

# Automatic control of the depth of anesthesia - clinical results

Filipa Nunes Nogueira \* Teresa Mendonça \*\* Paula Rocha \*

\* Faculdade de Engenharia da Universidade do Porto, Porto, Portugal

\*\* Faculdade de Ciências da Universidade do Porto, Porto, Portugal

## Abstract:

This paper presents clinical results of the implementation of an automatic controller previously designed by the authors for the BIS level of patients subject to general anesthesia. Since the controller has a state feedback component, an observer is introduced in order to estimate the state.

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**Keywords:** Positive systems, control, DoA, anesthesia, clinical cases

## 1. INTRODUCTION

General anesthesia consists of three components: areflexia, hypnosis and analgesia. These latter two components contribute to the depth of anesthesia (DoA) which may be measured by the bispectral-index (BIS) (Tirén et al. (2005), Grindstaff and Tobias (2004), Ekman et al. (2004), Wodey et al. (2005), Whyte and Booker (2003)). The BIS value is computed according to the measurements of an electroencephalogram and ranges between 0 and 97.7. When the BIS level is 97.7 the patient is completely awake and alert and when the BIS value is 0 there are no brain activity. During general anesthesia it is usually required that the BIS ranges between 40 and 60.

In Nogueira et al. (2014) a control law was proposed for automatic control of the BIS of patients undergoing surgical procedures by means of the administration of the hypnotic propofol and the analgesic remifentanyl. This control law makes use of the patient's state, which is not completely available for measurement. Therefore it 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 of the patient and the amounts of administered drugs. This observer, together with the control law proposed in Nogueira et al. (2014), was tested in real clinical cases, and the corresponding results are presented here. These results encourage the use of our observer-controller scheme for the control of the depth of anesthesia, a problem that has lately deserved much attention (Hemmerling et al. (2010), Ionescu et al. (2008), Dumont (2012), Furutani et al. (2005), Soltesz et al. (2011)).

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 state observer is proposed and clinical results are presented. Conclusions are drawn in Section 5.

## 2. MODEL DESCRIPTION

The BIS response of a patient to the administration of propofol and remifentanyl may be modeled by a Wiener model with a small number of parameters recently introduced in the literature Silva et al. (2010) and known as the parameter parsimonious model (PPM). According to this model, the linear relations between the propofol and remifentanyl dosages and the corresponding effect concentrations ( $c_e^p$  and  $c_e^r$ ) are modeled by the transfer functions:

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

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

respectively, where  $\alpha$  and  $\eta$  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 remifentanyl,  $u^r(t)$ , in  $mg\ min^{-1}$ . The corresponding BIS level,  $z(t)$ , usually given by the generalized Hill equation Minto et al. (2000), is approximated in Silva et al. (2010) by the nonlinear equation:

$$z(t) = \frac{97.7}{1 + (\mu \frac{c_e^p}{EC_{50}^p} + \frac{c_e^r}{EC_{50}^r})^\gamma}, \quad (3)$$

where  $\mu$  and  $\gamma$  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 remifentanyl 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 Mendonça et al. (2012), to which we refer for further explanation.

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

$$\begin{cases} \dot{x}(t) &= Ax(t) + Bu(t) \\ \begin{bmatrix} c_e^p(t) \\ c_e^r(t) \end{bmatrix} &= \begin{bmatrix} 0 & 0 & 1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 1 \end{bmatrix} x(t) \\ U(t) &= Cx(t) := [0 \ 0 \ 0.1\mu \ 0 \ 0 \ 100] x \\ z(t) &= \frac{97.7}{1 + U^\gamma}, \end{cases} \quad (4)$$

where

$$\begin{aligned} A^p &= \begin{bmatrix} -10\alpha & 0 & 0 \\ 9\alpha & -9\alpha & 0 \\ 0 & \alpha & -\alpha \end{bmatrix}, \\ A^r &= \begin{bmatrix} -3\eta & 0 & 0 \\ 2\eta & -2\eta & 0 \\ 0 & \eta & -\eta \end{bmatrix}, \\ B^p &= \begin{bmatrix} 10\alpha \\ 0 \\ 0 \end{bmatrix}, \quad C^p = [0 \ 0 \ 1], \\ B^r &= \begin{bmatrix} 3\eta \\ 0 \\ 0 \end{bmatrix}, \quad C^r = [0 \ 0 \ 1]. \\ A &= \begin{bmatrix} A^p & 0 \\ 0 & A^r \end{bmatrix} \quad \text{and} \quad B = \begin{bmatrix} B^p & 0 \\ 0 & B^r \end{bmatrix}. \end{aligned} \quad (5)$$

This specific form of the state space realization has compartmental structure. This has the advantage of allowing the use of the positive control law defined in the next section.

### 3. CONTROLLER DESCRIPTION

In Nogueira et al. (2014) (see also Nogueira et al. (2012)) a nonlinear controller was designed in order to track a desired reference value for the BIS level, by means of simultaneous administration of propofol and of remifentanyl. 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:

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

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

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

and

$$E = \begin{bmatrix} \rho \\ 1 \end{bmatrix} \frac{1}{\alpha\rho + 300\eta}, \quad (8)$$

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

$$K = [0.1 \ 0.1 \ 0.1 \ 100 \ 100 \ 100], \quad (10)$$

$z^*$  is the desired BIS level, and  $\lambda$  and  $\rho$  are positive design parameters that do not affect the tracked reference value and can be chosen according to clinical criteria. The parameter  $\lambda$  influences the convergence speed to the desired reference value and the parameter  $\rho$  can be interpreted as the proportion between the doses of propofol and remifentanyl.

For more details about this controller and its tracking properties, the reader is referred to Nogueira et al. (2014).

### 4. AUTOMATIC BIS CONTROL

The knowledge of the state of the model (4) is required in order to use the controller (7). In the simulations presented in [Nogueira et al. (2014)], it was assumed that the state of the BIS model was available for measurement, however in clinical practice this is not the case. Thus, here we consider that the state of the patient is approximated by the state of the corresponding model, and introduce an observer in order to estimate the state of the patient model (PPM) based on the measurements of the BIS response of the patient and the amounts of administered drugs. The application of an observer with this characteristics is challenging and entails some problems. First of all, the PPM with the observer-controller scheme is not positive, so we have to use a positive restriction for the estimation of the state. Secondly, the use of the estimated state of the PPM model rather than the actual patient's state leads to some misfit. Nevertheless, it may be proven that the errors produced by the estimation of the state of the PPM are bounded and the patient BIS converges to an interval that contains the desired value for the BIS, when the proposed observer is used. Furthermore, when the patient is well modeled, the BIS level converges to a value close to the desired one. The study of the errors produced by the observer will be presented in a future work. Here we focus on the observer design and in the clinical results.

#### 4.1 Observer design

Consider the PPM, as described in (4). The estimation of the state  $\hat{x}$ , of the PPM, based on the measurement of the patient BIS level,  $BIS_{patient}$ , may be obtained by the following equations:

$$\begin{cases} \dot{\hat{x}}(t) = A\hat{x}(t) + B\hat{u}(t) \\ U(t) = C\hat{x}(t) \\ U_{patient}(t) = \sqrt[3]{\frac{97.7}{BIS_{patient}} - 1} \\ \dot{\hat{x}}(t) = (A - LC)\hat{x}(t) + B\hat{u}(t) + LU_{patient}(t) \\ \hat{x}(t) = \max\{0, \hat{x}(t)\} \end{cases}, \quad (11)$$

where  $L$  is a matrix gain of the observer for the state.

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