2019 18th European Control Conference (ECC)
Napoli, Italy, June 25-28, 2019

An Explicit Reference Governor Scheme for Closed-Loop Anesthesia

Mehdi Hosseinzadeh, *Member, IEEE*, Klaske van Heusden, Guy A. Dumont, *Life Fellow, IEEE*, and Emanuele Garone, *Member, IEEE*

***Abstract*— This paper proposes a constrained control scheme for the control of the depth of hypnosis in clinical anesthesia. The proposed scheme guarantees overdosing prevention while taking into account infusion rate limits and safety constraints on the plasma concentration. The core idea is to formulate anesthesia as a constrained control problem and design a closed-form control scheme based on the explicit reference governor philosophy. More precisely, the proposed architecture consists of a stabilizing control loop and of an add-on control unit that is able to ensure the constraints satisfaction at all times. In this paper, this architecture has been implemented within the iControl system, a platform for clinical evaluation of control schemes. The proposed scheme is evaluated on a simulated surgical procedure for 44 patients. The results demonstrate that the proposed scheme can deliver propofol to yield induction time of (mean) 6.24 [min], while satisfying the imposed safety constraints.**

I. INTRODUCTION

Anesthesia means lack of ability to sense, or a state of being unable to feel nor recall anything. During clinical surgeries, anesthesiologists adjust the dose of anesthetic drug to reach an acceptable level of anesthesia. Current clinical practice can be interpreted as manual feedback control. Automating drug delivery in anesthesia, referred as closed-loop anesthesia, has gained much attention in recent years.

In general, anesthesia consists of three components [1]: (i) hypnosis (*i.e.,* loss of consciousness and lack of awareness), (ii) analgesia (*i.e.,* lack of nociceptive reactivity), and (iii) neuromuscular blockade (*i.e.,* immobilization). The main goal of this paper is to propose a propofol delivery system that can control the depth of hypnosis within predefined safety constraints, by manipulating the infusion rate of propofol.

Propofol hypnosis can be divided into three temporal phases [2]: (i) induction (bringing the patient from total awareness to a desired depth of hypnosis), (ii) maintenance (keeping the desired depth of hypnosis during the surgery), and (iii) emergence (returning the patient to consciousness). One of the main challenges in propofol delivery is to safely administer the drug during the induction phase despite the patients' inherent drug response variability without overdosing them. Overdoses are usually associated with a lack of balance between the anesthetic regimen and the patient's pharmacological needs, and might eventually provoke a cardiovascular collapse. To cope with this problem, some approaches to decrease the risk of overdosing have been proposed in the literature, *e.g.*, increasing the robustness of the system [3], [4], adding a set-point prefilter to smooth the reference signal and reduce possible overshoots [5], nonlinear adaptive controller [6], model predictive control scheme [7], and model-based controller [8].

Recently, the need to use constrained control schemes in closed-loop anesthesia to prevent patient's overdosing has been highlighted in [9], [10]. These studies showed that, by defining some suitable safety constraints, one can formulate the overdosing problem, as well as other safety issues, as constraints on patient's states based on the therapeutic window of propofol.

In this paper, based on results in [9]–[11], we first reformulate the control of depth of hypnosis as a constrained control problem. Then we propose a control architecture to guarantee safety constraints satisfaction. In particular, we will make use of the recently introduced Explicit Reference Governor (ERG) framework [12]–[16]. The main idea behind the ERG framework is to determine an invariant set (in particular, a Lyapunov level set) that would contain the state trajectory if the currently auxiliary reference were to remain constant. If the distance between this invariant set and the boundary of the constraints is strictly positive, it follows from continuity that the derivative of the auxiliary reference can be nonzero without leading to constraint violations. If this distance is zero, the satisfaction of the constraints is ensured by maintaining the current reference constant. One of the main strengths of the ERG is that it requires very limited computational capabilities since, unlike other constrained control schemes, it does not make use of online optimization, making its implementation simple, robust, and easily certifiable.

The rest of the paper is organized as follows. Section II describes the models used in the propofol delivery system. Section III presents the details of the iControl system and the proposed ERG scheme. In Section IV, simulations are carried out using the proposed scheme and their results are discussed. Finally, section V concludes the paper.

II. MODELLING OF THE SYSTEM

The model which is normally used to explain the response of a patient to administered aesthetic drug (propofol in this study) consists of two parts: (i) PharmacoKinetic (PK) model, and (ii) PharmacoDynamic (PD) model. The

This research has been funded by the FNRS MIS "Optimization-free Control of Nonlinear Systems subject to Constraints", Ref. F.4526.17.

M. Hosseinzadeh and E. Garone are with Service d'Automatique et d'Analyse des Systèmes (SAAS), Université Libre de Bruxelles (ULB), Brussels, Belgium mehdi.hosseinzadeh@ieee.org; egarone@ulb.ac.be.

