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Inversion-based propofol dosing for intravenous induction of hypnosis

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ABSTRACT

In this paper we propose an inversion-based methodology for the computation of a feedforward action for the propofol intravenous administration during the induction of hypnosis in general anesthesia. In particular, the typical initial bolus is substituted with a command signal that is obtained by predefining a desired output and by applying an input–output inversion procedure. The robustness of the method has been tested by considering a set of patients with different model parameters, which is representative of a large population.

1. Introduction

There has been a significant interest in the last decades for the feedback control of drug dosing (see, for example, [1]). In particular, the closed-loop control of anesthesia during surgery has been investigated thoroughly [2–5], because it results in a reduced workload for the anesthesiologist (who has in any case to supervise the overall surgery) [6]. It may also provide many advantages for the patient such as an increased safety and a reduced post operative recovery time interval because of a reduced amount of drug employed.

General anesthesia for surgery can be classified into three functional components, namely, hypnosis, analgesia and immobility, and each component can be induced by specific drugs. In this paper we focus on the control of the depth of hypnosis (DoH) by means of the intravenous administration of propofol. The controlled variable is the bispectral index scale (BIS, Aspect Medical Systems, Norwood, USA), which measures the brain activity based on a bispectral analysis of a simplified EEG of the patient [2,3,7–9] (note that an alternative similar measure is provided by the wavelet-based index WAV_{CNS} [10–12]).

The BIS has been chosen here because it is a widespread system to measure of the DoH and it is widely accepted in the clinical practice. Nevertheless, the use of the BIS involves a strong nonlinearity in the system and this makes the control task very challenging. During the surgery, three phases typically occur. Initially (induction phase), the patient is transitioned from consciousness to the required hypnotic state. This phase is usually very rapid, deep unconsciousness is reached in a short time from the start of the propofol intravenous bolus. Reduction of systemic blood pressure can be a common side-effect

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[13]. From a control systems point of view, a fast transition from the initial BIS value to the target one should be performed without the occurrence of a possibly dangerous overshoot [9,14,15]. Then (maintenance phase), the specified hypnotic level has to be kept despite the occurrence of disturbances, typically related to noxious stimuli. Finally, in the emergence phase the patient recovers from the anesthesia, usually by simply stopping the administration of the drugs.

A well-known pharmacokinetic-pharmacodynamic model can well describe the effect of propofol on the DoH. In particular, a three compartment model (represented by a third-order linear time invariant system) describes the relation between the propofol infusion rate and the plasma concentration, a fourth compartment (represented by a first-order linear time invariant system) links the plasma concentration with the effect site and, finally, a nonlinear Hill function describes the relation between the effect site and the sensor signal [16–18]. Based on this model, the target controlled infusion (TCI) has been devised and adopted in clinical practice. In particular, the anesthesiologist selects the plasma or the effect site concentration and the model-based open-loop control system aims at achieving it by selecting an appropriate bolus (whose duration can be also selected) in the induction phase. In standard practice, the anesthesiologist closes the loop manually in order to cope with the unavoidable modeling uncertainties. Indeed, a large interpatient variability, that is, a large model uncertainty has to be considered in this context.

Many different closed-loop control strategies have been proposed in the literature and also applied in practical cases [19].

The most selected option is the use of a simple proportional-integral-derivative (PID) controller [10–12,20–28]. In each paper the tuning issue has been addressed differently and often empirically and only in a few cases the robustness issue is handled explicitly. In this context, it has to be considered that the BIS signal is very noisy. To cope with this issue, in [23,29] the BIS value is disregarded by the feedback controller if the signal quality index is smaller than a given threshold. In general, the presence of noise makes the use of the derivative action critical.

It has also to be stressed that it is difficult to handle both the DoH induction and maintenance phases with the same PID parameters. For this reason, in some cases only the maintenance phase is controlled in closed-loop [2,7,22,30]; alternatively, a feedforward action is employed during the maintenance phase to increase the aggressiveness of the controller when a significant increment of the BIS occurs [29]. The use of a two-degree-of-freedom controller, which can be seen as the most sensible option, has been proposed in [10]. However in this case the filter used on the set-point to reduce the overshoot has also the effect of increasing the rise time.

Other more advanced methodologies, such as internal model control [31], Bayesian-based adaptive control [32], fuzzy control [33–36], model predictive control [27,37,38], adaptive control [39], fractional control [10,40] (using WAV_{CNS}) and μ-synthesis [12], have also been proposed as alternatives to PID control.

This paper focuses on the induction phase and proposes a new methodology to obtain a fast and smooth transition from the initial state of wakefulness to deep unconsciousness, that is, from the initial BIS value to the target one. In particular, we propose to apply an approach based on an input–output inversion technique. Dynamic inversion has been already investigated in the literature (see, for example, [41–45]) but it has not been applied to the control of anesthesia yet. The main idea consists in first defining a suitable smooth desired output transition of the system. For this purpose, a transition polynomial, parametrized by the transition time τ, is chosen, as it ensures (in the nominal case) a monotonic transition and it allows the user to arbitrarily select the degree of continuity of the control signal [46]. Then, the input–output inversion approach is applied to the closed-loop system where a PI feedback controller is employed in order to compensate for possible disturbances and to improve the robustness of the system. In this way, the command signal (which substitutes the typical set-point step signal) to be applied to the control system is determined.

Actually, the proposed approach is essentially a feedforward one but it differs from the standard TCI technique because instead of targeting a final value of the effect site (or plasmatic) concentration, in the inversion-based method a specific monotonic transition of the effect site concentration is pursued. This implies that the infusion rate does not exhibit abrupt changes, that is, an impulsive behavior as in the TCI, which is appreciable from a clinical point of view (see Section 4). Further, on the contrary of the TCI, the inversion based feedforward signal is designed by taking explicitly into account the feedback controller, which results in an improved robust performance.

The input–output inversion methodology applied here was originally developed for linear systems and it has been suitably adapted in order to cope with the presence of the nonlinearity. Basically, only the difference between the expected output (computed explicitly considering the nonlinearity) and the actual one is fed back to the controller. It is worth stressing that this approach is suitable for any possible nonlinear system that can be obtained by substituting the Hill function with any other nonlinear algebraic function.

The effectiveness of the method in coping with uncertainties is demonstrated by considering a population of 12 patients, which can be seen as representative of a large population as very different kinds of patients are included [37].

The paper is organized as follows. The pharmacokinetic-pharmacodynamic model is described in Section 2. The inversion-based methodology is proposed in Section 3. Simulation results are given and discussed in Section 4. Concluding remarks are in Section 5.

