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Robustness of a new nonlinear positive controller for BIS tracking

(Invited Paper)

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***Abstract*—In this paper, the study of the robustness of the positive control law introduced in [1] in the presence of parameter uncertainties is made. This controller was developed to track a desired reference level for the BIS of a patient by means of the simultaneous administration of *propofol* and of *remifentanil*. Here, it is proven that in the presence of uncertainties in the BIS model, the controller still has a good performance and the BIS of the patient converges to clinically acceptable values. These results are illustrated by simulations.**

I. Introduction

General anesthesia has three components: neuromuscular blockade, analgesia and hypnosis. These two latter components constitute the depth of anesthesia (DoA), which may be measured ([2], [3], [4], [5], [6]) by the Bispectral index (BIS). The BIS is a neurophysiologic value obtained through electroencephalogram analysis, ranged from 0 (no brain activity) to 97.7 (patient completely awake). Usually the clinical desired BIS level is defined within an interval, according to the clinical surgical procedure.

A nonlinear automatic positive control law to track a desired BIS level, by means of the administration of the analgesic *remifentanil* and the hipnotic *propofol*, was designed in [1]. This controller, already successfully implemented in clinical environment, is based on the parameter parsimonious model (PPM) (see [7]). As the identification of the model parameters influences the performance of this control law, a method for parameter identification was developed in [8]. The problems raised by the presence of uncertainties in the parameters of the nonlinear part of the PPM was studied in [9] and a retuning strategy in order to overcome this problem was developed in [10].

Here, it is proven that in the presence of uncertainties in the parameters of the linear part of the BIS model, the controller still has a good performance and the BIS of the patient converges to clinically acceptable values. These results are illustrated by simulations.

The structure of this paper is as follows. Section 2 is devoted to the explanation of the PPM while the control law is presented in Section 3. In Section 4 the theoretical study of the robustness of the controller in the presence of parameter uncertainties is made. Simulation results are presented in Section 5 and conclusions are drawn in Section 6.

II. Model description

The patient BIS response to the administration of *propofol* and of *remifentanil* has been recently modeled in [7] by a Wiener model with a small number of parameters, known as parameter parsimonious model (PPM). According to this model, the linear relations between the *propofol* and *remifentanil* dosages and the corresponding effect concentrations (c_e^p and c_e^r) are modeled by the transfer functions:

$$H^p(s) = \frac{k_1 k_2 k_3 \alpha^3}{(k_1\alpha + s)(k_2\alpha + s)(k_3\alpha + s)} u^p(s), \qquad (1)$$

$$H^r(s) = \frac{l_1 l_2 l_3 \eta^3}{(l_1\eta + s)(l_2\eta + s)(l_3\eta + s)} u^r(s), \qquad (2)$$

respectively, where α and η are patient dependent parameters, without any physiological meaning, and $u^p(s)$ and $u^r(s)$ are the Laplace transforms of the administered doses of *propofol*, $u^p(t)$, and of *remifentanil*, $u^r(t)$, in $mg\,min^{-1}$. The corresponding BIS level, $z(t)$, usually given by the generalized Hill equation [11], is approximated in [7] by the nonlinear equation:

$$z(t) = \frac{z_0}{1 + (\mu \frac{c_e^p}{EC_{50}^p} + \frac{c_e^r}{EC_{50}^r})^\gamma}, \qquad (3)$$

where μ and γ are patient dependent parameters, without any physiological meaning, z_0 is the BIS level at zero concentration, and EC_{50}^p and EC_{50}^r respectively denote the *propofol* and *remifentanil* concentrations that produce half the maximal effect when the drug acts isolated. The parameters EC_{50}^p and EC_{50}^r are taken to be fixed, namely

$EC_{50}^p = 10\ mg/ml$ and $EC_{50}^r = 0.01\ mg/ml$. These values were obtained in the work developed in [12], to which we refer for further explanation.