K. van Heusden and G. A. Dumont are with the Department of Electrical and Computer Engineering, The University of British Columbia, Vancouver, Canada klaskeh@ece.ubc.ca; guyd@ece.ubc.ca.

PK model relates the drug plasma concentration with the administered dose. Most propofol PK models consider three compartments [17]: (i) plasma compartment, (ii) shallow peripheral compartment, and (iii) deep peripheral compartment. Denoting the propofol concentration in the plasma, fast peripheral, and slow peripheral compartments as C_1, C_2, and C_3 (all in [mg/l] or [μg/ml]), respectively, and the volume in the aforementioned compartments as V_1, V_2, and V_3 (all in [l]), respectively, the state-space representation of the PK model can be expressed as

$$\begin{bmatrix}\dot{C}_1\\ \dot{C}_2\\ \dot{C}_3\end{bmatrix} = \begin{bmatrix}-(k_{10}+k_{12}+k_{13}) & k_{12} & k_{13}\\ k_{21} & -k_{21} & 0\\ k_{31} & 0 & -k_{31}\end{bmatrix}\begin{bmatrix}C_1\\ C_2\\ C_3\end{bmatrix} + \begin{bmatrix}\frac{1}{V_1}\\ 0\\ 0\end{bmatrix} I, \tag{1}$$

where $I(t)$ is the infusion rate (in [mg/s]), and k_{10}, k_{12}, k_{21}, k_{13}, and k_{31} are computed as

$$k_{10} = \frac{Cl_1}{V_1},\ k_{12} = \frac{Cl_2}{V_1},\ k_{21} = \frac{Cl_2}{V_2},\ k_{13} = \frac{CL_3}{V_1},\ k_{31} = \frac{Cl_3}{V_3}, \tag{2}$$

with Cl_1 as the elimination clearance, and Cl_2 and Cl_3 as inter-compartmental clearances, respectively. Parameters Cl_i and V_i, $i = 1,2,3$ are determined using the relations presented in [17].

The PD model relates the plasma concentration with the pharmacological end-effect. The PD model is typically described as a first-order plus time-delay system in the following form [18]

$$PD(s) = \frac{C_e(s)}{C_p(s)} = e^{-T_d s}\frac{k_d}{s+k_d}, \tag{3}$$

where $C_p(t) = C_1(t)$, and T_d (in [s]) and k_d (in [s^{-1}]) are transport delay and rate of propofol distribution between the plasma concentration and the brain. In addition, a nonlinear saturation function is used to describe the relation between $C_e(t)$ and the clinical hypnotic effect $E_o(t)$, as

$$E_o(t) = \frac{(C_e(t))^{\gamma}}{EC_{50}^{\gamma} + (C_e(t))^{\gamma}}, \tag{4}$$

where γ is the cooperativity coefficient, and EC_{50} (in [mg/l] or [μg/ml]) is the steady-state plasma concentration to obtain 50% of the hypnotic effect. Note that $E_o(t)$ is bounded between 0 and 1, where 0 means no hypnotic effect (state of full wakefulness), and 1 is associated with the maximum effect of hypnosis that can be identified.

Finally, the drug-response relationship of the propofol can be expressed by combining the PK and PD models to come up with a PKPD model, as shown in Fig. 1. Note that PK model is a known model, since its parameters depend on only weight, height and age of the patient, and their exact values can be determined before anesthetizing the patient. On the contrary, the PD model is an unknown model, since its parameters cannot be easily determined based on patient's characteristics, although they belong to an interval with known bounds.

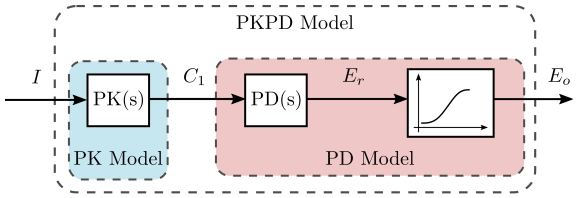

Fig. 1. PKPD model block diagram.

III. CONTROL ARCHITECTURE

This section discusses the development of a constrained control scheme for closed-loop anesthesia. The first step is to pre-stabilize the system. For this step, the iControl system is used. The next step is to augment it with the ERG to enforce constraints satisfaction.

A. Pre-stabilizing the Propofol Delivery System

To prestabilize the system we will use the so-called iControl system. iControl is a platform developed for the clinical evaluation of the controller design [19]. This software is approved for clinical evaluation by Health Canada[1]. The iControl platform uses feedback from the NeuroSENSE DOH monitor and propofol is delivered through an Alaris TIVA infusion pump (CareFusion, San Diego, USA) connected to an intravenous line. The system is operated through a touchscreen interface and was subject to an extensive usability study prior to the clinical study. The complete system is shown in Fig. 2.

