear system that links the propofol infusion rate to the concentration in the effect-site compartment (C_e), and obeys the following system of differential equations:

$$\begin{cases} \dot{q}_1(t) = -(k_{10} + k_{12} + k_{13})q_1(t) + k_{21}q_2(t) \\ \qquad\quad +k_{31}q_3(t) + u(t) \\ \dot{q}_2(t) = k_{12}q_1(t) - k_{21}q_2(t) \\ \dot{q}_3(t) = k_{13}q_1(t) - k_{31}q_3(t) \\ \dot{C}_e(t) = k_{1e}(q_1(t)/V_1) - k_{e0}C_e(t), \end{cases} \tag{1}$$

where $u(t)$ is the mass flow of infused propofol, expressed in mg/s, $q_1(t)$, $q_2(t)$ and $q_3(t)$ are the drug masses, in mg, in the primary, fast and slow compartment, respectively. Then, k_{12}, k_{13}, k_{21}, k_{31} and k_{1e} are the drug transfer rates between compartments, expressed in s^{-1}, $C_e(t)$ is the drug concentration in the effect-site compartment expressed in mg/ℓ, k_{10} and k_{e0} are the drug elimination rates, expressed in s^{-1}, from the primary compartment and from the effect-site compartment, respectively, and V_1 is the volume of the primary compartment expressed in ℓ. Note that k_{10}, k_{12} and k_{21} are, in general, functions of the patient height, weight, age and gender. In particular $k_{10} = f(weight, height, gender)$, $k_{12} = f(age)$ and $k_{21} = f(age)$. The relationship between C_e and the BIS value is described by a Hill function (Vanluchene et al., 2004)

$$BIS(t) = E_0 - E_{max}\left(\frac{C_e(t)^\gamma}{C_e(t)^\gamma + C_{e_{50}}^\gamma}\right), \tag{2}$$

where E_0 is the baseline value for the BIS measured before the drug infusion, $E_0 - E_{max}$ is the maximum effect on the BIS achievable by the drug infusion, γ is the maximum steepness of the function, and $C_{e_{50}}$ is the concentration in the effect-site compartment required to reach half of the maximum effect. With the exception of E_0, which can be measured before induction, the other parameters of the Hill function are not known a priori and are not related with the patient demographic parameters. Therefore, in this work, the following average values of the parameters are considered for design purposes (Vanluchene et al., 2004): $E_{max} = 87.5$, $\gamma = 2.69$ and $C_{e_{50}} = 4.92$.

2.3 Control Specifications

The control objective consists of minimizing the anesthesia induction time, that is, the transition time of $y(t)$ from its

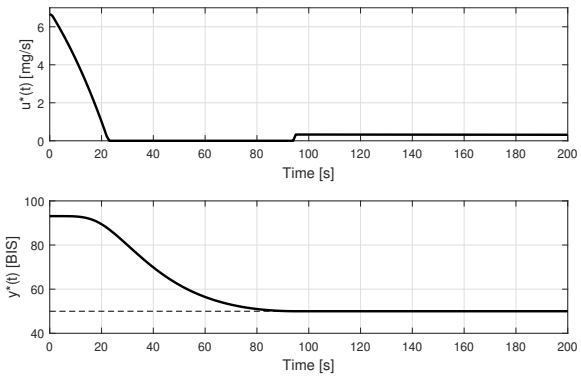

Fig. 3. Optimized feedforward action $u^*(t)$ and expected output trajectory $y^*(t)$ calculated for a 38-year-old female patient, 169 cm, 65 kg.

initial value E_0, which is close to 100 for an awake patient, to a value less than 60. Note that when the BIS is below this latter value, the risk of awareness during endotracheal intubation is reduced (Ekman et al., 2004), thus allowing the anesthesiologist to quickly instrument and secure the patient's airway. At the same time, excessively low BIS values must be avoided, thus imposing a limitation on the admissible undershoot. In particular, BIS values between 40 and 60 are recommended for most kind of surgeries (Rosow and Manberg, 2001), hence a sensible choice is to set the BIS target value to 50. Short-lasting undershoots of the BIS to values up to 30 are quite common in the clinical practice, while BIS values below this threshold should be avoided since they are correlated with the onset of EEG burst suppression (Bruhn et al., 2000) that has been associated with postoperative delirium (Soehle et al., 2015). The proposed control solution also aims at mimicking the infusion profile commonly used in the clinical practice to rapidly induce hypnosis, which consists of an initial propofol bolus followed by a continuous infusion.

