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IFAC PapersOnLine 58-7 (2024) 192–197

PIDA control of depth of hypnosis in total intravenous anesthesia

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Abstract: In this paper we discuss the use of a Proportional-Integral-Derivative-Acceleration (PIDA) controller for the Depth-of-Hypnosis (DoH) control in total intravenous anesthesia (TIVA). In particular, the infusion rate of the hypnotic drug propofol is the control variable and the bispectral index (BIS) is the controlled variable. The PIDA controller is tuned by using a population-based approach and its robustness is evaluated with a Monte Carlo method. The noise amplification is reduced by means of suitably designed low-pass filters. A comparison with a PID controller is performed, showing that the addition of the acceleration action allows us to design a more aggressive controller, thus reducing the risk of awareness of the patient in the maintenance phase.

Keywords: Anesthesia control, Depth of Hypnosis, PIDA control, Tuning, Robustness.

1. INTRODUCTION

Closed-loop control of anesthesia has emerged as an interesting research topic because of the advantages it can provide for both the patients and the anesthesiologists (Ghita et al., 2020). In fact, if properly designed, control systems can improve the effectiveness of anesthesia as they help to avoid under- and overdosing episodes (Brogi et al., 2017). Moreover, they decrease the workload of the anesthesiologist, so that he/she can focus on other tasks and the possibility of human errors is reduced.
In this context, total intravenous anesthesia (TIVA) is usually considered, where drugs are administered in order to obtain the required level of hypnosis, analgesia and paralysis, in addition to controlling hemodynamic variables (Ionescu et al., 2021). In particular, the automatic control of the Depth-of-Hypnosis (DoH) can be implemented by measuring the bispectral index (BIS), which is a processed electroencephalogram (pEEG) sensor (Rampil, 1998), and by using the infusion rate of the hypnotic drug propofol as control variable. Different solutions have been proposed in this scenario. Proportional-Integral-Derivative (PID) control has been extensively studied (Soltesz et al., 2013; Padula et al., 2017; van Heusden et al., 2019; Schiavo et al., 2021), since it is the standard option in process control, and also more advanced techniques, such as fuzzy control (Mendez et al., 2016, 2018), fractional control (Dumont et al., 2009; Copot et al., 2017; Paolino et al., 2023), event-based control (Merigo et al., 2017) have been considered. It is worth mentioning that also Model Predictive Control (MPC) techniques have been applied as they have the advantage of explicitly taking into account the system constraints (Ionescu et al., 2008; Naşcu et al., 2017; Pawlowski et al., 2022). However, MPC needs an accurate Pharmacokinetic/Pharmacodynamic (PK/PD) model, which might not be available. It is therefore relevant to investigate new advanced techniques that retain the same relative simplicity of PID control (that is, they are not model-based) but they are able to improve the performance. Recently, Proportional-Integral-Derivative-Acceleration (PIDA) controllers, also called Proportional-Integral-Double-Derivative controllers (PIDD or PIDD2), have been proposed as a valid alternative to PID controllers when the process dynamics are of integral type or of high-order (Huba et al., 2021; Visioli and Sanchez-Moreno, 2024). The addition of a control action that is proportional to the double derivative of the control error increases the order of the controller and allows the designer to increase the bandwidth while keeping the robustness at a reasonable level (Milanesi et al., 2022). It has been shown that possible problems associated to the amplification of the measurement noise and to the occurrence of kicks in the control action can be solved by suitably designed low-pass filters (Ferrari and Visioli, 2022). In this paper we investigate the application of a PIDA algorithm to the control of DoH in both the induction and maintenance phases of TIVA. In the induction phase, the BIS value has to be lowered as fast as possible to the required set-point value without a significant undershoot. In the maintenance phase, the BIS value has to be kept at the required set-point value despite the presence of noxious stimuli, and awareness episodes have to be avoided. The tuning of the controller has been performed by applying a procedure that has already been shown to be successful in process control. In particular, a genetic algorithm has been employed to minimize the worst-case integrated absolute error for a set of patients that are representative of a wide population. The robustness of the approach against inter- and intra-patient variability has then been tested by applying a Monte Carlo method. The paper is organized as follows. The problem is formulated in Section 2 and the design of the controller is

10.1016/j.ifacol.2024.08.033

described in Section 3. Simulation results are presented and discussed in Section 4 and, finally, conclusions are given in Section 5.