From the control viewepoint, the iControl system makes use of a robust PID that stabilizes the propofol delivery system [20]. The block diagram of the propofol control structure is shown in Fig. 3, where $G_{ff}(s)$ and $G_c(s)$ are

$$G_{ff}(s) = k + \frac{k_i}{s}, \tag{5}$$

$$G_c(s) = \frac{k_d N s}{s+N}, \tag{6}$$

where N, called filter coefficient, is a large constant (in this paper, $N = 10^5$).

The PID parameters are calculated based on Lean Body Mass (LBM) which can be computed [22] as

$$\begin{cases} LBM = 0.3281\cdot W + 0.33929\cdot H - 29.5336, & \text{if male}\\ LBM = 0.29569\cdot W + 0.41813\cdot H - 43.2933, & \text{if female}\end{cases} \tag{7}$$

where W is the weight (in [kg]) and H is the height of the patient (in [cm]). Once the LBM of the patient is computed, the corresponding PID parameters can be calculated as

$$k = 0.0243\cdot LBM, \tag{8}$$

$$k_i = 0.000165\cdot LBM, \tag{9}$$

$$k_d = 1.35\cdot LBM. \tag{10}$$

Since it is necessary to protect the controller from integrator windup, particularly when the infusion rate is nil, a back-calculation anti-windup scheme is also implemented in

[1]Investigational Testing Authorization- Class III. Application#168968.

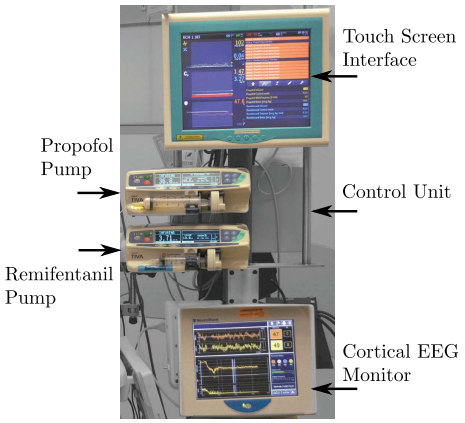

Fig. 2. The iControl closed-loop anesthesia system [21].

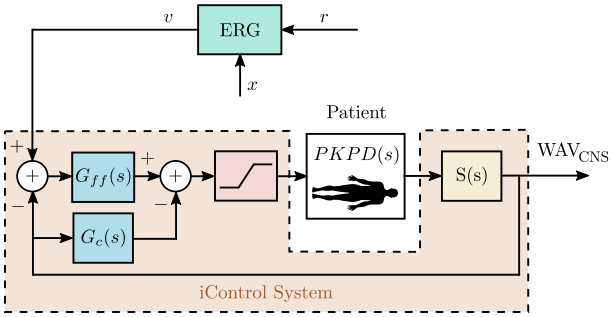

Fig. 3. Block diagram of the propofol control system.

the iControl system that resets the integrator dynamically with a time constant $T_t = 60$ [s].

The clinical hypnotic effect is measured through the WAV_{CNS} index, which provides linear time invariant dynamics [23]. The dynamics of the WAV_{CNS} monitor is usually modeled as a second-order low-pass filter [5]:

$$S(s) = \frac{Y(s)}{E_o(s)} = \frac{1}{(8s+1)^2}, \tag{11}$$

where $Y(s)$ is the Laplace transform of the WAV_{CNS} index. Note that since WAV DOH monitor defines awake as 100 and no activity as 0, to match the scaling depth of hypnosis $DOH(t)$ is defined as

$$DOH(t) = 100 \cdot (1 - y(t)), \tag{12}$$

where $DOH(t) = 100$ represents a wakeful state and $DOH(t) = 0$ represents the maximum level of hypnosis.

Since the infusion pump has a lower bound $I_{min} = 0$ [ml/h] and an upper bound $I_{max} = 1200$ [ml/h], the saturation block is used to represent this limitation.

For notational compactness, the overall dynamic model of the pre-stabilized propofol delivery system will be denoted as

$$\begin{cases} \dot{x}(t) = f(x(t), v(t)) \\ y(t) = h(x(t), v(t)) \end{cases}, \tag{13}$$

where $x \in \mathbb{R}^n$ is the state of the system, $y(t) \in [0,1]$ is the output of the system representing the depth of hypnosis, and $v \in [0,1]$ is the desired level of hypnosis.

B. Enforcing Constraints Handling Capability

As mentioned, clinical anaesthesia can be seen as a constrained control problem which includes a number of constraints that must be taken into account.

