Improvement of the BIS reference tracking performance in the presence of parameters uncertainties

Abstract—In this paper two controllers in parallel, each of them as proposed in [1] for the control of the total mass in SISO compartmental systems, are used to control the depth of anesthesia in patients (DoA) by means of the administration of propofol and remifentanil. These controllers are based on a parameter parsimonious Wiener model recently introduced in the literature. A strategy to solve the problem raised by the existence of uncertainties in the parameters of the patients models is presented. This technique significantly improves the performance of the controller.

I. INTRODUCTION

A surgery cannot be successful if the patient is not well anesthetized. 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, hypnosis, and analgesia. The depth of anesthesia (DoA) is related to the intensity of these two latter components, which may be measured, according to several studies ([2], [3], [4], [5], [6]) and clinical practices, 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 fully awake and alert). A BIS value between 40 and 60 indicates an appropriate level for general anesthesia.

Here, a control law is presented to administer the hypnotic agent propofol and the opioid analgesic remifentanil to patients during surgery in order to achieve a desired level of unconsciousness (DoA), along with a retuning strategy to overcome the presence of uncertainties in the model parameters. This is measured in terms of the BIS level, here denoted by $z(t)$, which is a feature that can be related to the quantities of administered drugs as explained in the next section.

II. CONTROL OF THE DEPTH OF ANESTHESIA

In what concerns DoA, the response for the administration of hypnotics and analgesics is commonly modeled as a high order pharmacokinetics/pharmacodynamics (PK/PD) Wiener model (see [7]). However, a new Wiener
model with a reduced number of parameters (parameter parsimonious model - PP model) describing the joint effect of propofol and of remifentanil has been introduced in [8]. Similarly to the previously proposed models, the PP model also presents a compartmental structure in the linear part; however, not all variables are directly related to the usual physiological variables. The main goal of this section is to design a controller for the DoA based on this new model.

More concretely, the model introduced in [8] consists of two independent state space models, describing the effect concentration of each drug, as shown below (where the indexes \( p \) and \( r \) stand for propofol and remifentanil, respectively, and \( \alpha \) and \( \eta \) are patient dependent parameters). The effect concentration of propofol (\( c_p^e \)) and of remifentanil (\( c_r^e \)) are then given by the state space models (see [8]):

\[
\begin{align*}
\dot{x}_i &= A_i x_i + B_i u_i, \\
c_p^e &= \left[ \begin{array}{rrr} 0 & 0 & 1 \end{array} \right] x_p, \\
c_r^e &= \left[ \begin{array}{rrr} 0 & 0 & 1 \end{array} \right] x_r,
\end{align*}
\]

where

\[
i = p, r,
\]

\[
x_i = \begin{bmatrix} x_i^1 \\ x_i^2 \\ x_i^3 \end{bmatrix},
\]

\[
A_p = \begin{bmatrix} -10\alpha & 0 & 0 \\ 9\alpha & -9\alpha & 0 \\ 0 & \alpha & -\alpha \end{bmatrix},
\]

\[
A_r = \begin{bmatrix} -3\eta & 0 & 0 \\ 2\eta & -2\eta & 0 \\ 0 & \eta & -\eta \end{bmatrix},
\]

\[
B_p = \begin{bmatrix} 10\alpha \\ 0 \end{bmatrix} \quad \text{and} \quad B_r = \begin{bmatrix} 3\eta \\ 0 \end{bmatrix}.
\]

When propofol and remifentanil are simultaneously administered, the corresponding BIS level, \( z(t) \), is approximately given by the expression (see [8]):

\[
z(t) \approx \frac{z_0}{1 + (\mu U^p + U^r)\gamma},
\]

where \( \mu, \gamma \) are parameters, and \( z_0 \) is the effect at zero concentration. \( U^p \) and \( U^r \) respectively denote the potencies of propofol and remifentanil, which are obtained by normalizing the effect concentrations with respect to the concentrations that produce half the maximal effect when the drug acts isolated (denoted by \( EC_{50}^p \) and \( EC_{50}^r \), respectively), i.e., (see [8]):

\[
U^p = \frac{c_p^e}{EC_{50}^p} \quad \text{and} \quad U^r = \frac{c_r^e}{EC_{50}^r}.
\]