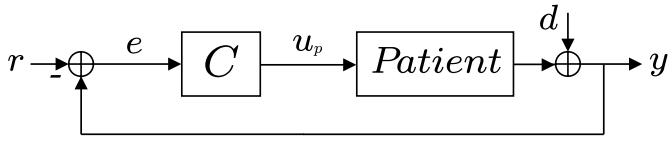


Fig. 1. The DoH control scheme.

2. PROBLEM FORMULATION

We consider the standard unity-feedback control scheme of Figure 1, where the set-point and load disturbance signals are denoted as r and d respectively, the propofol infusion rate is denoted as u_p [mg/s], the BIS value is denoted as y and the control error is calculated as $e = y - r$. The patient can be modelled with a typical mamillary three-compartmental PK/PD model, that results in a fourth-order dynamic linear part in series with a static nonlinear Hill function. In particular, the parameters of the linear part depend, with a given uncertainty, on the demographics of the patient (weight, height, age and gender), while the parameter of the nonlinear Hill function are not known a priori. All the details about the model can be found in (Schnider et al., 1998; Ionescu et al., 2008, 2015; Padula et al., 2017). The controller C is of PIDA type with transfer function

$$C(s) = K_p \left(1 + \frac{1}{sT_i} + \frac{T_d s}{1 + \frac{T_d}{N_1} s} + \frac{T_a s^2}{\left(1 + \frac{T_a}{N_2} s\right)^2} \right) \quad (1)$$

where K_p is the proportional gain, T_i is the integral time constant, T_d is the derivative time constant, N_1 is the coefficient of the first-order low-pass filter applied to the derivative action, T_a is the double derivative (acceleration) time constant (with a slight abuse of notation, since its units is s^2) and N_2 is the parameter of the second-order low-pass filter applied to the acceleration action. Note that if $T_a = 0$, then we have a standard PID controller. A conditional integration technique ha also been employed to avoid integrator windup (Visioli, 2006).

Two specific control tasks have to be considered in the anesthesia process. In the induction phase, the BIS level should be brought from the initial level (when the patient is awake) to the required value of 50 in a short time (less than 5 minutes) without an excessive undershoot (the BIS should not go below the indicative value of 30) to avoid possibly dangerous hypotension. This is indeed a set-point following task from the process control point of view. During the maintenance phase, the BIS value should be kept as much as possible in the range between 40 and 60 despite the presence of noxious stimuli, modelled as step disturbances on the process output (Soltesz, 2013). From a process control point of view, this is a disturbance rejection task. In general, underdosing and overdosing should be avoided as much as possible. The former might yield awareness during the surgery, which can be very traumatic for the patient, while the latter can yield delirium and/or post-operative nausea and vomiting after the surgery, which leads to a serious discomfort for the patient and a prolonged recovery time.

3. TUNING METHODOLOGY

Following the same approach as in (Padula et al., 2017), the tuning of the controller is performed with a genetic algorithm that minimizes the worst-case Integrated Absolute Error (IAE) for the individuals in a dataset of 13 patients that have been proven to be representative of a wide population (Ionescu et al., 2008). The choice of the IAE, defined as

$$IAE = \int_0^\infty |r(t) - y(t)| dt, \quad (2)$$

is justified as fast transients without excessive under and overshoots are required. Formally, the following optimization problem has been solved:

$$\min_{K_p, T_i, T_d, T_a} \max_{k \in \{1,\dots,13\}} \mathrm{IAE}_k (K_p, T_i, T_d, T_a), \quad (3)$$

where k ranges over the patients in the dataset.

