Two-degree-of-freedom control scheme for depth of hypnosis in anesthesia ⋆

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Abstract: In this work, a Proportional-Integral-Derivative (PID) controller based two-degree-of-freedom control scheme for Depth of Hypnosis (DoH) in general anesthesia is proposed. This approach uses the Bispectral Index Scale (BIS) as a controlled variable and propofol administration as a control variable. The developed structure applies a new compensation scheme, which reduces the influence of the nonlinear element. In this context, we exploit the linear part of the patient model, that can be obtained from the demographics of each individual patient. The parameters are tuned using the optimization procedure based on a genetic algorithm. The evaluation of the proposed technique is performed using intra-patient variability with a Monte Carlo method. Additionally, the performance of the analyzed system has been verified using several indexes. The simulation results show that desired characteristics are obtained for both induction and maintenance phases.

Keywords: Depth-of-hypnosis, PID control, two-degree-of-freedom control, optimization, robustness.

1. INTRODUCTION

During general anesthesia process it is required to maintain a desired level of DoH by administrating drugs like propofol. In the conventional approach, the anesthesiologist doses the drug based on patient vital indexes (e.g. the BIS signal) and his/her experience (Bailey and Haddad, 2005). The DoH in general anesthesia can be divided into three temporal phases, namely: induction, maintenance and emergence (Soltesz et al., 2013, 2016), where the first two phases require specific propofol dosage profile to obtain desired clinical effect (Vanluchene et al., 2004). Moreover, there exists a huge difference in response to drug infusions for each individual due to intra- and inter-patient variability. For these reasons, even experienced anesthesiologist can commit mistakes, which could result in an inadequate dosage of the drug. In fact, underdosing as well as overdosing can provoke severe health consequences and need to be avoided (Padula et al., 2016). Considering the aforementioned aspects, the safety margins can by improved using a proper control technique together with automatized drug administration and monitoring of the patient. The application of an adequate control approach can reduce the side effect of the drugs as well as limit the workload of the anesthesiologist resulting in decreased susceptibility for fatigue and distraction (Merigo et al., 2017b; Pawlowski et al., 2017).

In the last few decades, the DoH control in anaesthesia has been widely investigated by the research community. The DoH control problem was approached with different methodologies and techniques. For example, works that provide a solution using purely industrial control techniques, such as PID controllers (Dumont et al., 2009; Hahn et al., 2012; Padula et al., 2015) can be found. Based on the provided outcomes, it was shown that this methodology can provide satisfactory results under certain conditions. From the DoH point of view, the most important advantages of this methodology are related to the well established background and the wide spectrum of the successful applications. On the contrary, due to their simplicity, it is difficult to address the specific issues of the anesthesia process such as the presence of a strong nonlinearity. On the other hand, the application of a Model Predictive Control (MPC) technique can overcome many limitations of simple controllers and provide good overall performance (Ionescu et al., 2008; Sawaguchi et al., 2008; Krieger and Pistikopoulos, 2014; Nascu et al., 2015). Additionally, this technique takes advantage of the optimization procedure and can handle process constraints. Nevertheless, the MPC approach suffers important performance decrements when noise and unmeasurable disturbances are considered (Cardoso and Lemos, 2008). Recently, event-

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based control techniques have been also applied for the DoH control providing an interesting solution that mimics the anesthesiologist way of actuation, which is based on events rather that on time progress (Merigo et al., 2017a; Pawlowski et al., 2017).

In any case, a satisfactory control algorithm for the DoH needs to be very flexible in order to handle patient variability and to meet all the clinical requirements. As previously mentioned, the DoH is divided in different phases, which are characterized by changes in nonlinear dynamics and also by different requirements for the control technique. The objective in induction phase is to bring the patient DoH to the desired setpoint without significant overshoot (Soltesz et al., 2013). When the reference value is achieved, the control system needs to be adapted for maintenance phase, when the surgery takes place. In this case, the controller needs to quickly attenuate unmeasured disturbances keeping the drug administration in safety range (avoiding under- and over-dosing). In order to handle this behavior, two different controllers are designed for induction and maintenance phase, and swapped using appropriate switching/gain scheduling technique (Soltesz et al., 2013). However, special attention and actions need to be considered during this procedure to guarantee bumpless change and robustness.

