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Positive state observer for the automatic control of the depth of anesthesia - clinical results ☆

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Abstract

In this paper, a positive state observer is designed for the implementation of a control law proposed for the automatic administration of *propofol* and of *remifentanil* in order to track a desired level for the bispectral index (BIS). The BIS is used as a measure of the depth of anesthesia. It is proved and illustrated by simulations that the controller-observer scheme has a very good performance. This control scheme was implemented, tested and evaluated in real patients during surgical procedures. A set of clinical results are here presented.

Keywords:

Positive systems, control, state observer, DoA, anesthesia.

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1. Introduction

General anesthesia enables a patient to tolerate surgical procedures that would otherwise inflict unbearable pain, potentiate extreme physiologic exacerbations, and result in unpleasant memories. The components of general anesthesia are areflexia (paralysis), hypnosis (unconsciousness and amnesia), and analgesia (absence of any sensation, including pain). The depth of anesthesia (DoA) is related to the intensity of these two latter components and is achieved by the administration of two drugs: a hypnotic and an analgesic. According to several studies (Tirén et al. [1], Grindstaff and Tobias [2], Ekman et al. [3], Wodey et al. [4], Whyte and Booker [5]) the DoA may be measured by means of the bispectral index (BIS). This index is a single dimensionless number, which is computed from the electroencephalogram (EEG) and ranges from 0 (equivalent to EEG silence) to 100 (equivalent to a fully awake and alert state). A BIS value between 40 and 60 is clinically desirable for general anesthesia purposes. This is usually achieved manually by the anesthesiologists. However, due to the high complexity of this procedure an automated system for drug administration would be a good support for the clinicians (see Meijler [6]). The development of controllers for the automatic administration of drugs in patients has deserved the attention of several researchers and led to a number of contributions and controllers namely a predictive control in Ionescu et al. [7], an adaptive model-based controller in Mortier et al. [8] and Simanski et al. [9], a PID in Padula et al. [10], a neural in Ortolani et al. [11], a fuzzy logic in Shieh et al. [12], a model predictive control in Sawaguchi et al. [13] and Chang et al. [14], but in these contributions the control of the DoA is not fully automatic. More concretely, the

administration of the hypnotic is made automatically, but the administration of the analgesic is manually made by a clinician. A detailed introduction to anesthesia as a control problem together with a good overview of the state of the art can be found in Lemos et al. [15] and Chang et al. [16].

In Nogueira et al. [17] a control law was proposed for the BIS tracking of patients, during general anesthesia, by means of the automatic administration of both the hypnotic (*propofol*) and the analgesic (*remifentanil*). Moreover, this controller has the advantage of allowing different combinations of the two drugs in order to obtain the same value for the BIS level, and allows the changing of the desired reference value for the BIS during the surgical procedure. However the corresponding control law makes use of the state of the patient, which is not completely available for measurement. Therefore the controller cannot be directly implemented in the operation room. To overcome this drawback, in this paper, we introduce a state observer in order to estimate the state of the patient model based on the measurements of the BIS response and the amounts of administered drugs. This observer, together with the controller proposed in [17], was used in clinical environment under the supervision of an anesthetist, and the corresponding results are presented here. These results encourage the use of the proposed controller-observer scheme for the control of the depth of anesthesia.

The structure of this paper is as follows. Section 2 is devoted to the explanation of the BIS model, while the control law is presented in Section 3. In Section 4 a positive state observer is proposed and its performance is

illustrated in Section 5. Clinical case are presented in Section 6. Conclusions are drawn in Section 7.

2. Model description

The patient BIS level obtained by means of the administration of the hypnotic *propofol* and of the analgesic *remifentanil* may be modeled by a new Wiener model recently introduced in the literature Silva et al. [18] and known as the 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:

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

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

respectively, where α and η are patient dependent parameters, without any explicit physiological meaning, k_1, k_2, k_3 and l_1, l_2, l_3 are adimensional constants whose values were identified in Silva et al. [18] from a real patient database, as: $k_1 = 10$, $k_2 = 9$, $k_3 = 1$, $l_1 = 3$, $l_2 = 2$, $l_3 = 1$. The complex functions $u^p(s)$ 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 Minto et al. [19], is approximated in Silva et al. [18] by the nonlinear equation:

$$z(t) = \frac{97.7}{1 + U^{\gamma}}, \tag{3}$$

where $U = \mu \frac{c_e^p}{EC_{50}^p} + \frac{c_e^r}{EC_{50}^r}$, and μ and γ are patient dependent parameters, without any physiological meaning, 97.7 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 in isolation. 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 Mendonça et al. [20].

The PPM may be also represented by the following state space representation:

$$\begin{cases} \dot{x}(t) & = Ax(t) + Bu(t) \\ \begin{bmatrix} c_e^p(t) \\ c_e^r(t) \end{bmatrix} & = \begin{bmatrix} 0 & 0 & 1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 1 \end{bmatrix} x(t) \\ U(t) & = Cx(t) \\ z(t) & = \dfrac{97.7}{1 + U^{\gamma}}, \end{cases} \tag{4}$$

where

$$
C = \begin{bmatrix} 0 & 0 & 0.1\mu & 0 & 0 & 100 \end{bmatrix},
$$

$$
A = \begin{bmatrix} A^p & 0 \\ 0 & A^r \end{bmatrix}, \quad B = \begin{bmatrix} B^p & 0 \\ 0 & B^r \end{bmatrix},
$$

$$
A^p = \begin{bmatrix} -10\alpha & 0 & 0 \\ 9\alpha & -9\alpha & 0 \\ 0 & \alpha & -\alpha \end{bmatrix}, \quad A^r = \begin{bmatrix} -3\eta & 0 & 0 \\ 2\eta & -2\eta & 0 \\ 0 & \eta & -\eta \end{bmatrix}, \tag{5}
$$

$$
B^p = \begin{bmatrix} 10\alpha \\ 0 \\ 0 \end{bmatrix}, \quad B^r = \begin{bmatrix} 3\eta \\ 0 \\ 0 \end{bmatrix}.
$$

This state space model is more suited to model based control, since it has a reduced number of parameters to be identified. However, contrary to what happens with PK/PD models, most of the state components lack a physiological meaning. Nevertheless, model (4)-(5) exhibits a compartmental structure, which has the advantage of allowing the use of the positive control law defined in the next section.

