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A minimum Time-to-Target MPC approach for depth of hypnosis in total intravenous anesthesia

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Abstract: In this paper we propose a new approach for the Depth-of-Hypnosys (DoH) control in Total Intravenous Anesthesia (TIVA), where the bispectral index (BIS) is the process variable and the infusion rate of propofol is the control variable. In particular, a Proportional-Integral-Derivative (PID) controller is employed when the BIS is inside the specified range from 60 to 40. Then, a model predictive control (MPC) technique is employed when the BIS is higher than 60 with the aim of minimizing the time-to-target, thus reducing the risk of awareness for the patient during the maintenance phase. The same approach is also effective in the induction phase, reducing its duration. Simulation results show the effectiveness of the methodology.

Keywords: Anesthesia control, DoH control, MPC, PID control, optimization.

1. INTRODUCTION

Automatic control of the anesthesia process has been shown to offer numerous benefits over manual control both from the perspective of the patient and the anesthesiologist (Ghita et al., 2020). In fact, an effective automatic control system can increase patient safety by preventing underdosing and overdosing, which might yield side effects (e.g., delirium, post-operative nausea and vomiting in case of overdosing and traumatic awareness episodes in the case of underdosing). Furthermore, a lighter workload means that anesthesiologists are less likely to make mistakes because they are distracted or tired, freeing them up to concentrate on other duties and enhancing the procedure overall quality.

The primary responsibilities of the anesthesiologist in total intravenous anesthesia generally involve controlling Depth-of-Hypnosis (DoH), analgesia (Schumacher and Fukuda, 2020) and neuromuscular blockade by suitably administering specific drugs. In particular, hypnosis is typically accomplished by administering propofol. The availability of a DoH sensor makes it possible to create a feedback controller. The bispectral index (BIS), which is a processed electroencephalogram signal that provides a number ranging from 100, indicating a fully awake patient, to 0, indicating a flat electroencephalogram, is the most commonly used one. The ideal BIS value during operation is typically 50, but values between 60 and 40 are acceptable and this range is the actual target of the control task. The anesthesia procedure is divided into two stages: during the first one, known as induction, the patient's DoH level must be increased, which implies that the BIS value has to decrease from the starting value to 50 as fast as possible and in any case in less than five minutes. This is therefore a set-point following task that requires minimizing the transient time while avoiding significant undershoots, as these can result in potentially hazardous hypotension episodes. After induction is finished, the second phase, known as maintenance, begins. Its goal is to maintain the BIS value in the range from 40 to 60 despite the presence of disturbances caused by the surgical activity. In this case the controller has therefore to accomplish a disturbance rejection task where it is essential to avoid awareness episodes. Indeed, it has to be avoided that the BIS raises above 70 for a significantly large time interval, as this can be traumatic for the patient. For this reason, in manual control, the anesthesiologist performs a bolus of propofol when awareness can be expected during the maintenance phase. With a similar reasoning, a bolus is usually applied also in the induction phase to accelerate the BIS decrement and to avoid discomfort for the patient.

The design of an automatic control system is challenging because the patient (that is, the relationship between the propofol infusion rate and the BIS value) is described by a Wiener model where a linear part is in series with a static nonlinearity (Schnider et al., 1999). Further, it is of utmost importance to guarantee the required robustness, since a satisfactory performance must be achieved for all the patients.

In this context, many automatic control strategies have been proposed in the literature. In particular, Proportional-Integral-Derivative (PID) have been proven to be effective and research has focused on tuning methods and modifications of the basic algorithm (for example by considering event-based or fractional-order techniques) (Reboso et al., 2012; Soltesz et al., 2013; Padula et al., 2017; van Heusden et al., 2019; Schiavo et al., 2022; Merigo et al., 2017; Paolino et al., 2023). It is worth stressing that a gain scheduling strategy is usually applied, namely, the set of PID parameters for the induction phase is different from that of the maintenance phase, since the two control tasks are different.

