A simple PK/PD model identification procedure for controller design in anesthesia

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Abstract

In this paper a new estimation procedure for the parameters of the PK/PD model for the simultaneous administration of propofol and remifentanil introduced in [1] is presented. This model has the advantage of being parsimoniously parameterized, which allows a simple parameter estimation procedure, based on the patient's step response. It is shown that the parameter estimates obtained in this way provide good results when used to tune the positive control law introduced in [2].

1. INTRODUCTION

The depth of anesthesia (DoA) is an important factor during surgery. It is achieved by the combination of two drug types, an hypnotic and an analgesic, and can be measured by the bispectral index (BIS) - a feature that is extracted from the patient's EEG. Models for the effect of drug administration have been widely studied in the literature, see for instance [3], [4], [5], [6]. More recently a new PK/PD model has been introduced in [1] for the combined effect of the analgesic *remifentanil* with the hypnotic *propofol*. Although its structure does not have a complete physical interpretation, this model (known as parsimonious parameter model - PPM) has the advantage of involving a smaller number of parameters as the previously considered ones, without compromising the modeling capacity. This constitutes an advantage for parameter estimation, which in turn is crucial to tune automatic controllers.

On the other hand, the simplicity of the PPM corresponds to a simple analytic expression for the model response. In this paper this aspect is exploited in order to derive a simple estimation procedure for the model parameters, based on the administration of constant doses of *remifentanil* and of *propofol*. The corresponding estimates are used to tune the controller proposed in [2], yielding promising results.

The structure of this paper is as follows. Section 2 is devoted to the explanation of the proposed estimation technique. In Section 3, for the sake of completeness, the form of controller for the DoA introduced in [2] is recalled. Simulation results are presented in Section 4, and, finally, conclusions are drawn in Section 5.

2. MODEL IDENTIFICATION

A simple technique to identify the parameters of the parsimonious PK/PD model introduced in [1] is presented in Subsection 2.2, based on the patient's response to the administration of fixed drug doses. For this purpose, the parsimonious parameter model is first described in the next subsection.

2.1. Model description

The depth of anesthesia (DoA) induced by the administration of the hypnotic drug *propofol* and of the analgesic drug *remifentanil* is usually modeled by a pharmacokinetic/pharmacodynamic (PK/PD) Wiener model ([3], [6], [4], [5], [7]). This model has a compartmental linear part that depends on several parameters, corresponding to compartment volumes, micro-constant rates for mass transfer between compartments and drug clearance in the human body. This is an undesirable situation, as some of the parameters are unidentifiable. For this reason, mean values of the parameters are often considered. However, this does not always lead to adequate models, for instance, for control purposes. To overcome this situation, a new

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parameter parsimonious PK/PD Wiener model (PPM) describing the join effect of *propofol* and of *remifentanil* has been introduced in [1], allowing a less complex parameter identification procedure together with an easier automatic controller design.

In the parameter parsimonious model (PPM) the relation between the *propofol* and *remifentanil* dosages and the corresponding effect concentrations (c_e^p and c_e^r) are modeled by the transfer functions (see [1]):

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

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

respectively, where α and η are patient dependent parameters. The corresponding BIS level, $z(t)$, usually given by the generalized Hill equation [7], is approximated in [1] by the nonlinear equation:

$$z(t) = \frac{z_0}{1 + (\mu U^p + U^r)^\gamma}, \quad (3)$$

where μ and γ are patient dependent parameters, z_0 is the BIS level at zero concentration, and 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.:

$$U^p = \frac{c_e^p}{EC_{50}^p} \text{ and } U^r = \frac{c_e^r}{EC_{50}^r}. \quad (4)$$

The parameters EC_{50}^p and EC_{50}^r are taken to be fixed, namely $EC_{50}^p = 10$ and $EC_{50}^r = 0.01$. These values were obtained in the work developed in [8], to which we refer for further explanation.

This is the model to be used in the sequel for our identification procedure.

2.2. A strategy to identify the parameters of the PPM

To identify the parameters γ, η, μ, α, a constant dose (step) of *remifentanil* is administered as a single drug during the first t_1 minutes, after which a constant dose (step) of *propofol* is cumulatively delivered during the next t_2 minutes. This is in accordance with what happens in many surgeries, where, to avoid patient discomfort, the administration of the analgesic *remifentanil* precedes the one of the hypnotic *propofol*.

The step response for the effect concentration of *remifentanil*, $c_{step}^r(t)$, by administering *remifentanil*, is obtained by the inverse Laplace transform

$$c_{step}^r(t) = \mathcal{L}^{-1}\left(H^r(s)\frac{1}{s}\right)$$

$$= 3e^{-2\eta t} - 3e^{-\eta t} - e^{-3\eta t} + 1. \quad (5)$$

Equivalentely, the step response for the effect concentration of *propofol*, $c_{step}^p(t)$, by administering *propofol*, is obtained by the inverse Laplace transform

$$c_{step}^p(t) = \mathcal{L}^{-1}\left(H^p(s)\frac{1}{s}\right)$$

$$= \frac{5}{4}e^{-9\alpha t} - \frac{5}{4}e^{-\alpha t} - e^{-10\alpha t} + 1. \quad (6)$$