3. Controller description

The nonlinear controller presented in Nogueira et al. [17] was designed for the automatic administration of *propofol* and of *remifentanil* in order to control the BIS level of a patient. This control law, which results from a combination

of a linear controller with a positivity constraint for the drug doses, is defined by:

$$u(t) = \begin{bmatrix} u^p(t) \\ u^r(t) \end{bmatrix} = \begin{bmatrix} max(0, \tilde{u}^p(t)) \\ max(0, \tilde{u}^r(t)) \end{bmatrix}, \tag{6}$$

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

$$\tilde{u}(t) = \begin{bmatrix} \tilde{u}^p(t) \\ \tilde{u}^r(t) \end{bmatrix} = E\left(-KAx(t) + \lambda(M^* - Kx(t))\right), \tag{7}$$

and

$$E = \begin{bmatrix} \rho_1 \\ \rho_2 \end{bmatrix} \frac{1}{\alpha\rho_1 + 300\eta\rho_2}, \tag{8}$$

$$M^* = \frac{3(0.1\rho_1 + 100\rho_2)}{0.1\mu\rho_1 + 100\rho_2} \left(\frac{97.7}{z^*} - 1\right)^{\frac{1}{\gamma}}, \tag{9}$$

$$K = \begin{bmatrix} 0.1 & 0.1 & 0.1 & 100 & 100 & 100 \end{bmatrix}, \tag{10}$$

with ($\rho_1 \geq 0$ and $\rho_2 = 1$) or ($\rho_1 = 1$ and $\rho_2 \geq 0$). In (9), z^* is the desired BIS level, and λ, ρ_1 and ρ_2 are positive design parameters. The parameter λ does not affect the achieve steady state value but does influence the convergence speed to the desired reference value. The parameters ρ_1 and ρ_2 do not affect the tracking performance. When $\rho_1 = 1$ the parameter ρ_2 can be interpreted

as the proportion between the doses of *remifentanil* and *propofol*, and when $\rho_2 = 1$ the parameter ρ_1 can be interpreted as the proportion between the doses of *propofol* and *remifentanil*. This allows choosing ρ_1 and ρ_2 according to clinical criteria. In fact, this type of reasoning can be also followed for the simultaneous administration of any other two drugs.

In the particular case of the administration of *propofol* and *remifentanil* to induce depth of anesthesia, it is more convenient to consider $\rho_1 = 1$ and to define $\rho := \rho_2 \geq 0$; this corresponds to the case where the dose of *propofol* is not constantly zero, which is more in accordance with clinical practice. The case $\rho_2 = 1$ and $\rho := \rho_1 \geq 0$ can be dealt with in a completely analogous way.

For more details about this controller and its tracking properties, the reader is referred to Nogueira et al. [17].

4. State Observer

To control the DoA of a patient in the previous section, we assumed that all the state components of the model could be measured. However this does not happen in practice. In order to overcome this handicap, here, an observer Ω is designed to estimate the states of the PPM, by observing the BIS of a real patient and the administered doses of *propofol* and *remifentanil*.
Consider the PPM, as described in (4)

$$\begin{cases} \dot{x}(t) = Ax(t) + Bu(t) \\ U(t) = Cx(t) = \begin{bmatrix} 0 & 0 & 0.1\mu & 0 & 0 & 100 \end{bmatrix} x \\ z(t) = \frac{z_0}{1+U^\gamma}, \end{cases} \tag{11}$$

The observability matrix of the PPM has rank 6; therefore the state x is completely observable from the input u and the output $U(t)$. This allows to design an observer with gain L for the state of this model. However, instead of using the output $U(t)$ of the model, we estimate the state from the real BIS response of a patient, from which a value of the real combined drug potency, $U_{patient}(t)$, can be computed by inversion of the Hill equation. Due to model misfit and to the presence of noise in the measurement of the BIS level, the values of $U_{patient}(t)$ and $U(t)$ do not coincide. Letting

$$\varepsilon(t) = U_{patient}(t) - U(t) \tag{12}$$

the PPM state observer based on the measurement of the patient BIS level is described by the following equations:

$$\begin{cases} \dot{x}(t) = Ax(t) + Bu(t) \\ U(t) = Cx(t) \\ U_{patient}(t) = Cx(t) + \varepsilon(t) \\ \dot{\tilde{x}}(t) = (A - LC)\tilde{x}(t) + Bu(t) + LU_{patient}(t), \end{cases} \tag{13}$$

where $\tilde{x}$ is the (not necessarily positive) estimate of the state.
Denoting the estimation error by $e = (x - \tilde{x})$ one has that:

$$\dot{e}(t) = (A - LC)e(t) - L\varepsilon(t). \tag{14}$$

Moreover, $e(0) = 0$, because when the process starts the state $x(0)$ of the PPM is zero (as no drugs were administered) and the initial condition $\tilde{x}(0)$ for the state estimate is set to zero.

Due to the stability of $A - LC$, if $|\varepsilon(t)|$ is bounded, so is $||e(t)||$. If the patient is well modeled by the PPM we may assume that this is the case, i.e., $|\varepsilon(t)| < \bar{\varepsilon}$, for some small value $\bar{\varepsilon}$, which implies that $||e(t)|| \leq \bar{e}$, with $\bar{e} = \|g\|_1 \bar{\varepsilon}$, $g(\tau) = e^{(A-LC)\tau} L$, and $\|g\|_1 := \int_0^\infty g(\tau) d\tau$.

Now, since the state of the PPM is always positive, instead of taking the estimate $\tilde{x}$, the positive estimate $\hat{x}(t) = max\{0,\ \tilde{x}(t)\}$ is considered, where the maximum is taken componentwise. Note that $\|x - \hat{x}\| \leq \|x - \tilde{x}\| \leq \bar{e}$, because $\|x - \hat{x}\| = \sqrt{\sum_{i=1}^{6} (x_i - \hat{x}_i)^2}$ and $x_i - \hat{x}_i \leq x_i - \tilde{x}_i$, since, if $\tilde{x}_i < 0$ then $\hat{x}_i = 0$ and $x_i - \hat{x}_i = x_i < x_i - \tilde{x}_i$. If $\tilde{x}_i \geq 0$ then $\hat{x}_i = \tilde{x}_i$ and $x_i - \hat{x}_i = x_i - \tilde{x}_i$.

