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Feedback law with probabilistic certification for Propofol-based control of BIS during anesthesia

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Summary

This paper proposes a new control strategy for Propofol injection during anesthesia in patients undergoing surgery and where the Bispectral Index (BIS) is considered to be the regulated variable. The proposed control shows the nice feature of being completely independent of the knowledge of the pharmacokinetics that govern the diffusion of the drug. This paper also proposes a certification framework that gives a probabilistic guarantee regarding the containment of the BIS inside the desired interval as well as for the time needed for the BIS to be steered to this interval. Moreover, this certification is given for realistic (and hence very high) level of uncertainties on the parameters that define the unknown-to-the-controller dynamics. This last feature is checked using a widely employed model.

KEYWORDS

anesthesia, BIS, performance certification, Propofol, robust feedback

1 | INTRODUCTION

When it comes to using feedback strategies to monitor drug delivery on humans, the concept of robustness cannot be overestimated. This is because, unlike human designed technological systems that can be tightly modeled using well-established principles, modeling the dynamics of the underlying biological processes is very difficult. Even when potentially faithful models are derived (which is rather rare), the parameters that such models involve are highly uncertain. Therefore, any candidate model-based feedback strategy that is intended to rationalize the drug delivery has to assess the robustness of its performance against these unavoidable and particularly high uncertainties.

The automatic control of anesthesia makes no exception. Many advances have been achieved since the early expert systems.[1] The benefit from a successful automated process is twofold (1) It avoids the dramatic consequence of a possible transient lack of attention of the anesthetist. (2) It reduces the sensitivity to initial estimation of the specific patient responsiveness to the drug (or even ideally suppresses the need for it). This second feature needs the feedback strategy to not heavily rely on the knowledge of the specific patient parameters.

This paper is focused on the control of deep anesthesia via Propofol injection. More precisely, as there is no direct measurement of the depth of anesthesia, the Bispectral Index (**BIS**), which is a commercially available electroencephalography-based index, is used as a surrogate measure for the depth of anesthesia. Notice, however, that the BIS is one among multiple indicators that the anesthetist keeps monitoring during the operation.[2,3]

Since the early works by Bickford,[4] Mortier et al,[5] Ritchie et al,[6] Ross et al,[7] and Schwilden et al[8] that assessed the benefit from closed-loop feedback mode when compared to standard practices, several feedback design strategies have been proposed for the above problem. More precisely, a predictive control strategy based on a nominal linear model is proposed in the work of Ionescu et al.[9] The robustness of the resulting closed-loop behavior is tested by simulating a dozen of different sets of parameters used in the model. The performance and the robustness of this law showed to be comparable to the adaptive controller proposed in the works of Gentilini et al,[10] De Smet et al,[11] and Vishnoi and Roy,[12] which is based on online adaptation of the underlying model through a preliminary (open-loop) induction phase.

More recently, robust PID and fractional-order control strategies have been designed and applied that are based on linear models depending on the patients age as a parameter, in the works of Dumont et al,[13] and Van Heusden et al.[14] In the work of Liu et al,[15] the performance of a closed-loop co-administration of Propofol and Remifentanil guided by the BIS for induction and maintenance of anesthesia is evaluated. The control consists of an heuristic controller emulating the PID controller and has been applied in several clinical tests; see, for instance, the work of Le Guen et al.[16] The results are compared, under different criteria, with the analogous manual anesthesia operations. Furthermore, in the works of Agarwal et al[17] and Biswas et al,[18] a closed-loop anesthesia delivery system is proposed and compared with manual anesthesia to show the benefits of applying automatic control methods to regulate Propofol concentration. Reboso et al[19] design and implement on clinical tests a PI controller based on the identification of the linear discrete-time transfer function between the infusion rate and the BIS. Rocha et al[20] proposes a drug delivery method alternative to the standard target controlled infusion TCI system that is based on pharmacokinetic and pharmacodynamic models for regulating the drug concentration. Méndez et al[21] consider the problem of parametric uncertainties for the control design, proposing an adaptive fuzzy model for the BIS dynamics whose parameters are determined by a genetic algorithm. Such models are then used online to compute the prediction for feeding a model predictive control to regulate the BIS through the drug infusion rate. Finally, a dynamic decoupling approach is used in the work of Zabi et al[22] where a linear matrix inequality (LMI) that handles polytopic uncertainties is used to design a robust feedback law. The robustness is assessed through several simulations with various parameter sets.

Most of the above cited works are based on the use of linear model structure. This assumption simplifies the controller design but also enables rigorous robustness certification (as far as the linearity assumption is relevant) via LMIs or set-invariance frameworks. In most of these works, focus is made on the proof of stability although this is intrinsically an asymptotic property. For finite-time processes such as the one we are interested in where finite-time surgery is involved, the asymptotic stability is not the appropriate paradigm. Instead, one should focus on the time needed to reach the desired region for BIS and whether or not the latter remains inside this region for the remaining time. Moreover, the robustness in the above cited works is taken in the *traditional* worst-case sense, which is generally too stringent as even potentially extremely unlikely configuration of parameters is taken into account.