Thus, when the step of *remifentanil*, u_{step}^r, is administered, note that in this case $c_e^p = 0$ and hence $U^p = 0$, the BIS response of the PPM, $z(t) = z_{step}^r(t)$, is given by the expression

$$z_{step}^r(t) = \frac{z_0}{1 + \left(\frac{c_e^r(t)}{0.01}\right)^\gamma} \quad (7)$$

where

$$c_e^r(t) = c_{step}^r(t). \quad (8)$$

yielding

$$z_{step}^r(t) = \frac{z_0}{1 + \left(\frac{3e^{-2\eta t} - 3e^{-\eta t} - e^{-3\eta t} + 1}{0.01}\right)^\gamma}. \quad (9)$$

Now, the estimates $\hat{\gamma}$ and $\hat{\eta}$ for the parameters γ and η, respectively, are obtained by fitting the curve $z_{step}^r(t)$ to the patient response in the interval $0 < t < t_1$ by means of a nonlinear least squares procedure.

Subsequently, at time t_1, a constant dose (step) of *propofol* is added in order to estimate the remaining parameters μ and α, by a similar procedure. More concretely, the BIS response of the PPM,

$z(t) = z_{step}^{r+p}(t)$, to the combined doses of *propofol* and *remifentanil* is computed as:

$$z_{step}^{r+p}(t) = \frac{z_0}{1 + \left(\mu \frac{c_e^p(t)}{10} + \frac{\hat{c}_e^r(t)}{0.01}\right)^{\hat{\gamma}}}, \qquad (10)$$

where $c_e^p(t) = c_{step}^p(t - t_1)$, for $t \geq t_1$, and $c_e^p(t) = 0$, for $0 < t < t_1$, and $\hat{c}_e^r$ is the estimate for the effect concentration of *remifentanil*, obtained by replacing η with $\hat{\eta}$ in (5). The parameters μ and α are then estimated by fitting the curve $z_{step}^{r+p}(t)$ to the patient response in the interval $t_1 < t < t_2$, again by means of nonlinear least squares.

In this way the parameter estimation procedure is complete, and a controller can be designed based upon the identified model.

3. DEPTH OF ANESTHESIA CONTROL

In order to perform the automatic control of the depth of anesthesia (DoA) a nonlinear controller developed in [2] resulting from the combination of a linear control law with a positivity constraint for the drug doses is used. This controller is based on the state space realizations $\Sigma^p = (A^p, B^p, C^p)$ of the transfer function $H^p(s)$ and $\Sigma^r = (A^r, B^r, C^r)$ of $H^r(s)$. The matrices of such realizations are as follows:

$$\begin{aligned}
A^p &= \begin{bmatrix} -10\alpha & 0 & 0 \\ 9\alpha & -9\alpha & 0 \\ 0 & \alpha & -\alpha \end{bmatrix}, \\
B^p &= \begin{bmatrix} 10\alpha \\ 0 \\ 0 \end{bmatrix}, \\
C^p &= \begin{bmatrix} 0 & 0 & 1 \end{bmatrix}, \\
A^r &= \begin{bmatrix} -3\eta & 0 & 0 \\ 2\eta & -2\eta & 0 \\ 0 & \eta & -\eta \end{bmatrix}, \\
B^r &= \begin{bmatrix} 3\eta \\ 0 \\ 0 \end{bmatrix}, \\
C^r &= \begin{bmatrix} 0 & 0 & 1 \end{bmatrix}.
\end{aligned} \qquad (11)$$

Further, the states of Σ^p and of Σ^r are respectively denoted by x^p and x^r.

The controller is then defined by:

$$u(t) = \begin{bmatrix} u^p(t) \\ u^r(t) \end{bmatrix} = \begin{bmatrix} max(0, \tilde{u}^p(t) \\ max(0, \tilde{u}^r(t) \end{bmatrix}, \qquad (12)$$

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

$$\begin{bmatrix} \tilde{u}^p \\ \tilde{u}^r \end{bmatrix} = E\left(-KAx + \lambda(M^* - Kx)\right), \qquad (13)$$

where

$$x = \begin{bmatrix} x^p \\ x^r \end{bmatrix}, \qquad (14)$$

$$A = \begin{bmatrix} A^p & 0 \\ 0 & A^r \end{bmatrix}, \qquad (15)$$

$$E = \begin{bmatrix} \rho \\ 1 \end{bmatrix} \frac{1}{\alpha\rho + 300\eta}, \qquad (16)$$

$$M^* = \frac{3(\theta^p\rho + \theta^r)}{\mu\theta^p\rho + \theta^r} \left(\frac{z_0}{z^*} - 1\right)^{\frac{1}{\gamma}}, \qquad (17)$$

$$K = \begin{bmatrix} 0.1 & 0.1 & 0.1 & 100 & 100 & 100 \end{bmatrix}, \qquad (18)$$

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*.

For more details about this controller and its tracking properties, the reader is referred to [2].