2. Patient model

The patient model describes the relationship between the drug infusion rate and the drug effect by means of a pharmacokinetic-pharmacodynamic model. Pharmacokinetics (PK) refers to the infusion, distribution and elimination of the

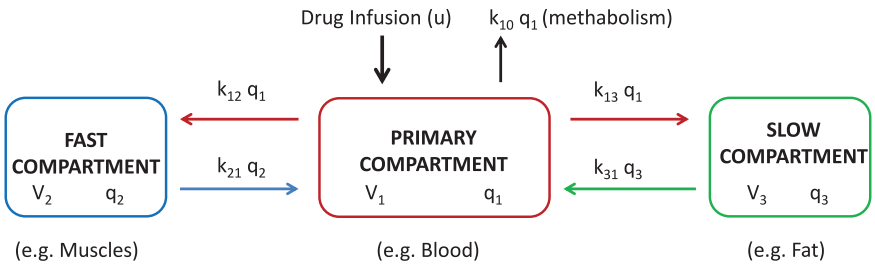

Fig. 1. The mamillary three-compartmental model representing the PK of a patient.

drug in the body, while pharmacodynamics (PD) describes the relationship between blood concentration of a drug and its clinical effect.

The overall effect of the propofol drug infused in the human body can be then modeled by matching the linear dynamics of the pharmacokinetics and pharmacodynamics in series with a static nonlinear function [16–18,37]. Pharmacokinetics is usually described by means of a mamillary compartmental model, where it is assumed that each compartment presents homogeneous properties, in particular the drug distribution inside a compartment is uniform. A schematic block diagram of the three-compartmental model typically employed for propofol is shown in Fig. 1.

This model is described by a first-order derivative system where mass fluxes in output for a compartment denote the input of a second or a third compartment. The general formulation of three-compartmental model is:

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

where $q_1(t)$ [mg] expresses the quantity of the drug over the time in the central blood compartment, $q_2(t)$ [mg] denotes the quantity in the peripheral fast compartment, which includes well perfused body tissues like muscles and tendons, $q_3(t)$ [mg] expresses the amount in the slow dynamics compartment, which includes poor perfused body tissues like fat and bones, the parameters k_{ij} are constants expressing the amount of the mass flow from the ith to the jth compartment, with the exception of k_{10} which represents the elimination rate of the drug (metabolism), and $u(t)$ [mg/min] is the infusion rate of the drug into the plasmatic circulation, thus it is the input of the model.

The parameters of the model can be obtained, as suggested in [17], starting from the values of the weight, height, and lean body mass of the patient. Note that the parameters are based on population averages, hence the real patient parameters are distributed according to the variances also reported in [17]. The corresponding transfer function representation can be written as:

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

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

$$\begin{cases} p_1+p_2+p_3 = k_{10}+k_{12}+k_{13}+k_{21}+k_{31}\\ p_1p_2+p_1p_3+p_2p_3 = k_{10}k_{21}+k_{13}k_{21}+k_{10}k_{31}+k_{12}k_{31}+k_{21}k_{31}\\ p_1p_2p_3 = k_{10}k_{21}k_{31}\end{cases} \tag{3}$$

The output of (2) is the plasmatic concentration of the propofol drug C_p calculated as $C_p(t) = q_1(t)/V_1$.

Pharmacodynamics is characterized by a first-order delay-free function which relates the drug concentration in the central compartment to a fictitious one known as effect-site compartment:

$$PD(s) = \frac{C_e(s)}{C_p(s)} = \frac{k_{e0}}{s+k_{e0}}. \tag{4}$$

where C_e is the effect-site concentration and k_{e0} [min^{-1}] is the parameter that characterizes the equilibration time constant between the plasma concentration and the corresponding drug effect. Its value is estimated in the literature [17] as:

$$k_{e0} = 0.459. \tag{5}$$

Then, the relation between effect-site drug concentration and clinical effect can be mathematically expressed by the means of a nonlinear sigmoid function, known also as Hill function, which models the bispectral index scale (BIS), a dimensionless parameter normalized between 0 and 100, indicating isoline EEG and fully awake patient respectively:

$$BIS(t) = E_0 - E_{max}\left(\frac{C_e(t)^\gamma}{C_e(t)^\gamma + C_{e_{50}}^\gamma}\right), \tag{6}$$

Table 1
Characteristic variables for the considered set of patients (H: height, W: weight) (as from [37]).

Id	Age	H [cm]	W [kg]	Gender	$C_{e_{50}}$	γ	E_0	E_{max}
1	40	163	54	F	6.33	2.24	98.8	94.10
2	36	163	50	F	6.76	4.29	98.6	86.00
3	28	164	52	F	8.44	4.10	91.2	80.70
4	50	163	83	F	6.44	2.18	95.9	102.00
5	28	164	60	M	4.93	2.46	94.7	85.30
6	43	163	59	F	12.00	2.42	90.2	147.00
7	37	187	75	M	8.02	2.10	92.0	104.00
8	38	174	80	F	6.56	4.12	95.5	76.40
9	41	170	70	F	6.15	6.89	89.2	63.80
10	37	167	58	F	13.70	1.65	83.1	151.00
11	42	179	78	M	4.82	1.85	91.8	77.90
12	34	172	58	F	4.95	1.84	96.2	90.80
13	38	169	65	F	7.42	3.00	93.1	96.58

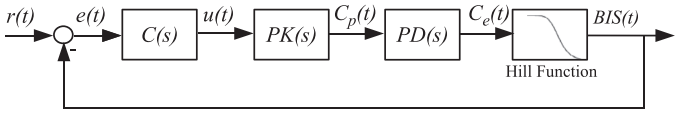

Fig. 2. The considered control scheme.

where E_0 is the baseline value representing the initial infusion-free state of the patient, $E_0 - E_{max}$ is the maximum reachable effect achieved by the infusion, γ denotes the slope of the curve (*i.e.*, 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.

It is worth stressing that the Hill function is highly nonlinear. In fact, at the beginning of the infusion, the curve presents a *plateau*, where the presence of little quantities of the drug in the effect compartment does not affect the clinical effect until the drug concentration reaches a certain value. The final saturation expresses the impossibility to overcome the maximum achievable value E_{max} regardless of the amount of hypnotic infused.

In other words, in the first phase, despite the evolution of the system state, the system output does not change because of the nonlinearity the Hill function. Hence, during this part of the hypnosis induction, the output (BIS) does not contain information about the system states to be fed back to the controller, that is, the state evolution during the first part of the induction has to be dealt with by using a feedforward signal. On the contrary, when the drug concentration in the effect site reaches a value that is sufficient to exit from the plateau of the Hill function (i.e., the derivative of the Hill function starts to decrease), it is worth feeding the output back to the controller. Thus, in this phase the role of the feedback loop is very important and a suitable correcting input is needed, as it will be clarified in the next sections. In this context, the proposed dynamic inversion methodology is implicitly capable to cope with this nonlinear behavior by explicitly taking into account the Hill function in the inverting signals.