In this work, a different approach is adopted in which the linearity assumption is dropped and certification is obtained by means of randomized optimization. More precisely, the recently developed control scheme,[23] originally developed for saturated control of unknown scalar systems, is used in a somehow backstepping form. The parameters of the resulting control scheme are then optimized via the randomized optimization framework[24] in order to get certified closed-loop performance in terms of the following:

- the maximal time needed before entering the final (40-60) region for the BIS indicator;
- the effective invariance of this terminal BIS region;
- the fact that BIS is kept above 40 all the time.

The certification mentioned above needs a simulation model (that is unknown to the controller) in order to perform the randomized optimization. To this end, some existing models are used to derive highly uncertain simulators in order to support the certification claims. The results suggest extremely high robustness to the parameters of the pharmacokinetics model (up to 50% of uncertainties on all parameters).

This paper is organized as follows. Section 2 states the problem addressed in this paper. A brief sketch of the solution is derived in Section 3. Since the proposed solution is based on two ingredients, which are the control framework of Alamir[23] and the randomized certification framework of Alamo et al,[24] these two results are recalled in Section 4. The proposed feedback strategy is derived in Section 5 while Section 6 gives extensive closed-loop simulations and the certification results. Finally, Section 7 concludes this paper and gives hints for further investigations.

2 | PROBLEM STATEMENT

In this paper, we consider the problem of steering and maintaining the BIS level to and inside the interval

$$\mathcal{I} := [50 - \delta_B, 50 + \delta_B] \tag{1}$$

by means of appropriate feedback-based Propofol injection strategy. It is assumed that a nonlinear static map, denoted hereafter by Ψ_B, links the BIS to the drug concentration C_e (mg/L) in the *effect site compartment*, namely,[9,25]

$$\text{BIS} = \Psi_B(C_e|\ p_B), \tag{2}$$

where p_B are uncertain modeling parameters. The map Ψ_B is supposed to be invertible so that one can write

$$C_e = \Psi_B^{-1}(\text{BIS}|\ p_B). \tag{3}$$

The dynamics of C_e is governed by[25]

$$\dot{C}_e(t) = k_{e0}\left[C_p(t) - C_e(t)\right], \tag{4}$$

in which C_p represents the concentration (mg/L) of drug in the *central compartment* (blood). This is a common modeling compartmental approach in which only the drug quantity inside the *effect site* compartment is effective while Equation (4) models the transfer between the blood and the site effect compartment. This models the diffusion-induced dynamics between the injection of the drug and its effect on the BIS indicator.

Finally, the dynamics of C_p is given by

$$\dot{C}_p(t) = \Phi\left(\xi(t), C_e(t), C_p(t)\right) + v(t), \tag{5}$$

where $\xi \in \mathbb{R}^{n_\xi}$ is a varying nonmeasured quantity with unknown dynamics while Φ is an unknown function. This term gathers the *leaks* of drug from the blood to the well and the poorly perfused body tissues. v stands for the drug injection intensity (mg/min), which belongs to the admissible set $\mathbb{V} := [0, \bar{v}]$, where $\bar{v}$ is the maximum injection intensity.

This paper is about designing a feedback law that does not use any knowledge regarding the term $\Phi(\cdot)$ involved in (5). Nevertheless, in order to support simulations AND certification tasks, we need relevant realization of this term. Concrete choices for such realizations are described in Section 6. At this stage of the presentation and in order to keep the problem statement at a generic level, the following definition is needed.

Definition 1. (Relevant Model Completion)
Consider the following items:

(1) A dynamic equation of the form

$$\dot{\xi} = F(\xi, C_e, C_p, v, p_\phi) \quad ; \quad \xi \in \mathbb{R}^{n_\xi}, \tag{6}$$

where $p_\phi \in \mathbb{P} \subset \mathbb{R}^{n_\phi}$ is a vector of parameters that belongs to an admissible set $\mathbb{P}$. Note that all the arguments of F are not necessarily present in the explicit expression of F, they are all used here to avoid loss in generality;
(2) A static map $\Phi : \mathbb{R}^{n_\xi} \times \mathbb{R}^2 \to \mathbb{R}$;
(3) A probability distribution $\mathcal{P}_\phi$ that enables to get random realizations of the parameter vector p_ϕ inside the admissible set $\mathbb{P}$;
(4) Two probability distributions $\mathcal{P}_B$ and $\mathcal{P}_{e0}$ that enables to get random realizations of p_B and k_{e0} involved in Equations (2) and (4), respectively.

We say that the preceding items define a Relevant Model Completion (RMC) if the family of dynamic models defined by (2), (4), (5) *completed* by (6) is a relevant model to describe the Propofol-based action on the BIS indicator including the inter-patient variability as far as p_B, k_{e0}, and p_ϕ are *fired* according to the probability distributions $\mathcal{P}_B$, $\mathcal{P}_{e0}$, and $\mathcal{P}_\phi$, respectively.

Based on the description above, the control problem addressed in the present paper can be described as follows.
Problem statement. Assuming that:

- ✓ The BIS is measured;
- ✓ An RMC is given;
- ✓ A duration T for the surgery is given.