The optimization problem has been solved separately for the set-point following and for the disturbance rejection task. This allows us to investigate the best performance achievable by the PIDA controller in the two phases of anesthesia separately. For the calculation of the IAE, a step has been applied to the set-point signal r from the initial BIS value to the target BIS value of 50 for the induction phase and a step of amplitude 10 followed by another one of amplitude -10 after 4 min have been applied to the disturbance signal d for the maintenance phase. In order to take into account actuator saturation constraints, in each control task the lower saturation limit has been set to zero, whereas the upper limit has been set to 6.67 mg/s. These specifications have been derived from the Graseby™ 3500 pump, a common surgical device that is found in operating rooms.

The genetic algorithm has been used to tune the controller parameters in a noise-free setting. However, to ensure a suitable filtering, N_1 and N_2 have been set to 5. In fact, given the high noise level of the real BIS signal, this choice helps preventing significant fluctuations in the pump infusion rates.

For the sake of comparison, the same tuning procedure has also been applied to a PID controller (again with $N_1 = 5$), so that the improvement achievable with the addition of the acceleration action can be clearly assessed.

4. SIMULATION RESULTS

The control system evaluation is performed for the induction and maintenance phases focusing on the medical specifications. Moreover, the robustness analysis concerning the inter- and intra-patient variability is shown, by comparing the results using specific performance indexes.

4.1 Tuning dataset

The controller performance is first analyzed by considering the response of the PIDA control scheme to the set-point change from the initial BIS value to the desired BIS level of 50 (induction phase). The results of the GA optimization are shown in Table 1, together with those obtained for PID control. It appears that they are similar and the performance improvement achieved by the PIDA controller is only of 3.1% in terms of the worst-case IAE. The inability of the PIDA controller to significantly improve the performance compared to the PID controller is confirmed by analyzing the responses obtained for the 13 patients of the tuning dataset shown in Figure 2.

Results regarding the maintenance phase are shown in Table 2. In this case, the determined optimal parameters yield a PIDA controller that is more aggressive than the PID controller (with an improved worst-case IAE). The PIDA controller achieves a faster positive-step rejection than the PID controller, while both controllers show similar performances in the negative step (see Figure 3). As already mentioned, this type of behaviour is desirable in anesthesia, despite the small undershoot that occurs, as it minimizes the risk of awareness episodes for the patient. This is achieved thanks to the double derivative action, which provides a larger control action and mimics the manual control action of an anesthesiologist in such a scenario (who generally provides an additional bolus of propofol if awareness is expected). On the contrary, when a negative step occurs, the performance of the two controllers is comparable since it is limited by the lower saturation of the actuator yielding almost the same results in terms of overshoot and settling time.

Table 1. Tuning parameters in the setpoint following task.

Controller	K_p	T_i	T_d	T_a	worst-case *IAE*
PID	0.049	303.077	23.25	-	3063.17
PIDA	0.045	270.58	26.90	6.70	2968.52

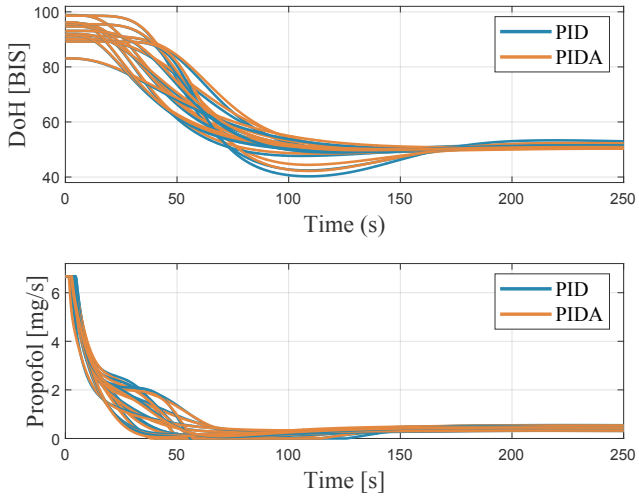


Fig. 2. Simulation responses obtained with the 13 patients used in the tuning procedure for the set-point following task.

