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Nonlinear controller for bispectral index tracking: Robustness and on-line retuning ☆

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ABSTRACT

In this paper, the performance of a control law designed for the automatic administration of *propofol* and of *remifentanil* in order to track a desired level for the bispectral index (BIS), used as a measure of the depth of anesthesia, is analyzed under the presence of model parameters uncertainties. It is theoretically proved and illustrated by simulations that under these circumstances the controller has a very good performance as the BIS converges to a value contained in a neighborhood of the desired BIS level. A retuning strategy in order to improve the BIS tracking under the presence of uncertainties was also theoretically deduced. Simulations show that this strategy leads to BIS tracking improvement. The performance of the controller in clinical environment is illustrated by a clinical case.

1. Introduction

Correct administration of anesthesia drug is crucial for the success of surgery. In this regard, the controllers developed for automatic administration of drugs have to be extensively studied. It is important to study the performance of the controller under the presence of modeling errors as the complex nature of the human body and the inter- and intra-individual variability do not allow obtaining an exact description of the drug effect in each patient. In this sense, it is also crucial to develop retuning techniques to calibrate the controller in order to address possible misfits between the obtained results and the desired values, arising not only from modeling errors, but also from noisy measurements.

Here, the focus is the administration of the hypnotic *propofol* and of the analgesic *remifentanil*. These drugs are used for the control of the depth of anesthesia (DoA). The DoA is related to the intensity of two components of general anesthesia: analgesia and hypnosis. According to several studies (Ekman, Lindholm, Lennmarken, & Sandin, 2004; Grindstaff & Tobias, 2004; Tirén, Anderson, Barr, Owall, & Jakobsson, 2005; Whyte & Booker, 2003; Wodey et al., 2005) 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 fully awake and alert). According to clinical experience, a BIS value between 40 and 60 is desirable for general anesthesia purposes, as it usually corresponds to an adequate state of unconsciousness during surgical procedures. 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. This question has deserved the attention of several researchers and led to a number of contributions and controllers namely a predictive control in Ionescu et al. (2008), an adaptive model-based controller in Mortier, Struys, De Smet, Versichelen, and Rolly (1998) and Simanski, Sievert, Janda, and Bajorat (2013), a PID in Padula et al. (2015), a neural in Ortolani et al. (2002), a fuzzy logic in Shieh, Linkens, and Asbury (2005), a model predictive control in Sawaguchi, Furutani, Shirakami, Araki, and Fukuda (2008) and Chang, Krieger, Astolfi, and Pistikopoulos (2014), but in these contributions the control of the DoA is not fully automatic. More concretely, the administration of

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the hypnotic is made automatically, however the administration of the analgesic is made manually by the anesthetic. 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. (2014).

In Nogueira, Mendonça, and Rocha (2014a) a control law was proposed for the BIS tracking of patients, during general anesthesia, by means of the automatic administration of *propofol* and of *refimentanil*. This controller has the advantage of allowing different combinations of drugs in order to obtain the same value for the BIS level, it allows the changing of the desired reference value for the BIS during the surgical procedure, and it is already used in clinical practices, with good performance according to the anesthesiologists. The big difference between this controller and the aforementioned controllers cited above is that: in the referred works the BIS is controlled by the automatic administration of one single drug (the hypnotic) together with the manual administration of the other drug (the analgesic), by the anesthesiologist, whereas in Nogueira et al. (2014a) these two drugs are automatically administered, without any intervention of the anesthesiologist.

The aim of this work is to study the performance of the controller proposed in Nogueira et al. (2014a) under the presence of model parameters uncertainties. It is theoretically proved that under these circumstances, the BIS level converges to a value contained in a neighborhood of the desired BIS level. This fact allows a retuning strategy in order to recalibrate the controller for BIS tracking improvement. The theoretical deduction of this strategy is here presented.

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 the robustness of the controller is analyzed and in Section 5 an on-line retuning strategy is theoretically deduced. Simulations are illustrated in Section 6 while a clinical case is presented in Section 7. Conclusions are drawn in Section 8.

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, Mendonça, and Wigren (2010) 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:

$$H^p(s) = \frac{k_1k_2k_3\alpha^3}{(k_1\alpha+s)(k_2\alpha+s)(k_3\alpha+s)}u^p(s), \tag{1}$$

$$H^r(s) = \frac{l_1l_2l_3\eta^3}{(l_1\eta+s)(l_2\eta+s)(l_3\eta+s)}u^r(s), \tag{2}$$

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 dimensionless constants whose values were identified in Silva et al. (2010) 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. (2000), is approximated in Silva et al. (2010) 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, Alonso, Silva, Esteves, and Seabra (2012).

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

$$\begin{aligned} &C = [0\ \ 0\ \ 0.1\mu\ \ 0\ \ 0\ \ 100], \\ &A = \begin{bmatrix} A^p & 0 \\ 0 & A^r \end{bmatrix}, \quad B = \begin{bmatrix} B^p & 0 \\ 0 & B^r \end{bmatrix}, \\ &A^p = \begin{bmatrix} -10\alpha & 0 & 0 \\ 9\alpha & -9\alpha & 0 \\ 0 & \alpha & -\alpha \end{bmatrix}, \quad A^r = \begin{bmatrix} -3\eta & 0 & 0 \\ 2\eta & -2\eta & 0 \\ 0 & \eta & -\eta \end{bmatrix}, \\ &B^p = \begin{bmatrix} 10\alpha \\ 0 \\ 0 \end{bmatrix}, \quad B^r = \begin{bmatrix} 3\eta \\ 0 \\ 0 \end{bmatrix}. \end{aligned} \tag{5}$$

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

The nonlinear controller presented in Nogueira et al. (2014a) 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:

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

and

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

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

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