In this work, we propose a Two-Degree-of-Freedom (TDoF) control structure exploiting a new scheme for the nonlinearity compensation. In the developed structure we use only one PID controller for both DoH phases, which simplifies the design of the whole system. The proposed structure applies a new compensation scheme, which reduces the influence of the nonlinear element (Sánchez et al., 2011). In this context, we exploit the linear part of the patient model, that can be obtained from the characteristics of each individual patient. The developed structure combines the simplicity of the PID controller and the efficacy of the model-based approach. The resulting system is firstly tuned in order to optimize the performance in the disturbance attenuation problem using a genetic algorithm. Once the PID design parameters are fixed, a second optimization is performed to find the desired value for two additional filters related to reference and feedback signals, respectively. The analyzed system is evaluated through a simulation study, where a set of patients that is representative of a wide range of population is considered and each individual is represented by the nonlinear realistic pharmacokinetic-pharmacodynamic (PK-PD) model (Schinder et al., 1999; Merigo et al., 2017b). Additionally, the validation of the proposed technique is performed using intra-patient variability with Monte Carlo method for an average patient. The performance of the tested configurations has been verified using several indexes.

2. PHARMACOKINETIC-PHARMACODYNAMIC MODEL

This section presents a brief introduction to the BIS response to propofol adminstration using realistic patient model basing on pharmacokinetic-pharmacodynamic (PK-PD) response to the drug infusion (Schinder et al., 1999; Merigo et al., 2017b). The patient model considers correlation between the drug dosage rate and the drug effect by

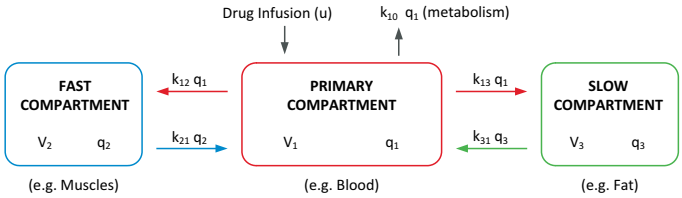

Fig. 1. The mamillary three-compartment for the PK model representation.

means of pharmacokinetics and pharmacodynamics terms. The PK refers to the infusion, distribution and elimination of the drugs in the body, while the PD characterizes the relationship between blood concentration of a drug and its clinical effect. The propofol dosage effect on the human body can be modelled using linear dynamics for PK and PD connected in series with a static nonlinear element.

The PK term describes a mamillary compartment model, assuming that each compartment is homogeneous with uniform drug distribution. This structure was introduced and validated on real patients by using blood samples during anesthesia in (Schinder et al., 1999). Figure 1 shows the structure of schematic diagram of the three-compartment model frequently used for propofol. The compartments are interconnected by a mass flux exchange, so that the following system results:

$$\begin{aligned} \dot{q}_1(t) &= -(k_{10}+k_{12}+k_{13})q_1(t) + k_{21}q_2(t) + \\ &\quad + k_{31}q_3(t) + u(t) \\ \dot{q}_2(t) &= k_{12}q_1(t) - k_{21}q_2(t) \\ \dot{q}_3(t) &= k_{13}q_1(t) - k_{31}q_3(t) \end{aligned} \tag{1}$$

where $q_i(t)$ $[mg/min]$ is the quantity of the drug over the time for each compartment. Notice that $q_1(t)$ refers to primary blood compartment, $q_2(t)$ refers to the peripheral fast compartment that includes well perfused body tissues like muscles, and $q_3(t)$ refers to slow dynamics compartment that includes poor perfused body tissues like fat. The input of the model is $u(t)$ $[mg/min]$ and represents the infusion rate of the drug. The parameters k_{ij} for $i \neq j$ refer to the drug transfer frequency from the ith to the jth compartment (Schinder et al., 1999). The resulting output of the PK term is the plasmatic concentration of the drug, obtained as $C_p(t) = q_1(t)/V_1$ and it is also the input of the pharmacodynamical term of the model. The resulting PK transfer function has the following form:

$$PK(s) = \frac{C_p(s)}{U(s)} = \frac{1}{V_1}\frac{(s+k_{21})(s+k_{31})}{(s+p_1)(s+p_2)(s+p_3)} \tag{2}$$

where p_1, p_2, p_3 are related to k_{ij} for $i \neq j$ through:

$$\begin{cases} p_1+p_2+p_3 &= k_{10}+k_{12}+k_{13}+k_{21}+k_{31} \\ p_1p_2+p_1p_3+p_2p_3 &= k_{10}k_{21}+k_{13}k_{21}+k_{10}k_{31} \\ & \quad +k_{12}k_{31}+k_{21}k_{31} \\ p_1p_2p_3 &= k_{10}k_{21}k_{31} \end{cases}$$

The value of the parameters depend on the characteristics of the patient (age, weight, height, gender) (Schnider et al., 1998).

In the PD term, a fictitious compartment called effect-site compartment is added to represent the lag between the plasma concentration and the corresponding drug effect. The drug concentration in the effect-site compartment is denoted as C_e, where $\dot{C}_e(t) = k_{1e}C_p(t) - k_{e0}C_e(t)$.

Following (Schinder et al., 1999), the propofol transfer frequency k_{1e} can be considered constant and equal to the frequency of drug removal from the effect-site compartment with $k_{1e} = k_{e0} = 0.456\ [min^{-1}]$. The resulting transfer functions is:

$$PD(s) = \frac{C_e(s)}{C_p(s)} = \frac{k_{e0}}{s + k_{e0}} \tag{3}$$

Last, a static nonlinear sigmoidal function, known as Hill function, needs to be added to correlate the effect-site drug concentration and clinical effect, given by the BIS index (Vanluchene et al., 2004; Ionescu et al., 2008). This nonlinear function can be written as:

$$NL = E_0 - E_{max}\left(\frac{C_e(t)^\gamma}{C_e(t)^\gamma + C_{e_{50}}^\gamma}\right), \tag{4}$$

where E_0 is the baseline value representing the BIS level of the patient in the initial state before the infusion, E_{max} is the maximum reachable effect achieved by the infusion, γ denotes the steepness of the curve that represents the receptiveness of the patient to the drug, and $C_{e_{50}}$ is the necessary concentration of the drug to reach the half maximal effect. Figure 2 shows the block diagram of the complete propofol response model.

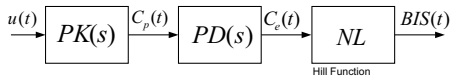

Fig. 2. Schematic representation on the patient PK-PD model for propofol dosage response.

The DoH induced by the propofol administration is therefore usually modelled by means of a Wiener model, where a linear model is connected in series with a static nonlinear function (Vanluchene et al., 2004; Marsh et al., 2004; Schinder et al., 1999). Indeed, the Wiener model is obtained grouping the linear part of PK and PD :

$$H(s) = \frac{C_e(s)}{U(s)} = PK(s)PD(s)$$

and connecting in series a nonlinear element NL (sigmoidal Hill function).

3. TWO-DEGREE-OF-FREEDOM CONTROL SCHEME FOR DOH

In this section a detailed description of the developed TDoF control scheme for the DoH is provided. The main objective of such a system is to regulate the propofol infusion rate to reach the desired BIS reference during induction phase and to maintain its value during the maintenance phase. The desired BIS level is therefore the set-point of the control scheme and it is set to 50 in accordance with clinical practice. The block diagram of the proposed control scheme is shown in Figure 3, where $r(t)$ is the reference signal, $u(t)$ is the control signal that represents the propofol administration volume, $d(t)$ represents the disturbances and $y(t)$ is the BIS signal representing the controlled variable. In such a scheme, we exploit the patient model that was presented previously in Section 2. In particular, we assume that the linear part H can be obtained with good precision based on the demographics of each individual patients (more information regarding this topic can be found in Merigo et al. (2017a)). Nevertheless,