Finally, in order to address the intrapatient variability, the dataset of patients presented in [37] has been employed. In addition to the set of 12 patients, a thirteenth individual has been considered as the average patient of the group, calculating for each available parameter its algebraic mean. This can serve as the nominal model on which the inversion-based methodology described in the next section can be applied (see Section 4 for the related results). The values of the model parameters for the considered population are presented in Table 1.

It is worth stressing that the Hill curve (and its parameters) is not related to the a rigorous physical modeling of the drug effect. Nevertheless, it is useful to describe the propofol behavior in a range that is interesting for the clinical effect, *i.e.*, for the BIS ranging approximatively from E_0 to 20. In this context, the set of patients whose parameters are given in Table 1 are representative of a wide range of people with different characteristics and can be therefore used to prove the robustness of the proposed approach.

3. Inversion-based control system design

The aim of the induction phase is to provide a transition from the initial BIS value E_0 to a target one, denoted as $\bar{E}$, which is usually selected as $\bar{E} = 50$. As already mentioned, this transition should be as fast as possible but without the occurrence of large overshoots, which can be critical for the patient safety.

In order to satisfy this control requirement, the control scheme of Fig. 2 is proposed. First, the feedback controller is chosen as an output filtered PI controller with transfer function

$$C(s) = K_p\left(1 + \frac{1}{sT_i}\right)\frac{1}{(T_f s + 1)^2} \tag{7}$$

Table 2
Resulting values of $C_{e,f}$ for the different patients of Table 1.

Patient	1	2	3	4	5	6	7	8	9	10	11	12	13
$C_{e,f}$	6.5438	7.1856	8.5272	5.8737	5.1266	8.0137	6.6624	7.2060	6.5803	6.3440	5.2175	5.0457	6.9050

where K_p is the proportional gain, T_i is the integral time constant and T_f is the filter time constant. The derivative action has not been employed because the BIS signal is very noisy. Indeed, from real BIS data it has been determined that the noise can be considered as white Gaussian signal with zero mean value and a standard deviation equal to 6.2721. For the same reason a second-order filter has been used to significantly reduce the effect of the noise on the control variable, that is, in order to reduce unnecessary fast changes in the infusion rate that would occur just because of the noise. The PI controller has been tuned by employing a genetic algorithm [47] in order to minimize the integrated absolute error defined as

$$IAE = \int_0^\infty |e(t)|dt \tag{8}$$

in the worst case step response, when all the patients of Table 1 are considered. Actually, the minimization of (8) yields a PID controller that is sensible although the overshoot is not minimized explicitly. The resulting controller parameters are $K_p = 0.0334$, $T_i = 314$ and $T_f = 0.0062$ in the noise-free case. In the presence of noise, the value of T_f has been substituted with $T_f = 4.246$. This value has been calculated so that the resulting integrated absolute error is worsened of 30% (again, when a set-point step signal is used) but, obviously, a strong noise filtering is achieved [48]. Note that it is not worth including the filter time constant in the optimization procedure with noise because the system acts as a low-pass filter and therefore noise in the true output is in any case almost negligible and does not influence the value of (8).

The inversion-based methodology is then proposed in order to determine a suitable command signal r to be applied to the closed-loop system in order to improve the transient response. First, the desired output function has to be selected. This represents the desired evolution of the effect-site concentration from zero to the desired steady-state value normalized to one. For this purpose, the simple but powerful transition polynomial investigated in [46] has been chosen. The normalized τ-parametrized $\bar{y}(t,\tau)$ function is:

$$\bar{y}(t,\tau) = \begin{cases} 0 & \text{if } t < 0 \\ \dfrac{(2n+1)!}{n!\tau^{2n+1}} \displaystyle\sum_{i=0}^{n} \frac{(-1)^{n-i}\tau^i t^{2n-i-1}}{i!(n-i)!(2n-i-1)} & \text{if } 0 \le t \le \tau \\ 1 & \text{if } t > \tau \end{cases} \tag{9}$$

Note that $\bar{y}(t,\tau)$ is continuous until the order n, that is, $\bar{y}(\cdot;\tau) \in C^n$ and it monotonically increasing, that is, it does not present overshooting nor undershooting.

In order to apply the desired output function to the induction phase, the initial and final steady-state values have to be defined as the initial and final effect-site concentrations of propofol, which determine the desired BIS effect. The initial concentration $C_{e,i}$ is usually set equal to zero, by assuming that propofol has not been already infused in the patient. The final concentration $C_{e,f}$ can be calculated from (6), by knowing the value $\bar{E}$ of the BIS target:

$$C_{e,f} = C_{e_{50}} \sqrt[\gamma]{\frac{\bar{E} - E_0}{E_0 - \bar{E} - E_{max}}}. \tag{10}$$

The resulting values of $C_{e,f}$ for the different patients are shown in Table 2.

It is worth stressing that the sensitivity of the calculated value of $C_{e,f}$ with respect to γ is quite low, as it is shown in Fig. 3 where the average patient 13 in Table 1 has been considered and the percentage error between the value of $C_{e,f}$ calculated for the nominal value of γ (denoted as $\bar{\gamma}$) and the value of $C_{e,f}$ calculated for different values in the range [1.5,5] is plotted. Thus, the actual desired output function is selected as

$$\bar{p}(t;\tau) = \left(C_{e,f} - C_{e,i}\right)\bar{y}(t;\tau). \tag{11}$$

Now, we determine the command signal $r(t;\tau)$ that causes (in the nominal case) the desired output function (11). For this purpose, because of the presence of the nonlinear Hill function in the feedback loop, it is worth considering initially the open-loop transfer function

$$H(s) = C(s) \cdot PK(s) \cdot PD(s) \tag{12}$$

and determining the input signal $r_{ol}(t;\tau)$ that, applied to $H(s)$, causes $\bar{p}(t;\tau)$ as output. The Laplace transform of $R_{ol}(s;\tau)$ is given by

$$R_{ol}(s;\tau) = H^{-1}(s)\bar{P}(s;\tau) \tag{13}$$

The inverse transfer function is calculated, through polynomial division, as:

$$H^{-1}(s) = \gamma_\rho s^\rho + \gamma_{\rho-1}s^{\rho-1} + \cdots + \gamma_1 s + \gamma_0 + H_0(s), \tag{14}$$