When instead of the state x the estimate $\hat{x}$ is used in the control law (7), a control input $\hat{u}(t)$ is obtained, which is described by the following expressions:

$$\hat{u}(t) = max(0, \hat{\tilde{u}}(t)), \tag{15}$$

with

$$\begin{aligned} \hat{\tilde{u}}(t) &= \tilde{u}(t) + \begin{bmatrix} 1 \\ \\ \rho \end{bmatrix} (KAe(t) + \lambda Ke(t)) \frac{1}{\alpha + 300\eta\rho}, \\ &= \tilde{u}(t) + \bar{u}(t), \end{aligned} \tag{16}$$

where $\lambda > 0$ and

$$\bar{u}(t) = \begin{bmatrix} 1 \\ \rho \end{bmatrix} (KAe(t) + \lambda Ke(t)) \frac{1}{\alpha + 300\eta\rho} \tag{17}$$

$$= Re(t), \tag{18}$$

with $R = \begin{bmatrix} 1 \\ \rho \end{bmatrix} \frac{1}{\alpha + 300\eta\rho} K (A + \lambda I_n)$.

As will be proved next, the error $\Delta u(t) = u(t) - \hat{u}(t)$ in the computed drug doses is bounded. For this purpose we consider four different cases separately.

Case one - Both $\tilde{\mathbf{u}}(\mathbf{t})$ and $\hat{\tilde{\mathbf{u}}}(\mathbf{t})$ are negative

When $\tilde{u}(t)$ and $\hat{\tilde{u}}(t)$ are both negative, $u(t) = \hat{u}(t) = 0$, then $\Delta u(t) = 0$, which means that $\hat{u}(t)$ presents no errors.

Case two - Both $\tilde{\mathbf{u}}(\mathbf{t})$ and $\hat{\tilde{\mathbf{u}}}(\mathbf{t})$ are positive

When $\tilde{u}(t)$ and $\hat{\tilde{u}}(t)$ are both positive, the error $\Delta u(t)$ is given by:

$$\Delta u(t) = -Re(t), \tag{19}$$

and $\|\Delta u(t)\|$ is bounded by:

$$\|\Delta u(t)\| \leq \|-R\| \, \|e(t)\| \tag{20}$$

$$\leq \|R\| \, \bar{e}, \tag{21}$$

where the notation $v < w$, for two vectors $v = \begin{bmatrix} v_1 \\ \vdots \\ v_j \end{bmatrix}$ and $w = \begin{bmatrix} w_1 \\ \vdots \\ w_j \end{bmatrix}$, means that $v_i < w_i$, for $i = 1 \cdots j$.

Case three - $\tilde{\mathbf{u}}(\mathbf{t}) < \mathbf{0}$ and $\hat{\tilde{\mathbf{u}}}(\mathbf{t}) > \mathbf{0}$

In this case $u(t) = 0$ and $\hat{u}(t) = \hat{\tilde{u}}(t) > 0$.

Since $\hat{\tilde{u}}(t) = \tilde{u}(t) + \bar{u}(t)$, one has that

$$0 < \hat{\tilde{u}}_j(t) = \tilde{u}_j(t) + \bar{u}_j(t) < \bar{u}_j(t), \qquad j = 1, 2. \tag{22}$$

Thus,

$$\begin{aligned} \|\Delta u(t)\| &= \|u(t) - \hat{u}(t)\| && (23)\\ &= \left\|0 - \hat{\tilde{u}}(t)\right\| && (24)\\ &= \left\|\hat{\tilde{u}}(t)\right\| && (25)\\ &= \sqrt{\sum_{j=1}^{2} (\hat{\tilde{u}}_j(t))^2} && (26)\\ &< \sqrt{\sum_{j=1}^{2} (\bar{u}_j(t))^2} && (27)\\ &= \|\bar{u}(t)\| && (28)\\ &= \|Re(t)\| && (29)\\ &\leq \|R\|\, \bar{e}. && (30) \end{aligned}$$

Case four - $\tilde{\mathbf{u}}(\mathbf{t}) > \mathbf{0}$ and $\hat{\tilde{\mathbf{u}}}(\mathbf{t}) < \mathbf{0}$

In this case $u(t) = \tilde{u}(t)$, $\hat{u}(t) = 0$, and $\Delta u(t) = \tilde{u}(t)$.
Since $\hat{\tilde{u}}(t) = \tilde{u}(t) + \bar{u}(t) < 0$, one has that

$$0 < \tilde{u}_j < -\bar{u}_j, \qquad j = 1, 2, \tag{31}$$

and hence

$$\begin{aligned} \|\Delta u(t)\| &= \|\tilde{u}(t)\| && (32)\\ &= \sqrt{\sum_{j=1}^{2} (\tilde{u}_j(t))^2} && (33)\\ &< \sqrt{\sum_{j=1}^{2} (-\bar{u}_j(t))^2} && (34)\\ &= \|\bar{u}(t)\| && (35)\\ &\leq \|R\|\, \bar{e}. && (36) \end{aligned}$$