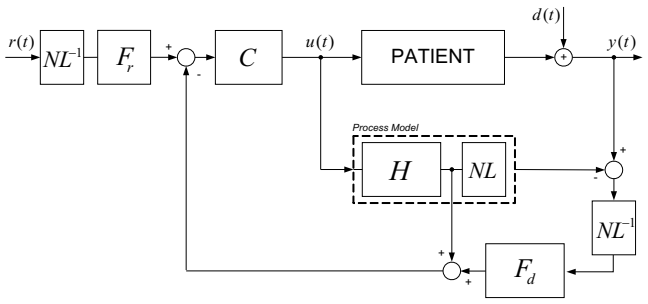

Fig. 3. TDoF control scheme with compensation of nonlinear component

the nonlinear part NL of the Wiener model can not be easily estimated for an individual patient and in this work we use the average values of parameters obtained from statistical distribution of population (Schnider et al., 1998; Schinder et al., 1999). The inverse of the nonlinear function, NL^{-1}, is obtained by calculating the inverse function of the BIS index from equation (4):

$$NL^{-1} = C_{e_{50}} \sqrt[\gamma]{\frac{\bar{E} - E_0}{E_0 - \bar{E} - E_{max}}}$$

where $\bar{E}$ refers to the current $BIS(t)$ value.

From the presented scheme (see Figure 3), it can be observed that the DoH control problem is reduced to a linear case, where the controlled system H is affected by the difference between the patient and the considered model response. In case of perfect knowledge of the patient model and of the nonlinear function, the resulting difference is zero in steady- state condition. Otherwise, non zero signal is feed though F_d when unmeasurable disturbances and/or difference between the model and the real process exists. The F_d role consists of attenuation of the disturbance signal that usually is originated by the surgical stimuli and has a step like profile. Additionally, the F_r filter is used to obtain a smooth reference profile avoiding an aggressive response of the controller. The error between the desired reference inverse and the filtered feedback inverse is compensated by the controller C.

In this case, we consider the PID controller as the feedback controller, such that:

$$C(s) = K_p\left(1 + \frac{1}{sT_i} + sT_d\right) \tag{5}$$

where K_p is the proportional gain, T_i is the integral time constant and T_d is the derivative time constant. Moreover, the derivative action is filtered (with $N = 10$) to provide proper controller structure (Åström and Hägglund, 2006). Furthermore, anti-windup technique was implemented in order to take into account to the control signal saturation.

Using this structure we can obtain, on the one hand, the desired performance for disturbance compensation and, on the other hand, the presence of the filters allows an additional degree of freedom to adjust the system response to setpoint changes as in the standard TDoF approach. Following this philosophy, we use two additional elements, apart from the feedback controller, that influence the control system performance. In order to obtain smooth and

overshoot free response to step changes in the reference signal, we consider a first-order filter of the form:

$$F_r(s) = \frac{1}{sT_{F_r} + 1}$$

where its time constant, T_{F_r} is used for tuning procedure. Moreover, as mentioned previously, the response of the control system to the disturbances can be modified using the F_d filter placed in the feedback loop:

$$F_d(s) = \frac{1}{(sT_{F_d} + 1)^2}.$$

In this case, we propose the use of a second-order low-pass filter, where the filter cut-off frequency (and consequently the T_{F_d} parameter) can be adjusted.

In order to analyze the developed control scheme, we consider the inter-patient variability, taking into account a set of patients, which provide representative data for a wide range of population (Struys et al., 2003; Ionescu et al., 2008; Nascu et al., 2015). The values of model parameters for thirteen individuals can be found in (Merigo et al., 2017a) (note that the 13th patient represents an average patient and for this case the model parameters are calculated as algebraic means of whole group).

3.1 Tuning

For the presented approach, it is not possible to apply the conventional tuning rules for the PID parameters due to the DoH process and control system complexity. For this reason, the values for the control system parameters are determined, considering clinical specifications and required robustness, by application of a genetic algorithm optimization (Padula et al., 2015).