The objective is twofold:

(1) Define a dynamic control feedback of the form

$$\dot{z} = g(z, \text{BIS}) \tag{7a}$$

$$v = K(z, \text{BIS}) \tag{7b}$$

that is designed to steer the BIS inside the interval $\mathcal{I}$ after a finite time τ_r and maintain it inside $\mathcal{I}$ over the remaining time $[\tau_r, T]$ while never cross the lower bound $50 - \delta_B = 40$ on the BIS level.

(2) Provide an acceptably small upper bound $\bar{\tau}_r > 0$ such that the following condition holds on the probability of τ_r being lower than $\bar{\tau}_r$:

$$\Pr[\tau_r \leq \bar{\tau}_r] \geq 1 - \eta \tag{8}$$

with a very small η.

In the following section, the general guidelines of the proposed methodology to address this problem are first sketched to get the *whole picture* before a detailed derivation is given in later sections.

3 | SKETCH OF THE PROPOSED SOLUTION

The proposed methodology can be summarized in two steps:

(1) design a feedback control law;
(2) certify the properties of the corresponding closed-loop behavior.

The following two sections explain these two steps.

3.1 | Feedback design

Let us denote $y = \text{BIS}$ the only measured quantity. Denote by $x := (C_e, C_p)^\top$ the state vector of the following dynamic model that is used in the control design and that is derived from (4)-(5):

$$\dot{x}_1 = k_{e0}(-x_1 + x_2) \quad k_{e0} \text{ uncertain} \tag{9a}$$

$$\dot{x}_2 = \Phi + v \qquad \Phi \text{ unknown.} \tag{9b}$$

Moreover, Φ can possibly be time varying. Let us also denote by p the vector that concatenates all the uncertain parameters while p_c gathers the uncertain parameters that are not associated to Φ, namely,

$$p := \begin{bmatrix} p_c \\ p_\phi \end{bmatrix} \quad ; \quad p_c := \begin{bmatrix} p_B \\ k_{e0} \end{bmatrix}. \tag{10}$$

Finally, the notation $\mathcal{P}$ designates the probability distribution of p that is induced by $\mathcal{P}_B$, $\mathcal{P}_{e0}$, and $\mathcal{P}_\phi$.

Assume a nominal parameter vector $p_c^{\text{nom}} := (p_B^{\text{nom}}, k_{e0}^{\text{nom}})$ of p_c. Using p_B^{nom}, Equation (3) can be used as a measurement equation for $x_1 = C_e = \Psi_B^{-1}(y \mid p_B^{\text{nom}})$. This *measurement* together with (9a) can be used to estimate x_2. More precisely, a Luenberger observer can be designed to produce an estimation $\hat{x}_2$ of x_2, namely,

$$\dot{\hat{x}} = \begin{bmatrix} -k_{e0}^{\text{nom}} & k_{e0}^{\text{nom}} \\ 0 & 0 \end{bmatrix} \hat{x} + \begin{bmatrix} 0 \\ v \end{bmatrix} + \begin{bmatrix} L_1 \\ L_2 \end{bmatrix} \left[\Psi_B^{-1}\left(y \mid p_B^{\text{nom}}\right) - \hat{x}_1 \right], \tag{11}$$

where the matrix $L = [\, L_1 \;\; L_2 \,]^\top$ is a standard Luenberger observer gain.[26] Note that, in this observer, the assumption $\Phi = 0$ is used, which can still lead to acceptable observer performance provided that sufficiently high gain L is used. This is a standard practice in extended state-based observer.

Now that x_1 is measured and x_2 can be reconstructed, one can focus on the design of a state feedback for (9a)-(9b) knowing that, once such a feedback is designed, the estimated state can be used. The objective of the control design will be to steer the state x to the *desired* steady state that is defined by

$$x^d := \begin{bmatrix} 1 \\ 1 \end{bmatrix} \Psi_B^{-1}\left(50 | p_B^{\text{nom}}\right), \tag{12}$$

which is simply the steady state of (9a)-(9b) that is compatible with the desired BIS value, namely, 50.

The design of the control law uses a technique that is inspired by the well-known *backstepping* approach. In order to better understand the idea, let us rewrite (9a)-(9b) in the following form:

$$\dot{x}_1 = k_{e0}\left[-x_1 - e_2 + x_2^{\text{ref}}\right] \tag{13a}$$

$$\dot{x}_2 = \Phi + v, \tag{13b}$$

where $e_2 = x_2^{\text{ref}} - x_2$ in which x_2^{ref} is some reference value for x_2 to be designed in the sequel. In the backstepping approach, one views x_2^{ref} as a control signal that regulates x_1 at x_1^d and views v as a control signal that regulates x_2 at x_2^{ref}. By doing so, the control problem can be split into two scalar control problems in each of which the dynamic scalar controlled system takes the following form:

$$\dot{x}_i = \alpha_i[u_i - h_i], \tag{14}$$

where α_i and h_i are given by

$$(\alpha_1, \alpha_2) = (k_{e0}, 1) \quad ; \quad (h_1, h_2) = (x_1 + e_2, -\Phi). \tag{15}$$

Therefore, one can apply the above backstepping inspired idea provided that a feedback design can be systematically obtained for systems of the form (14) in which α_i and h_i are partially unknown. This is because Φ, e_2, and k_{e0} are supposed to be (partially or totally) unknown for their respective controllers.