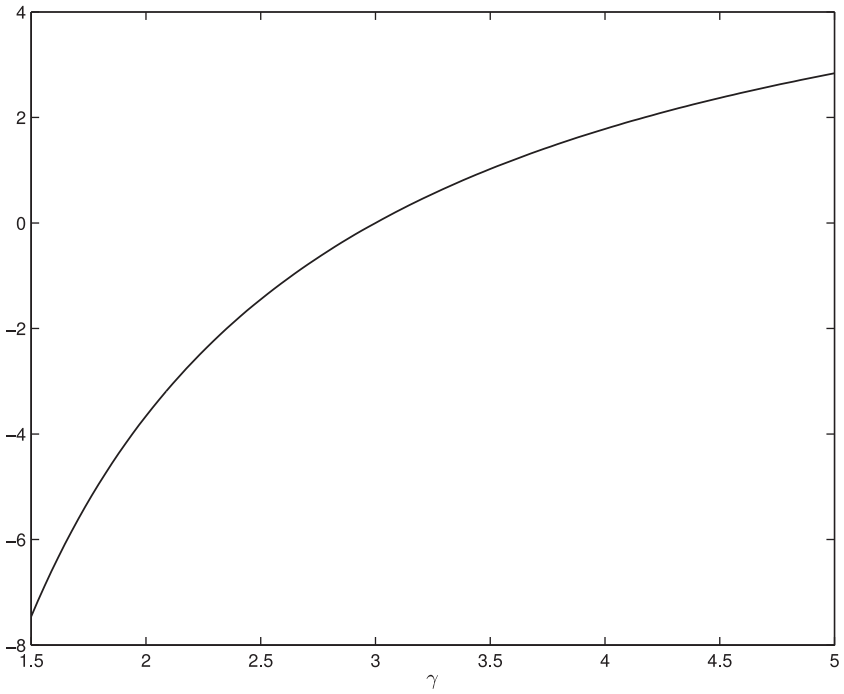

Fig. 3. The percentage error $(C_{e,f}(\bar{\gamma}) - C_{e,f}(\gamma))/C_{e,f}(\gamma)$ where $\bar{\gamma}$ is the nominal value for patient 13 in Table 1 and $\gamma \in [1.5, 5]$.

where ρ is the relative order of $H(s)$ and $H_0(s)$ is a strictly proper transfer function which represents the zero dynamics of the system. By considering the Laplace transform properties, we can obtain

$$r_{ol}(t;\tau) = \gamma_\rho D^\rho \bar{p}(t;\tau) + \gamma_{\rho-1} D^{\rho-1} \bar{p}(t\tau) + \cdots + \gamma_1 D\bar{p}(t;\tau) + \gamma_0 \bar{p}(t;\tau) + \int_0^t \eta_0(t-\xi)\bar{p}(\xi;\tau)d\xi \tag{15}$$

where $\eta_0(t) = \mathcal{L}^{-1}\{H_0(s)\}$, being $\mathcal{L}$ the Laplace transform operator. The terms of (15) can be analytically determined by considering that the transition polynomial (9) can be alternatively represented as:

$$\bar{y}(t;\tau) = \begin{cases} 0 & \text{if } t < 0 \\ \dfrac{(2n+1)!}{n!\tau^{2n+1}} \displaystyle\sum_{i=0}^{n} \frac{(-1)^{n-i}\tau^i t^{2n-i+1}}{i!(n-i)!(2n-i+1)} & \text{if } 0 \le t \le \tau \\ \dfrac{(2n+1)!}{n!\tau^{2n+1}} \displaystyle\sum_{r=0}^{n} \frac{(-1)^{n-i}\tau^i}{i!(n-i)!(2n-i+1)} & \\ \times\left[t^{2n-i+1} - \displaystyle\sum_{j=0}^{2n-i+1} \binom{2n-i+1}{j}(t-\tau)^{2n-i+1-j}\tau^j\right] + 1(t-\tau) & \text{if } t > \tau \end{cases} \tag{16}$$

where $1(\cdot)$ is the Heaviside function. By exploiting the previous expression, the derivative of the transition function (9) for $\alpha \in \mathbb{N}$, $\alpha < n+1$ can be calculated as:

$$D^\alpha \bar{y}(t;\tau) = \begin{cases} 0 & \text{if} \quad t < 0 \\ \dfrac{(2n+1)!}{n!\tau^{2n+1}} \displaystyle\sum_{i=0}^{n} \frac{(-1)^{n-i}\tau^r (2n-i+1)!}{i!(n-i)!(2n-i+1)(2n-i+1-\alpha)!} t^{2n-i+1-\alpha} & \text{if} \quad 0 \le t \le \tau \\ \dfrac{(2n+1)!}{n!\tau^{2n+1}} \displaystyle\sum_{i=0}^{n} \frac{(-1)^{n-i}\tau^i (2n-i+1)!}{i!(n-i)!(2n-i+1)} & \\ \times\left(\dfrac{t^{2n-i+1-\alpha}}{(2n-i+1-\alpha)!} - \displaystyle\sum_{j=0}^{n-i} \frac{\tau^j (t-\tau)^{2n-i+1-j-\alpha}}{j!(2n-i+1-j-\alpha)!}\right) & \text{if} \quad t > \tau. \end{cases} \tag{17}$$

Then, by expressing the partial fraction of $H_0(s)$ as

$$H_0(s) = \sum_{i=1}^{m} \frac{g_i}{(s-\lambda_i)^{k_i+1}} \tag{18}$$

we have that

$$\eta_0(t) = \sum_{i=1}^{m} \frac{g_i}{k_i!} t^{k_i} \frac{d^{k_i}}{d(\lambda_i t)^{k_i}} e^{\lambda_i t} \tag{19}$$

and the convolution integral in (15) is determined as:

$$\begin{aligned}\int_0^t \eta_0(t-\xi)\bar{y}(\xi;\tau)d\xi = &\sum_{i=1}^{m} \frac{g_i}{k_i!} \frac{(2n+1)!}{n!\tau^{2n+1}} \sum_{h=0}^{n} \frac{(-1)^{n-h}\tau^h}{h!(n-h)!(2n-h+1)} (2n-h+1)! \\ &\times \left[t^{k_i+2n-h+2} \frac{d^{k_i}}{d(\lambda_i t)^{k_i}} \left[\frac{1}{(\lambda_i t)^{2n-h+2}} \left(e^{\lambda_i t} - \sum_{l=0}^{2n-h+1} \frac{(\lambda_i t)^l}{l!} \right) \right] \right. \\ &\left. - \begin{cases} 0 & \text{if } 0 \le t \le \tau \\ \sum_{j=0}^{n-h} \frac{\tau^j}{j!} (t-\tau)^{k_i+2n-h+2-j} \frac{d^{k_i}}{d(\lambda_i(t-\tau))^{k_i}} \left[\frac{1}{(\lambda_i(t-\tau))^{2n-h+2-j}} \left(e^{\lambda_i(t-\tau)} - \sum_{l=0}^{2n-h+1-j} \frac{(\lambda_i(t-\tau))^l}{l!} \right) \right] & \text{if } t > \tau \end{cases} \right]\end{aligned} \tag{20}$$

It is important to stress that, $r_{ol}(\cdot\,;\tau) \in C^k$, $k \in \mathbb{N}$ if and only if $\bar{p}(\cdot;\tau) \in C^{k+\rho}$ where ρ is the relative order of $H(s)$ [46]. Thus, as the relative order of $PD(s)$ and $PK(s)$ is one, and the relative order of $C(s)$ is two, in order to obtain a continuous command signal (that is, $r_{ol}(\cdot\,;\tau) \in C^0$) we have to select the value of the transition polynomial as $n = 4$.