The control scheme analyzed in this work requires the tuning of the PID controller parameters, K_p, T_i and T_d, as well as proposed filters parameters, T_{F_r} and T_{F_d}. Due to the TDoF approach, the tuning procedure is divided into two steps. In the first step we adjust the controller parameters to be optimal for disturbance compensation which is related with the DoH maintenance phase. For this reason both filters are disabled ($T_{F_r} = 0$, $T_{F_d} = 0$) in this stage, in order to obtain best performance in disturbance attenuation. During this phase, the control system has to suppress the effect of unmeasurable disturbances due to noxious stimuli. In the presented methodology we follow the same approach as in (Merigo et al., 2017a, 2018), where disturbances have been modeled as a step signal of amplitude 10 in the BIS level followed by another step after 10 [min] of amplitude -10. In this case, the BIS signal should be maintained in the range from 40 to 60 in order to minimize the possibility of health complications for the patient. The second stage of tuning procedure consists of filters adjustment by keeping the PID controller parameters fixed. This stage focuses on the induction phase where the control system needs to achieve the desired DoH in terms of the BIS signal. For this part, the reference signal was fixed to 50 and, by following the clinical specifications, it should be achieved in around 5 minutes avoiding an excessive undershoot.

The values obtained for all tuning parameters are shown in Table 1 and have been determined in order to minimize the worst-case Integral Absolute Error (IAE) of the process output by considering the entire data set of patients. In this way, as the patient data set represents a wide population, the inter-patient robustness is ensured. The IAE performance index is defined as $\int_0^\infty |r(t)-y(t)|$. Notice that applying the proposed control scheme it is possible to use only one controller for induction and maintenance phases. On the contrary, in many previously proposed solutions for the DoH, two different controllers (or sets of parameters) were required for each phase.

Table 1. Tuning for proposed TDoF scheme

K_p	T_i	T_d	T_{F_r}	T_{F_d}
22.64	915.2	20.43	12.60	11.44

4. SIMULATION RESULTS

In this section, the developed control scheme is evaluated through simulations using a set of patients models. In the first part, the evaluation of the obtained tuning is provided focusing on the disturbance attenuation and setpoint tracking problems. Afterwards, intra-patient variability is analyzed considering the average patient. Moreover, in all analyzed systems, the control action $u(t)$ is the propofol infusion rate [mg/s], bounded by the saturation block between a minimum value of 0 [mg/s] and a maximum value of 6.67 [mg/s], considering a standard propofol concentration (Propofol 20 [mg/ml]) (Merigo et al., 2017a).

The proposed methodology has been tested on the considered data set of patients. In order to evaluate the performance, the following indexes, proposed in (Ionescu et al., 2008), have been computed for the induction phase (set-point following tuning):

- TT: observed time-to-target (in minutes) required for reaching for the first time the target interval of 45-55 BIS values;
- BIS-NADIR: the lowest observed BIS value during the induction phase;
- ST10: settling time, defined as the time interval for the BIS to reach and stay within the BIS range between 45 and 55 (that is, the target value of 50 $\pm$ 5);

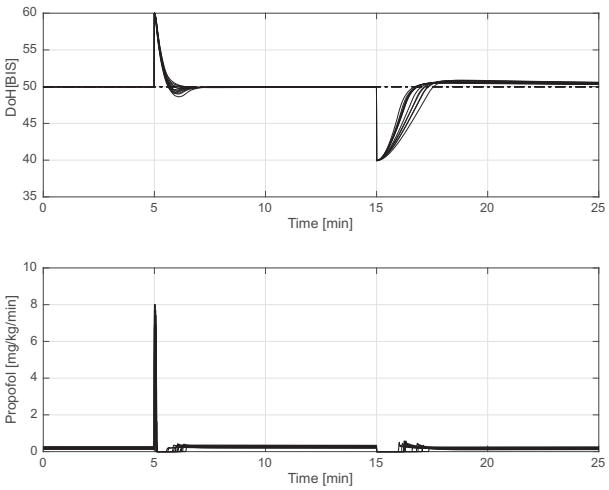

Fig. 4. Simulation results for maintenance phase considering all patients.