The controller considered in this paper is based on state space methods, which implies taking state space realizations of the transfer functions $H^p(s)$ and $H^r(s)$. Here, we respectively realize these transfer functions by means of the state space models $\Sigma^p = (A^p, B^p, C^p)$ and $\Sigma^r = (A^r, B^r, C^r)$, where

$$\begin{aligned} A^p &= \begin{bmatrix} -10\alpha & 0 & 0 \\ 9\alpha & -9\alpha & 0 \\ 0 & \alpha & -\alpha \end{bmatrix}, \\ B^p &= \begin{bmatrix} 10\alpha \\ 0 \\ 0 \end{bmatrix}, \quad C^p = \begin{bmatrix} 0 & 0 & 1 \end{bmatrix}, \\ A^r &= \begin{bmatrix} -3\eta & 0 & 0 \\ 2\eta & -2\eta & 0 \\ 0 & \eta & -\eta \end{bmatrix}, \\ B^r &= \begin{bmatrix} 3\eta \\ 0 \\ 0 \end{bmatrix}, \quad C^r = \begin{bmatrix} 0 & 0 & 1 \end{bmatrix}. \end{aligned} \tag{4}$$

The states of Σ^p and of Σ^r are respectively denoted by x^p and x^r; the third components of these vectors correspond to the effect concentrations of *propofol* and of *remifentanil*, respectively, whereas the other components have no physiological meaning. The specific form of the realizations Σ^p and Σ^r was chosen so as to have state space systems with a compartmental structure. As should be seen, this has the advantage of allowing the use of the positive control law defined in the next section.

This yields the following equations:

$$\begin{cases} \dot{x}(t) & = Ax(t) + Bu(t) \\ \begin{bmatrix} c_e^p(t) \\ c_e^r(t) \end{bmatrix} & = \begin{bmatrix} 0 & 0 & 1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 1 \end{bmatrix} x(t) \\ z(t) & = z(t) = \frac{z_0}{1+(\mu \frac{c_e^p}{EC_{50}^p} + \frac{c_e^r}{EC_{50}^r})^\gamma}, \end{cases} \tag{5}$$

with

$$x = \begin{bmatrix} x^p \\ x^r \end{bmatrix}, \tag{6}$$

$$A = \begin{bmatrix} A^p & 0 \\ 0 & A^r \end{bmatrix} \quad \text{and} \tag{7}$$

$$B = \begin{bmatrix} B^p & 0 \\ 0 & B^r \end{bmatrix}, \tag{8}$$

where the entries 0 should be interpreted as null submatrices of adequate dimensions.

III. Depth of anesthesia controller

In order to track a desired reference value for the BIS level, by means of simultaneous administration of *propofol* and of *remifentanil*, a nonlinear controller was presented in [1] (see also [13]). This controller results from a combination of a linear control law with a positivity constraint for the drug doses. More concretely, the controller is defined by:

$$u(t) = \begin{bmatrix} u^p(t) \\ u^r(t) \end{bmatrix} = \begin{bmatrix} max(0, \tilde{u}^p(t) \\ max(0, \tilde{u}^r(t) \end{bmatrix}, \tag{9}$$

where u^p is the input of *propofol* and u^r is the input of *remifentanil*, with:

$$\begin{bmatrix} \tilde{u}^p \\ \tilde{u}^r \end{bmatrix} = \tilde{u} = E\left(-KAx + \lambda(M^* - Kx)\right), \tag{10}$$

and

$$E = \begin{bmatrix} \rho \\ 1 \end{bmatrix} \frac{1}{\alpha\rho + 300\eta}, \tag{11}$$

$$M^* = m_{\rho,\mu}\left(\frac{z_0}{z^*} - 1\right)^{\frac{1}{\gamma}}, \tag{12}$$

$$m_{\rho,\mu} = \frac{3(0.1\rho + 100)}{0.1\mu\rho + 100} \tag{13}$$

$$K = \begin{bmatrix} 0.1 & 0.1 & 0.1 & 100 & 100 & 100 \end{bmatrix}, \tag{14}$$

z^* is the desired BIS level, and λ and ρ are positive design parameters that do not affect the tracked reference value and can be chosen according to clinical criteria. The parameter λ influences the convergence speed to the desired reference value and the parameter ρ can be interpreted as the proportion between the doses of *propofol* and *remifentanil*.
Note that the matrix E is such that

$$KBE = 1. \tag{15}$$

For more details about this controller and its tracking properties, the reader is referred to [1].