Taking into account that a nominal pharmacokinetic/pharmacodynamic (PK/PD) model of propofol is available, Model Predictive Control (MPC) has also been proposed, in order to exploit its capability to handle the constraints. In general, the

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nominal static nonlinearity of the system is inverted in order to apply a linear MPC strategy (Ionescu et al., 2008; Sawaguchi et al., 2008; Chang et al., 2014; Nascu and Pistikopoulos, 2017; Pawlowski et al., 2022, 2023). In general, the cost function to be minimized in an MPC strategy involves the minimization of the predicted control error and of the control effort.
In this paper we propose a different control approach. A PID controller is used when the BIS value is between 60 and 40, that is, when the DoH is satisfactory. When the BIS is outside this range, and, in particular, when the BIS value is above 60 and there is a clear risk of awareness, an MPC strategy is applied where the cost function to be minimized is the time to target, that is, the time required for the BIS to be driven below 60.
The paper is organized as follows. In Section 2 the problem is formulated, the PK/PD model is briefly reviewed and the control strategy is explained. Simulation results are then presented in Section 3. Conclusions are given in Section 4.

2. MATERIALS AND METHODS

2.1 Problem formulation

The two distinct phases of clinical anesthesia have different requirements for the control system. The first part of the procedure, known as the induction phase, consists in driving the BIS level to the reference value, which is defined as *BIS*=50, in less than five minutes, preferably in only two. Furthermore, it is necessary to prevent an undershoot of less than 30 since it may cause burst suppression (Bruhn et al., 2000), which is linked to postoperative delirium. Maintaining the BIS value as much as possible within the safe range of 40 to 60 is the aim of the second stage, known as the maintenance phase. It is also necessary to take into account the actuation system's physical limits. In particular, if a standard infusion pump is employed (Smiths Medical: Graseby 3400, London, UK), the upper saturation limit is $6.67\,mg/s$.

2.2 Patient model

The depth of hypnosis induced by propofol administration is usually modelled by means of a PK/PD model, which is a Wiener model composed of the series of a linear system and a static nonlinear function. The linear part of the model consists of a fourth-order system, whose parameters depend on the total body weight, height, age and gender of the patient. By defining the state vector as $x(t) = [q_1(t), q_2(t), q_3(t), C_e(t)]^T$, where q_i, $i = 1,2,3$ is the quantity of drug in the ith compartment and C_e is the effect-site concentration. The discretized model subject to either noise or disturbances can be written as:

$$\begin{cases} x(k+1) &= A_D x(k) + B_D u(k) \\ BIS(k) &= h(x(k)) \end{cases},$$

where $A_D = e^{AT_s}$ and $B_D = \int_0^{T_s} e^{A\tau} B \, \mathrm{d}\tau$ with

$$A = \begin{bmatrix} -(k_{10}+k_{12}+k_{13}) & k_{21} & k_{31} & 0 \\ k_{12} & -k_{21} & 0 & 0 \\ k_{13} & 0 & -k_{31} & 0 \\ k_{1e}/V_1 & 0 & 0 & -k_{e0} \end{bmatrix}, \quad B = \begin{bmatrix} 1 \\ 0 \\ 0 \\ 0 \end{bmatrix}, \tag{1}$$

where $V_1 = 4.27\,\mathrm{L}$ is the volume of the primary compartment, $T_s = 1\,s$ is the sampling period and h is the nonlinear output function defined as:

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

In equation (2), γ is the maximum steepness of the function h, while $C_{e_{50}}$ is the concentration in the effect-site compartment required to reach half of the maximum effect. It is worth stressing that, while the nominal parameters of the linear part of the model are known because they depend on the demographics of the patient, the parameters of the Hill function are unknown.

2.3 Control system

The proposed control structure is shown in Figure 1. It comprises a selector, a PID controller, an MPC and a Kalman filter. The PK/PD model used by the MPC is obtained individually for each patient based on their gender, height, age and weight, while the nonlinearity is compensated by inverting the patient's Hill function (see Section 2.3.3), thus enabling the use of a linear model in the optimizer.

Controller Selector The primary responsibility of the controller selector is to discern between employing either the MPC control action u_{MPC} or the PID one u_{PID}. The MPC is used to drive the patient within a safe operational range from 40 to 60, while the PID controller takes over within this interval. This strategic choice is motivated by the capability of MPC to provide a bolus-like control action. This is obtained by embedding a minimum time objective function subject to constraints. Conversely, the PID controller is deployed to mitigate model mismatches and small disturbances. Indeed, obtaining a high performance by using MPC only would require that an accurate PK/PD model of the patient is available, which is very challenging in practice.

