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# A simplified control scheme for the Depth of Anesthesia

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**Abstract:** In this paper a new simplified control scheme for the depth of anesthesia that only requires the knowledge of the half of the model parameters is proposed. Two control laws are designed in parallel to control the amount of the hypnotic dose and the amount of the analgesic dose. Furthermore, an identification procedure to obtain the necessary model parameters is implemented. The results were validated by simulations based on real data collected during surgeries.



*Keywords:* Control design, identification method, depth of anesthesia.

## 1. INTRODUCTION

The recent technological advances in the monitoring devices for biomedical systems justify the increasing focus on the research of dedicated automatic control systems. In this context, the automatic control of drug administration during general anesthesia is one application of particular interest. During general anesthesia, several drugs are administered to induce and maintain areflexia, hypnosis and analgesia. In this paper we focus on these two last components. Hypnosis is defined as the absence of consciousness and the inability of the patient to recall intra operative events. This is achieved by the administration of hypnotics, e.g., propofol, and is measured by the electroencephalographic activity. The Bispectral Index (BIS), T. J. Gan (1997), is the most widely used index to infer the hypnosis of a patient. It is related to the responsiveness level and the probability of recalling intra operative events, and ranges from 97.7 (fully awake and alert state) to 0 (total absence of brain activity). During a standard general anesthesia, the BIS level should vary between 40 and 60. Analgesia is obtained by the administration of analgesics, e.g., remifentanil, and it allows the loss of the pain. The level of analgesia cannot be measured directly and must be estimated based on autonomic reactions, such as changes in blood pressure and heart rate, sweating, pupil reactivity and the presence of tears, Guignard (2006). It turns out that hypnotics and analgesics interact in such way that their effect is enhanced when administered together. In this way, both types of drugs contribute to the depth of anesthesia (DoA). It is commonly accepted that the DoA is also well described by the BIS level, T. J. Gan (1997).

In order to describe the drug absorption, distribution and biotransformation in the patients body, Pharmacokinetic/Pharmacodynamic (PK/PD) models are the most commonly used, Haddad (2010). These models have a Wiener structure: a linear part, usually represented as compartmental models, in series with a nonlinear static function for the drug effect. The compartmental models are positive linear models composed by a finite number of interconnected homogeneous, well-mixed subsystems called compartments.

Due to the large number of patient dependent parameters present in the PK/PD models, in this paper a simplified compartmental MISO Wiener model will be used to describe the relation between the hypnotic and analgesic doses with the BIS level. This model was proposed by M. M. Silva (2014) and uses only four parameters to characterize the patient while keeping a good modeling accuracy, M. M. Silva (2013).

Based on this, here a positive control law is designed to control the BIS level in line with the work presented in F. N. Nogueira (2014). However, whereas in F. N. Nogueira (2014) all the four model parameters are used to design the controller, here a new simplified control law that only requires the knowledge of two of the four model param-

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eters is proposed. Moreover, an identification procedure to obtain the two necessary parameters is implemented. Our results are illustrated by simulations based on data collected during general anesthesia in one surgery.

This paper is organized as follows. Section 2 presents the model used to design the control scheme, the proof of the parameter independence in the mass convergence and the identification procedure. The obtained results are shown in Section 3 and the conclusions are drawn in Section 4.

## 2. PARAMETER INDEPENDENCE IN THE MASS CONVERGENCE

This section presents our new positive control law for the BIS level that uses a compartmental description of the system. The BIS model used in this paper is first introduced.

### *2.1 MISO Wiener model*

The BIS model proposed in M. M. Silva (2014) for the description of the joint effect of hypnotics and analgesics in the human body consists of two linear parts: one for the relationship between the hypnotic dose and its effect concentration and another for the effect concentration of the analgesic. These linear sub-models are connected in parallel and then followed by a nonlinear static equation that describes the drug interaction and corresponding effect.