Defining \( \theta^p = \frac{1}{EC_{50}^p} \), \( \theta^r = \frac{1}{EC_{50}^r} \) and \( U = \mu U^p + U^r \) (that can corresponds to the potency of the drug combination) yields

\[
z(t) \approx \frac{z_0}{1 + U\gamma}, \quad (1)
\]

with \( U = \mu \theta^p c_p^e + \theta^r c_r^e \). This leads to the following model

\[
\begin{align*}
\dot{x}(t) &= Ax(t) + Bu(t) \\
U(t) &= \mu \theta^p c_p^e(t) + \theta^r c_r^e(t) \\
z(t) &\approx \frac{z_0}{1 + U\gamma},
\end{align*}
\]

where

\[
x(t) = \begin{bmatrix} x_p(t) \\ x_r(t) \end{bmatrix}, \quad A = \begin{bmatrix} A_p & 0_{3 \times 3} \\ 0_{3 \times 3} & A_r \end{bmatrix},
\]

\[
B = \begin{bmatrix} B_p & 0_{3 \times 1} \\ 0_{3 \times 1} & B_r \end{bmatrix}.
\]

As mentioned before, for surgery purposes it is desirable to maintain the BIS close to a certain reference level \( z^* \) between 40 and 60. Taking (1) into account one easily concludes that this can be achieved by designing a control law that forces \( U(t) \) to follow the reference level

\[
U^* = \left( \frac{z_0}{z^*} - 1 \right) \frac{\theta}{\gamma}.
\]

For this purpose, we use two controllers in parallel, one for each model, as proposed in [1] for the control of the total mass \(^1\) in SISO compartmental systems. Thereby, the extra output

\[
M(t) = \begin{bmatrix} M_p \\ M_r \end{bmatrix} = C_M x(t),
\]

where

\[
M_p(t) = \begin{bmatrix} 1 & 1 & 1 \end{bmatrix} x_p(t),
\]

\[
M_r(t) = \begin{bmatrix} 1 & 1 & 1 \end{bmatrix} x_r(t)
\]

respectively denote the total system mass for propofol and remifentanil, and

\(^1\) The total system mass is defined as the sum of all the states. This designation is due to the fact that, usually, the states correspond to the existing mass in each compartment. However, it may not have this meaning, as happens in our case, where the states are concentrations in virtual compartments.
\[ C_M = \begin{bmatrix} C & 0_{1 \times 3} \\ 0_{1 \times 3} & C \end{bmatrix}, \]
\[ C = \begin{bmatrix} 1 & 1 & 1 \end{bmatrix}, \]

is considered. A connection between the reference value \( U^* \) and an adequate reference value \( M^* = \begin{bmatrix} M^{p*} \\ M^{r*} \end{bmatrix} \) for \( M \) is established, in such a way that when \( \dot{M}(t) \rightarrow M^* \), \( U(t) \rightarrow U^* \) and \( z(t) \rightarrow z^* \), as desired.

It as been proved in [9] that the total mass of the compartmental part of a PP model

\[
\begin{align*}
\dot{x} &= Ax + Bu \\
M &= Cx,
\end{align*}
\]

controlled by means of

\[
\begin{align*}
u &= \max(0, \tilde{u}), \\
\tilde{u} &= (CB)^{-1}[-CAx + \lambda(M^* - M)] \\
\text{and } \lambda, M^* > 0,
\end{align*}
\]

as proposed in [1], converges to \( M^* \), whereas the corresponding effect concentration of the administered drug \( c_r = \begin{bmatrix} 0 & 0 & 1 \end{bmatrix} x \) converges to \( \frac{M^*}{3} \), independent of the value of the system parameter.

Therefore, applying the control law

\[
\begin{align*}
u &= \begin{bmatrix} u^p \\ u^r \end{bmatrix} = \begin{bmatrix} \max(0, \tilde{u}^p) \\ \max(0, \tilde{u}^r) \end{bmatrix}, \text{ with } \\
\tilde{u}^p &= (CBp)^{-1}[-CA^p x^p + \lambda^p(M^p - M^p)] \\
\text{and } \lambda^p > 0, \\
\tilde{u}^r &= (CBr)^{-1}[-CA^r x^r + \lambda^r(M^r - M^r)] \\
\text{and } \lambda^r > 0,
\end{align*}
\]

(3)

(4)

to the system (2), the effect concentrations \( c_r^p \), of propofol, and \( c_r^r \), of remifentanil, converge respectively to \( \frac{M^p}{3} \) and \( \frac{M^r}{3} \), regardless of the values of the parameters \( \alpha, \eta \). This is equivalent to say that \( U^p \) converges to \( \tilde{U}^p = \mu \theta^p \frac{M^p}{3} \) and \( U^r \) converges to \( \tilde{U}^r = \theta^r \frac{M^r}{3} \).