PID Controller The PID controller is implemented by discretizing the standard ideal form:

$$u_{PID}(k) = P(k) + I(k) + D(k) = K_p\, e(k) + \frac{K_p\, T_s + T_i\, I(k-1)}{T_i} + \frac{2\,T_d\, N\, K_p\,(BIS(k) - BIS(k-1)) - (T_s N - 2\,T_d) D(k-1)}{T_s N + 2\,T_d}$$

where $e(k) = BIS(k) - BIS^R(k)$ is the error. The values for the proportional, integral, and derivative tuning parameters (K_p, T_i and T_d, respectively), as well as the time constant of the low-pass filter of the derivative action N, have been selected as in (Schiavo et al., 2022) for the maintenance phase. They are: $K_p = 0.2013$, $T_i = 385.8701$, $T_d = 13.7577$, and $N = 5$. A conditional integration anti-windup strategy is also implemented.

Model Predictive Controller The nonlinearity introduced by the Hill equation is inverted so that the equivalent reference effect site concentration C_e^R and the estimated effect-site concentration $\widehat{C}_e$ are obtained in terms of the target BIS value $BIS^R(t)$ and of the output $BIS(t)$ value, respectively:

$$C_e^R = h^{-1}(BIS^R) = C_{e_{50}}\left[\frac{E_0 - BIS^R}{E_0 - E_{\max} + BIS^R}\right]^{1/\gamma} \tag{3}$$

$$\widehat{C}_e = h^{-1}(BIS) = C_{e_{50}}\left[\frac{E_0 - BIS}{E_0 - E_{\max} + BIS}\right]^{1/\gamma} \tag{4}$$

It is worth noting that the Hill parameters are unknown a priori, with the exception of E_0 which can be measured before the induction. Therefore, for the induction phase, we utilize the average parameter values reported in (Vanluchene et al., 2004),

which are $E_{\max} = 87.5$, $\gamma = 2.69$, and $C_{e_{50}} = 4.92$. On the other side, in the maintenance phase, in order to obtain a more aggressive controller and therefore to better prevent awareness, the parameters of the nominal Hill function are selected as $E_{\max} = 100$, $\gamma = 1.65$ and $C_{e_{50}} = 7.42$.
Then, at each sampling time $\tilde{k}$, the optimal control action $u_{MPC}(\tilde{k})$ is calculated as the one that solves the following optimization problem:

$$\min_{0\le\bar{k}\le N_P} \quad \bar{k} \tag{5}$$

$$\begin{aligned}
\textbf{s.t.} \quad & 0 \le u(k) \le u_M, \quad k = 0,\dots,N_C && \text{(5a)}\\
& x(k+1) = A_D x(k) + B_D u_{MPC}(k), \quad k = 0,\dots,N_P && \text{(5b)}\\
& x_4(k) \le h^{-1}(\text{BIS}_{\min}), \quad k = 0,\dots,N_P && \text{(5c)}\\
& x_4(k) \ge h^{-1}(\text{BIS}_{\max}), \quad k = \bar{k},\dots,N_P && \text{(5d)}\\
& x_4(k) \ge C_e^R, \quad k = \bar{k},\dots,N_P && \text{(5e)}\\
& x(0) = x_{KF}(\tilde{k}-1), && \text{(5f)}\\
& u_{MPC}(k) - u_{MPC}(k-1) \le \text{SR}, \quad k = 1,\dots,N_C && \text{(5g)}\\
& && \text{(5h)}
\end{aligned}$$

Parameter	Value	Description
u_M	6.67	Saturation upper limit in terms of $[mg/s]$
N_P	120	Prediction horizon
N_C	120	Control horizon
$\text{BIS}_{\max}$	60	Maximum admissible BIS level
$\text{BIS}_{\min}$	40	Minimum admissible BIS level
SR	0.1	Slew Rate Induction Phase
	0.4	Slew Rate Maintenance Phase

A detailed explanation of the specified constraints is provided as follows:

- (5a) represents input limitations;
- (5b) represents the patient dynamics, that is the MPC model (see (1));
- (5c) guarantees that the calculated *BIS* signal never falls below $BIS_{\min}$ along the prediction horizon;
- (5d) states that the calculated *BIS* signal must be above threshold $BIS_{\max}$ at all samples greater than or equal to $\bar{k}$.
- (5e) expresses that the effect-site concentration must be above the target effect-site target concentration C_e^R at all samples in the prediction horizon time instants greater than or equal to $\bar{k}$;
- (5f) is a condition that imposes the initial condition $x(0)$ to be equal to the predicted states resulting from the Kalman filter at the previous iteration $x_{KF}(\tilde{k}-1)$;
- (5g) – (5h) represent the constraints on the rate of change of the drug dosage (slew-rate), adjusted based on the anesthesia phase. Specifically, only the positive change in dosage is limited, to give to the MPC the chance to immediately set to zero the propofol infusion.