Table 2. Disturbance rejection performance indexes for all patients.

Patient	TT_p	BIS-NADIR$_p$	TT_n	BIS-NADIR$_n$
1	0.47	49.48	1.02	50.05
2	0.35	49.71	0.77	50.1
3	0.44	49.5	0.79	49.95
4	0.43	49.48	0.87	50
5	0.41	49.47	1.07	50.1
6	0.45	49.47	0.79	49.94
7	0.5	49.45	0.95	49.97
8	0.4	49.53	0.79	49.97
9	0.34	49.95	0.7	50.14
10	0.59	49.44	1.04	49.95
11	0.59	49.41	1.28	50.02
12	0.48	49.44	1.14	50.07
13	0.4	49.48	0.8	49.97
Mean	0.45	49.53	0.92	50.02
Std. Dev.	0.075	0.142	0.167	0.065
Min.	0.34	49.41	0.7	49.94
Max.	0.59	49.95	1.28	50.14

- ST20: the same of ST10 but it considers a wider BIS range from 40 to 60;
- US45: undershoot, defined as the maximum amount of BIS value that exceeds the BIS lower limit 45.

For the maintenance phase (disturbance rejection tuning) only the TT and the BIS-NADIR indices are considered and they have been calculated separately for the positive and for the negative step (represented by $_p$ and $_n$ subindexes, respectively).

Following the TDoF philosophy, in the first step the developed control system has been evaluated for the maintenance phase focusing on the disturbance attenuation performance. Figure 4 shows the obtained results for the whole patients set. From this figure it can be observed that the proposed control system obtains satisfactory performance in disturbance compensation independently on the step direction. For both step changes (positive and negative), the control system achieves the steady state approximately after 2.5 minutes fulfilling the clinical requirements. The performance indexes for the maintenance phase considering individual patients are shown in Table 2. As can be observed, for all the analyzed individuals the

Table 3. Setpoint tracking performance indexes for all patients.

Patient	TT	BIS-NADIR	ST10	ST20	US45
1	1.39	49.27	1.39	1.1	0
2	1.11	45.29	1.11	1	0
3	1.6	49.32	1.6	1.34	0
4	1.32	49.24	1.32	1.05	0
5	1.1	49.22	1.1	0.9	0
6	1.76	49.28	1.76	1.43	0
7	1.57	49.26	1.57	1.23	0
8	1.3	49.32	1.3	1.09	0
9	1.01	40	2.27	1.69	5
10	1.8	49.31	1.8	1.32	0
11	1.39	49.21	1.39	1.02	0
12	1.25	49.21	1.25	0.95	0
13	1.41	49.26	1.41	1.16	0
Mean	1.38	48.25	1.48	1.18	0.38
Std. Dev.	0.236	2.604	0.31	0.213	1.332
Min.	1.01	40	1.1	0.9	0
Max.	1.8	49.32	2.27	1.69	5

TDoF control system provides the necessary performance, by satisfying the control objectives.

In the next step, the response of the system to the setpoint change in the induction phase has been analyzed. In Figure 5 the simulation results are shown for complete set of the patients. It can be observed that for the analyzed group the proposed control system is able to achieve the desired level of DoH in the required time. Additionally, the excessive undershoot is avoided for all patients, keeping the controlled variable inside the band (setpoint $\pm$ 5). Table 3 summarizes the performance indexes for the induction phase. Considering the obtained values, it can be observed that a satisfactory performance is also obtained for this DoH phase. Further, the disturbance rejection is not worsen by the presence of the filters.

The results for intra-patient variability, considering the average patient, are shown in Figure 6. In this case, a Monte Carlo method has been applied by considering the uncertainty in the parameters of the model representing the patient shown in (Schnider et al., 1998; Vanluchene et al., 2004). In particular a set of 200 models have been generated in order to test the robustness of the developed TDoF control system.