Therefore, in steady state, we obtain for the value of \( U \)

\[ \tilde{U} = \mu \tilde{U}^p + \tilde{U}^r = \mu \theta^p \frac{M^p}{3} + \theta^r \frac{M^r}{3} \]

(5)

whereas the steady state value of \( z \) is given by

\[ \tilde{z} = \frac{z_0}{1 + U^r}. \]

(6)

In order to obtain a certain BIS value, \( z^* \), during a surgery, using the controller above described, we first calculate \( \tilde{U} = U^* \), using the equation (6) for \( \tilde{z} = z^* \), which gives

\[ U^* = \left( \frac{z_0}{z^*} - 1 \right)^{\frac{1}{\gamma}}. \]

As a next step, adequate values \( M^{p*} \), of \( \tilde{M}^p \), and \( M^{r*} \), of \( \tilde{M}^r \), to be used in the control laws (4) need to be computed from \( U^* \), using equation (5). This yields to the relation

\[ \mu \theta^p \frac{M^{p*}}{3} + \theta^r \frac{M^{r*}}{3} = U^* \]

(7)

where clearly one degree of freedom exists.

In order to eliminate this degree of freedom we take

\[ M^{p*} = \rho M^{r*} \]

(8)

with \( \rho \geq 0 \). This is motivated by the fact that the steady state input doses of propofol and of remifentanil are respectively given by:

\[ u^{p*} = \frac{M^{p*}}{3} \text{ and } u^{r*} = \frac{M^{r*}}{3}. \]

Indeed, for \( \tilde{M}^r = M^{r*} \) and \( \tilde{M}^p = M^{p*} \), the states of the closed-loop system converges to

\[ x^* = \begin{bmatrix} x^{p*} \\ x^{r*} \end{bmatrix} \text{ with, } x^{p*} = \frac{M^{p*}}{3} \begin{bmatrix} 1 \\ 1 \\ 1 \end{bmatrix} \]

\[ x^{r*} = \frac{M^{r*}}{3} \begin{bmatrix} 1 \\ 1 \\ 1 \end{bmatrix}, \text{ (9)}, \]

which implies that:

\[ u^{p*} = (CBp)^{-1}(-CA^p x^{p*}) = \frac{1}{10\alpha} \begin{bmatrix} \alpha & 8\alpha & \alpha \end{bmatrix} x^{p*} = \frac{1}{10\alpha} \begin{bmatrix} \alpha & 8\alpha & \alpha \end{bmatrix} \begin{bmatrix} 1 \\ 1 \\ 1 \end{bmatrix} = \frac{M^{p*}}{3} = \frac{M^{p*}}{3}. \]

Analogously \( u^{r*} = \frac{M^{r*}}{3} \).
Thus imposing (8), a proportion $\rho$ between the steady state drug doses can be achieved, i.e.,

$$u^{p*} = \rho u^{r*}.$$  

This may constitute an advantage from the clinical point of view. Combining (7) and (8) leads to

$$M^{r*} = \frac{3U^*}{\mu b^p \rho + \theta r} = \frac{3}{\mu b^p \rho + \theta r} \frac{1}{\gamma}$$

and $M^{p*} = \rho M^{r*}$

### III. Parameter Uncertainty

In practice, the real value of $\gamma$ is unknown and a nominal value $\bar{\gamma}$ is used, instead of $\gamma$. Thus we obtain a nominal value $\bar{U}^*$, for $U^*$, which is given by

$$\bar{U}^* = \left( \frac{z_0}{z^*} - 1 \right)^{\bar{\gamma}^{-1}}.$$  

Moreover, the real value of $\mu$ is also unknown and a nominal value $\bar{\mu}$ is used instead. In this way, an approximate value $\bar{M}^{r*}$, for $M^{r*}$, given by

$$\bar{M}^{r*} = \frac{3\bar{U}^*}{\bar{\mu} b^p \bar{\rho} + \theta r} = \frac{3}{\bar{\mu} b^p \bar{\rho} + \theta r} \frac{1}{\bar{\gamma}}$$

is obtained.