In a single iteration, a bisection problem is solved. We start by setting $\bar{k} = N_P$ and then check the feasibility of the problem formulated by the objective function (5) subject to constraints (5a) to (5h) using a standard linear programming solver such as GUROBI (Gurobi Optimization, LLC, 2023). If it is feasible, we halve $\bar{k}$ and repeat the test until we find the minimum value of $\bar{k}$ that makes Problem (5)–(5h) feasible. This value is the optimal value of $\bar{k}$. The control actions are computed for the entire control horizon N_C, however, only the first control action is applied.
The plot in Figure 2 illustrates the evolution of parameter C_e over the prediction horizon resulting from the optimization, with each curve corresponding to a distinct time step. Specifically, the initial curve corresponds to time $k = 0$, while subsequent curves are generated at intervals of 10 iterations. The dashed line is the ultimate target C_e^R to be reached. The intersection point between these lines, represented by the symbol $*$, denotes the value of $\bar{k}$ derived from the bisection problem. Each curve originates from the initial state predicted by the Kalman filter, with the optimization procedure starting from this initial condition. The problem translates itself in a minimum Time-to-Target objective function, that is the time needed for the BIS level to reach for the first time the target BIS value of 60.
Finally, a receding horizon strategy is applied so that only the first calculated value of $u_{MPC}(k)$ is applied and then the optimization problem is solved again at the next sampling time.

2.4 Kalman Filter

In the MPC algorithm, the optimal control law is obtained based on the predicted initial condition provided by the state estimator, as shown in the *KF* block of Figure 1. Initially, all four states are set to zero since there is no presence of drug in the patient's body. Then, the PK/PD model of four states are estimated by means of a Kalman filter, employing the drug concentration in the effect-site compartment $\hat{C}_e$ (see (4)). The values for the measurement noise and the process noise covariances have been selected as in (Ntouskas and Sarimveis, 2021). Additionally, the covariance matrix is set to a 4 by 4

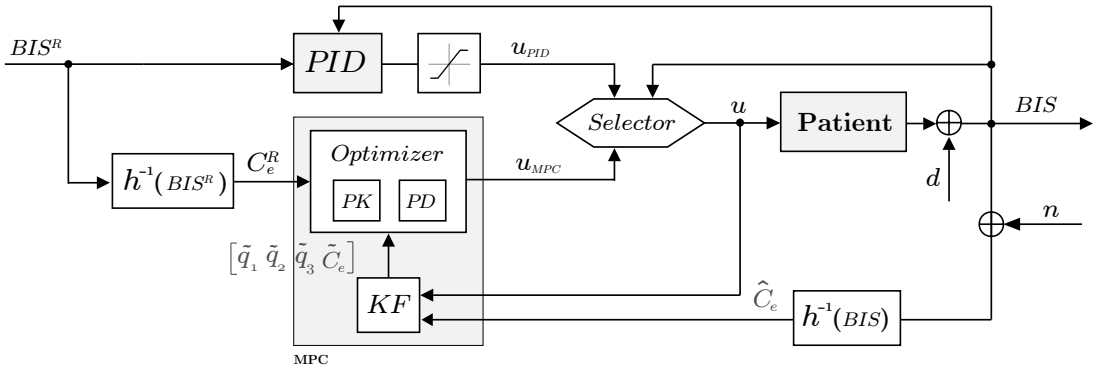


Fig. 1. Closed loop control scheme for DoH.

diagonal matrix of 0.1, because of the relatively low level of uncertainty in the initial state estimates since no drug is present inside the patient's body.