Constraints on the amplitude of the propofol infusion rate $I(t)$ are mostly due to hard physical constraints of the system [24] and to safety requirements: the infusion rate can obviously not be negative, and the maximum infusion rate is limited to keep hemodynamics changes bounded. Assuming that propofol 10 [mg/ml] is being used as the hypnotic drug, the infusion rate is typically constrained between 0 and 1.67 [mg/s] (between 0 and 600 [ml/h]) [25], *i.e.*,

$$0 \leq I(t) \leq 1.67 \text{ [mg/s]}. \tag{14}$$

Safety bounds on the propofol plasma concentration $C_p(t)$ and effect-site concentration $C_e(t)$ can be defined using the therapeutic window [26] for propofol. Safety bounds on $C_p(t)$ and $C_e(t)$ are [27]

$$0 \leq C_p(t) \leq 10 \text{ [}\mu\text{g/ml]}, \tag{15}$$

$$1.5 \leq C_e(t) \leq 8 \quad \text{[}\mu\text{g/ml]}. \tag{16}$$

Hypnosis levels between 40 and 60 [%] are typically associated with adequate anesthesia, while values below 40 [%] may indicate a risk of overdosing [1]. Accordingly, it is reasonable to define the safety constraint $DOH(t) \geq 40$ to ascertain overdosing prevention, or equivalently:

$$y(t) \leq 0.6. \tag{17}$$

In the following, we will address how one can add the constraint-handling capability to the iControl system to enforce constraints (14)-(17). This will be done by using the ERG framework, as shown in Fig. 3, to generate the auxiliary reference $v(t)$ so that the trajectories of the pre-stabilized propofol delivery system are always contained in a suitable invariant set. As shown in [14], an intuitive choice for the invariant set is the invariant level set defined by the Lyapunov theory. Thus, to ensure satisfaction of constraints (14)-(17) at all times, it is sufficient to manipulate the auxiliary reference $v(t)$ so that the Lyapunov function is always smaller than a suitably defined upper-bound. This can be done by manipulating the auxiliary reference $v(t)$ according to the following differential equation:

$$\dot{v}(t) = \kappa \cdot \Delta(x,v) \cdot \rho(r,v), \tag{18}$$

where $\kappa > 0$ is a tuning parameter, and $\Delta(x,v)$ and $\rho(r,v)$ are the two fundamental components of the ERG scheme, called the Dynamic Safety Margin (DSM) and the Navigation Field (NF), respectively.

The NF represents the direction along a feasible path that leads from the current auxiliary reference v to the desired reference r. Since in closed-loop anesthesia the reference is mono-dimensional, it is sufficient to choose the NF as

$$\rho(r,v) = \frac{r-v}{\max\{|r-v|, \eta\}}, \tag{19}$$

where $\eta > 0$ is a smoothing factor.

The DSM can be defined as follows:

$$\Delta(x,v) = \Gamma(v) - V(x,v), \tag{20}$$

where $V(x,v)$ is a Lyapunov function that proves the stability of the point of equilibrium associated to the constant reference v. Also, $\Gamma(v)$ is the aforementioned upper-bound, and is such that for any v, the set $\{x|V(x,v) \leq \Gamma(v)\}$ is wholly contained in the constraints. Ideally, $\Gamma(v)$ is the maximum value of the Lyapunov function such that the Lyapunov level set touches but does not violate the constraints.

Finding the stabilizing Lyapunov function for the propofol delivery system (13) is not straightforward. Hence, in what follows, we will first approximate the propofol delivery system (13) with a linear model. Then, we will study how to find the optimal $\Gamma(v)$ and to construct the DSM in a closed-form. Finally, we will propose a procedure to compensate approximation error and to guarantee constraints satisfaction even in the presence of approximation error.

From extensive simulations, it is concluded that the system (13) can be well approximated with the following linear system:

$$\begin{cases} \dot{\hat{x}}(t) = A\hat{x}(t) + Bv(t) \\ \hat{y}(t) = C\hat{x}(t) \end{cases}, \tag{21}$$

where

$$A = \begin{bmatrix} A_1 & 0 & 0 & 0 & -B_1C_5 \\ 0 & A_2 & 0 & 0 & 0 \\ B_3C_1 & -B_3C_2 & A_3 & 0 & -B_3(D_1+D_2)C_5 \\ 0 & 0 & B_4C_3 & A_4 & 0 \\ 0 & 0 & 0 & B_5C_4 & A_5 \end{bmatrix}, \tag{22}$$

$$B = \begin{bmatrix} B_1 & 0 & B_3D_1 & 0 & 0 \end{bmatrix}^T, \tag{23}$$

$$C = \begin{bmatrix} 0 & 0 & 0 & 0 & C_5 \end{bmatrix}, \tag{24}$$

with (A_1,B_1,C_1,D_1), (A_2,B_2,C_2,D_2), (A_3,B_3,C_3,D_3), (A_4,B_4,C_4,D_4), and (A_5,B_5,C_5,D_5) as the state-space realization matrices of the feedforward controller $G_{ff}(s)$, the feedback controller $G_c(s)$, the PK model, the PD model, and the monitor, respectively. Note that to compute (A_4,B_4,C_4,D_4), the time-delay operator in (3) is approximated by a second-order Padè approximant.