2.4 Controller Design

The reference signal $r(t)$ is obtained by taking the feedforward action $u^*(t)$ calculated as explained in (Schiavo et al., 2021a) and by performing a dynamic inversion of the PID controller.

In particular, the feedforward control law is the solution of a minimum-time control problem obtained by solving a sequence of linear programming problems. This technique is based on the offline simulation of the patient's response to propofol infusion obtained by exploiting the nominal model. The optimization procedure is applied to calculate the optimal open-loop bolus $u^*(t)$ required to bring the theoretical patient BIS level $y^*(t)$ from E_0 to 50 without undershoot. Since the parameters of the model employed in the optimization procedure depend on patient's demographic data, as described in Section 2.2, the resulting optimized feedforward bolus $u^*(t)$ is personalized. An example of the feedforward action $u^*(t)$ and of the corresponding theoretical output trajectory $y^*(t)$ obtained on the nominal model is shown in Figure 3. For a detailed explanation regarding the computation of $u^*(t)$ the reader is referred to (Schiavo et al., 2021a).

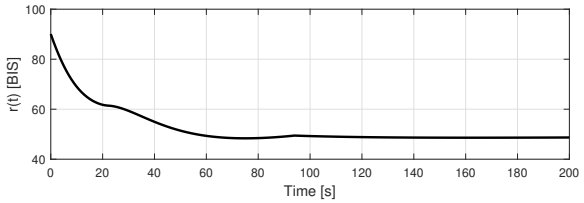

Fig. 4. Reference signal $r(t)$ obtained by inversion of the optimal feedforward bolus $u^*(t)$ by considering a PID controller with $K_p = 0.06$ mg/s, $T_i = 333$ s and $T_d = 34$ s.

Then $u^*(t)$ is used to determine the corresponding optimized reference command input $r(t)$, which is obtained by dynamic inversion of the PID controller, defined as:

$$U^*(s) = K_p \left(1 + \frac{1}{sT_i} + sT_d\right) E(s) \tag{3}$$

where $E(s)$ is the Laplace transform of $e(t) = r(t) - y^*(t)$ and $U^*(s)$ is the Laplace transform of $u^*(t)$. Then, K_p is the proportional gain, T_i is the integral time constant, T_d is the derivative time constant. By doing so, in the nominal case, when $r(t)$ is given as input to the PID controller the resulting control action $u(t)$ is equal to $u^*(t)$. Since there are unavoidable model uncertainties, the actual control action $u(t)$ will be different from the theoretical one $u^*(t)$, as the PID controller will act in order to compensate for them. An example of the reference signal $r(t)$ is shown in Figure 4.

With the proposed technique, the tuning of the PID controller plays a key role since the reference signal depends on the controller dynamics. Although in the nominal case the obtained control variable is obviously the same optimized feedforward bolus as in (Schiavo et al., 2021a), the approach proposed in this paper is expected to add robustness and to make the performance of the overall control system less dependent on the tuning of the PID controller itself. In order to investigate this aspect, two different sets of PID tuning parameters have been considered in this work. Both of them have been obtained with the optimization-based approach presented in (Padula et al., 2017), which is based on the minimization of the integral absolute error of the worst-case simulated step response of the 12 patients of (Ionescu et al., 2008) plus a thirteenth one obtained by calculating for each available parameter its algebraic mean. The first set of PID parameters is the one presented in (Padula et al., 2017) for set-point following: $K_p = 0.06$ mg/s, $T_i = 333$ s and $T_d = 34$ s. The second set of PID parameters has been obtained by performing the same procedure but also considering the presence of the reference command $r(t)$ in the optimization. It results $K_p = 0.05$ mg/s, $T_i = 288$ s and $T_d = 23$ s. This represents an optimal combination of tuning parameters for the whole feedforward/feedback system since $r(t)$ depends on K_p, T_i and T_d. The performance obtained with this latter tuning can be considered as the best performance achievable with this control solution since it has been shown that the design of both the feedback and feedforward part plays a key role in achieving the required performance and therefore using a combined approach gives a significant advantage (Piccagli and Visioli, 2011). For the sake of brevity, in the rest of the paper we will refer to these two tuning sets as tuning 1 and tuning 2, respectively.