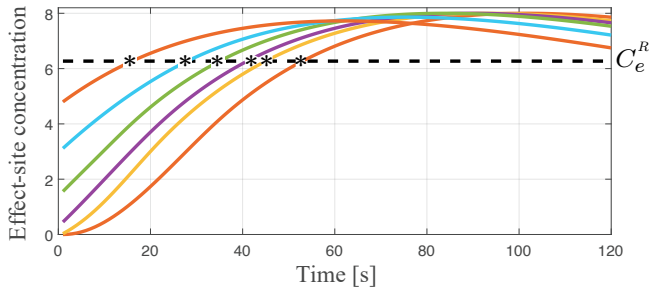


Fig. 2. Effect site concentration outputs computed every 10-time-steps intervals, showcasing the result of the optimizer in some iterations.

3. SIMULATION RESULTS

The control system evaluation is performed for the induction and the maintenance phases focusing on the medical specifications fulfilment. We first examine the response to a set-point change from the initial BIS value to the desired hypnosis level of $BIS = 50$. In addition, we apply two different positive step disturbances d to simulate the surgical stimuli that affect the DoH level. One disturbance has an amplitude of 20, and the other has an amplitude of 30. This choice is made to evaluate the ability of the controller to prevent awareness, as the MPC serves to bring back the patient's depth of hypnosis within the safe range between 40 and 60 in a minimum Time-to-Target, while the PID controller subsequently adjusts it to the desired BIS level.
Two performance indexes are considered:

- TT: refers to time-to-target required for reaching the first time the target interval of $40 \div 60$ BIS values;
- BIS_{NADIR}: which represents the lowest BIS value reached;

3.1 Test on a sample dataset

The control approach was first tested on a dataset of 13 patients that has been widely employed to design anesthesia control systems (Ionescu et al., 2008). The thirteenth patient in this set is a special case, as it has been obtained through the computation of the algebraic mean of the parameters of the other 12 patients.
Simulation results are shown in Figure 3 for the induction phase and in Figures 4a and 4b for the maintenance phase. For the average patient, the response is shown with a black solid line, and the control action is plotted on a separate graph to highlight the PID control actions and the role of the selector.
The performance achieved for all the patients in the dataset in the induction phase is satisfactory from the clinical point of view. The BIS level reaches the set-point value without undershooting and with a low settling time. This is confirmed by the indexes analysis. Clinical requirements are also satisfied in the maintenance phase, where it appears that, even with large disturbances, the DoH level is quickly driven to the safe range without relevant undershoots. The performance indexes are shown in Table 1.

Table 1. Performance indexes for the induction and maintenance phase for the 13 patients dataset.

	Induction Phase		**Maintenance phase 20**		**Maintenance Phase 30**	
	TT[s]	BIS_{NADIR}	TT[s]	BIS_{NADIR}	TT[s]	BIS_{NADIR}
mean μ	66	45.8	22	48.6	45	50
std σ	16	3.8	6	1.7	13	0
min	45	34	16	45.7	30	50
max	98	52.9	35	50	68	50