IV. DoA controller robustness

In this section, the robustness of the control law (9) under the presence of uncertainties in the parameters of the linear part of the PPM is analyzed. The description of the controller action under parameter uncertainties is made in the next subsection and its robustness is studied in the following one.

A. Controller with uncertainties

In practice, the true values of α and η of the PPM are unknown and estimated values $\hat{\alpha}$ and $\hat{\eta}$ are used instead. This means that estimated control doses $\hat{u}^p$ of *propofol* and $\hat{u}^r$ of *remifentanil* are used. These doses are computed as

$$\begin{bmatrix} \hat{u}^p(t) \\ \hat{u}^r(t) \end{bmatrix} = \hat{u}(t) = \hat{u}(x(t)) = \begin{bmatrix} max(0, \hat{\hat{u}}^p(t) \\ max(0, \hat{\hat{u}}^r(t) \end{bmatrix}, \quad (16)$$

with:

$$\hat{\hat{u}} = \begin{bmatrix} \hat{\hat{u}}^p \\ \hat{\hat{u}}^r \end{bmatrix} = \hat{E}\left(-K\hat{A}x + \lambda(M^* - Kx)\right), \quad (17)$$

where

$$\hat{A} = \begin{bmatrix} -10\hat{\alpha} & 0 & 0 & 0 & 0 & 0 \\ 9\hat{\alpha} & -9\hat{\alpha} & 0 & 0 & 0 & 0 \\ 0 & \hat{\alpha} & -\hat{\alpha} & 0 & 0 & 0 \\ 0 & 0 & 0 & -3\hat{\eta} & 0 & 0 \\ 0 & 0 & 0 & 2\hat{\eta} & -2\hat{\eta} & 0 \\ 0 & 0 & 0 & 0 & \hat{\eta} & -\hat{\eta} \end{bmatrix}, \quad (18)$$

and

$$\hat{E} = \begin{bmatrix} \rho \\ 1 \end{bmatrix} \frac{1}{\hat{\alpha}\rho + 300\hat{\eta}},$$

For technical reasons we define

$$k = \frac{\alpha\rho + 300\eta}{\hat{\alpha}\rho + 300\hat{\eta}} \quad (19)$$

and write the matrix $\hat{E}$ as:

$$\hat{E} = Ek. \quad (20)$$

Then $\hat{\hat{u}}$ may be written as

$$\hat{\hat{u}} = \hat{\hat{u}}(x) = \hat{E}k\left(-K\hat{A}x + \lambda(M^* - Kx)\right). \quad (21)$$

B. Robustness analysis

In order to study the robustness of the DoA controller under parameter uncertainty, the following auxiliary output is considered:

$$M(x) = Kx. \quad (22)$$

It was proven in [1] that if in steady state $M(x) = \bar{M}$, then the steady state BIS of the patient, $\bar{z}$, is equal to

$$\bar{z} = \left(\frac{z_0}{1 + \left(\frac{\bar{M}}{m_{\rho,\mu}}\right)^{\gamma}}\right). \quad (23)$$

This implies that, when $M(x)$ converges to M^* (as in equation (12)), the BIS of the patient converges to the reference value z^*.