Table 2. Tuning parameters in the load disturbance rejection task.

Controller	K_p	T_i	T_d	T_a	worst-case *IAE*
PID	0.0989	631.53	18.72	-	1284.60
PIDA	0.14	3103.65	18.35	0.3839	1108.70

4.2 Robustness evaluation

To test the robustness of the controller, a much more extensive group of patients has been considered. In particular, as already done in (Schiavo et al., 2021), to evaluate the performance against inter-patient variability, a Monte Carlo approach has been implemented to generate a set of 500 patients with different demographics. Further, in order to address the intra-patient variability, using a similar approach, additional 500 patients have been created from each one of the 13 patients in the original dataset (thus, overall, 6500 patients have been simulated to test intra-patient robustness).

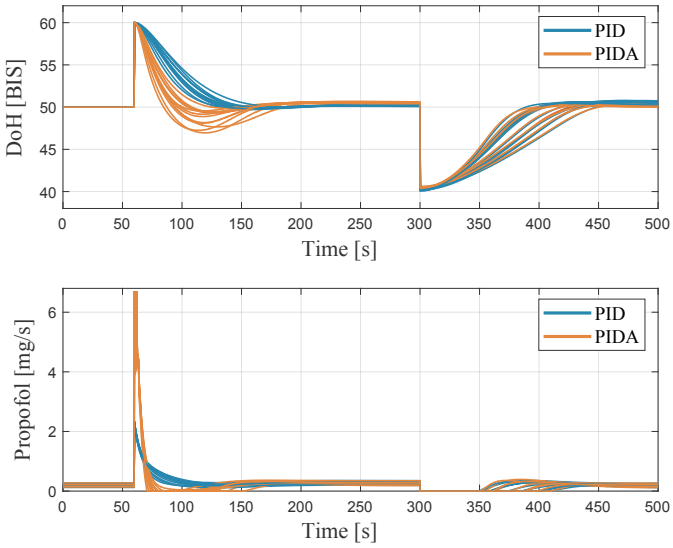


Fig. 3. Simulation responses obtained with the 13 patients used in the tuning procedure for the load disturbance rejection task.

In order to provide a rigorous assessment, the performance indexes proposed in Ionescu et al. (2008) have been evaluated. For the induction phase they are:

- TT: observed time-to-target required for reaching the first time the target interval of $[45 \div 55]$ BIS values;
- $BIS - NADIR$: the lowest observed BIS value;
- ST_{10}: settling time at 10%, representing the time interval for BIS to settle within the $50 \pm 5\%$ range.
- ST_{20}: settling time at 20%, which means taking into account a BIS range between 40 and 60.