Constraints (14)-(17) can be rewritten with respect to the states of the linear system (21) in the following form:

$$\beta_i^T\hat{x}(t) + \alpha_i v(t) \leq \theta_i,\ i = 1,\cdots,7, \tag{25}$$

where $\alpha_1 = -\alpha_2 = D_1$, $\alpha_3 = \cdots = \alpha_7 = 0$, $\beta_1 = -\beta_2 = \begin{bmatrix} C_1 & -C_2 & 0 & 0 & -D_2C_5 \end{bmatrix}^T$, $\beta_3 = -\beta_4 = \begin{bmatrix} 0 & 0 & C_3 & 0 & 0 \end{bmatrix}^T$, $\beta_5 = -\beta_6 = \begin{bmatrix} 0 & 0 & 0 & C_4 & 0 \end{bmatrix}^T$, $\beta_4 = \begin{bmatrix} 0 & 0 & 0 & 0 & C_5 \end{bmatrix}^T$, $\theta_1 = 0$, $\theta_2 = 600$, $\theta_3 = 0$, $\theta_4 = 10$, $\theta_5 = -1.5$, $\theta_6 = 8$, and $\theta_7 = 0.6$. Note that the first constraint in (25) represents the lower bound of constraint (14), the second one represents the upper bound of constraint (14), the third one represents the lower bound of constraint (15), the forth one represents the upper bound of constraint (15), the fifth one represents the lower bound of constraint (16), the sixth one represents the upper bound of constraint (16), and the seventh constraint represents constraint (17).

In the case of linear systems, it is well known that a possible Lyapunov function is the quadratic form:

$$V(\hat{x},v) = (\hat{x} - \overline{x}_v)^T P(\hat{x} - \overline{x}_v), \tag{26}$$

where $\overline{x}_v$ is the equilibrium point of the linear system (21) (*i.e.,* $\overline{x}_v = -A^{-1}Bv$), and $P = P^T > 0$ is a solution of the Lyapunov inequality $A^TP + PA \leq 0$.

For quadratic Lyapunov function (26) and linear constraints (14)-(17), it follows from [13], [14] that $\Delta(\hat{x},v)$ can be defined as follows:

$$\Delta(\hat{x},v) = \min_{i\in\{1,\cdots,7\}}\{\Gamma_i(v)\} - V(\hat{x},v), \tag{27}$$

where $\Gamma_i(v)$ can be calculated as follows:

$$\Gamma_i(v) = \frac{(\beta_i^T\overline{x}_v + \alpha_i v - \theta_i)^2}{\beta_i^T P^{-1}\beta_i},\ i = 1,\cdots,7. \tag{28}$$

From (28), it is obvious that the performance of the proposed ERG will strongly depend on the selection of the matrix P. Hence, a systematic design method should be proposed for choosing the most suitable Lyapunov function.

As shown in [13], it is convenient to select P so that the resulting Lyapunov level set that corresponds to $\Gamma(v)$ is as large as possible. Hence, one can find DSM individually for each constraint in (25), and select the minimum DSM as the final one, *i.e.*,

$$\Delta(v) = \min_{i\in\{1,\cdots,7\}}\{\Gamma_i(v) - V_i(\hat{x},v)\}, \tag{29}$$

where

$$V_i(\hat{x},v) = (\hat{x} - \overline{x}_v)^T P_i(\hat{x} - \overline{x}_v), \tag{30}$$

with $P_i = P_i^T > 0$, and $A^TP_i + P_iA \leq 0$, $i = 1,\cdots,7$. It is proved in [13, Proposition 3.1] that the optimal P_i can be found by solving the following off-line convex problem:

$$P_i = \begin{cases} \min & \log\det P_i \\ \text{s.t.} & A^TP_i + P_iA \leq 0 \\ & P_i \geq \beta_i\beta_i^T \\ & P_i > 0 \end{cases}. \tag{31}$$

Finally, to compensate the effect of aforementioned approximation, it is only needed to further restrict the DSM (29) with an additional static safety bound δ_0, as follows

$$\Delta(\cdot) = \max\left\{\min_{i\in\{1,\cdots,7\}}\{\Gamma_i(\cdot) - V_i(\cdot) - \delta_0\}, 0\right\}. \tag{32}$$

Remark 3.1: By defining approximation error as $e(t) = y(t) - \hat{y}(t)$, the value of δ_0 can be determined as

$$\delta_0 = \max_{v\in[0,0.5]}\sup_t|e(t)|. \tag{33}$$

From extensive simulation studies, as shown in Fig. 4, the value of δ_0 is calculated as 0.08.