In the next section, a recent result[23] is recalled regarding a systematic control design for uncertain systems of the form (14). This result is then used to give an explicit feedback design. For the time being and in order to keep the general overview of the proposed solution, let us assume that some dynamic output feedback design is achieved so that a dynamic control of the form (7) is obtained leading to the following closed-loop system (recall that $y = \text{BIS}$):

$$\dot{x}_1 = k_{e0}(-x_1 + x_2) \tag{16a}$$

$$\dot{x}_2 = \Phi + K(z, y) \tag{16b}$$

$$\dot{z} = g(z, y). \tag{16c}$$

Notice that the definition of this system is incomplete as the dynamics of Φ is unknown. However, the definition of the feedback $K(z, y)$ does not involve any knowledge regarding this dynamics. Now, as soon as an RMC is defined in the sense of Definition 1, Equations (16a)-(16c) can be completed to yield an autonomous closed-loop system for each choice of the parameter vector p, namely,

$$\dot{x}_1 = k_{e0}(-x_1 + x_2) \tag{17a}$$

$$\dot{x}_2 = \Phi(\xi, x_1, x_2) + K(z, y) \tag{17b}$$

$$\dot{z} = g(z, y) \tag{17c}$$

$$\dot{\xi} = F\left(\xi, x_1, x_2, K(z, y), p_\phi\right) \tag{17d}$$

$$y = \text{BIS} = \Psi_B(x_1 | p_B), \tag{17e}$$

which is a complete simulator for the specific closed-loop *patient* that is defined by the value of $p := (p_B^\top, k_{e0}, p_\phi)^\top$.

Remark 1. Note that nominal values k_{e0}^{nom} and p_B^{nom} used in the design of the observer (see (11)) and the definition of the desired state x^d (see (12)) are implicitly contained in the functions $K(z, y)$ and $g(z, y)$.

The complete definition of the feedback law is given in Section 5.

3.2 | Probabilistic certification

The simulator defined by (17a)-(17e) gives the evolution of the BIS indicator during the surgery when the feedback law is applied and for a specific value p of the vector of parameters that is related to a specific patient. Let us denote by $y(t|p)$, $t \in [0, T]$ the resulting trajectory for the BIS indicator. Therefore, it is possible to define the response time $\tau_r(p)$ for that specific value of p by

$$\tau_r(p) := \begin{cases} t^* := \min\left\{\bar{t} |\ y(t|p) \in \mathcal{I}\ \forall t \in [\bar{t}, T]\right\}, & \text{if } t^* \text{exists} \\ 2T, & \text{otherwise,} \end{cases} \tag{18}$$

that is to say, if there is $\bar{t}$ such that, for all $t \in [\bar{t}, T]$, the BIS remains inside the targeted region $\mathcal{I}$ (see (1)), then $\tau_r(p)$ is set to the least of such values; otherwise, it is set to $2T$. Note that the use of $2T$ in the second branch of (18) is arbitrary and simply means that the control task is not achieved.

The probabilistic certification paradigm is linked to the possibility to have something to say about the issue of the operation on the whole population of patients, represented by the possible values of p associated to the probability distribution $\mathcal{P}$ defined by the RMC under interest. More precisely, one seeks a way to be able to certify that the following probability holds:

$$\Pr_{\mathcal{P}}\left[\tau_r(p) \leq \bar{\tau}_r\right] \geq 1 - \eta \tag{19}$$

with sufficiently small upper bound $\bar{\tau}_r$ and sufficiently small probability of failure η. The way such a result can be obtained is based on the probabilistic certification framework that is recalled in Section 4.

4 | RECALLS ON SOME RELEVANT RESULTS

This section contains some recalls on two results that are used to complete the proposed solution. The first one concerns the control design for scalar uncertain systems of the form (14). The second one concerns the concept of probabilistic certification. These are the subject of the following two sections.

4.1 | Constrained feedback of uncertain scalar systems

Let us consider a general system of the form (14)

$$\dot{x} = \alpha[u - h], \tag{20}$$

in which α and h are unknown and possibly time varying, $u \in [u_{\min}, u_{\max}]$. It is assumed that $\alpha \geq \alpha_{\min} > 0$ while $h \in [h_{\min}, h_{\max}]$ where the bounds are assumed to be known and such that the following inequalities hold:

$$u_{\max} - h_{\max} \geq \varrho_+ > 0 \tag{21a}$$

$$h_{\min} - u_{\min} \geq \varrho_- > 0 \tag{21b}$$

with some positive scalars ϱ_+ and ϱ_-. It simply means that the control has sufficient *authority*. Consider the following saturation function on the control variable:

$$S(u) := \begin{cases} u_{\max,} & \text{if } u \geq u_{\max} \\ u_{\min,} & \text{if } u \leq u_{\min} \\ u, & \text{otherwise.} \end{cases} \tag{22}$$

Using the above notation and assumptions, the following result can be proved[23].