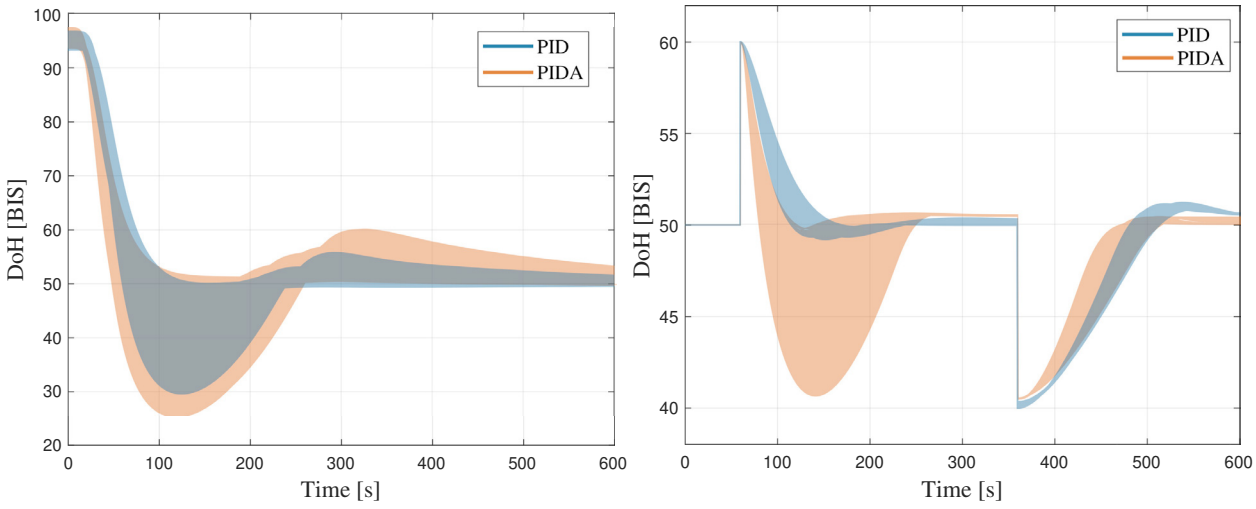
For the maintenance phase, the only meaningful indexes are TT and $BIS - NADIR$ and they are calculated separately for the positive and for the negative step, represented as *pos* and *neg* subscripts, respectively.

The responses obtained for the induction phase are shown in Figure 4 and they clearly show that there is no point in using the acceleration action for this case as the slight decrement of the TT value is paid for by an increment of the undershoot. This is also confirmed by the performance indexes shown in Figure 5 where it appears that PIDA controllers provide a lower TT, but the values of ST_{10} and ST_{20} are comparable for PIDA and PID control schemes (in all cases the clinical requirements are met). However, by looking at the $BIS - NADIR$ value, it appears that even if the interquartile range is kept in the range $40 \div 30$ for both controllers, PIDA controllers tend to fall below the minimum level of 30, with some outliers going even lower. For this reason, intra-patient variability is not further considered for the setpoint following case.

On the contrary, results related to the maintenance phase show the advantage of using the acceleration action in providing a faster compensation of the disturbance, as it can be observed in Figure 4 related to inter-patient variability, where, despite the large variability, the undershoot is kept inside the required range. By considering the performance indexes in Figure 6, we note that, in terms of time-to-target indexes, PIDA controllers have an advantage over PID controllers. This difference is more significant for the positive step, where the performance is not

limited by the lower saturation. In particular, in all 500 patients tested, the time-to-target in the positive step (TT_{pos}) is always less with PIDA controllers than with PID controllers. Although the PIDA controller is more aggressive than the PID and larger undershoots occur (see the $BIS - NADIR_{pos}$), these remain within clinically acceptable bounds. In general, results show that the control system is robust to the inter-patient variability and the clinical specifications are always met.

Similar considerations apply to intra-patient variability (see Figures 8 and 7). The PIDA controller has a lower TT_{pos} for all the 13 patients, while the difference in the TT_{neg} is smaller, but still the PIDA controller shows better performance. By examining the $BIS - NADIR$ indices, it can be observed that in the case of the positive index, there is a greater variability for the PIDA controllers, whereas for the negative index, the variability is reduced. However, for all 13 patients, the BIS level is always kept within the required range from 40 to 50.



(a) Induction phase

(b) Maintenance phase

Fig. 4. Responses obtained with the 500 patients used to test robustness to inter-patient variability.