Remark 3.2: Since the states of the system are not directly measured during the experiments, to determine the Lyapunov function $V_i(\cdot)$, $i = 1,\cdots,7$ an estimator is needed. For this

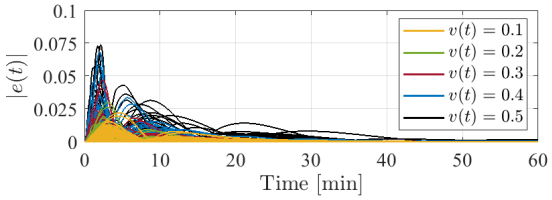

Fig. 4. Approximation error for different hypnosis levels.

purpose, a linear Kalman Filter (KF) can be utilized. Since the PKPD parameters (in particular PD parameters, as discussed in Section II) of the patient are unknown, to design the KF we have to use nominal PKPD parameters. As discussed in [28], patients' age can be used as a criterion to reduce the inter-individual variability of the PKPD parameters. Thus, to build the KF, first, patients were grouped based on their ages, and then nominal parameters for each group were identified.

Remark 3.3: To make sure that obtained matrix P_i through (31) is valid Lyapunov matrix for all patients, one possible way is to use Kharitonov theory [29], and replace the constraint $A^T P_i + P_i A \leq 0$ with the resulting four Kharitonov's-based constraints.

IV. Results and Discussion

In this section, we illustrate the effectiveness of the proposed ERG scheme in preventing overdosing and maintaining the predicted states of patients within the pre-defined safe zone using simulation results. We consider a set of 44 patient models identified in [18], in patients 18 to 60 years old. Using a 10-years bracket, the 44 patients are divided into four age groups, as Group 1: 18-29 years, Group 2: 30-39 years, Group 3: 40-49 years, and Group 4: 50-60 years. Then, for each age group, a nominal model based on average parameters is identified.

The unconstrained responses of the patients are presented in Fig. 5, where 26 patients are in danger of overdosing.

The simulated responses for the case that the proposed ERG scheme is added to the unconstrained closed-loop anesthesia is shown in Fig. 6. The results are obtained using the values $\kappa = 10$, $\eta = 0.01$, covariance matrix of process noise $Q = 0.1I$, and covariance matrix of observation noise $R = 0.01I$, with I as the identity matrix with appropriate size. Since δ_0 should cover approximation error as well as the error caused by KF, $\delta_0 = 0.1$ was used in simulations.

As seen in Fig. 6, the proposed ERG scheme guarantees constraints (14)-(17) satisfaction, while DOH of 50% is achieved for all the patients.

As seen in the bottom figure of Fig. 6, the ERG scheme manipulates the auxiliary reference $v(t)$ only when the manipulation does not lead to constraints violations. In simple terms, by using the ERG, instead of applying the desired reference instantly, we apply the auxiliary reference $v(t)$ that automatically converges to the desired level of hypnosis so that constraints satisfaction is guaranteed at all times.

Comparing the obtained results with those obtained with unconstrained control scheme reveals that enforcing constraints (14)-(17) satisfaction increases the time required for induction of anesthesia. TABLE I shows the induction time obtained with the unconstrained structure and with the ERG scheme. Note that the induction of anesthesia is completed if a measure of DOH(t) reaches 60 [%] and stays below that more than 30 seconds. As seen in TABLE I, the trade-off for avoiding constraints violations during induction of anesthesia is a slower induction for patients.

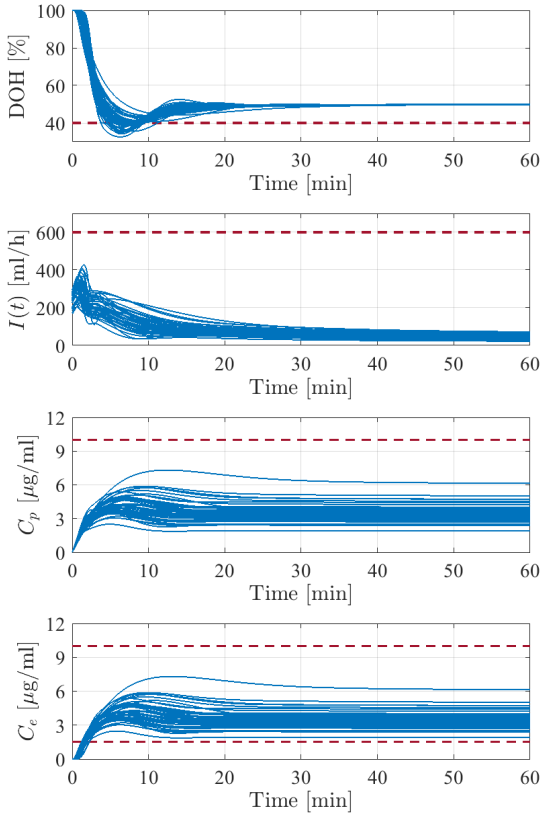

Fig. 5. The unconstrained simulated responses of the 44 patients.

TABLE I
Comparison of the Obtained Induction Time.

	Unconstrained	With ERG
Induction Time mean±STD[2] [min, max]	3.11±0.38 [2.53, 4.46]	6.24±7.51 [4.98, 8.96]

V. Conclusion

This paper proposed a control scheme structure based on explicit reference governor framework to control the depth of hypnosis. Using the proposed scheme, it was shown that it is possible to develop an automatic propofol delivery system that can be proven to guarantee safety constraint satisfaction, while completing induction of anesthesia within (mean) 6.24 minutes. The proposed scheme was validated on 44 simulated surgeries based on data identified on clinically. The results showed the scheme's effectiveness in controlling the depth of hypnosis and safety constraints satisfaction.