For discrete-time implementation, we used the following form of the PID controller (see eq. (1.39) of Visioli (2006))

$$u^*(k+1)-u^*(k) = K_1 e(k)+K_2 e(k-1)+K_3 e(k-2), \quad (4)$$

where $e(k) = r(k) - y^*(k)$ and

$$K_1 = K_p\left(1+\frac{T_s}{T_i}+\frac{T_d}{T_s}\right)$$
$$K_2 = -K_p\left(1+2\frac{T_d}{T_s}\right)$$
$$K_3 = K_p\frac{T_d}{T_s}.$$

By solving (4) with respect to $r(k)$, we obtain that r is the solution of

$$\begin{aligned} r(k) \quad &= y^*(k) + K_1^{-1}\left(u^*(k+1) - u^*(k) + \right. \\ &\quad +K_2(y^*(k-1) - r(k-1)) + \\ &\quad \left. K_3(y^*(k-2) - r(k-2))\right) \\ r(-1) \; &= r(-2) = E_0. \end{aligned}$$

The numerical solution of this difference equation gives the reference signal r.

3. SIMULATION RESULTS

In this section, simulation results obtained for the proposed control methodology are shown and compared with those obtained by employing the PID controller proposed in (Padula et al., 2017) with a step reference input and the optimized feedforward bolus proposed in (Schiavo et al., 2021a). For the sake of clarity, in the rest of the paper we will indicate as (a) the control scheme with PID controller and a step reference signal, (b) the control system with a feedforward bolus and a feedback PID controller, (c) the novel control system with the determined reference input and the PID controller with tuning 1 and (d) the novel control system with the determined reference input and the PID controller with tuning 2. All the control systems have been initially tested on the tuning dataset of the 13 patients (Padula et al., 2017) and then on a much wider population obtained by means of a Monte Carlo method, in order to evaluate the controllers robustness to intra-patient and inter-patient variability. For the purpose of evaluating the effectiveness of the proposed approach, the performance indexes proposed in (Ionescu et al., 2008) have been employed:

- TT: is the time-to-target, hence the time required for the BIS to reach the value of 55 for the first time;
- ST10: is the settling time at 10%, hence the time required for the BIS to enter and remain between the range 45-55;
- ST20: is the settling time at 20%, hence the time required for the BIS to enter and remain between the range 40-60;
- BIS-NADIR: is the lowest BIS value observed.

The anesthesia induction response has been first simulated on the tuning dataset of 13 patients. A comparison between mean, minimum and maximum values of the performance indexes is shown in Figure 5. It can be observed that with all the feedforward strategies it is possible to reduce the TT with respect to the PID controller. In particular, there is a reduction of TT of 27% with (b), of 15% with (c) and of 9% with (d). However, the significant reduction in TT obtained with (b) is achieved at the expense of a

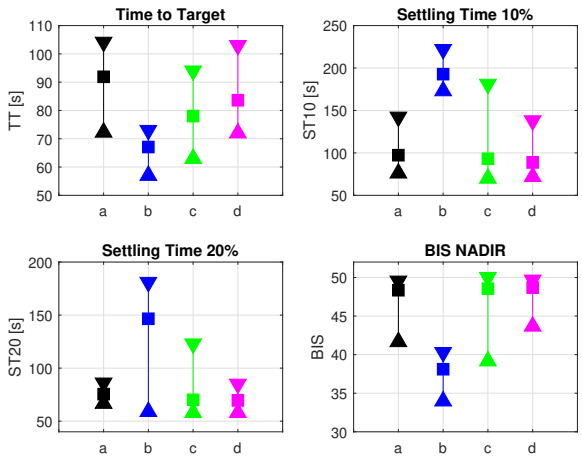

Fig. 5. Comparison of mean, minimum and maximum values of performance indexes for the 13 patients of the tuning dataset. ■ : mean value, ▲ : minimum value, ▼ : maximum value. (a) PID controller, (b) feedforward bolus, (c) optimized reference with tuning 1, (d) optimized reference with tuning 2.

significant increase in the undershoot with a consequent increment of the settling times ST10 and ST20 with respect to (a). On the other hand (c) shows only a slight increment in the minimum value of undershoot with a consequent increment in the maximum values of the settling times but the mean values remain close to that of (a). Conversely, with (d) there is a reduction also the minimum value of undershoot and the maximum values of the settling times with respect to (a).