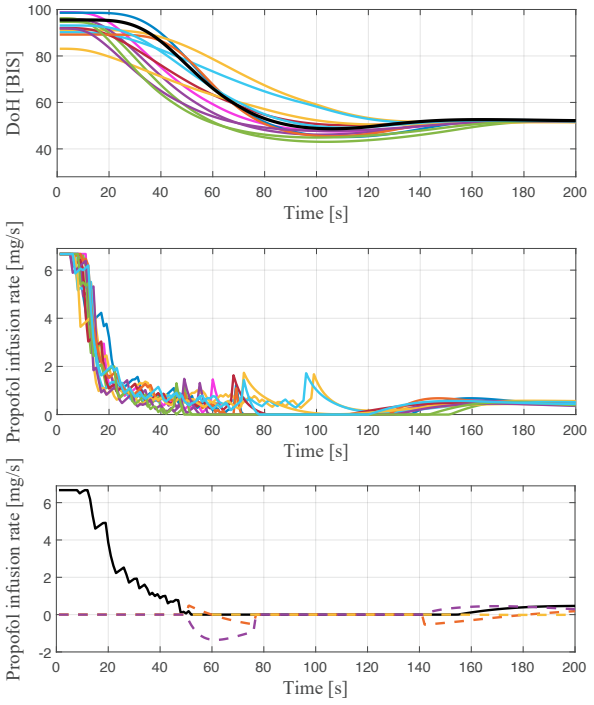


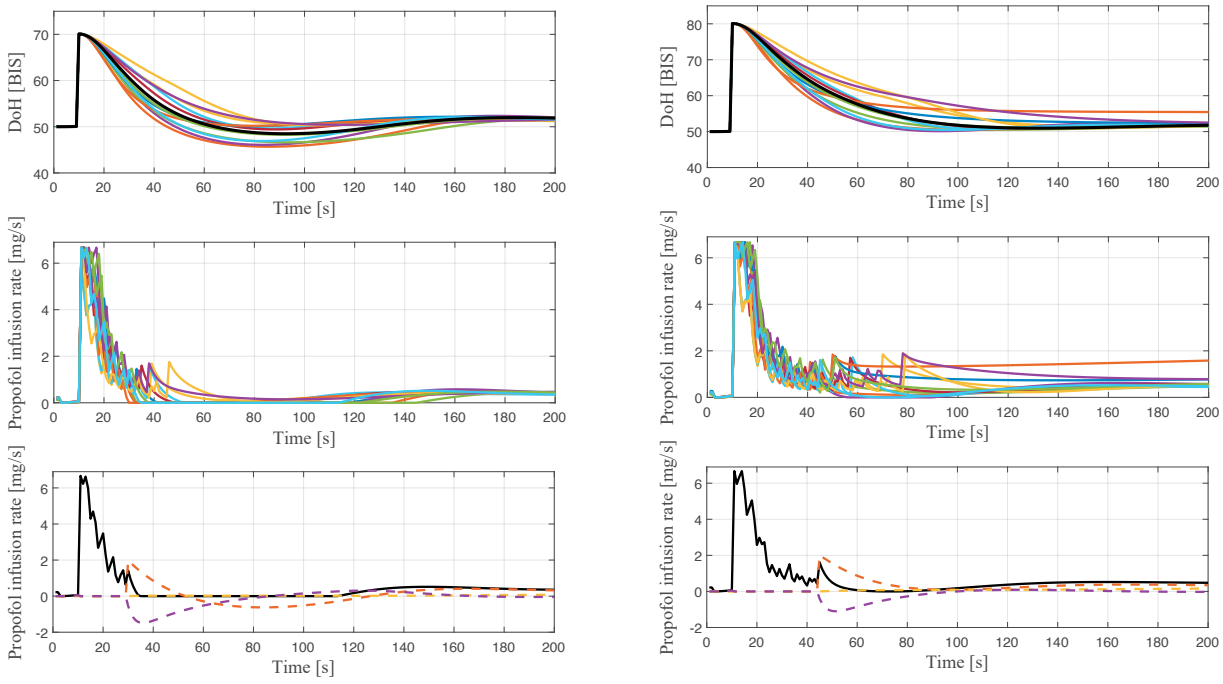
Fig. 3. Simulation responses obtained for the dataset of 13 patients (top) and the control action for the average patient 13 (bottom) for the induction phase. The control actions in the bottom plot are represented by different lines: resulting control action ——, proportional action - - -, integral action - - - and derivative action - - -.

3.2 Test on a wide population

Since the MPC is a model-based approach, it is essential to test its performance on a more extensive population to verify its effectiveness. We have therefore tested the controller on a dataset of 500 patients as in (Pawlowski et al., 2022). Results are presented in Figures 5-6 and the performance indexes can be found in Table 2.
The same considerations done for the dataset of the 13 patients can also be made in this case, the use of MPC allows the BIS to attain the required range in a short time and then the PID controller keeps the DoH at the required level, both in the induction and in the maintenance phase.

Table 2. Performance indexes for the induction and maintenance phase for the wide population dataset.