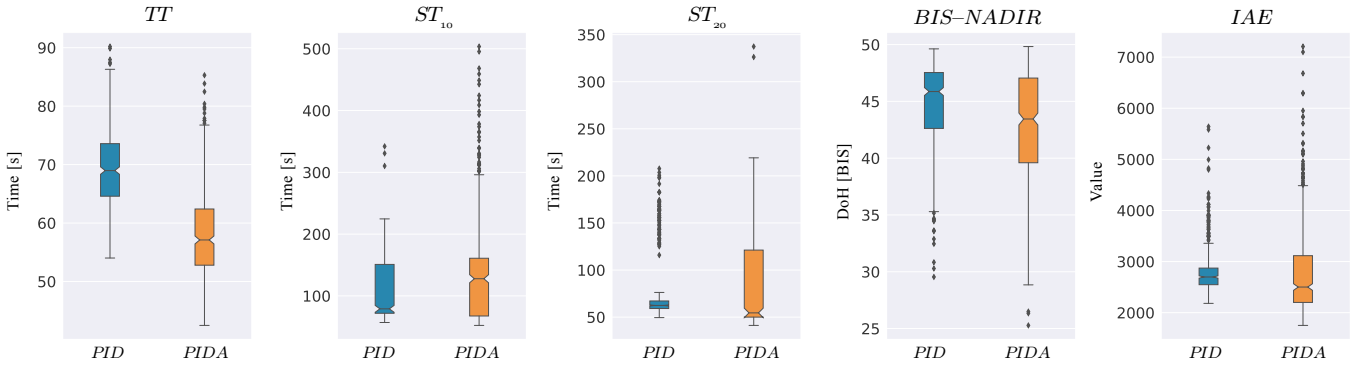


Fig. 5. Performance indexes for inter-patient variability (induction phase).