This proves that the norm of the error, $\|\Delta u\|$, of the computed drug doses to be administered is bounded by $\bar{u}_{\bar{e}} := \|R\|\, \|g\|_1 \bar{\varepsilon}$. The effect that this error produces in the controlled BIS of a patient is analyzed next.
In a first step, the influence of the input error Δu on the model BIS is studied. Recalling the first two equations of (13), the model response $\hat{U}(t)$ to the input $\hat{u}(t) = u(t) - \Delta u(t)$ is given by:

$$\hat{U}(t) = Ce^{At}x(0) + \int_0^t Ce^{A\tau}B\hat{u}(t-\tau)d\tau, \tag{37}$$

whereas the model response $U(t)$ to the input $u(t)$ is given by:

$$U(t) = Ce^{At}x(0) + \int_0^t Ce^{A\tau}Bu(t-\tau)d\tau. \tag{38}$$

Thus, the error $\Delta U(t) = U(t) - \hat{U}(t)$ is:

$$\Delta U(t) = \int_0^t Ce^{A\tau}B(u(t-\tau) - \hat{u}(t-\tau))d\tau \tag{39}$$

$$= \int_0^t Ce^{A\tau}B\Delta u(t-\tau)d\tau. \tag{40}$$

Consequently, since $\|\Delta u(t-\tau)\| < \|R\|\,\bar{e} = \|R\|\,\|g\|_1\bar{\varepsilon}$,

$$|\Delta U(t)| \leq \|h\|_1\,\|R\|\,\|g\|_1\bar{\varepsilon}, \tag{41}$$

with $h(\tau) = Ce^{A\tau}B$, i.e.,

$$|U(t) - \hat{U}(t)| \leq \Lambda\bar{\varepsilon}, \tag{42}$$

for $\Lambda = \|h\|_1\,\|R\|\,\|g\|_1$.

Since $\lim_{t\to\infty} U(t) = U^*$, for sufficiently large t, we may assume that $|U^* - \hat{U}(t)| \leq \Lambda\bar{\varepsilon}$.

As $\hat{U}(t) = \hat{U}_{patient}(t) - \varepsilon(t)$, where $\hat{U}_{patient}(t)$ is the patient combined drug potency response corresponding to the administration of the dose $\hat{u}(t)$, one concludes that

$$|U^* - \hat{U}_{patient}(t) + \varepsilon(t)| \leq \Lambda\bar{\varepsilon}, \tag{43}$$

i.e.,

$$U^* + \varepsilon(t) - \Lambda\bar{\varepsilon} \quad \leq \quad \hat{U}_{patient} \quad \leq \quad U^* + \varepsilon(t) + \Lambda\bar{\varepsilon} \tag{44}$$

$$U^* - |\varepsilon(t)| - \Lambda\bar{\varepsilon} \quad \leq \quad \hat{U}_{patient} \quad \leq \quad U^* + |\varepsilon(t)| + \Lambda\bar{\varepsilon} \tag{45}$$

$$U^* - \bar{\varepsilon} - \Lambda\bar{\varepsilon} \quad \leq \quad \hat{U}_{patient} \quad \leq \quad U^* + \bar{\varepsilon} + \Lambda\bar{\varepsilon} \tag{46}$$

$$U^* - (1+\Lambda)\bar{\varepsilon} \quad \leq \quad \hat{U}_{patient} \quad \leq \quad U^* + (1+\Lambda)\bar{\varepsilon}. \tag{47}$$

Since the patient BIS response to $\hat{U}_{patient}$, $\hat{z}_{patient}$, is a decreasing function of $\hat{U}_{patient}$, one has that

$$f(U^* + (1+\Lambda)\bar{\varepsilon}) \ \leq \ \hat{z}_{patient} \ \leq \ f(U^* - (1+\Lambda)\bar{\varepsilon}), \tag{48}$$

with

$$f(U) = \frac{z_0}{1+U^\gamma}. \tag{49}$$

Since

$$f(U^* + \Delta) \simeq f(U^*) + \frac{df}{dU}|_{U=U^*}\Delta \tag{50}$$

$$= z^* + \frac{df}{dU}|_{U=U^*}\Delta, \tag{51}$$

(48) implies that

$$z^* - \frac{\gamma z_0 (U^*)^{\gamma-1}}{(1+(U^*)^\gamma)^2}(1+\Lambda)\bar{\varepsilon} \quad \leq \ \hat{z}_{patient} \ \leq \quad z^* + \frac{\gamma z_0 (U^*)^{\gamma-1}}{(1+(U^*)^\gamma)^2}(1+\Lambda)\bar{\varepsilon}. \tag{52}$$

This means that when our proposed control law is combined with a state observer based on the BIS patient measurements, the patient BIS level converges to the interval

$$I = \left]z^* - \frac{\gamma z_0 (U^*)^{\gamma-1}}{(1+(U^*)^\gamma)^2}(1+\Lambda)\bar{\varepsilon}\,,\; z^* + \frac{\gamma z_0 (U^*)^{\gamma-1}}{(1+(U^*)^\gamma)^2}(1+\Lambda)\bar{\varepsilon}\right[. \qquad (53)$$

As expected, the desired steady state value z^* is not achieved, but the patient BIS remains in a neighborhood of this target value, whose radius decreases with $\bar{\varepsilon}$. Thus, if the modeling error and measurement noise are sufficiently small, the patient achieved BIS level is close to z^*.

5. Observer Performance

Here, the performance of the DoA control of a simulated patient using an observer in order to estimate the state of the corresponding model, as previously explained (see equation (13)), is illustrated by simulations. For this purpose, the control law is applied to a simulated patient that was set up based on the data of a real patient (Patient 13 of the database presented in Appendix B), a woman, with 68 years of age, a height of 158 cm, and 113 Kg who was subject to general anesthesia under *propofol* and *remifentanil* administration during a breast surgery. The DoA was monitored by the BIS and was manually controlled around clinically accepted values by the anesthetist. Alaris GH pumps were used to administer both drugs, *propofol* and *remifentanil*. Infusion rates, BIS values and other physiological variables were acquired every five seconds ([20]).

For this patient, a PK/PD Wiener model was obtained as follows. The

linear part was modeled according to [21], [22], and [23] based on the relevant patient characteristics. This corresponding model is summarized in Appendix A, in equation (A.1). The nonlinear part was taken to coincide with the generalized Hill equation (3) and the corresponding parameters γ and μ were identified in [20] from the surgery data, being given by: $\gamma = 1.09$ and $\mu = 2.40$.

The controller (7) is first tuned assuming that the simulated patient is modeled by the parsimonious parameter Wiener model of [18], with parameters $\alpha = 0.0759$, $\eta = 0.5825$, $\gamma = 1.09$, and $\mu = 2.40$. These values are the average of the values for α, η, γ, and μ taken from a bank of identified values for eighteen real patients obtained in the work developed in [20] (see Table B.2).