[2]STD stands for standard deviation.

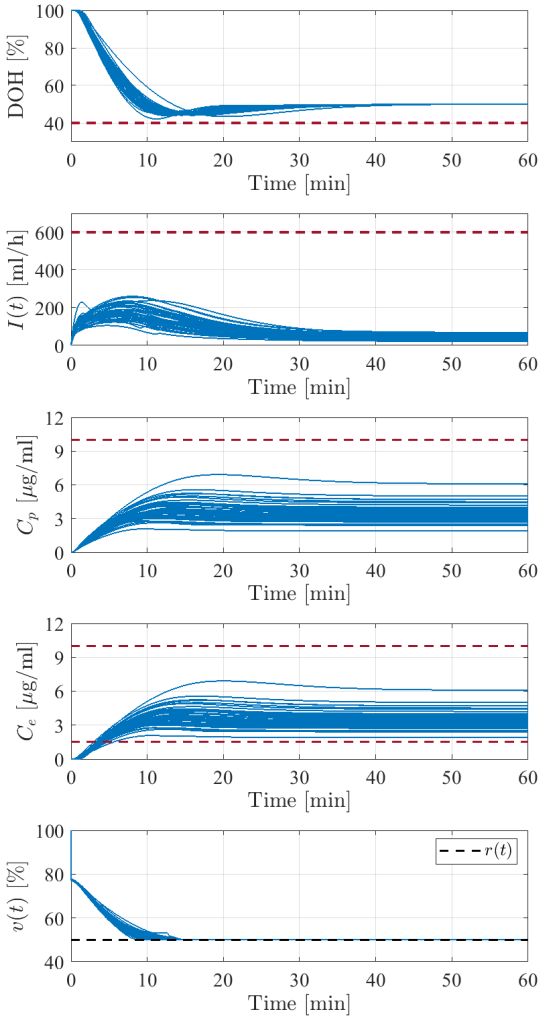

Fig. 6. The simulated responses of the 44 patients with the ERG scheme.

REFERENCES

[1] S. Bibian, C. R. Ries, M. Huzmezan, and G. Dumont, "Introduction to automated drug delivery in clinical anesthesia," *Eur. J. Control*, vol. 11, no. 6, pp. 535-557, 2005.

[2] K. Soltesz, J. O. Hahn, G. A. Dumont, and J. M. Ansermino, "Individualized PID control of depth of anesthesia based on patient model identification during the induction phase of anesthesia, in *Proc. 50th IEEE Conf. Decision and Control and European Control Conf.*, Orlando, USA, Dec. 12-15, 2011, pp. 855-860.

[3] J. O. Hahn, G. A. Dumont, and J. M. Ansermino, "Robust closed-loop control of hypnosis with propofol using WAV_{cns} index as the controlled variable," *Biomed. Signal Process. Control*, vol. 7, no. 5, pp. 517-524, Sep. 2012.

[4] N. Sadati, M. Hosseinzadeh, and G. A. Dumont, "Multi-model robust control of depth of hypnosis," *Biomed. Signal Process. Control*, vol. 40, pp. 443-453, Feb. 2018.

[5] G. A. Dumont, A. Martinez, and J. M. Ansermino, "Robust control of depth of anesthesia," *Int. J. Adapt. Control Signal Process.*, vol. 23, no. 5, pp. 435-454, May 2009.

[6] J. M. Bailey, and W. M. Haddad, "Drug dosing control in clinical pharmacology," *IEEE Control Syst. Mag.*, vol. 25, no. 2, pp. 35-51, Apr. 2005.

[7] Y. Sawaguchi, E. Furutani, G. Shirakami, M. Araki, and K. Fukuda, "A model-predictive hypnosis control system under total intravenous anesthesia," *IEEE Trans. Biomed. Eng.*, vol. 55, no. 3, pp. 874-887, Mar. 2004.

[8] E. Mortier, M. Struys, T. D. Smet, L. Versichelen, and G. Rolly, "Closed-loop controlled administration of propofol using bispectral analysis," *Anaesthesia*, vol. 53, pp. 749-754, 1998.

[9] K. van Heusden, N. West, A. Umedaly, J. M. Ansermino, R. N. Merchant, and G. A. Dumont, "Safety, constraints and anti-windup in closed-loop anesthesia," in *Proc. 19th IFAC World Congress,* Cape Town, South Africa, Aug. 24-29, 2014, pp. 6569-6574.

[10] M. Yousefi, K. van Heusden, I. M. Mitchell, J. M. Ansermino, and G. A. Dumont, "A Formally-Verified Safety System for Closed-Loop Anesthesia," in *Proc. 20th IFAC World Congress,* Toulouse, France, Jul. 9-14, 2017, pp. 4424-4429.