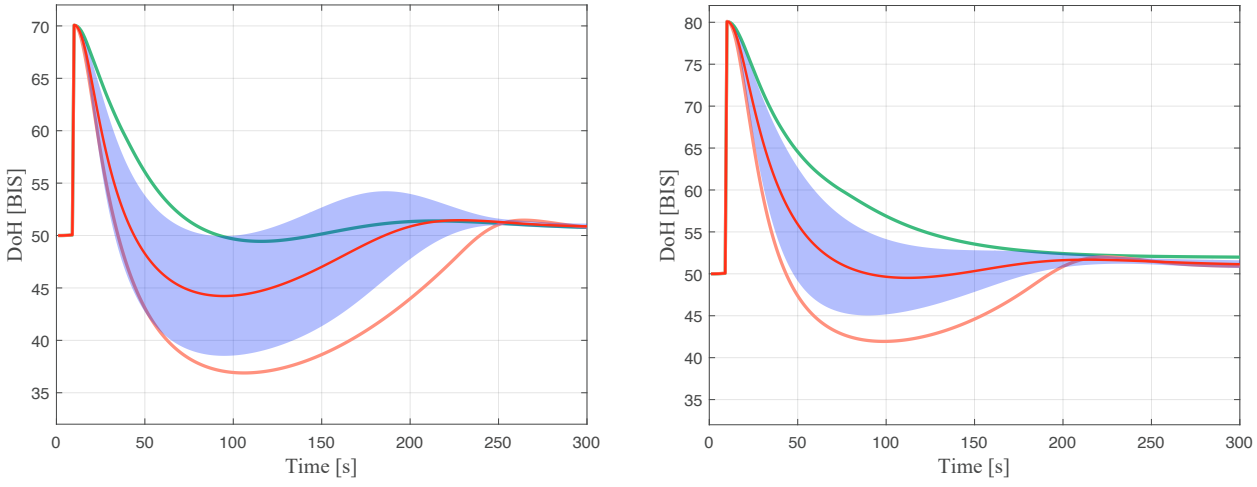
	Induction Phase		**Maintenance phase 20**		**Maintenance phase 30**	
	TT[s]	BIS_{NADIR}	TT[s]	BIS_{NADIR}	TT	BIS_{NADIR}
mean μ	58	45.8	18	44.2	32	49
std σ	9	3.8	4	2.8	8	2
min	35	34	12	36.9	20	42
max	89	52.9	34	50	71	50



(a) Maintenance phase 20

(b) Maintenance phase 30

Fig. 4. Simulation responses obtained for the dataset of 13 patients (top) and the control action for the average patient 13 (bottom) for the maintenance phase with a step disturbance of amplitude 20 and 30. The control actions in the bottom plot are represented by different lines: resulting control action ——, proportional action - - -, integral action - - - and derivative action - - - .



(a) Maintenance phase 20

(b) Maintenance phase 30

Fig. 5. Responses for the maintenance phase with a step disturbance of amplitude 20 and 30 obtained for the 500 patients representative of a wider population. The mean value (μ) is illustrated by the solid red line ——, while the shaded region ▭ represents $\mu \pm 2\sigma$ standard deviations (σ) around the mean. Additionally, the response for the worst-case patient is highlighted in terms of TT —— and BIS_{NADIR} ——.

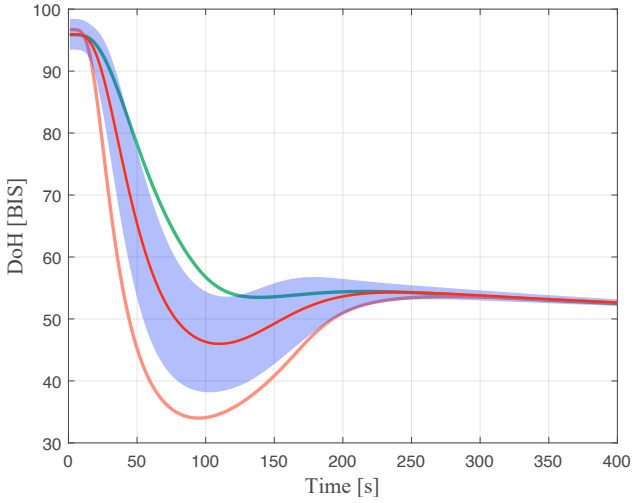


Fig. 6. Responses for the induction phase obtained for the 500 patients representative of a wider population. The mean value (μ) is illustrated by the solid red line, while the shaded region represents $\mu \pm 2\sigma$ standard deviations (σ) around the mean. Additionally, the response for the worst-case patient is highlighted in terms of TT and BIS_{NADIR}.

4. CONCLUSIONS

In this paper we have presented a new DoH control algorithm for total intravenous anesthesia. Its main feature is that a selector is employed so that when the BIS level is inside the required range a PID controller is used, while when the BIS is outside the range, an MPC controller is used to minimize the time-to-target. Most of all, this allows a fast recovery of the hypnosis when the BIS is too high, thus preventing awareness episodes that might be traumatic for the patient. Simulation results have shown that the control system meets the clinical requirements.

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