In order to evaluate the robusness of the controllers to intra-patient variability, for each of the 13 patients of the tuning dataset, a set of 500 perturbed models has been created by a Monte Carlo method based on the statistical properties of the PK model parameters given in (Schnider et al., 1998). By doing so each controller has been tested on a set of 6500 perturbed models and the comparison between the obtained mean, minimum and maximum values of the performance indexes is shown in Figure 6. The same considerations made with the tuning dataset hold true even in case of intra-patient variability. With respect to the nominal situation there is a decrease in the BIS NADIR minimum values for each controller but it never falls below 30 thus ensuring patient's safety.

Finally, in order to validate the robustness with respect to inter-patient variability, another Monte Carlo simulation has been performed. In particular, 500 patients have been generated by randomly selecting gender, by considering a uniform distribution of age between 20 and 70, of the Body Mass Index (BMI) between 18.5 kg/m^2 and 29.9 kg/m^2, and of the height between 165 cm and 190 cm for males and between 150 cm and 175 cm for females. For each generated patient, the weight has been calculated according to the selected height and BMI in order to consider sensible height and weight combinations. The parameters of the Hill function has been generated by considering the statistical properties given in (Vanluchene et al., 2004). A comparison between the obtained mean, minimum and maximum values of the performance indexes is shown in

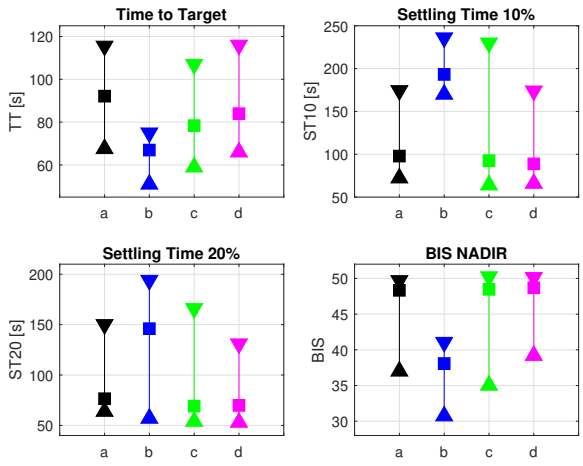

Fig. 6. Comparison of mean, minimum and maximum values of performance indexes for the 13 patients of the tuning dataset subject to intra-patient variability. ■ : mean value, ▲ : minimum value, ▼ : maximum value. (a) PID controller, (b) feedforward bolus, (c) optimized reference with tuning 1, (d) optimized reference with tuning 2.

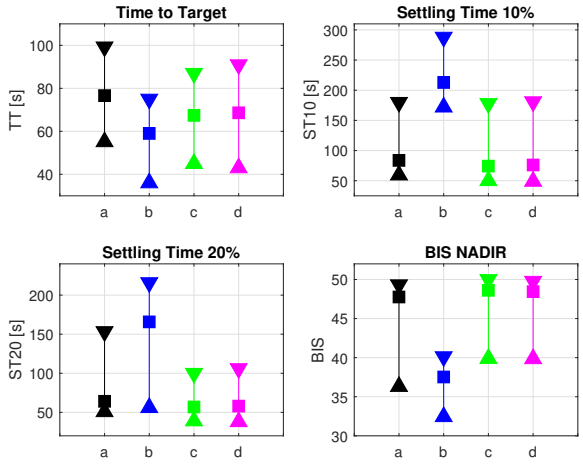

Fig. 7. Comparison of mean, minimum and maximum values of performance indexes for the inter-patient Monte Carlo simulation. ■ : mean value, ▲ : minimum value, ▼ : maximum value. (a) PID controller, (b) feedforward bolus, (c) optimized reference with tuning 1, (d) optimized reference with tuning 2.

Figure 7. Even in presence of inter-patient variability the feedforward strategies are still able to reduce the TT with respect to the PID controller. In particular there is a reduction of TT of 23% with (b), of 12% with (c) and of 10% with (d). Even in this case the significant reduction of TT obtained with (b) is accompanied by a significant increase in the undershoot with a consequent lengthening of the settling times ST10 and ST20. Conversely, (c) and (d) are able also to reduce the undershoot and to shorten the settling times ST10 and ST20 with respect to (a). In particular, with (c) and (d) the BIS NADIR never falls below the lower threshold of the recommended range 40-60. It is wort stressing that even with (a) and (b) the BIS NADIR never falls below 30, hence guaranteeing patient's safety even in presence of inter-patient variability.