The matrix L of the observer, described in (13), was considered to be:

$$L = \begin{bmatrix} -0.5720 \\ 21.1536 \\ -2.2715 \\ 0.0013 \\ -0.0040 \\ 0.0156 \end{bmatrix}, \tag{54}$$

so that the eigenvalues of $A - LC$ are approximately 30% faster then the ones of A. In the following simulations the BIS evolution of the patient is

illustrated in the presence of Gaussian white noise, with zero mean and standard deviation $\sigma_{noise} = 3$. In order to improve the performance of the control procedure in the presence of noise, a filter was applied to the noisy BIS signal.

In Figures 1 and 2 the evolution of the DoA of the simulated patient during 120 min is illustrated. In Fig. 1 the desired value for the BIS was set to be 50 during the whole procedure and in Fig. 2 the desired value for the BIS was set to be 50 from the beginning till $t = 50\, min$, then was set to be 40 from $t = 50\, min$ till $t = 120\, min$, and finally was again set to be 50 from then on. As we can see, in both cases the behavior of the controlled output of the patient is clinically acceptable.

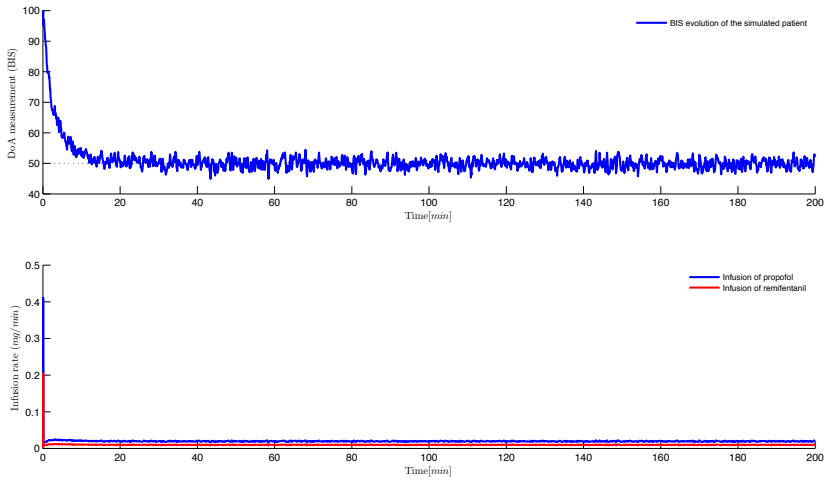

Figure 1: Top graph: BIS evolution, in the presence of noise of a simulated patient, using an observer. The reference value for the BIS level was set to be 50. Bottom graph: Administered doses of *propofol* and of *remifentanil*.

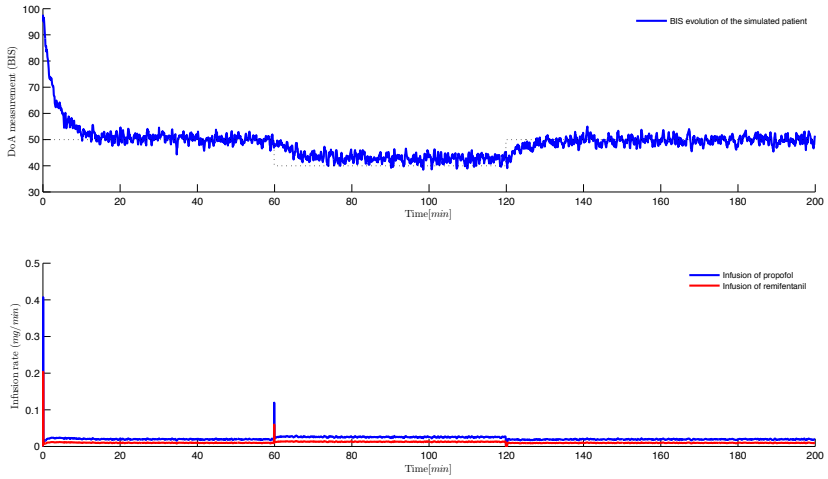

Figure 2: Top graph: BIS evolution, in the presence of noise of a simulated patient, using an observer and assuming changes in the reference profiles ($z^* = 50$ from the beginning till $t = 50\,min$, $z^* = 40$ from $t = 50\,min$ till $t = 120\,min$, and $z^* = 50$ from then on). Bottom graph: Administered doses of *propofol* and of *remifentanil*.

6. Clinical Cases

The control law (6) was integrated in the Galeno platform ([24]) and was used for the automatic administration of *propofol* and *remifentanil* to real patients during surgical procedures. This platform was developed in the framework of the portuguese funding agency (FCT) project Galeno, and incorporates several identification and control procedures for automation in anesthesia. This supervisory automatic drug administration system Galeno is currently implemented in a surgery room at the ULSM (Pedro Hispano

Hospital, Matosinhos, Portugal), working under medical surveillance, where the data here presented were collected. Manual drug administration is ready to be switched on both under clinical decision or in case of failure of the automatic controller. The results obtained in the surgery room are presented in this section.

Patient 1, a man of 86 years of age, 50kg of weight and 1.65m of height was subject to general anesthesia, for a total gastrectomy. Patient 2, a man of 85 years of age, 80kg of weight and 1.72m of height was subject to general anesthesia, for a partial gastrectomy. The DoA was monitored by the BIS and Alaris GH pumps were used for both *propofol* and *remifentanil*. Infusion rates, BIS values and other physiological variables were acquired with a sampling time of five seconds. The neuromuscular blockade (NMB) was controlled manually by bolus administration.

The controller (7) was tuned assuming that the patients were modeled by the parsimonious parameter Wiener model (PPM), always with the same parameters $\alpha = 0.0759$, $\eta = 0.5825$, $\gamma = 1.09$, and $\mu = 2.40$. These values are the average of the values for α, η, γ, and μ taken, as usual, from the bank of identified values of Table B.2 (see Appendix B). The state of the PPM used in the control law was estimated from the patient BIS, by means of an observer, as described in (13), with matrix L as in (54).