Since there is a relation between the output $M(x)$ and the BIS of the patient, in a first step, the influence of the parameter uncertainties on the auxiliary output $M(x)$ is studied. More concretely, we shall prove that, for suitable values of the design parameter λ, when the estimated control law (16) is applied to the PPM given by (5) with true parameters α and β, $M(x)$ converges to an interval I_M, which contains M^*. For this purpose we define:

$$\Delta_\alpha = \alpha - \hat{\alpha}, \qquad r = \max\{8\hat{\alpha}, \hat{\eta}\}, \quad (24)$$

$$\Delta_\eta = \eta - \hat{\eta}, \qquad s = \max\{|8\Delta_\alpha|, |\Delta_\eta|\}, \quad (25)$$

and $\Delta_{KA} = KA - K\hat{A}$.

Taking into account that:

$$K\hat{A} = -\begin{bmatrix} 0.1\hat{\alpha} & 0.1(8\hat{\alpha}) & 0.1\hat{\alpha} & 100\hat{\eta} & 100\hat{\eta} & 100\hat{\eta} \end{bmatrix}, \quad (26)$$

and that

$$\Delta_{KA} = \quad (27)$$
$$-\begin{bmatrix} 0.1\Delta_\alpha & 0.1(8\Delta_\alpha) & 0.1\Delta_\alpha & 100\Delta_\eta & 100\Delta_\eta & 100\Delta_\eta \end{bmatrix},$$

the following inequalities, that will be useful later on, hold:

$$|K\hat{A}|x \leq rKx = rM(x); \quad (28)$$

$$|\Delta_{KA}|x \leq sKx = rM(x). \quad (29)$$

Let

$$I_M = \left[\bar{M}_{min}\,,\, \bar{M}_{max}\right], \quad (30)$$

with

$$\bar{M}_{min} = \frac{k\lambda}{k\lambda + \Delta_{ks}} M^*, \quad (31)$$

$$\bar{M}_{max} = \frac{k\lambda}{k\lambda - \Delta_{ks}} M^*, \quad (32)$$

$$\Delta_{ks} = |1 - k|r + s. \quad (33)$$

$$(34)$$

We next prove that $M(x)$ converges to I_M. For this purpose, we apply the LaSalle's invariance principle (see [14]) to the Lyapunov function $V : \mathbb{R}^n \longrightarrow \mathbb{R}$ defined by:

$$V(x) = \begin{cases} \frac{1}{2}(M(x) - \bar{M}_{min})^2 & \text{if } M(x) < \bar{M}_{min} \\ \frac{1}{2}(M(x) - \bar{M}_{max})^2 & \text{if } M(x) > \bar{M}_{max} \\ 0 & \text{otherwise.} \end{cases} \quad (35)$$

$V(x)$ is a LaSalle-Lyapunov function of the system on $\mathbb{R}^n_+$ because it is continuous and its time derivative along the close-loop system trajectories, $\dot{V}(x)$, satisfies $\dot{V}(x) \leq 0$, $\forall x \in \mathbb{R}^n_+$, as shown next. Indeed, $\dot{V}(x)$ is given by:

$$\dot{V}(x) = \begin{cases} (M(x) - \bar{M}_{min})\dot{M} & \text{if } M(x) < \bar{M}_{min} \\ (M(x) - \bar{M}_{max})\dot{M} & \text{if } M(x) > \bar{M}_{max} \\ 0 & \text{otherwise,} \end{cases} \quad (36)$$

with $\dot{M}(x) = K\dot{x} = KAx + KB\hat{u}$.

The study of the non positivity of $\dot{V}$ is divided into two cases. First we consider $M(x) < \bar{M}_{min}$ and prove that in this case $M(x) > 0$, implying that $\dot{V} < 0$. Second, we analyze the case when $M(x) > \bar{M}_{max}$ and verify that in this case $M(x) < 0$ and then $\dot{V} < 0$, as well.