Proposition 1. *Take some $\lambda > 0$. Take any $\lambda_f > 0$ satisfying*

$$\lambda_f < \left[\min\left\{\frac{\min\{\varrho_+, \varrho_-\}}{u_{\max} - u_{\min}}, \frac{\alpha_{\min}}{4}\right\}\right] \times \lambda. \tag{23}$$

If *the following conditions hold:*

(1) x_d *is constant and*
(2) the dynamics of the unknown term h *satisfies*

$$\left|\frac{dh}{dt}\right| \leq \delta_h, \tag{24}$$

where $\delta_h > 0$ *is some upper bound,*
then *the dynamic state feedback law defined by*

$$\dot{z} = \lambda_f \left[S\left(\lambda(x_d - x) + z\right) - z\right] \tag{25a}$$

$$u = S\left(\lambda(x_d - x) + z\right) \tag{25b}$$

leads to a tracking error $e_x = x - x_d$ *that satisfies*

$$\lim_{t\to\infty} |x(t) - x_d| \leq \frac{\delta_h}{\lambda\lambda_f}. \tag{26}$$

Note that this result means that, for constant unknown h, asymptotic convergence results. Moreover, even with dynamic unknown h, the value of λ can always be taken sufficiently high to enforce any asymptotic small error. In Section 5, this result is used to derive a dynamic backstepping like state feedback for the system (13a)-(13b).

4.2 | Probabilistic certification

Recall that, according to the discussion of Section 3.2, one looks for a solution (if any) to the following optimization problem:

$$\min_{\bar{\tau}_r} J(\bar{\tau}_r) := \bar{\tau}_r \quad | \quad \Pr_{\mathcal{P}}\left[\begin{array}{c} \tau_r(p) \leq \bar{\tau}_r \\ \text{AND} \\ \min\limits_{t\in[0,T]} y(t|p) \geq 40 \end{array}\right] \geq 1 - \eta. \tag{27}$$

This is a rather intractable formulation as the probability depends on a rather high-dimensional vector p of random parameters. The idea of probabilistic certification is to replace this problem by the following more tractable one:

$$\min_{\bar{\tau}_r} J(\bar{\tau}_r) := \bar{\tau}_r \quad | \quad \sum_{i=1}^{N} I\left(\bar{\tau}_r, p^{(i)}\right) \leq m, \tag{28}$$

where

- $p^{(i)}$, $i = 1, \ldots, N$, are N random samples of p that are obtained according to the distribution $\mathcal{P}$.
- $I(\bar{\tau}_r, p^{(i)})$ is the constraint violation indicator

$$I\left(\bar{\tau}_r, p^{(i)}\right) := \begin{cases} 1, & \text{if } \tau_r(p) > \bar{\tau}_r \text{ or } \min_t y(t|p) < 40 \\ 0, & \text{otherwise.} \end{cases} \tag{29}$$

- m is some integer such that

$$\frac{m}{N} \leq \eta. \tag{30}$$

Roughly speaking, the condition (28) states that only m samples inside the population of N samples violate the constraint ($\tau_r(p) \leq \bar{\tau}_r$ and $\min_t y(t|p) \geq 40$). Now, intuitively, one would expect that, if a value $\bar{\tau}_r$ is found such that for a *sufficiently high* number of samples N, only a small number m satisfying (30) violates the constraint, then one can say that the probability that the constraint is violated is *close* to η.

The problem lies obviously in the terms (*sufficiently high N*) and (*close to* η). That is where the rigorous formalism of probabilistic certification[24] comes into action. This formulation computes the number of scenarios to simulate in order to be able to make a statement that is correct with a probability $1 - \delta$, where δ is called the confidence parameter. More precisely, the theory gives for a priori chosen m, a priori desired η, and a priori defined confidence parameter δ, the

TABLE 1 Evolution of the sample size N (number of samples needed to achieve the certification) as a function of the precision η and the cardinality n_r of the design parameter set $\mathbb{T}$ (confidence parameters $\delta = 10^{-3}$ and $m = 1$ are used)

n_r	$\eta = 0.1$	$\eta = 0.05$	$\eta = 0.01$	$\eta = 0.001$
1	132	264	1317	13164
5	154	308	1536	15354
10	163	326	1628	16280
100	193	386	1930	19299
1000	223	445	2225	22249
10 000	252	503	2515	25148

number of samples N that one has to use. Note that the confidence parameter δ is the probability with which (28) can hold while (27) is violated. In other words, $1 - \delta$ is the probability that one satisfies the intractable inequality (27) while checking only the tractable inequality (28).

Many results are given in the works of Alamo et al[24] under different conditions, and here, only a specific case of interest is considered in which the set of candidate values of $\bar{\tau}_r$ is supposed to belong to a discrete set of cardinality n_r, namely,

$$\bar{\tau}_r \in \mathbb{T} := \left\{ \bar{\tau}_1, \ \ldots, \bar{\tau}_{n_r} \right\}. \tag{31}$$

In this case, the number of samples N is given by the following formulae[24]:

$$N \geq \frac{1}{\eta} \left(m + \ln \left(\frac{n_r}{\delta} \right) + \left(2m \ln \left(\frac{n_r}{\delta} \right) \right)^{1/2} \right). \tag{32}$$

The corresponding values of N for $m = 1$ and the confidence parameter $\delta = 10^{-3}$ are given in Table 1.