The hypnotic linear dynamics is hence modelled by

$$C_e^P(s) = \frac{k_1\, k_2\, k_3 \alpha^3}{(s\, +\, k_1\alpha)\,(s\, +\, k_2\alpha)\,(s\, +\, k_3\alpha)}\, U^P(s) \qquad (1)$$

and the linear model for the effect concentration of the analgesic is similarly given by

$$C_e^R(s) = \frac{l_1\, l_2\, l_3 \eta^3}{(s\, +\, l_1\eta)\,(s\, +\, l_2\eta)\,(s\, +\, l_3\eta)}\, U^R(s) \qquad (2)$$

where $C_e^P(s)$ and $C_e^R(s)$ are the Laplace transforms of the effect concentration of the hypnotic and the analgesic, $c_e^P(t)$ and $c_e^R(t)$, respectively; $U^P(s)$ and $U^R(s)$ are the Laplace transforms of the input doses of the hypnotic (propofol) and the analgesic (remifentanil) $u^P(t)$ and $u^R(t)$, respectively. $k = [k1\ k2\ k3]$ and $l = [l1\ l2\ l3]$ are parameters that have been suitably determined in M. M. Silva (2014), and $\alpha$ and $\eta$ are patientdependent parameters. The state-space representation of the linear part for the hypnotic model is

$$\begin{cases} \dot{x}^P(t) = \alpha A^P x^P(t) \,+\, \alpha B^P u^P(t) \\ c_e^P(t) = [0\ 0\ 1]\, x^P(t) \end{cases} \qquad (3)$$

where the matrix $A^P$ and the vector $B^P$ are defined as

$$A^P = \begin{bmatrix} -k_3 & 0 & 0 \\ k_2 & -k_2 & 0 \\ 0 & k_1 & -k_1 \end{bmatrix},\ B^P = \begin{bmatrix} k_3 \\ 0 \\ 0 \end{bmatrix}$$

Similarly, the statespace representation of the linear part for the analgesic model is

$$\begin{cases} \dot{x}^R(t) = \eta A^R x^R(t) \,+\, \eta B^R u^R(t) \\ c_e^R(t) = [0\ 0\ 1]\, x^R(t) \end{cases} \qquad (4)$$

where the matrix $A^R$ and the vector $B^R$ are defined as

$$A^R = \begin{bmatrix} -l_3 & 0 & 0 \\ l_2 & -l_2 & 0 \\ 0 & l_1 & -l_1 \end{bmatrix},\ B^R = \begin{bmatrix} l_3 \\ 0 \\ 0 \end{bmatrix}$$

The nonlinear static equation proposed in M. M. Silva (2014) to describe the drug interaction and the relation between the effect concentration and the actual drug effect is given by

$$y(t) = \frac{y_0}{1 + z(t)^\gamma}, \qquad (5)$$

$z(t) = m\, U^P(t) \,+\, U^R(t)$, $U^P = \frac{c_e^P}{C_{50}^P}$ and $U^R = \frac{c_e^R}{C_{50}^R}$; $m$ and $\gamma$ are patient-dependent parameters and $C_{50}^P$ and $C_{50}^R$ have fixed values for all patients, this can be viewed as a simplified Hill equation; $y(t)$ is the level of BIS. The vector $\theta$ is the parameter array, $\theta = [\alpha\ \eta\ m\ \gamma]$.

### *2.2 Control law for the BIS level*

The positive control law introduced in this paper is inspired on the control law for the BIS level in F. N. Nogueira (2014). This is obtained by considering two controllers in parallel: one to control the administration of the hypnotic and another to control the administration of the analgesic. The main difference is that, here, the controllers are independent of parameters $\alpha$ and $\eta$, respectively, which constitutes a simplification with respect to the approach in F. N. Nogueira (2014). Our aim of tracking a desired BIS level is achieved by reaching and maintaining appropriate masses of propofol and remifentanil in the patient's body (or system).

More concretely, for the hypnotic and for the analgesic, the proposed control laws obtained are, respectively,

$$\begin{cases} u^P(t) = \max\left(0, \tilde{u}^P(t)\right) \\ \tilde{u}^P(t) = -\left(\sum_{i=1}^{3} b_i^P\right)^{-1} [[1\ 1\ 1]\, A^P x^P(t) \\ \qquad\qquad + \lambda\left(M(x^P) - M^{*P}\right)\Big] \end{cases} \qquad (6)$$

$$\begin{cases} u^R(t) = \max\left(0, \tilde{u}^R(t)\right) \\ \tilde{u}^R(t) = -\left(\sum_{i=1}^{3} b_i^R\right)^{-1} [[1\ 1\ 1]\, A^R x^R(t) \\ \qquad\qquad + \lambda\left(M(x^R) - M^{*R}\right)\Big] \end{cases} \qquad (7)$$

where $M(x) = \sum_{i=1}^{3} x_i(t)$ is the actual total system mass; $M^*$ is the desired system mass and the $b_i^P$ and $b_i^R$ are elements of the matrices $B^P$ and $B^R$, respectively.

In the same line of what was done in F. N. Nogueira (2014), and for each drug model we can conclude that the total