When the doses $u^p$ and $u^r$, computed according to (4) with $M = M^{r*}$ and $M = M^{r*}$, are administered the patient's BIS response follows the reference value $z^{*}_{ap}$,

$$z^{*}_{ap} = \frac{z_0}{1 + U^{*}_{ap}} \bar{\gamma},$$  

with

$$U^{*}_{ap} = \left( \frac{\mu b^p \bar{\rho} + \theta r}{\mu b^p \bar{\rho} + \theta r} \right) \left( \frac{z_0}{z^*} - 1 \right)^{\bar{\gamma}},$$  

instead of the desired value $z^*$. This leads to an error

$$\Delta z^* = z^* - z^{*}_{ap} = z^* - \frac{z_0}{1 + \left( \frac{\mu b^p \rho + \theta r}{\mu b^p \bar{\rho} + \theta r} \right) \left( \frac{z_0}{z^*} - 1 \right)^{\bar{\gamma}}},$$

where

$$\Delta \mu = \mu - \bar{\mu}, \Delta \gamma = \gamma - \bar{\gamma}.$$  

In order to find better approximations for the parameters $\mu$ and $\gamma$ we first obtain a good approximation for $\gamma$, and only after that improve the approximation for $\mu$. For this purpose, we initially consider $\rho = 0$, i.e., only remifentanil is administered. In this way only the parameter $\gamma$ is present in the Hill equation and (9) becomes

$$z^{*}_{ap} = \frac{z_0}{1 + \left( \frac{\hat{\mu}}{\hat{\mu}} \right) \left( \frac{z_0}{z^*} - 1 \right)^{\bar{\gamma}}},$$  

where $z^{*}_{1}$ corresponds to a initial target for the BIS level, fixed only during a short period of time for identification purposes. After the system settles down, say at time $t_1^{*}$, the value of the BIS level, $z(t_1^{*})$, is very close to $z^{*}_{ap}$. Thus, replacing this value in (11) and solving with respect to $\gamma$ yields a good estimate

$$\gamma \approx \bar{\gamma} \ln \left( \frac{z_0}{z^{*}_{ap}} - 1 \right) \ln \left( \frac{z_0}{z^{*}_1} - 1 \right)^{\bar{\gamma}},$$  

(12)

As a second step, once $\bar{\gamma}$ is obtained, the value of $\rho$ is taken to be nonzero (equal to the desired clinically one) and the target $z^*$ is set to the clinically desired value, $z_2^*$. Again (9) becomes

$$z(t_2^*) = \frac{z_0}{1 + \left( \frac{\mu b^p \rho + \theta r}{\mu b^p \bar{\rho} + \theta r} \right)^{\bar{\gamma}} \left( \frac{z_0}{z^*} - 1 \right)^{\bar{\gamma}}},$$  

where $z(t_2)$ is the computed steady state value of $z$. This yields

$$z(t_2^*) \approx \frac{z_0}{1 + \left( \frac{\mu b^p \rho + \theta r}{\mu b^p \bar{\rho} + \theta r} \right)^{\bar{\gamma}} \left( \frac{z_0}{z^*} - 1 \right)},$$  

since $\bar{\gamma} \approx 1$.

Solving (14) with respect to $\mu$, we obtain an improved
Finally with these values \( \hat{\gamma} \) and \( \hat{\mu} \), new estimates \( \hat{U}^\star \), \( \hat{M}^\star \), and \( \hat{M}^{p\star} = \rho \hat{M}^{r\star} \) are computed, and the control law is retuned by replacing the new values \( \hat{M}^{r\star} \), and \( \hat{M}^{p\star} \).