Then, in order to take the nonlinear Hill function into account, a corrector term, equal to the desired BIS output function, has to be added to $r_{ol}(t;\tau)$ in order to obtain the command signal $r(t;\tau)$ to be applied to the closed-loop system. This term can be computed as (see (6)):

$$r_c(t;\tau) = E_0 - E_{max}\left(\frac{\bar{p}(t;\tau)^\gamma}{\bar{p}(t;\tau)^\gamma + C_{e_{50}}^\gamma} \right) \tag{21}$$

Note that, thanks to this correction term, the nonlinearity is explicitly taken into account by feeding back to the controller only the difference between the expected output and the actual one. Indeed, as discussed in Section 2, this allows the implicit consideration of the Hill function plateau in the transition of the system output. The overall command signal is then easily computed as:

$$r(t,\tau) = r_{ol}(t;\tau) + r_c(t;\tau). \tag{22}$$

At this point it appears that the only design parameters in the proposed methodology is the transition time, that is the time required to achieve the desired BIS value. This can be selected, in general, in order to provide a fast transition time without exceeding the saturation limits of the actuator [46]. In this case, the saturation limits are related to the infusion rate, which has a trivial minimum value of 0 [mg/s] and a maximum value of 4 [mg/s], which is typical in clinical practice. By making clinical considerations related to usual induction time intervals and after having evaluated a large number of simulations, the value $\tau = 200$ [s] has been selected. Actually, lower values would cause the control variable to significantly saturate at the lower limit. In fact, as already mentioned, the Hill function presents an initial plateau, for which a large amount of propofol would be required in the first part of the transient to generate a reduction of the BIS value. This means that, in order to avoid the overshoot, the control variable would tend to assume negative value in the second part of the transient.

Remark 1. It is worth stressing that, by taking into account the control system of Fig. 2, the inversion-based method aims at achieving $C_e(t) = \bar{p}(\cdot;\tau)$. Thus, in the ideal case, that is, when there are no modeling errors, we have $BIS(t) = r_c(t;\tau)$ and the error signal is $e(t) = r_{ol}(t;\tau)$ (see (22)). Conversely, when the (unavoidable) model mismatches occur, $BIS(t)$ is no longer equal to $r_c(t;\tau)$, and the error signal becomes $e(t) = r_{ol}(t;\tau) + r_c(t;\tau) - BIS(t)$. Thus, the feedback error $e(t)$ is not the pure difference between the desired BIS value and the actual one, but the difference between the expected model response and the actual patient response. In other words, only the error depending on the model patient mismatch is really fed back to the controller.

4. Simulation results and discussion

The inversion based methodology has been first tested in the nominal cases, that is, by assuming that the models of the different patients (see Table 1) are known. In particular, the inversion-based command signal has been determined for each patient based on his/her model. Note that the PI controller (where $T_f = 0.0062$ as the noise-free case is considered) is the same for all the patients. The determined command signals are shown in Fig. 4 and the responses for the different patients

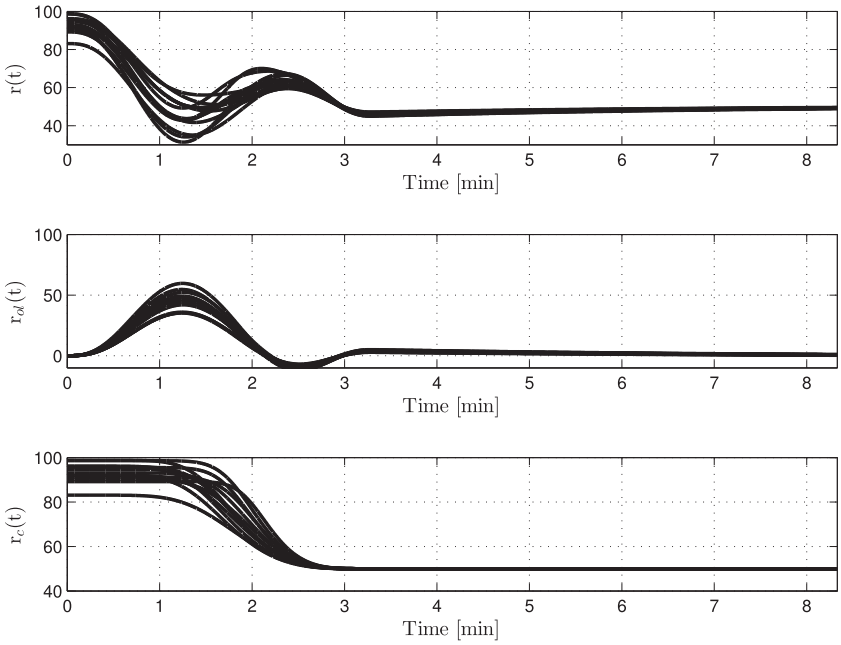

Fig. 4. The inversion-based command signals for the nominal cases.

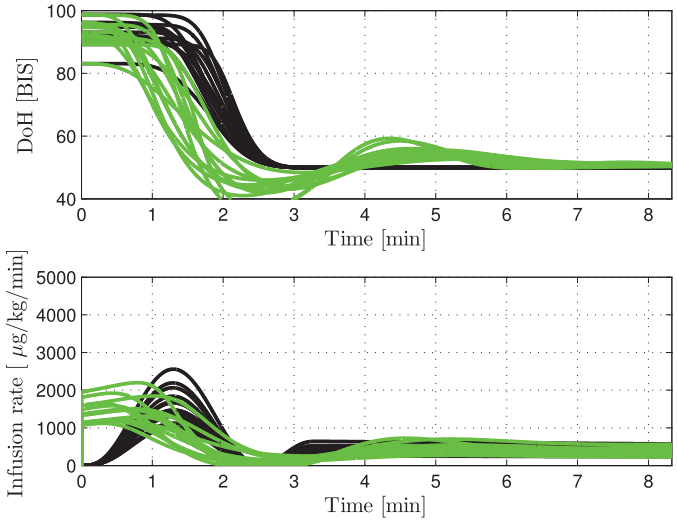

Fig. 5. Responses to propofol infusion for the nominal cases and in the absence of noise. Black: inversion-based command signals. Green: step set-point signal. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

are shown in Fig. 5, where the results are compared with those obtained by applying a step set-point signal. As expected, a smooth and monotonic response is obtained, while for the PI controller there are patients for which an overshoot (even if at a reasonable value) results. It has to be remarked that with the inversion-based methodology, on the contrary of the standard TCI, the propofol infusion rate does not present an abrupt change, that is, a rapid bolus is avoided. While, on one hand, this slightly increases the time of the overall induction phase, on the other hand this is appreciable as propofol rapid infusion may cause hemodynamic instability with vascular dilation and stroke volume reduction with harmful hypotension [49]. Moreover, a rapid injection of propofol aiming at reaching a predefined plasmatic drug concentration as with the TCI can lead to a BIS value well below the optimal level. Also in case of a difficult ventilation or intubation or in case of adverse events, the interruption of the drug administration when a rapid bolus is avoided could lead to a faster recovery of the spontaneous breathing. Moreover, despite the increased induction time, the rise time with the proposed method is more or less the same as the for the PI controller and, more important, the settling time is evidently reduced. The small initial delay in the induction does not yield clinical problems or discomfort to the patient, especially in case of elective procedures.