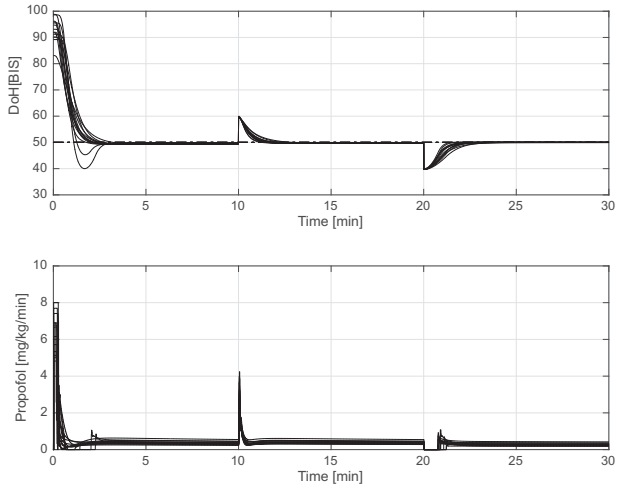

Fig. 5. Simulation results for induction phase considering all patients.

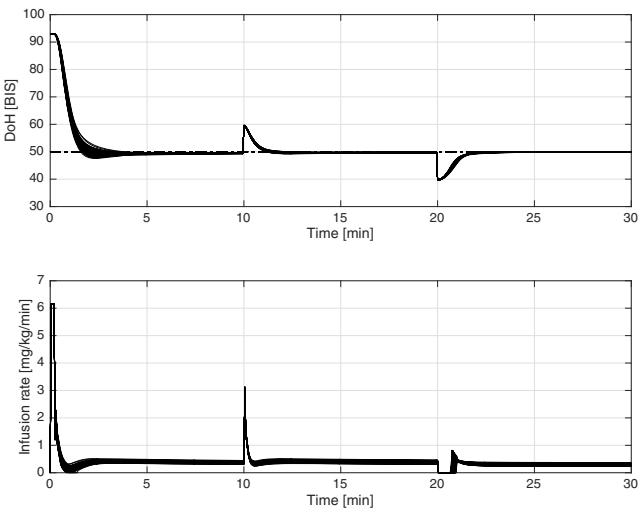

Fig. 6. Monte Carlo simulation results for the average patient.

Table 4. Setpoint tracking performance indexes for the average patient.

Index	TT	BIS-NADIR	ST10	ST20	US45
Mean	1.42	49.08	1.42	1.17	0
Std. Dev.	0.083	0.424	0.083	0.050	0
Min.	1.24	47.57	1.24	1.05	0
Max.	1.72	49.61	1.72	1.30	0

Table 5. Disturbance rejection performance indexes for the average patient.

Index	TT_p	BIS-NADIR$_p$	TT_n	BIS-NADIR$_n$
Mean	0.40	49.48	0.80	49.88
Std. Dev.	0.018	0.090	0.047	0.034
Min.	0.36	49.23	0.71	49.81
Max.	0.44	49.66	0.92	50.01

The performance indexes for the induction and maintenance phases are shown in Table 4 and Table 5, respectively. In both cases, a low variability of the considered indexes can be observed. This fact confirms a good performance of the proposed approach, even for significant modelling uncertainty. From this simulation, it can be deduced that the developed control scheme is able to handle the intra-patient variability assuring desired behavior of the controlled variable. This issue is highly important from the practical point of view, since the exact model of the patient can not be obtained and only the approximated one can be used.

5. CONCLUSIONS

In this work a TDoF control scheme for the DoH in general anesthesia has been introduced and analyzed. The presented solution uses a nonlinear compensation scheme to improve the control system performance. The developed structure enables the possibility to meet clinical requirements during the whole anesthesia process using only one controller. This is possible by a suitable tuning of such control system that considers disturbance attenuation and setpoint tracking simultaneously. The provided evaluation shows that the proposed scheme can obtain the desired control performance without requiring a controller commutation between induction and maintenance phases.

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