[11] M. Hosseinzadeh, and E. Garone, "Constrained Control in Closed-Loop Anesthesia," in *Proc. 238th Benelux Meeting on Systems and Control*, Lommel, Belgium, Mar. 19-21, 2019.

[12] E. Garone, and M. M. Nicotra, "Explicit reference governor for constrained nonlinear systems," *IEEE Trans. Autom. Control*, vol. 61, no. 5, pp. 1379-1384, May 2016.

[13] E. Garone, M. M. Nicotra, and L. Ntogramatzidis, "Explicit reference governor for linear systems," *Int. J. Control*, vol. 91, no. 6, pp. 1415-1430, Jun. 2018.

[14] M. M. Nicotra, E. Garone, "The Explicit Reference Governor: A General Framework for the Closed-Form Control of Constrained Nonlinear Systems," *IEEE Control Syst. Mag.*, vol. 38, no. 4, pp. 89-107, Aug. 2018.

[15] E. Hermand, T. W. Nguyen, M. Hosseinzadeh, and E. Garone, "Constrained Control of UAVs in Geofencing Applications," in *Proc. 26th Mediterranean Conference on Control and Automation*, Zadar, Croatia, Jun. 19-22, 2018, pp. 217-222.

[16] M. Hosseinzadeh, E. Garone, "An Explicit Reference Governor for the Intersection of Concave Constraints," *IEEE Trans. Autom. Control*, 2018.

[17] J. Schuttler, and H. Ihmsen, "Population pharmacokinetics of propofol a multicenter study," *Anesthesiology*, vol. 92, pp. 727-738, Mar. 2000.

[18] S. Bibian, "Automation in clinical anesthesia," Ph.D. dissertation, Univeristy of British Columbia, 2006.

[19] K. van Heusden, G. A. Dumont, K. Soltesz, C. L. Petersen, A. Umedaly, N. West, and J. M. Ansermino, "Design and Clinical Evaluation of Robust PID Control of Propofol Anesthesia in Children," *IEEE Trans. Control Syst. Technol.*, vol. 22, no. 2, pp. 491-501, 2014.

[20] K. van Heusden, J. M. Ansermino, G. A. Dumont, "Robust MISO Control of Propofol-Remifentanil Anesthesia Guided by the NeuroSENSE Monitor," *IEEE Trans. Control Syst. Technol.*, vol. 26, no. 5, pp. 1758-1770, Sep. 2014.

[21] N. West, K. van Heusden, M. Görges, S. Brodie, A. Rollinson, C. L. Petersen, G. A. Dumont, J. M. Ansermino, R. N. Merchant, "Design and evaluation of a closed-loop anesthesia system with robust control and safety system," *Anesthesia & Analgesia*, vol. 127, no. 4, pp. 883-894, Nov. 2018.

[22] R. Hume, "Prediction of lean body mass from height and weight," *J. Clin. Pathol.*, vol. 19, no.4, pp. 389-391, Jul. 1966.

[23] S. Bibian, G. A. Dumont, and T. Zikov, "Dynamic behavior of BIS, Mentropy and neuroSENSE brain function monitors," *J. Clin. Monit. Comput.*, vol. 25, no. 1, pp. 81-87, Feb. 2011.

[24] M. Hosseinzadeh, and M. J. Yazdanpanah, "Robust adaptive passivity-based control of open-loop unstable affine nonlinear systems subject to actuator saturation," *IET Control Theory A.*, vol. 11, no. 16, pp. 2731-2742, Nov. 2017.

[25] S. Khosravi, "Constrained Model Predictive Control of Hypnosis," Ph.D. dissertation, Univeristy of British Columbia, 2015.

[26] J. Vuyk, M. J. Mertens, E. Olofsen, A. G. Burm, and J. G. Bovill, "Propofol anesthesia and rational opioid selection: determination of optimal EC50-EC95 propofol-opioid concentrations that assure adequate anesthesia and a rapid return of consciousness," *Anesthesiology*, vol. 87, no. 6, pp. 1549-62, Dec. 1997.

[27] G. E. van Poucke, L. J. Bravo, and S. L. Shafer, "Target controlled infusions: targeting the effect site while limiting peak plasma concentration," *IEEE Trans. Biomed. Eng.*, vol. 51, no. 11, 2004.

[28] T. W. Schnider, C. F. Minto, S. L. Shafer, P. L. Gambus, C. Andresen, D. B. Goodale, and E. J. Youngs, "The influence of age on propofol pharmacodynamics," *Anesthesiology*, vol. 90, no. 6, Jun. 1999.

[29] M. Sánchez, and M. Bernal, "A Convex Approach for Reducing Conservativeness of Kharitonovs-Based Robustness Analysis," in *Proc. 20th IFAC World Congress*, Toulouse, France, Jul. 9-14, 2017.