IV. Simulations

In this section the performance of the previously described strategy to estimate the parameters \( \gamma \) and \( \mu \) is illustrated by means of several simulations. For this purpose, we consider a PP model with parameters: \( z_0 = 97.7 \), \( \alpha = 0.0687 \), \( \eta = 4.5413 \), \( \mu = 2.40 \), \( \gamma = 1.09 \), \( EC^{p}_{50} = 10 \), \( EC^{r}_{50} = 0.01 \), taken from the bank of identified values for eighteen real patients obtained in the work developed in [10], to which we refer for further explanation. These parameter values are only taken to simulate the patient’s response, and considered to be unknown for control purposes. We also assume that it is intended that the DoA of the patient corresponds to the reference value of 50 for the BIS and \( \lambda^p, \lambda^r = 1 \) (for larger values of \( \lambda^p \) and \( \lambda^r \) the convergence rate speed will be faster). The selected proportion between the two drugs was the corresponding average reported in the monitored real case, \( \rho = 374 \), which means that the steady state dosage of propofol is 374 times greater than one of remifentanil.

Figure 1 shows the BIS response of the patient using the controller (4), with nominal values for the parameters \( \hat{\gamma} = 1,88 \), and \( \hat{\mu} = 1,79 \). These correspond to the average values in the aforementioned bank. In this case, the BIS response of this patient converged for 46 instead for the desired reference value, \( z^* = 50 \), which means that the nominal parameters produced an error of 8%.

In order to apply our strategy, in the first three minutes of the BIS control, only remifentanil was administrated to the patient, i.e., \( \rho = 0 \), and the reference value of 85 was considered \( (z^*_1 = 85) \). The parameter \( \hat{\gamma} \) obtained, and calculated as explained in the previous section, was equal to the real \( \gamma \), i.e., \( \hat{\gamma} = \gamma = 1,09 \). Figure 2 shows the BIS response of the patient during these three minutes. As expected, the desired reference value is not achieved, and it is precisely the existence of a steady state error that allows to retune the value of \( \gamma \).

Figure 3 illustrates the controller performance when, after retuning the value of the parameter \( \gamma \), the values of \( \rho \) and \( z^* \) are set to the desired ones, i.e., \( \rho = 374 \) and \( z^* = z^*_2 = 50 \). Again as expected a steady state error can be observed, due to the error in the estimate \( \hat{\mu} \) of \( \mu \). Note, however, that some improvement is already achieved with respect to the initial case already shown in Figure 2 and repeated here for better comparison.
Based on the previously obtained steady state error, a retuning of the value of \( \mu \) is performed, thus completing the control strategy proposed in the previous section. This yields a new value for \( \mu, \hat{\mu} = 2.28 \), quite close to the real value \( \mu = 2.40 \).

The illustration of the BIS response of the patient with the complete strategy is presented in Figure 4. The BIS response of the patient converged to the reference value 49.4, corresponding to an error of 1%, which is a much better result than with the one of 8% obtained when only the nominal parameters \( \hat{\gamma} \) and \( \hat{\mu} \) where used.

\[\text{Fig. 3. Evolution of DoA, for } \lambda = 1, \rho = 0, \gamma = \hat{\gamma} = 1.88, \text{ and } z^* = 85 \text{ in the first 3 minutes and, from then on, } \rho = 374, \gamma = \hat{\gamma} = 1.09, \mu = \hat{\mu} = 1.79, \text{ and } z^* = 50 \text{ versus the evolution of DoA, for } \lambda = 1, \rho = 374, \gamma = \hat{\gamma} = 1.88, \mu = \hat{\mu} = 1.79, \text{ and } z^* = 50.\]

\[\text{Fig. 4. Evolution of DoA, for } \lambda = 1, \rho = 374, \gamma = \hat{\gamma} = 1.88, \mu = \hat{\mu} = 1.79, \text{ and } z^* = 50 \text{ versus the evolution of DoA, for } \lambda = 1, \rho = 374, \gamma = \hat{\gamma} = 1.09, \mu = \hat{\mu} = 1.79, \text{ and } z^* = 50.\]

V. Conclusion

In this paper, a nonlinear control law was proposed in order to control the BIS level of patients by means of simultaneous administration of propofol and remifentanil. This control law has a good performance for the control of the DoA and allows a retuning strategy to solve the problem raised by the existence of uncertainties in the parameters of the patients models. The simulations presented in this paper for one study case (taken from a bank of real patient models) show that this technique significantly improves the performance of the controller.

Similar results are obtained for the other patient models in the bank.

References