4. DISCUSSION

The proposed reference input design methodology provided satisfactory control performance when tested in simulation on the considered benchmark dataset. This approach provides a satisfactory performance even in presence of both intra-patient and inter-patient variability. In particular, it always guarantees the fulfillment of the control specifications, thus a fast anesthesia induction time without causing an excessive suppression of the BIS. In order to better understand the advantages and disadvantages that the proposed control solution can provide, the results obtained have been compared with those obtained with an optimally tuned PID controller and with those obtained with an optimal feedforward bolus strategy. When tested on a benchmark dataset of 13 patients the proposed solution is able to reduce the TT required for anesthesia induction with respect to the PID controller without causing excessive undershoots of the BIS value that in fact remain comparable to those of the PID controller. Indeed, the undershoot remains limited both in its amplitude, as shown by the BIS NADIR, and in its duration, as shown by the settling times ST10 and ST20. The shortest induction time TT is obtained with the optimized feedforward bolus but at expense of a larger undershoot. Although the undershoot never reaches critical values this situation is not desirable for every patient and for all clinical procedures. Hence, the proposed reference input design method can provide a good alternative to the feedforward bolus when it is desirable to reduce as much as possible the induction time without causing excessive suppression of the BIS. These evaluations hold true even in case of intra-patient and inter-patient variability. It is also interesting to observe the behaviour of the two different tuning set of the PID parameters that have been considered with the proposed reference command input. In particular the tuning 2 shows a reduced variability of the performance indexes on the dataset of 13 patients even in presence of intra-patient variability with respect to tuning 1. This difference is then no longer present when the control solutions are tested on the large population of 500 patients used to assess the inter-patient variability. Indeed in this case approximately the same performance is obtained with both the tuning sets. The difference in performance on the 13 patient dataset is justified by the fact that tuning 2 has been performed by considering the dataset itself, so this may have constituted a performance bias. The same consideration also applies to the case of intra-patient variability as the perturbed models were obtained starting from the nominal models of the same dataset of 13 patients. In the simulation on a larger population of 500 patients for inter-patient variability, however, this bias effect is not present as both controllers are tested for the first time on a new dataset. This shows the effectiveness of the proposed solution in making the performance of the control system less dependent on the PID calibration as its dynamics is taken into account during the inversion of the feedforward signal.

5. CONCLUSIONS

In this work a new reference input design strategy for the induction of general anesthesia has been proposed. The proposed solution is a modification of that proposed in (Schiavo et al., 2021a) as it allows to explicitly take into account the dynamics of the feedback PID controller in the calculation of the feedforward action. Promising results have been obtained in simulation since the proposed control solution has always guaranteed the fulfillment of the control specifications even in presence of intra-patient and inter-patient variability. The comparative analysis carried out with an optimally tuned PID controller and with the optimal feedforward bolus of (Schiavo et al., 2021a) shows that the proposed solution can provide a valid intermediate solution between the two control solutions. In fact, it is particularly suitable when it is desired to reduce the induction time obtainable with the PID controller without however causing a BIS suppression level such as that of the optimal feedforward bolus.

REFERENCES

Bibian, S., Ries, C.R., Huzmezan, M., and Dumont, G.A. (2005). Introduction to automated drug delivery in clinical anesthesia. *European Journal of Control*, 11, 535–557.

Blayney, M.R. (2012). Procedural sedation for adult patients: an overview. *Continuing Education in Anaesthesia, Critical Care & Pain*, 12(4), 176–180.

Brogi, E., Cyr, S., Kazan, R., Giunta, F., and Hemmerling, T.M. (2017). Clinical performance and safety of closed-loop systems: a systematic review and meta-analysis of randomized controlled trials. *Anesthesia & Analgesia*, 124(2), 446–455.

Bruhn, J., Bouillon, T.W., and Shafer, S.L. (2000). Bispectral index (BIS) and burst suppression: revealing a part of the BIS algorithm. *Journal of Clinical Monitoring and Computing*, 16(8), 593–596.