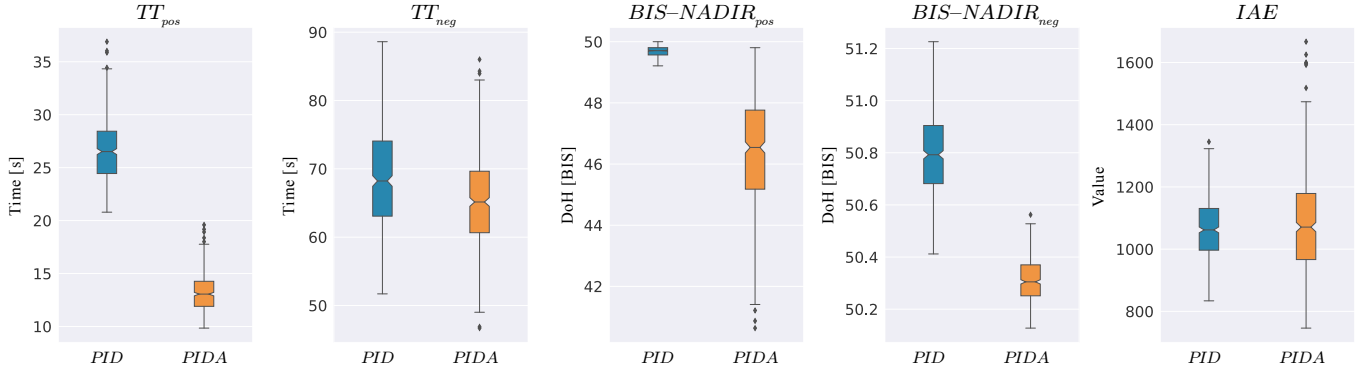
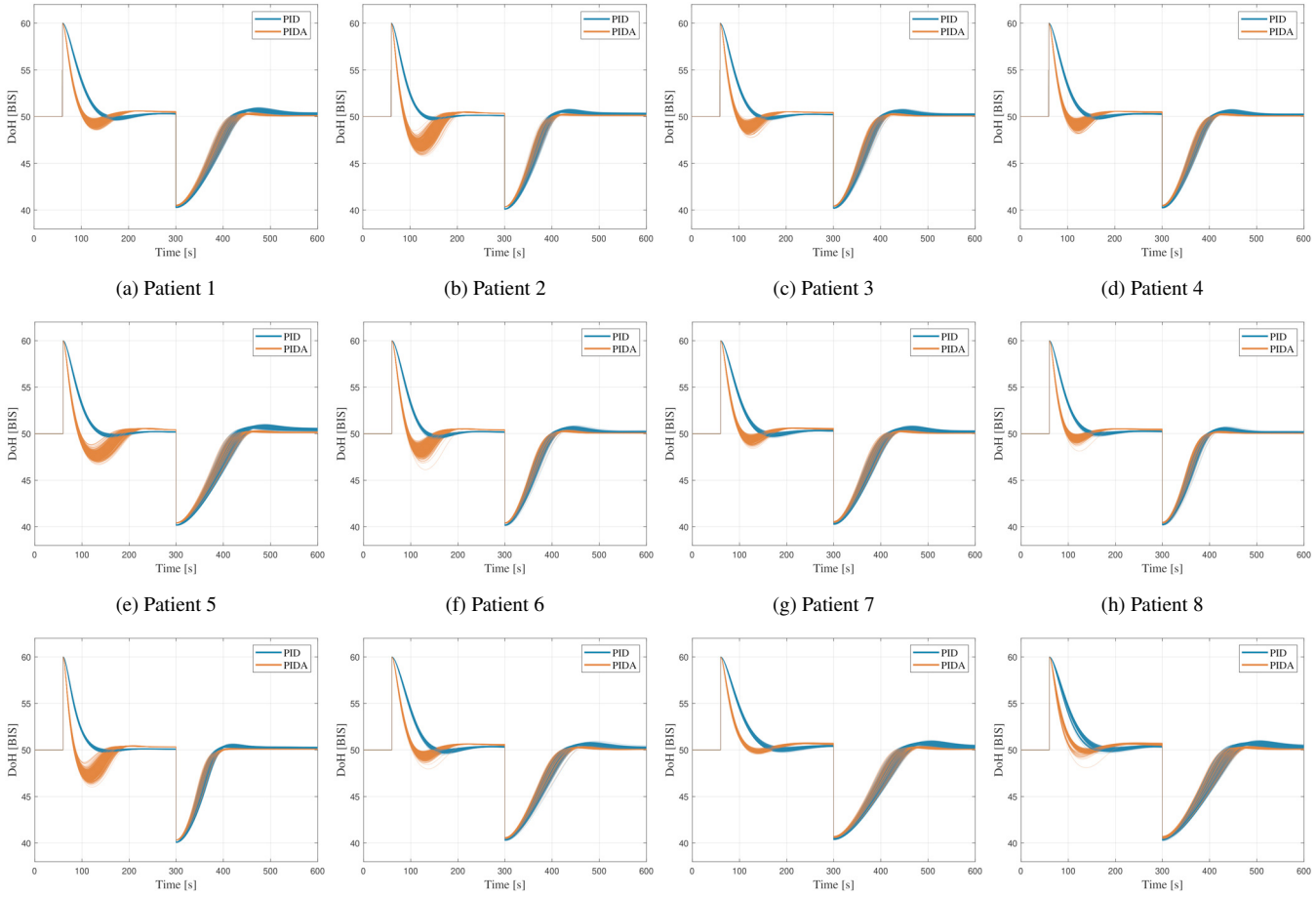


Fig. 6. Performance indexes for inter-patient variability (maintenance phase).



(a) Patient 1 (b) Patient 2 (c) Patient 3 (d) Patient 4

(e) Patient 5 (f) Patient 6 (g) Patient 7 (h) Patient 8

(i) Patient 9 (j) Patient 10 (k) Patient 11 (ℓ) Patient 12

Fig. 7. Load disturbance responses for intra-patient variability (patient 13 is omitted for brevity).