5 | THE PROPOSED FEEDBACK STRATEGY

As explained in Section 3.1, the dynamic feedback law (25) is applied to the following two scalar uncertain systems in a backstepping form.

(1) System (13a) in which the control is x_2^{ref}, the state is x_1, and the reference is x_1^d given by (12). The *virtual* control x_2^{ref} belongs to $[\underline{\gamma} x_2^d, \bar{\gamma} x_2^d]$, where $\underline{\gamma} \in (0, 1)$ and $\bar{\gamma} \in [1, 2]$. This obviously defines an interval of variation around the steady value x_2^d.
(2) System (13b) in which the control is v, the state is x_2, and the reference is x_2^{ref}. The control v belongs to $[0, \bar{v}]$.

Using (25a)-(25b) the controller is given by

$$\dot{z}_1 = \lambda_{f_1} \left[S_1 \left(\lambda_1 \left(x_1^d - x_1 \right) + z_1 \right) - z_1 \right] \tag{33a}$$

$$\dot{z}_2 = \lambda_{f_2} \left[S_2 \left(\lambda_2 \left(x_2^{\text{ref}}(x_1, z_1) - x_2 \right) + z_2 \right) - z_2 \right] \tag{33b}$$

$$v = S_2 \left(\lambda_2 \left(x_2^{\text{ref}}(x_1, z_1) - x_2 \right) + z_2 \right), \tag{33c}$$

where

$$x_2^{\text{ref}}(x_1, z_1) := S_1 \left(\lambda_1 \left(x_1^d - x_1 \right) + z_1 \right) \tag{33d}$$

$$S_1(r) := \begin{cases} \underline{\gamma} x_2^d, & \text{if } r < \underline{\gamma} x_2^d \\ \bar{\gamma} x_2^d, & \text{if } r > \bar{\gamma} x_2^d \\ r, & \text{otherwise} \end{cases} \tag{33e}$$

$$S_2(r) := \begin{cases} 0, & \text{if } r < 0 \\ \bar{v}, & \text{if } r > \bar{v} \\ r, & \text{otherwise.} \end{cases} \tag{33f}$$

Notice that the feedback defined by (33) depends on the following vector of parameters:

$$\theta_c := \left[\lambda_1 \;\; \lambda_2 \;\; \lambda_{f_1} \;\; \lambda_{f_2} \;\; \underline{\gamma} \;\; \bar{\gamma} \right]. \tag{34}$$

The feedback law given by (33c) can be put in the form $v = K(z, y)$ invoked in (16) and (17) once that (x_1, x_2) is replaced by $(z_3, z_4) := (\hat{x}_1, \hat{x}_2)$ whose dynamics is given by the observer equation (11).

The last modification that is needed to take into account the uncertainties on the parameter p_B consists in introducing an integral action. The need for this integral action comes from the bad knowledge of the precise values of the parameter vector p_B that can induce a bad reference value for x_1. This is done by modifying the definition of the desired state x^d from the original form (12) to the new form

$$x_1^d := \Psi_B^{-1}(50 + e | p_B^{\text{nom}}), \tag{35}$$

where the dynamics of the error e is defined by

$$\dot{e} = \begin{cases} \lambda_I(50 - y), & \text{if } y \in \mathcal{I} \\ 0, & \text{otherwise,} \end{cases} \tag{36}$$

where $\lambda_I > 0$ is the integrator constant. This conditional definition enables the integrator state to be updated only in the vicinity of the desired BIS. This completes the definition of the feedback scheme. In the next section, a specific widely used RMC is defined and the behavior of the resulting closed-loop system can be examined. In particular, certification results are obtained using the framework of Section 4.2.

6 | RESULTS

This section is organized as follows.

(1) A specific RMC is first defined to serve in the simulations and the certification. Note that this definition includes the definition of the unknown map Φ and F respectively given by (5) and (6), but also the definition of the admissible sets of the parameters p_c and p_ϕ and their probability distributions. Any other model can be used in the framework without any change in the feedback design. Only the behavior and the quantitative results of the assessment would be different.
(2) The set of control parameters defined by (34) and used in the feedback expression (33) is given. Note that these parameters can be *optimized* using the full randomized optimization framework of Alamo et al.[24] This would complicate the exposition of the methodology. Instead, we decided to assess the certification of the resulting closed loop for a specific hand-tuned control parameter. The very nice result suggests that optimization is not necessary here.
(3) Some temporal simulations for different parameter values p are shown in order to illustrate the widespread set of possible closed-loop trajectories.
(4) Finally, the upper bound $\bar{\tau}_r$ discussed in Section 4.2 is computed and the certification result is summarized.

These items are developed in the following sections.