Ekman, A., Lindholm, M.L., Lennmarken, C., and Sandin, R. (2004). Reduction in the incidence of awareness using BIS monitoring. *Acta Anaesthesiologica Scandinavica*, 48(1), 20–26.

Glen, J.B. (1998). The development of 'Diprifusor': a TCI system for propofol. *Anaesthesia*, 53(1), 13–21.

Hosseinzadeh, M., van Heusden, K., Dumont, G.A., and Garone, E. (2019). An explicit reference governor scheme for closed-loop anesthesia. In *2019 18th European Control Conference (ECC)*, 1294–1299. Naples, Italy.

Ionescu, C.M., Keyser, R.D., Torrico, B.C., Smet, T.D., Struys, M.M.R.F., and Normey-Rico, J.E. (2008). Robust predictive control strategy applied for propofol dosing using BIS as a controlled variable during anesthesia. *IEEE Transactions on Biomedical Engineering*, 55(9), 2161–2170.

Merigo, L., Beschi, M., Padula, F., Latronico, N., Paltenghi, M., and Visioli, A. (2017). Event-based control of depth of hypnosis in anesthesia. *Computer Methods and Programs in Biomedicine*, 147, 63–83.

Merigo, L., Padula, F., Pawlowski, A., Dormido, S., Guzman, J.L., Latronico, N., Paltenghi, M., and Visioli, A. (2018). A model-based control scheme for depth of hypnosis in anesthesia. *Biomedical Signal Processing and Control*, 42, 216–229.

Neckebroek, M., Ionescu, C.M., Amsterdam, K.V., 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(4), 675–686.

Padula, F., Ionescu, C., Latronico, N., Paltenghi, M., Visioli, A., and Vivacqua, G. (2016). Inversion-based propofol dosing for intravenous induction of hypnosis. *Communications in Nonlinear Science and Numerical Simulation*, 39, 481–494.

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.

Piccagli, S. and Visioli, A. (2011). PID tuning rules for minimum-time rest-to-rest transitions. *IFAC Proceedings Volumes*, 44(1), 5771–5776.

Rampil, I.J. (1998). A primer for eeg signal processing in anesthesia. *Anesthesiology*, 89, 980–1002.

Rosow, C. and Manberg, P.J. (2001). Bispectral index monitoring. *Anesthesiology Clinics of North America*, 19(4), 947–966.

Schiavo, M., Consolini, L., Laurini, M., Latronico, N., Paltenghi, M., and Visioli, A. (2021a). Optimized feedforward control of propofol for induction of hypnosis in general anesthesia. *Biomedical Signal Processing and Control*, 66, 102476.

Schiavo, M., Padula, F., Latronico, N., Merigo, L., Paltenghi, M., and Visioli, A. (2021b). Performance evaluation of an optimized PID controller for propofol and remifentanil coadministration in general anesthesia. *IFAC Journal of Systems and Control*, 15, 100121.

Schnider, T.W., Minto, C.F., Gambus, P.L., Andresen, C., Goodale, D.B., Shafer, S.L., and Youngs, E.J. (1998). The influence of method of administration and covariates on the pharmacokinetics of propofol in adult volunteers. *Anesthesiology*, 88, 1170–1182.

Schnider, T.W., Minto, C.F., Shafer, S.L., Gambus, P.L., Andresen, C., Goodale, D.B., and Youngs, E.J. (1999). The influence of age on propofol pharmacodynamics. *Anesthesiology*, 90(6), 1502–1516.

Soehle, M., Dittmann, A., Ellerkmann, R.K., Baumgarten, G., Putensen, C., and Guenther, U. (2015). Intraoperative burst suppression is associated with postoperative delirium following cardiac surgery: a prospective, observational study. *BMC Anesthesiology*, 15(1), 61.

Tramer, M., Moore, A., and McQuay, H. (1997). Propofol anaesthesia and postoperative nausea and vomiting: quantitative systematic review of randomized controlled studies. *British Journal of Anaesthesia*, 78(3), 247–255.

Vanluchene, A.L.G., Vereecke, H., Thas, O., Mortier, E.P., Shafer, S.L., and Struys, M.M.R.F. (2004). Spectral entropy as an electroencephalographic measure of anesthetic drug effect. a comparison with bispectral index and processed midlatency auditory evoked response. *Anesthesiology*, 101, 34–42.

Visioli, A. (2006). *Practical PID Control*, chapter Anti-windup strategies. Springer.