Notice that, the BIS signal is measured by an electroencephalogram that also detects muscle activity. Due to this fact, the measurement values may

present outliers and high frequency noise, since they may be influenced by more traumatic surgical procedures and/or by a decrease of the patient's neuromuscular blockade level. Therefore, in clinical practices some variations of the BIS around the pre-specified reference value is accepted.

Due to clinical constraints associated to the anesthetic procedures adjusted to the patient and also for safety reasons, the controller was not started at the beginning of the anesthetic procedure. The time for initialization of the automatic controller was defined by the anesthetists and is marked with a red arrow in the following figures. In some moments, we may notice the existence of a big tracking error in the BIS signal. This was due to the fact that the effect of muscle relaxants was decreasing, which led to "false" high BIS values. In these cases, after the administration of an extra bolus of a muscle relaxant the BIS values decreased almost immediately.

On the other hand, the lower BIS observed during some periods results from interruptions of the surgery due to a variety of clinical reasons. When the surgery procedure is more invasive, the BIS signal increases, so the controller also increases the administered drug doses. It turns out that the reference tracking is highly dependent on the invasive level of the surgery procedure. This relevant issue should be taken into account whenever the performance of automatic control is evaluated. A similar situation occurs during manual clinical control of the DoA.

In these two patients a change of the reference value for the BIS was suggested

by the anesthesiologist due to the overall physiological evaluation of the patients. As it can be observed, the automatic controller presented an adequate clinical behavior leading to the desired reference tracking. In patient 1, the proportion (ρ) between the administered drug doses had to be changed, due to clinical indication (this instant is marked with a red row in the graph of the drug doses of Fig. 3). This happened because although the BIS signal was within the recommended value, the anesthesiologist considered that the patient was probably in pain due to sudden changes in the blood pressure and in the heart rate. Thus it was necessary to increase the administered dose of the analgesic *remifentanil* without changing the BIS value. This fact was achieved by increasing the proportion between the doses of *remifentanil* and *propofol*, which corresponded to increasing the parameter ρ. This change may be observed by looking at the administered drug doses presented in Fig. 3, where the initial proportion between *remifentanil* and *propofol* is clearly lower than the final one. This situation highlights the controller ability of allowing different combinations of drug doses to obtain the same reference tracking value, dealing with a variety of clinical problems.

The proposed BIS controller performed in practice as theoretically expected leading to a good clinical performance under a variety of clinical situations, patients and surgery characteristics. The positive global assessment of the anesthesiologists concerning the controller features constitutes a strong encouragement to use it regularly in clinical practice.

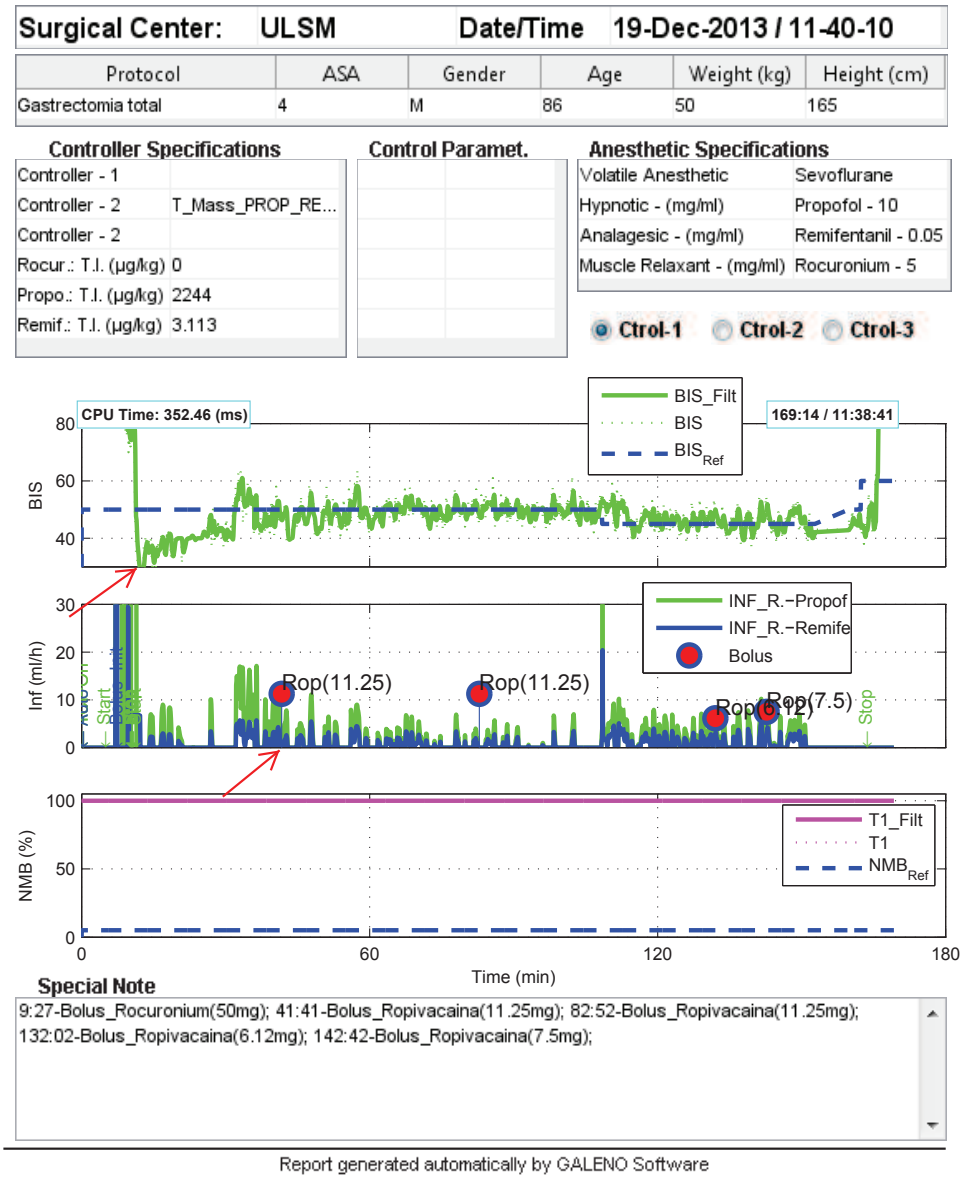

Figure 3: Printout of the final report of the clinical case of the patient 1. The dashed blue row on the top graph corresponds to the desired reference value for the BIS. The top red arrow marks the initialization of the automatic control. The bottom red arrow marks the increasing of the proportion between *remifentanil* and *propofol*. The NMB value is not presented, because it was manually controlled.