4. IDENTIFICATION STRATEGY PERFORMANCE FOR DoA CONTROL

In this section the performance of the identification strategy for control purposes is tested on a realistic

simulated patient. This is a necessary preliminary step before implementation in clinical environment. The simulated patient was set up based on the data of a real patient, a woman, with 45 years of age, a height of 155cm, and 58Kg, subjected to general anesthesia under *propofol* and *remifentanil* administration. The DoA was monitored by the BIS level and was manually controlled around clinically accepted values by the anesthetist. Alaris GH pumps were used for both *propofol* and *remifentanil*. Infusion rates, BIS values and other physiological variables were acquired every five seconds ([8]).

For this patient, a PK/PD Wiener model (other than the PPM) was obtained as follows. The linear part was modeled according to [4], [5], and [6] based on the relevant patient characteristics. These corresponding models are summarized in equation (1) of [9], which was used here with age $= 45$, height $= 155$cm and weight $= 58$Kg. The nonlinear part was taken to coincide with the generalized Hill equation (3) and the corresponding parameters γ and μ were identified in [8] from the surgery data, being given by: $\gamma = 0.9172$ and $\mu = 1$.

In order to identify the parameters of the PPM for this patient, a constant infusion of $0.001\,mg\,min^{-1}$ of *remifentanil* was administered during the first 5 minutes. The parameters η and γ were estimated as $\hat{\eta_1} = 0.02$ and $\hat{\gamma_1} = 1$, respectively. Subsequently, a constant dose of $1\,mg\,min^{-1}$ of *propofol* was added to the one of remifentanil during 5 more minutes, and the estimates $\hat{\alpha_1} = 0.1575$ and $\hat{\mu_1} = 1$ for the parameters α and μ were obtained. The choice of the estimation time of $10 = 5 + 5$ minutes was made so as not collide with clinical practice.

After the parameter estimation phase (first 10 minutes) the controller of the DoA presented in Section 3 is put in action, in order to track a desired reference BIS level of 50 (corresponding to the average between the maximum value of 60 and minimum value of 40 commonly used in clinical practice). The values $\rho = 300$ and $\lambda = 10$ are considered. Note that these are two design parameters: the former corresponds to the proportion between the drug doses and the latter is a parameter corresponding to the controller convergence speed.

In Fig. 1 the evolution of the level of the BIS patient during the whole procedure of estimation and control is presented. As we can see, during the control the BIS obtained $(50, 9)$ is very close to the desired one (50) which indicates that the model parameters were suitably estimated for control purposes.

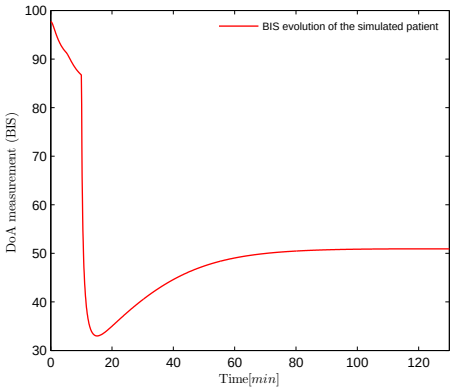

Figure 1. BIS evolution. In the first ten minutes the parameters are estimated and in the following the BIS is controlled with the estimated parameters for tracking the BIS level of 50.

The obtained estimates ($\hat{\alpha_1}$, $\hat{\eta_1}$, $\hat{\mu_1}$, and $\hat{\gamma_1}$) were compared with the ones from [8] ($\hat{\alpha_2} = 0.086$, $\hat{\eta_2} = 0.0212$, $\hat{\mu_2} = 1.4$, and $\hat{\gamma_2} = 0.98$). When our parameters are used, the patient BIS level converges to the value (50.9), which corresponds to an error of only 2%, whereas when the parameters from [8] are used the patient BIS level converges to the value (53), with an error of 6%, which indicates that our method produced better results. This is illustrated in Fig. 2.

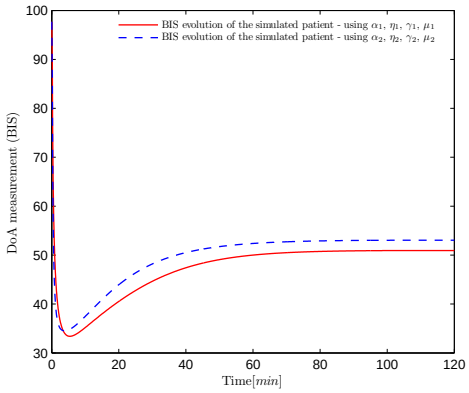

Figure 2. Comparison of BIS evolution of the patient controlled with the parameters estimated here (in red, solid line) and with the parameters estimated in [8] (in blue, dashed line).

5. CONCLUSION

In this paper, a simple method to estimate the parameters of a parameter parsimonious model was presented. The adequacy of this technique for control purposes was illustrated by tuning a controller for the BIS level of a realistic simulated patient, based on the obtained parameter estimates, yielding better results as previously obtained in other works with more elaborate tools. This also happens in other tested cases, showing that simplicity does not always imply a lack of quality. Although further validation is necessary, for instance with the inclusion of measurement noise, the obtained results seem to encourage the application of our method in clinical environment.

6. ACKNOWLEDGMENTS

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