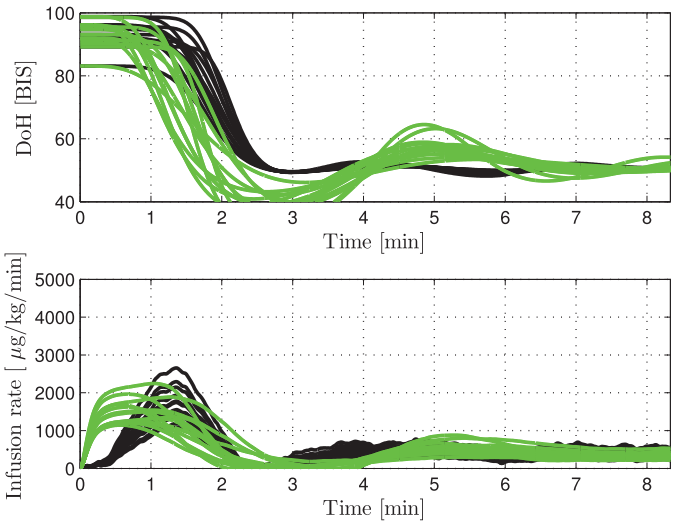

Fig. 6. Responses to propofol infusion for the nominal cases and in the presence of noise. Black: inversion-based command signals. Green: step set-point signal. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

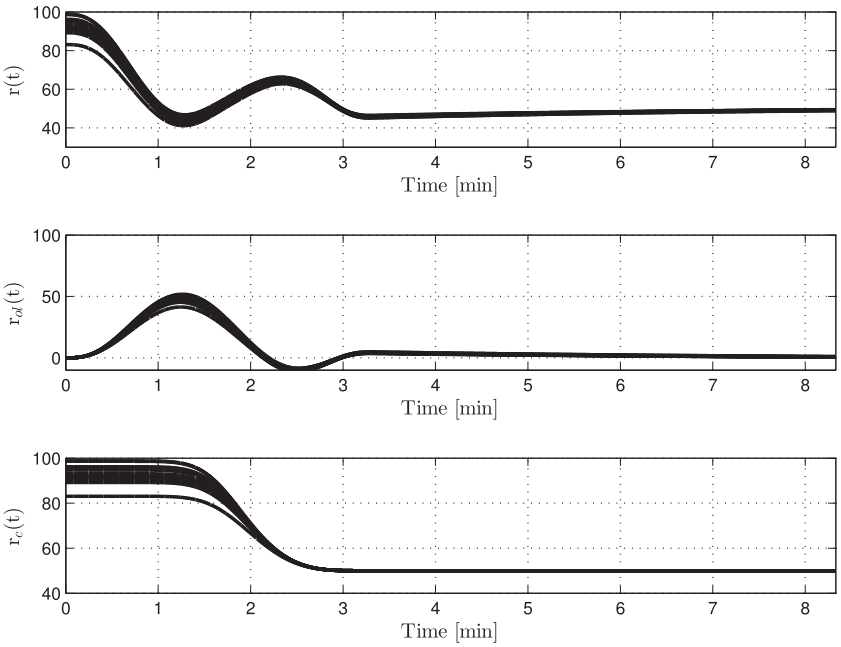

Fig. 7. The inversion-based command signals determined by considering the Hill function parameters of average patient 13.

In fact, during the infusion of anesthetics the patient is proxygenated and once he/she has reached the apnea he/she is manually ventilated until the adequate level of BIS is attained.

A similar test has then been performed by introducing noise in the feedback path and by changing the value of the filter time constant to $T_f = 4.246$. The results are shown in Fig. 6 (a comparison with the step set-point signal test is shown again), where it appears that, because of the filtering action, the effect of the noise on the actuator signal is acceptable. Further, because of the stronger influence of the noise filter on the controller dynamics, the difference between the worst-case result provided by the inversion-based command signal and the step set-point signal is more evident.

It has however to be highlighted at this point that the comparison provided above are quite unfair and the results obtained with the proposed methodology are unrealistic as it has been assumed that the model of the patient is perfectly known, which is never true in practical cases. In fact, while the age, the weight and the height of the patient can be easily measured, the parameters of the Hill functions are unknown. Hence, the proposed methodology must be able to deal with an uncertain set of nonlinear function obtained by parametrizing the Hill function. Clearly, a (suitable) single set of Hill

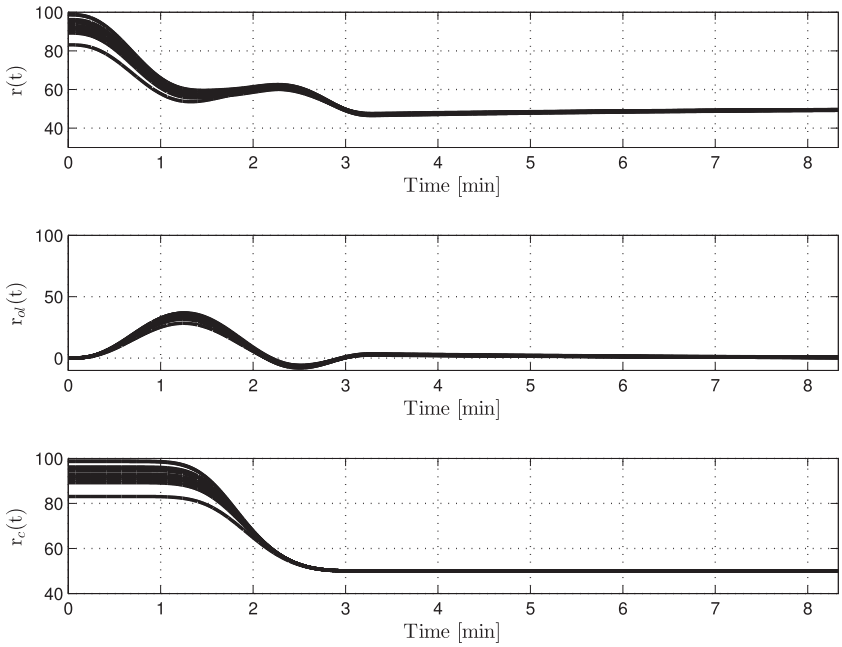

Fig. 8. The inversion-based command signals determined by considering the Hill function parameters of average patient proposed in [50].