6.1 | Definition of the RMC used for certification

As an RMC, we shall consider the widely used compartmental model describing the dynamics of the drug in the human body (see the works of Ionescu et al[9] and Zabi et al[22] and the references therein). In this model, the two states following dynamics is used to represent the unknown functions Φ and F

$$\dot{\xi}_1 = k_{12} x_2 - k_{21} \xi_1 \tag{37a}$$

$$\dot{\xi}_2 = k_{13} x_2 - k_{31} \xi_2 \tag{37b}$$

$$\Phi = -(k_{10} + k_{12} + k_{13}) x_2 + k_{21} \xi_1 + k_{31} \xi_2, \tag{37c}$$

where the coefficients k_{ij} are given by nominal expressions that depend on the gender (G), age (A), height (H), and weight (W) of the patient

$$k_{ij}^{\text{nom}} := F_{ij}(G, A, H, W). \tag{38}$$

Interested readers can consult the work of Ionescu et al[9] for the explicit expression of the functions F_{ij}. Recall that, in the previous discussion, the vector gathering these parameters is the one denoted by p_ϕ, namely,

$$p_\phi := \left[k_{10} \;\; k_{12} \;\; k_{21} \;\; k_{13} \;\; k_{31} \right]^\top \in \mathbb{R}^5. \tag{39}$$

Note that Equations (37a)-(37b) define the function F invoked in (6). In this work, the probability distribution ($\mathcal{P}_\phi$) associated to this parameter is defined by the following procedure to generate random samples.

(1) First, the gender parameter G is randomly chosen by equally probable Male/Female issue.
(2) Then, the continuous parameters $A \in [20, 60]$, $H \in [140, 200]$, $W \in [55, 90]$ are uniformly sampled inside the above defined intervals of age, weight, and height. Then, the corresponding parameter vector p_ϕ^{nom} is computed by (38).
(3) The results of the two previous steps are then randomly perturbed by multiplying each parameter $p_{\phi_i}, i = 1, \ldots, 5$ independently by a factor β_i that is uniformly randomly chosen in the interval $[\underline{\beta}, \bar{\beta}]$, where $\underline{\beta} \in (0, 1)$ and $\bar{\beta} > 1$,

$$p_{\phi_i} = \beta_i \times p_{\phi_i}^{\text{nom}}(G, A, H, W) \quad \beta_i \in [\underline{\beta}, \bar{\beta}]. \tag{40}$$

The values $\underline{\beta} = 0.5$ and $\bar{\beta} = 1.5$ are used in the following investigation. Note that this means that

> Each parameter can randomly take any value between 50% and 150% of its nominal value. These nominal values are themselves randomly obtained through random samples of G, A, H, and W.

The static map between the BIS and x_1 is classically defined by[9]

$$\text{BIS} = \Psi_B(x_1 |\, p_B) := 100 \left[1 - \frac{x_1^\gamma}{x_1^\gamma + E_{c50}^\gamma} \right], \tag{41}$$

which is a model that is defined by the parameter vector $p_B := (\gamma, E_{c50})$ for which, the following nominal value is used:

$$p_B^{\text{nom}} := (2.39, 5.6), \tag{42}$$

while the random sampling (distribution $\mathcal{P}_B$) is defined by a uniform sampling in the interval defined by ±15% around the nominal values of the components. Similarly, the nominal value $k_{e0}^{\text{nom}} = 0.474$ is used for k_{e0} involved in (9a) while the *real* value used in the simulation is uniformly randomly chosen in the ±30% interval around the nominal value. This defines the sampling probability $\mathcal{P}_{e0}$ invoked in Definition 1.

6.2 | Definition of the control parameters

The following control parameters are used in the definition of the dynamic feedback (33):

$$\begin{aligned} &\lambda_1 = 40 \quad ; \quad \lambda_2 = 10 \quad ; \quad \lambda_{f_1} = 0.01\lambda_1 \quad ; \quad \lambda_{f_2} = 0.1\lambda_2 \\ &\underline{\gamma} = 0.7 \quad ; \quad \bar{\gamma} = 1.3 \quad ; \quad \bar{\nu} = 100. \end{aligned}$$

The integrator constant is taken equal to $\lambda_I = 0.1$ in (36). The sampling period for the control is taken equal to $\tau = 6$ seconds. It is important here to highlight the fact that whether these parameters meet the theoretical requirements of Proposition 1 does not really matter. The last word is given by the certification phase, which evaluates the probability of success of the designed feedback regardless of whether it lies inside the theoretical, generally over-stringent, sufficient conditions of Proposition 1. The latter can be viewed as a source of inspiration of the control design that is candidate for certification statement.