<u>*Case one*</u> - $M(x) < \bar{M}_{min}$

When $M(x) < \bar{M}_{min}$, $M(x) < M^*$, and consequently $\hat{\hat{u}} > 0$. Then $\hat{u} = \hat{\hat{u}}$ and $\dot{M}(x)$ becomes:

$$\begin{aligned}
\dot{M}(x) &= KAx + KB\hat{\hat{u}} && (37)\\
&= KAx + \underbrace{KBE}_{1} k(-K\hat{A}x + \lambda(M^* - M(x)) && (38)\\
&= KAx - kK\hat{A}x + k\lambda(M^* - M(x))) && (39)\\
&= K\hat{A}x + \Delta_{KA}x - kK\hat{A}x + k\lambda(M^* - M(x)) && (40)\\
&= (1-k)K\hat{A}x + \Delta_{KA}x + k\lambda(M^* - M(x)) && (41)\\
&\geq -|1-k||K\hat{A}|x - |\Delta_{KA}|x + k\lambda(M^* - M(x)) && (42)\\
&\geq -|1-k|rM(x) - sM(x) + k\lambda(M^* - M(x)) && (43)\\
&= -|1-k|rM(x) - sM(x) + k\lambda M^* - k\lambda M(x) && (44)\\
&= k\lambda M^* - (k\lambda + |1-k|r + s)M(x) && (45)\\
&= k\lambda M^* - (k\lambda + \Delta_{ks})M(x) && (46)\\
&= (k\lambda + \Delta_{ks})\left(\frac{k\lambda}{k\lambda + \Delta_{ks}}M^* - M(x)\right) && (47)\\
&= (k\lambda + \Delta_{ks})\left(\bar{M}_{min} - M(x)\right) > 0. && (48)
\end{aligned}$$

The relation between expressions (41) and (42) is due to the fact that every $a \in \mathbb{R}$ satisfies $a \geq -|a|$, whereas the relation between expressions (42) and (43) results from (28) and (29).

<u>*Case two*</u> - $M(x) > \bar{M}_{max}$

Let $M(x) > \bar{M}_{max}$. If $\hat{\hat{u}} < 0$, then $\hat{u} = 0$ and

$$\begin{aligned}
\dot{M}(x) &= KAx && (49)\\
&= -\begin{bmatrix} 0.1\alpha & 0.8\alpha & 0.1\alpha & 100\eta & 100\eta & 100\eta \end{bmatrix} x\\
&\leq 0,
\end{aligned}$$

because all the components of x are nonnegative. If $\hat{\hat{u}} > 0$, then $\hat{u} = \hat{\hat{u}}$ and $\dot{M}(x)$ becomes (see equation (41)):

$$\begin{aligned}
\dot{M}(x) &= (1-k)K\hat{A}x + \Delta_{KA}x + k\lambda(M^* - M(x)) && (50)\\
&\leq |1-k||K\hat{A}|x + |\Delta_{KA}|x + k\lambda(M^* - M(x)) && (51)\\
&\leq |1-k|rM(x) + sM(x) + k\lambda(M^* - M(x)) && (52)\\
&= |1-k|rM(x) + sM(x) + k\lambda M^* - k\lambda M(x) && (53)\\
&= k\lambda M^* - (k\lambda - |1-k|r - s)M(x) && (54)\\
&= k\lambda M^* - (k\lambda - \Delta_{ks})M(x) && (55)\\
&= (k\lambda - \Delta_{ks})\left(\frac{k\lambda}{k\lambda - \Delta_{ks}}M^* - M(x)\right) && (56)\\
&= (k\lambda - \Delta_{ks})\left(\bar{M}_{max} - M(x)\right) < 0, && (57)
\end{aligned}$$

for $k\lambda > |\Delta_{ks}|$.