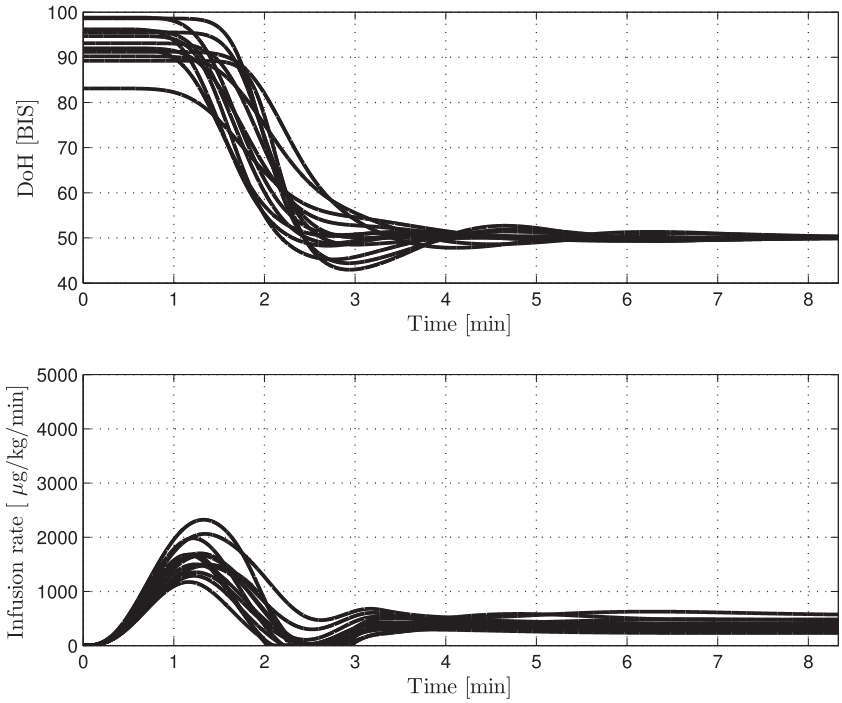

Fig. 9. Responses to propofol infusion for the set of patients of Table 1 with the command signals of Fig. 7.

function parameters must be chosen for the design of the inverting signals. For this reason, other simulations have been performed, where the inversion-based command signals have been determined by considering a unique Hill function for all the different patients. In particular, two cases have been considered, the first one where the parameters of the Hill function are those of the average patient 13 in Table 1 and the second one where the parameters of the Hill function are those of the average patient proposed in [50] (it is $C_{e_{50}} = 4.92$, $\gamma = 2.69$, and $E_{max} = 87.5$). The determined command functions are shown in Figs. 7 and 8 respectively, and the corresponding results are plotted in Figs. 9 and 10. In the first case the BIS drops below 60 in less than three minutes and, without never going below 40 in all cases, it settles around the required value of 50 in about six minutes. In the second case the transient is slightly more sluggish but the propofol infusion rate

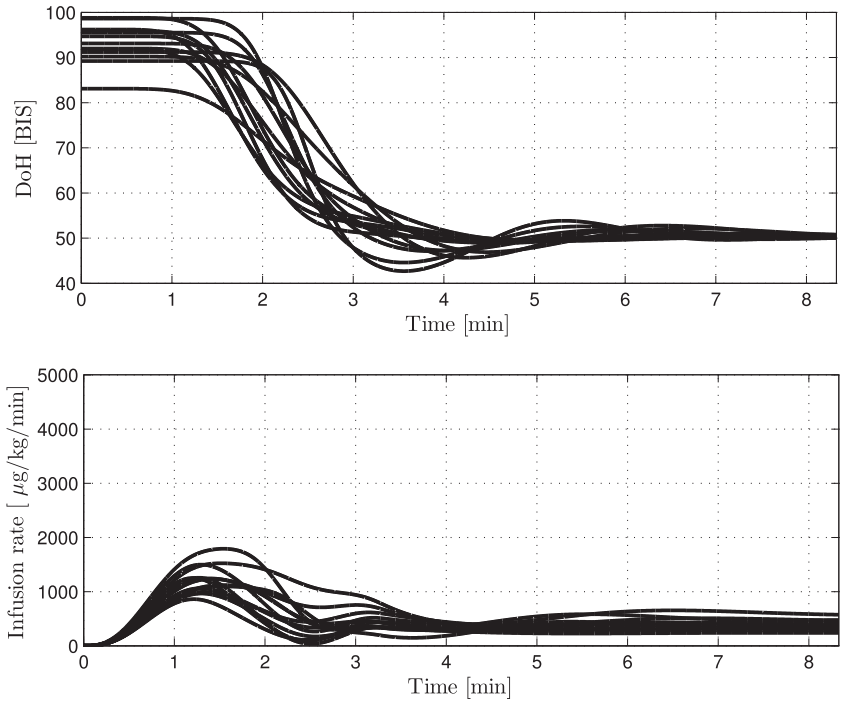

Fig. 10. Responses to propofol infusion for the set of patients of Table 1 with the command signals of Fig. 8.

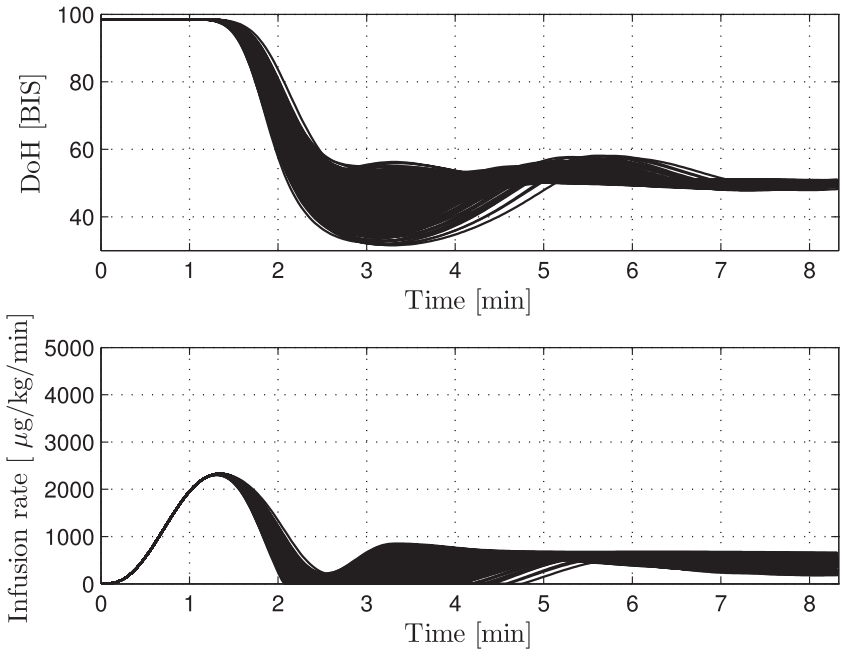

Fig. 11. Responses to propofol infusion for 1000 patients determined by the Monte Carlo method based on patient 2 with the corresponding command signal plotted in Fig. 7.

has the advantage of being smaller than in the other cases (note that the maximum value is always far below the value of 2000) as this kind of propofol infusion keeps haemodynamic parameters more stable.