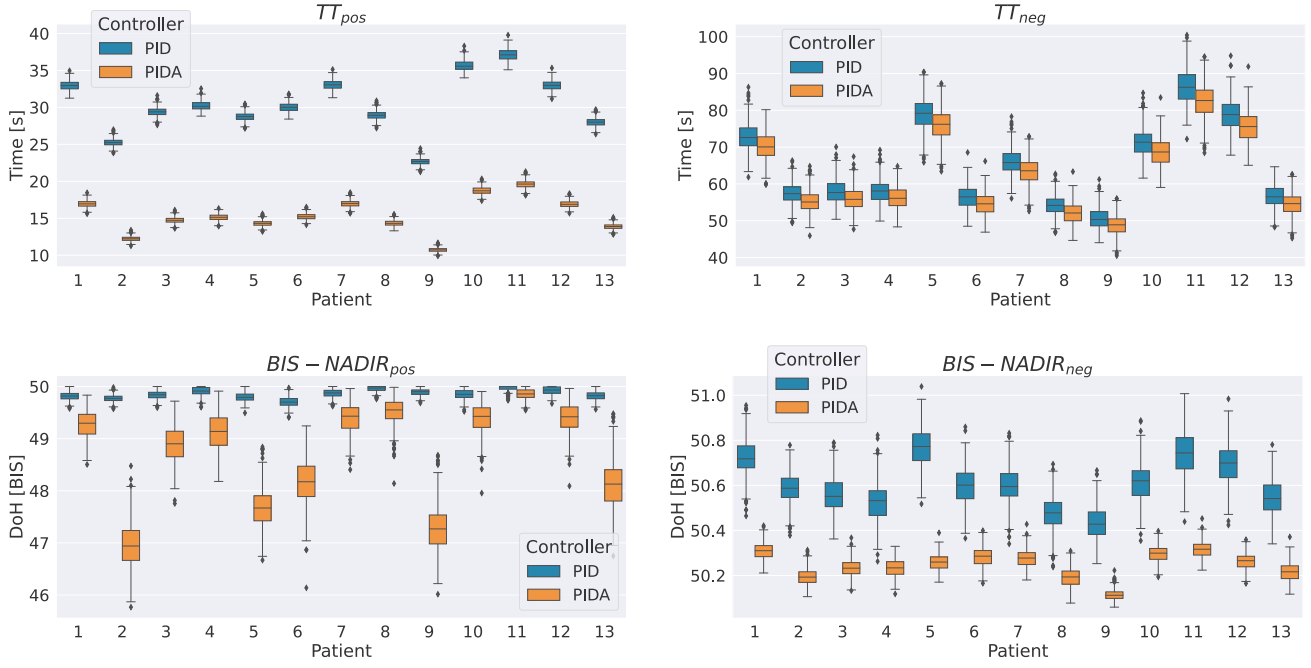


Fig. 8. Performance indexes for the load disturbance rejection task with the Monte Carlo method for intra-patient variability.

5. CONCLUSIONS

In this paper we have proposed the use of PIDA controllers for the control of DoH in TIVA. The tuning of the controller has been done by applying a population-based approach, that is, by minimizing the worst-case integrated absolute error in a dataset of 13 patients that are able to represent a wide population. A comparison with PID control has shown that the improvement in the induction phase is marginal, while the more aggressive control action in the maintenance phase reduces the risk of awareness for the patient. Further, the additional acceleration action does not impair the robustness of the system to inter- and intra-patient variability and the proper use of low-pass filters avoids a detrimental amplification of the measurement noise. Thus, PIDA controllers are good candidates to be employed in closed-loop control of anesthesia and future work will involve clinical trials to confirm these conclusions.

ACKNOWLEDGEMENTS

This work was partially supported by the European Union NextGeneration EU (PIANO NAZIONALE DI RIPRESA E RESILIENZA (PNRR) - MISSIONE 4 COMPONENTE 2, INVESTIMENTO 3.3—Decreto del Ministero dell'Università e della Ricerca n.352 del 09/04/2022). The grant of Nicola Paolino has been partially funded by CSMT Innovative Contamination Hub.

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