Thus $\dot{V}(x)$ is indeed nonpositive, provided that the value of the design parameter λ is taken larger than $\frac{|\Delta_{ks}|}{k}$, and by the LaSalle's invariance principle, all system trajectories, $x(t)$, converge to the largest set contained in

$$W = \{x \in \mathbb{R}^n_+ : \dot{V}(x) = 0\}, \quad (58)$$

which is forward-invariant under the closed-loop dynamics. It follows from (36) that $\dot{V}(x) = 0$ either when $u = \tilde{u}$ and ($M(x) = \bar{M}_{min}$ or $M(x) = \bar{M}_{max}$ or $M(x) = \frac{(1-k)K\hat{A}x + \Delta_{KA}x + k\lambda M^*}{k\lambda}$), or when $u = 0$, which implies that $M(x) > M^*$, and $KAx = 0$. So we get

$$\begin{aligned}
W =& I_1 \cup I_2 \cup I_3 \cup I_4 \text{ with} && (59)\\
I_1 =& \{x \in \mathbb{R}^n_+ : M(x) = \bar{M}_{min} \text{ and } \hat{\hat{u}}(x) > 0\} && (60)\\
I_2 =& \{x \in \mathbb{R}^n_+ : M(x) = \bar{M}_{max} \text{ and } \hat{\hat{u}}(x) > 0\} && (61)\\
I_3 =& \{x \in \mathbb{R}^n_+ : M(x) = \frac{(1-k)K\hat{A}x + \Delta_{KA}x}{k\lambda}\\
&\quad + M^* \text{ and } \hat{\hat{u}}(x) > 0\} && (62)\\
I_4 =& \{x \in \mathbb{R}^n_+ : KAx = 0 \text{ and } \hat{u}(x) = 0\}. && (63)
\end{aligned}$$

The set I_4 is not invariant. In fact, if $\hat{u}$ would remain equal to zero, at a certain time instant, $M(x)$ would become smaller than M^*, $\hat{\hat{u}}(x)$ would become positive, and $\hat{u}(x)$ would equal $\hat{\hat{u}}(x)$, so the trajectory $x(t)$ would leave the subset. On the other hand, both I_1, I_2 and I_3 are

subsets of I_M, which is invariant, indeed if $M(x) \leq \bar{M}_{min}$, then $\dot{M}(x) \geq 0$ and if $M(x) \geq \bar{M}_{max}$, then $\dot{M}(x) \leq 0$. Therefore, one may conclude that $M(x)$ converges to (a subset contained in) the interval I_M as previously claimed.

Since the patient BIS response to the administered drug doses $\hat{u}$ is a decreasing function of $M(x)$ (cf. equation (23)), the BIS level converges to the interval:

$$I_{BIS} =]BIS_{min}\ ,\ BIS_{max}[\,, \tag{64}$$

with

$$BIS_{min} = \frac{z_0}{1 + \left(\frac{\bar{M}_{max}}{m_{\rho,\mu}}\right)^{\gamma}} \text{ and} \tag{65}$$

$$\tag{66}$$

$$BIS_{max} = \frac{z_0}{1 + \left(\frac{\bar{M}_{min}}{m_{\rho,\mu}}\right)^{\gamma}}. \tag{67}$$

As expected, the desired steady state value z^* is not achieved, but the patient's BIS remains in a neighborhood of this target value. Moreover, when the errors in the parameters go to 0, and hence s goes to 0 and k goes to 1 (see the remark below), $\bar{M}_{min}$, $\bar{M}_{max}$ and $M(x)$ converge to M^*. This implies that the patient BIS converges to the desired value z^*, which means that the control law is robust with respect to parameter uncertainties. Moreover, as can be seen by expressions (31) and (32), increasing the parameter λ decreases the width of the interval I_M and consequentely the robustness of the controller is also increased.

Remark:

Recall that:

$$k = \frac{\alpha\rho + 300\eta}{\hat{\alpha}\rho + 300\hat{\eta}} \tag{68}$$

$$= \frac{\hat{\alpha}\rho + \Delta_\alpha\rho + 300\hat{\eta} + 300\Delta_\eta}{\hat{\alpha}\rho + 300\hat{\eta}} \tag{69}$$

$$= 1 + \frac{\Delta_\alpha\rho + 300\Delta_\eta}{\hat{\alpha}\rho + 300\hat{\eta}}, \tag{70}$$

thus, if Δ_α and Δ_η converge to zero k clearly converges to the value 1.