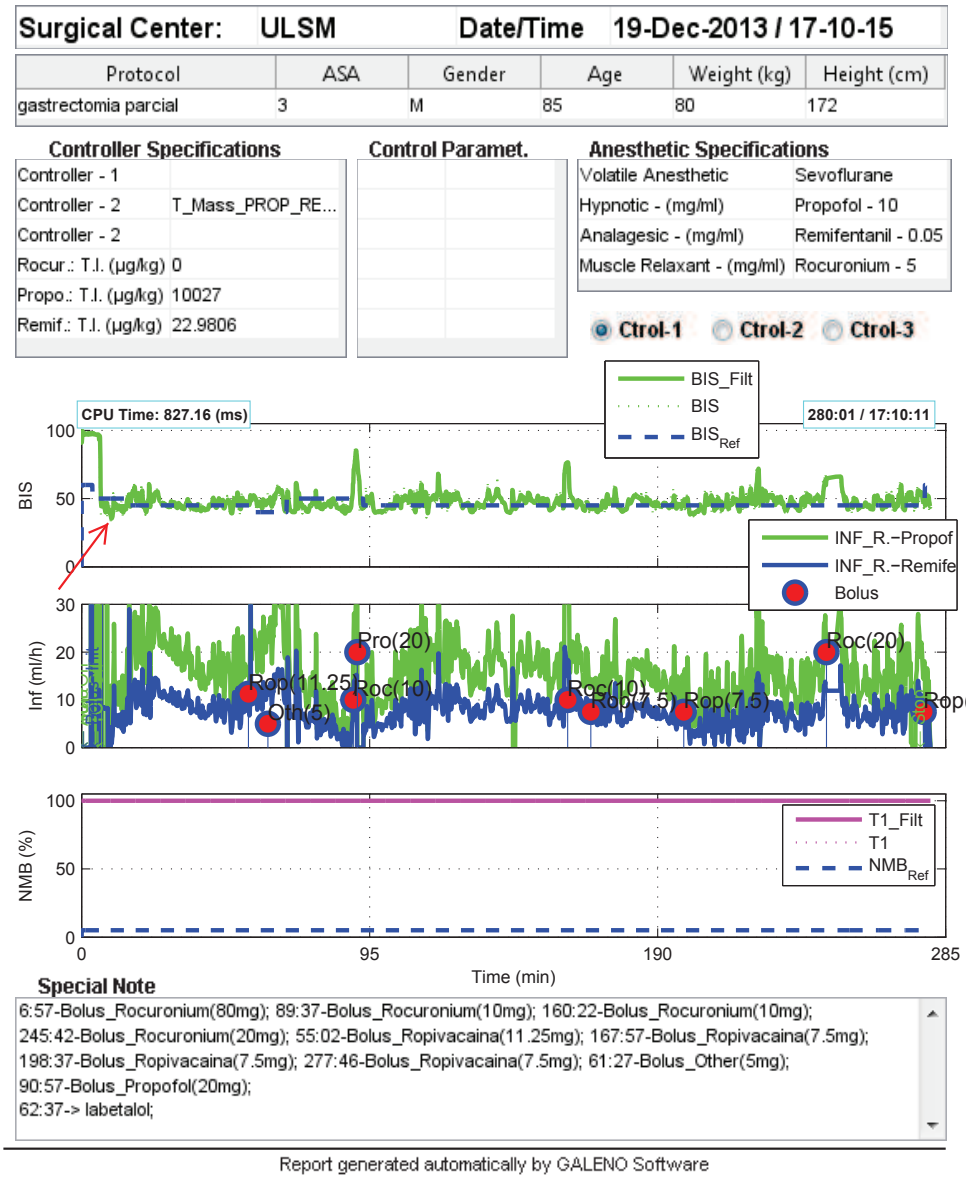

Figure 4: Printout of the final report of the clinical case of the patient 2. The dashed blue row on the top graph corresponds to the desired reference value for the BIS. The top red arrow marks the initialization of the automatic control. The NMB value is not presented, because it was manually controlled.

7. Conclusion

Here, a positive state observer was proposed in order to implement a control law developed for the administration of *propofol* and of *remifentanil* for tracking a desired BIS level. It was proved and illustrated by simulations that the controller-observer scheme has a very good performance as the BIS converges to a value in a neighborhood of the desired BIS level.

This controller-observer scheme was implemented and tested for a set of patients during surgical procedures. This testing showed that the performance of the proposed scheme was in accordance with the theoretical results presented here. Good clinical results were achieved under a variety of clinical situations, patients and surgery characteristics. Due to its satisfactory performance the anesthesiologists consider it as a potential candidate for integration into a personalized drug administration system in general anesthesia.

Appendix A. PK/PD Model Description

The effect concentration of *propofol* (c_e^p) and of *remifentanil* (c_e^r) can be modeled by the PK/PD state space model (see Bailey and Haddad [25], Marsh et al. [21], Minto et al. [22], and Schnider et al. [23] - These corresponding models are summarized in equation (1) of Ionescu et al. [26]):

$$\begin{cases} \dot{x^i} = A^i x^i + B^i u^i \\ c_e^i = \begin{bmatrix} 0 & 0 & 0 & 1 \end{bmatrix} x^i, \end{cases} \tag{A.1}$$

where

$$i = p, r,$$

$$x^i = \begin{bmatrix} x_1^i \\ x_2^i \\ x_3^i \\ x_4^i \end{bmatrix},$$

$$A^i = \begin{bmatrix} -k_{10} - k_{12} - k_{13} & k_{21}V_2/V_1 & k_{31}V_3/V_1 & 0 \\ k_{12}V_1/V_2 & -k_{21} & 0 & 0 \\ k_{13}V_1/V_3 & 0 & -k_{31} & 0 \\ k_{e0} & 0 & 0 & -k_{e0} \end{bmatrix}, \tag{A.2}$$

$$B^i = \begin{bmatrix} \frac{1}{V_1} \\ 0 \\ 0 \\ 0 \end{bmatrix}$$

Parameters related with the infusion of *propofol*.