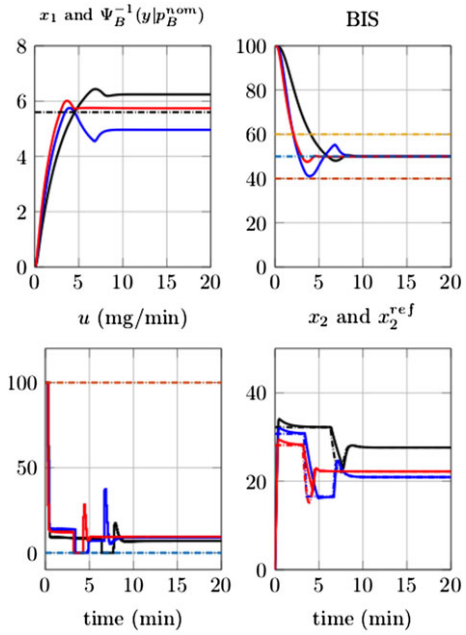

FIGURE 1 Closed-loop simulations of three randomly sampled patients with the uncertainty levels given by (43). Notice the drastically different closed-loop Propofol injection profiles. Note also the integrator induced adaptation of the stationary values of x_1 (mg/ml) in order to steer the Bispectral Index (BIS) to its desired value despite of the uncertainties on the parameters of the BIS-x_1 static relation [Colour figure can be viewed at wileyonlinelibrary.com]

6.3 | Time simulations for different patients

The aim of this section is to show how different closed-loop feedback Propofol injection time profiles might result when patients with highly different parameters are used in the simulation. This does not correspond to any certification but enables to get a feeling regarding the efficiency of the proposed feedback in handling the lack of knowledge of the patient's response to Propofol administration. To show this, three patients are considered with the following relative discrepancies w.r.t. the nominal values of the parameters (the expressions have to be interpreted componentwise):

$$\frac{p_\phi - p_\phi^{\text{nom}}}{|p_\phi^{\text{nom}}|} \in \left\{ \begin{bmatrix} 43\% \\ 5\% \\ 29\% \\ 12\% \\ 11\% \end{bmatrix}, \begin{bmatrix} -45\% \\ -1\% \\ -18\% \\ -11\% \\ -10\% \end{bmatrix}, \begin{bmatrix} 3.5\% \\ -13.3\% \\ -22\% \\ -2\% \\ 12\% \end{bmatrix} \right\}. \tag{43}$$

The closed-loop simulations for the three patients are given in Figure 1. One can easily notice the very different Propofol injection profiles for the three patients despite of the model-free design of the feedback law. The role of the integrator variable e introduced in (36) can also be observed on the fact that the stationary values of x_1 are corrected and hence become patient dependent so that the truly regulated BIS is steered to the desired value despite the unknown parameters of the specific patient.

6.4 | Probabilistic certification

In this section, the methodology described in Section 4.2 is applied. To do so, $n_r = 100$ values of the response time have been taken, which are uniformly distributed on the interval $[1, 20]$ minutes. The precision $\eta = 10^{-2}$ and the confidence parameter $\delta = 10^{-3}$ are used. From Table 1, it comes that the above choice leads to a number of samples $N = 1930$ that is necessary to give the certification result. Note that, since a single simulation needs less than 1 ms, the certification of a given value of the design parameter vector p needs less than 2 seconds. Figure 2 shows the histogram of the response

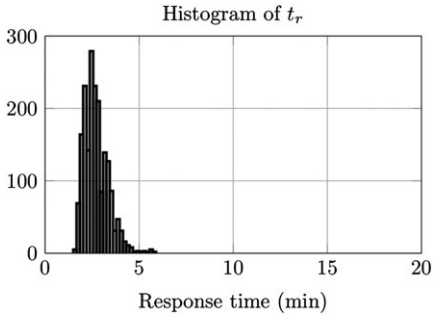

FIGURE 2 Histogram of the response times for the 1930 sampled patients used in the computation of the probabilistically certified response time

time corresponding to the randomly sampled population of patients. From this Figure, it comes clearly that a certifiable response time can be taken equal to $\bar{\tau}_r = 6$ minutes. Let us state the result more clearly.

> As far as the RMC described in Section 6.1 is relevant, under the proposed feedback, **the probability** that more than 1% of the patients **BIS** indicator remains outside the admissible domain after 6 min or gets their BIS lower than 40 **is lower than 0.1%**.

It is important to underline that the quantitative conclusion of the study is valid only for a given RMC. As far as clinical expectation is concerned, the results can only give an appreciation of the capacity of the method to handle high discrepancies. Now, if the results were too weak even for the RMC including in the certification phase, this would trigger justified doubts regarding the application in real life of the proposed algorithm. The maybe over-optimistic results reported in the paper can be weakened in real life but the margin is quite large and very good results should be expected. Note that the study can be conducted for different settings of the problem (different maximum injection intensity, different assumptions on the parameter dispersion, different models, different controller settings, etc) The *machinery* including the structure of the feedback law remains identical.

7 | CONCLUSION AND FURTHER WORK

In this paper, a complete framework for the design of certifiable dynamic output feedback law that can be used for Propofol-based anesthesia is proposed. The feedback formulation totally ignores the structure of the pharmacokinetic mechanisms. In spite of that, the certification results suggest that, despite an extremely high variability of the patient response to the drug, a reasonable response time (for 99% of patients) of less than 6 minutes can be probabilistically certified (with 99.9% of confidence) to be an upper bound of the time that would be necessary to steer any randomly sampled patient to the admissible 40-60 region of the BIS indicator. The natural extension of the current work is to apply the proposed framework on real patients under the supervision of an anesthetist in order to confirm the nice behavior of the control law in real-life situations.

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