V. Simulations

In this section, the performance of the control law (9) under the presence of uncertainties in the parameters on the linear part of the PPM is illustrated by means of simulations. For this purpose, a test patient was considered modeled by a PPM with realistic parameters: $\alpha = 0.068$, $\eta = 0.337$, $\mu = 1.14$, and $\gamma = 4.12$ (see [12]). On the other hand, the control law was tuned with $z_0 = 97.7$ and the design parameters $\lambda = 100$ and $\rho = 600$. The desired reference value for the BIS, z^*, was set to be 50.

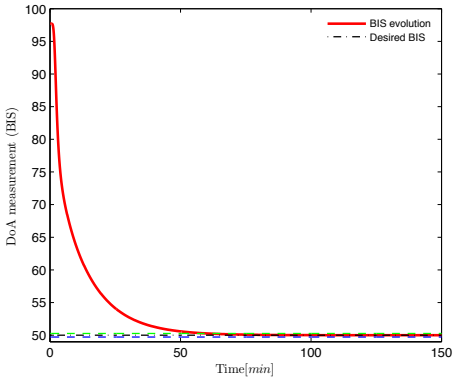

Fig. 1. BIS evolution in the presence of uncertainties, $\hat{\alpha} = \mathbf{0.5}\alpha$, $\hat{\eta} = \mathbf{0.5}\eta$. The reference value for the BIS level was set to be 50.

Figure 1 shows the BIS response of the patient using the controller (16) tuned for estimated parameters $\hat{\alpha} = 0.5\alpha = 0.034$ and $\hat{\eta} = 0.5\eta = 0.1685$. These values correspond to an estimation error of 50%. As theoretically proved, the BIS converged to the interval

$$I_{BIS} =]BIS_{min}\ ,\ BIS_{max}[\,, \tag{71}$$

with $BIS_{min} = 49.7$ and $BIS_{max} = 50.3$. In spite of the error of 50% in the parameters, the interval I_{BIS} is very narrow and the BIS nearly converged to the desired value 50.

The BIS evolution of the patient under the presence of an error of 90% in the estimation of the parameters is illustrated in Fig. 2. In this case, the controller (16) was tuned for estimated parameters $\hat{\alpha} = 1.9\alpha = 0.1292$ and $\hat{\eta} = 1.9\eta = 0.6403$. As in the previous simulation, the BIS of the patient also converged to the interval I_{BIS}, now with $BIS_{min} = 48.1$ and $BIS_{max} = 51.8$. Although the parameter estimates presents an error of 90%, the BIS of the patient also nearly converged to 50.

VI. Conclusion

In this paper, the robustness of the nonlinear control law proposed in [1], in order to control the BIS level of patients by means of simultaneous administration of *propofol* and *remifentanil*, was studied. It was theoretically proven that even in the presence of model uncertainties, the BIS of the patient converges to an interval that contains the desired reference value for the BIS. Moreover, the presented simulations suggest that, under these circumstances, the BIS also converges to a constant value within the expected range. A study of this conjecture is the subject of ongoing research.

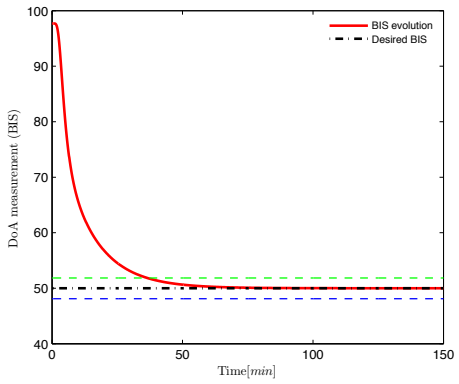

Fig. 2. BIS evolution in the presence of uncertainties, $\hat{\alpha} = \mathbf{1.9}\alpha$, $\hat{\eta} = \mathbf{1.9}\eta$. The reference value for the BIS level was set to be 50

VII. Acknowledgments

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