Then, in order to take into account the variability within a group with the same demographics, that is, the statistical distribution of the model parameters, a set of simulations based on Monte Carlo method has been performed. In particular, for each patient, we have considered the corresponding inversion based command signal of Fig. 7 and applied them to a set of 1000 patients determined by a Monte Carlo method based on the statistical properties of the model reported in [17]. For the sake of brevity, only the worst case (related to patient 2) is shown in Fig. 11, where it appears that, despite the intra-patient variability, the value of the settling time is still satisfactory.

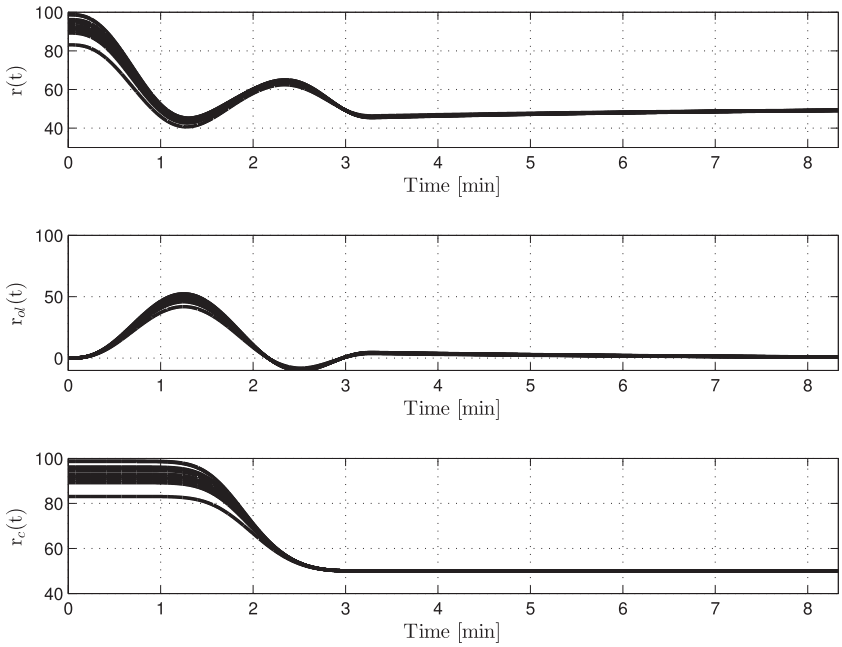

Fig. 12. The inversion-based command signals determined by considering the complete nominal model of patient 13.

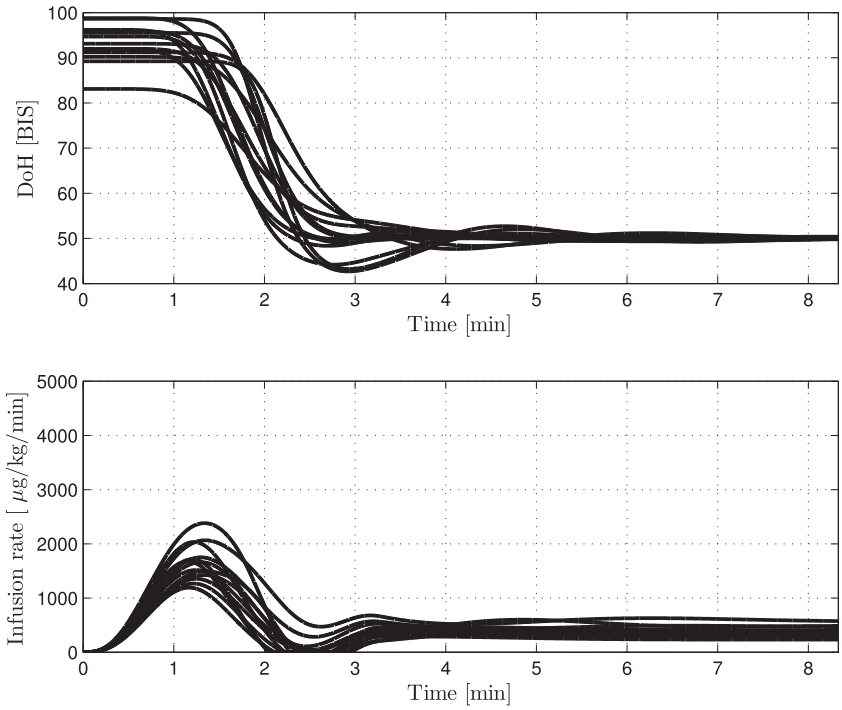

Fig. 13. Responses to propofol infusion for the set of patients of Table 1 with the command signals of Fig. 12.

Finally, in order to analyze better the robustness issue, the complete model of the average patient 13 (that is, both the linear and nonlinear parts) has been considered as the nominal model to calculate the inverting signals. These signals, which differ only because of the different values of E_0 that can be measured for each patient, are shown in Fig. 12. Their application to all the other patients of the set give the results shown in Fig. 13. The obtained results show that, in general, even if a significant uncertainty is considered in the model, the inversion based methodology is effective. This is because the command signal is applied to the closed-loop system where the feedback controller reduces the effect of the uncertainties

in the range of frequencies of the command signal (see, for example, [44]). Indeed, the BIS value does not drop in general below 40, and the ideal state of hypnosis is attained in the required time interval. Further, the more gradual propofol infusion reduces vasodilation and hypotension that sometimes could be dangerous and therefore reduces also the use of vasoconstrictors that the anesthesiologists could additionally infuse in order to avoid hypotensive episodes.

5. Conclusions

In this paper we have presented an inversion-based methodology for the propofol dosing in the induction of hypnosis in surgery. A suitable command signal is determined and applied to the closed-loop system instead of the typical step signal. Simulation results that have considered a population of significantly different patients have shown that this approach is robust and allows to achieve the BIS target value without significant overshoots and by means of a smooth propofol infusion rate, which increases the safety of the patient.

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