$$V_1 = 4.27\ [l]$$

$$V_2 = 18.9 - 0.391(age - 53)\ [l]$$

$$V_3 = 238\ [l]$$

$$C_1 = 1.89 + 0.0456(weight - 77) - 0.0681(lbm - 59) + 0.0264(height - 177)\ [l/m]$$

$$C_2 = 1.29 - 0.024(age - 53)\ [l/m]$$

$$C_3 = 0.836\ [l/m]$$

$$K_{e0} = 0.456\ [min^{-1}]$$

$$K_{10} = \frac{C_1}{V_1}\ [min^{-1}]$$

$$K_{12} = \frac{C_2}{V_1}\ [min^{-1}]$$

$$K_{13} = \frac{C_3}{V_1}\ [min^{-1}]$$

$$K_{21} = \frac{C_2}{V_2}\ [min^{-1}]$$

$$K_{31} = \frac{C_3}{V_3}\ [min^{-1}]$$

Parameters related with the infusion of *remifentanil*.

$$
\begin{aligned}
V_1 &= 5.1 - 0.0201(age - 40) + 0.072(lbm - 55)\ [l] \\
V_2 &= 9.82 - 0.0811(age - 40) + 0.108(lbm - 55)\ [l] \\
V_3 &= 5.42\ [l] \\
C_1 &= 2.6 - 0.0162(age - 40) + 0.0191(lbm - 55)\ [l/m] \\
C_2 &= 2.05 - 0.0301(age - 40)\ [l/m] \\
C_3 &= 0.076 - 0.00113(age - 40)\ [l/m] \\
K_{e0} &= 0.595 - 0.007(age - 40)\ [min^{-1}] \\
K_{10} &= \frac{C_1}{V_1}\ [min^{-1}] \\
K_{12} &= \frac{C_2}{V_1}\ [min^{-1}] \\
K_{13} &= \frac{C_3}{V_1}\ [min^{-1}] \\
K_{21} &= \frac{C_2}{V_2}\ [min^{-1}] \\
K_{31} &= \frac{C_3}{V_3}\ [min^{-1}]
\end{aligned}
$$

The lean body mass (lbm) for women and men are computed, respectively, by the equations

$$1.07 weight - 148 \frac{weight^2}{height^2} \quad \text{and} \quad 1.1 weight - 128 \frac{weight^2}{height^2}. \tag{A.3}$$

Appendix B. Database

This database was courteously provided by Galeno project (http://www2.fc.up.pt/galeno/).

The parameters presented in Table B.2 were identified in Mendonça et al. [20].

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Table B.1: Patient features

	Gender	**Age**	**Height (cm)**	**Weight (kg)**
Patient 1	F	56	160	88
Patient 2	F	48	158	52
Patient 3	F	51	165	55
Patient 4	F	56	160	65
Patient 5	F	64	146	60
Patient 6	F	59	159	110
Patient 7	F	29	163	59
Patient 8	F	45	155	58
Patient 9	F	51	163	55
Patient 10	F	32	172	56
Patient 11	F	68	160	64
Patient 12	F	50	161	68
Patient 13	F	68	158	113
Patient 14	F	70	161	78
Patient 15	F	73	160	75
Patient 16	F	34	162	57
Patient 17	F	43	155	62
Patient 18	F	66	155	74

Table B.2: PPM parameters

	α	η	γ	μ
Patient 1	0.0667	0.3989	1.7695	2.1502
Patient 2	0.0874	0.0670	0.9365	4.7014
Patient 3	0.0693	0.0482	2.8186	1.1700
Patient 4	0.0590	0.0425	2.7594	1.4077
Patient 5	0.0489	0.1269	1.5627	1.4171
Patient 6	0.0677	0.3373	4.1247	1.1444
Patient 7	0.0737	0.2793	0.7812	0.8986
Patient 8	0.0860	0.0212	0.9780	1.4203
Patient 9	0.0701	0.2837	1.0956	1.2164
Patient 10	0.1041	0.1038	1.2165	1.9085
Patient 11	0.0343	3.5768	1.7097	2.5451
Patient 12	0.0467	0.1254	2.4877	1.4884
Patient 13	0.0687	4.5413	1.0859	2.3951
Patient 14	0.0774	0.0397	1.4038	1.5460
Patient 15	0.0995	0.0377	1.3706	2.0485
Patient 16	0.0929	0.1205	4.5194	1.5565
Patient 17	0.0811	0.1033	2.1978	2.0338
Patient 18	0.1336	0.2307	1.0849	1.2061

Table B.3: PK/PD model parameters - Hill eq.

	EC_{50}^{p}	EC_{50}^{r}	γ	μ
Patient 1	13.94	0.042	2.0321	4.3266
Patient 2	13.88	0.040	1.0133	4.3845
Patient 3	20	0.028	2.0196	3.3133
Patient 4	20	0.052	1.8930	4.2273
Patient 5	14.85	0.1	1.0702	3.9505
Patient 6	20	0.09	2.6169	4.3774
Patient 7	17.08	0.061	3.7297	4.1494
Patient 8	3.35	0.1	0.9172	1.0000
Patient 9	12.17	0.031	1.8645	3.8367
Patient 10	16.91	0.014	1.4517	3.7978
Patient 11	15.52	0.1	0.9334	4.4496
Patient 12	20	0.1	1.6649	4.2860
Patient 13	5.41	0.035	0.9882	3.8094
Patient 14	7.2	0.037	3.8213	3.2302
Patient 15	12.41	0.016	1.6771	3.4726
Patient 16	20	0.046	3.9302	3.9983
Patient 17	20	0.05	1.6096	4.2064
Patient 18	3.43	0.1	1.5613	4.2411