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Automatic control of the depth of anesthesia - clinical results

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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.

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 remifentanil. 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 remifentanil 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 remifentanil dosages and the corresponding effect concentrations (c_e^p and c_e^r) are modeled by the transfer functions:

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

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

respectively, where α and η 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 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:

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

where 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 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:

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

where

$$A^p = \begin{bmatrix} -10\alpha & 0 & 0 \\ 9\alpha & -9\alpha & 0 \\ 0 & \alpha & -\alpha \end{bmatrix},$$

$$A^r = \begin{bmatrix} -3\eta & 0 & 0 \\ 2\eta & -2\eta & 0 \\ 0 & \eta & -\eta \end{bmatrix},$$

$$B^p = \begin{bmatrix} 10\alpha \\ 0 \\ 0 \end{bmatrix}, \quad C^p = [\,0\ 0\ 1\,], \tag{5}$$

$$B^r = \begin{bmatrix} 3\eta \\ 0 \\ 0 \end{bmatrix}, \quad C^r = [\,0\ 0\ 1\,].$$

$$A = \begin{bmatrix} A^p & 0 \\ 0 & A^r \end{bmatrix} \quad \text{and} \quad B = \begin{bmatrix} B^p & 0 \\ 0 & B^r \end{bmatrix}.$$

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 remifentanil. 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:

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

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

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

and

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

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

$$K = [\,0.1\ 0.1\ 0.1\ 100\ 100\ 100\,], \tag{10}$$

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 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:

$$\begin{cases} \dot{x}(t) = Ax(t) + Bu(t) \\ U(t) = Cx(t) \\ U_{patient}(t) = \sqrt[\gamma]{\dfrac{97.7}{BIS_{patient}} - 1} \\ \dot{\tilde{x}}(t) = (A - LC)\tilde{x}(t) + Bu(t) + LU_{patient}(t) \\ \hat{x}(t) = \max\{0,\ \tilde{x}(t)\} \end{cases}, \tag{11}$$

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

In our applications we considered that all the patients were modeled by the PPM and tuned with parameters $\alpha = 0.0759$, $\eta = 0.5825$, $\gamma = 1.09$, and $\mu = 2.40$. These values are the average of the values for α, η, γ, and μ taken from a bank of identified values for patients obtained in Mendonça et al. (2012) (see Table A.1). For these models we consider the observer gain L to be given by:

$$L = \begin{bmatrix} -0.5720 \\ 21.1536 \\ -2.2715 \\ 0.0013 \\ -0.0040 \\ 0.0156 \end{bmatrix}. \quad (12)$$

Then, the controller $\hat{u}$ used for the automatic BIS control by means of the administration of propofol and remifentanil can be described as

$$\hat{u} = max(0, \tilde{\hat{u}}), \quad (13)$$

with

$$\tilde{\hat{u}} = \begin{bmatrix} \rho \\ 1 \end{bmatrix} (-K\hat{x} + \lambda(M^* - K\hat{x})) \frac{1}{0.0759\rho + 174.75}, \quad (14)$$

and $\lambda > 0$.

4.2 Clinical cases

The automatic administration of propofol and remifentanil to real patients during general anesthesia was performed by the Galeno platform (Costa et al. (2014)), where the control law, $\hat{u}$, as proposed in the previous section was used.

The DoA was monitored by the BIS and Alaris GH pumps were used for both propofol and remifentanil. Infusion rates, BIS values and other physiological variables were acquired every five seconds.

Patient 1 is a male, with 86 years of age, a height of 1.65m, and 50Kg of weight. Patient 2 is a male, with 85 years of age, a height of 1.72m, and 80Kg of weight.

For safety reasons, the controller was not started at the beginning of the anesthetic procedure. The initialization of the automatic control was made empirically and is marked with a red row in the following figures.

It is noteworthy that the BIS signal is measured by an electroencephalogram that also detects muscle activity. Due to this fact, the measurement values do not always entirely correspond to the DoA, since they may be influenced by more traumatic surgical procedures and/or by a decrease of the patient's neuromuscular blockade level. Therefore, in clinical practices some variations of the BIS around the pre-specified reference value is accepted. In some moments, we may notice the existence of a big tracking error in the BIS signal. This was due to the fact that the effect of muscle relaxants was decreasing, which led to "false" high BIS values. In these cases, after the administration of an extra bolus of a muscle relaxant the BIS values decreased almost immediately. On the other hand, the lower BIS observed in some moments happened when the surgeons temporarily stopped their interventions. When the surgery is more invasive, the BIS signal increases, so the controller also increases the administered drug doses. Then, when the surgeons stop the invasive procedure, the BIS signal considerably decreases.

In both patients, a change of the reference value for the BIS was necessary, due to medical conditions. This goal was achieved successfully. In patient 1, the proportion between the administered drug doses had to be changed, this moment is marked with a red row in the graph of the drug doses of Fig. 1. Although the BIS level was accepted, the blood pressure and the heart beats were high, which usually indicates that the patient might be in pain. So, it was necessary to increase the administration of the analgesic without changing the BIS level. This goal was achieved by increasing the proportion, ρ, between the doses of propofol and of remifentanil. This fact did not affect the BIS signal, as desired and theoretically expected.

The proposed BIS controller performed in practice as theoretically expected and led to clinically acceptable values for the BIS, according to the anesthesiologists.

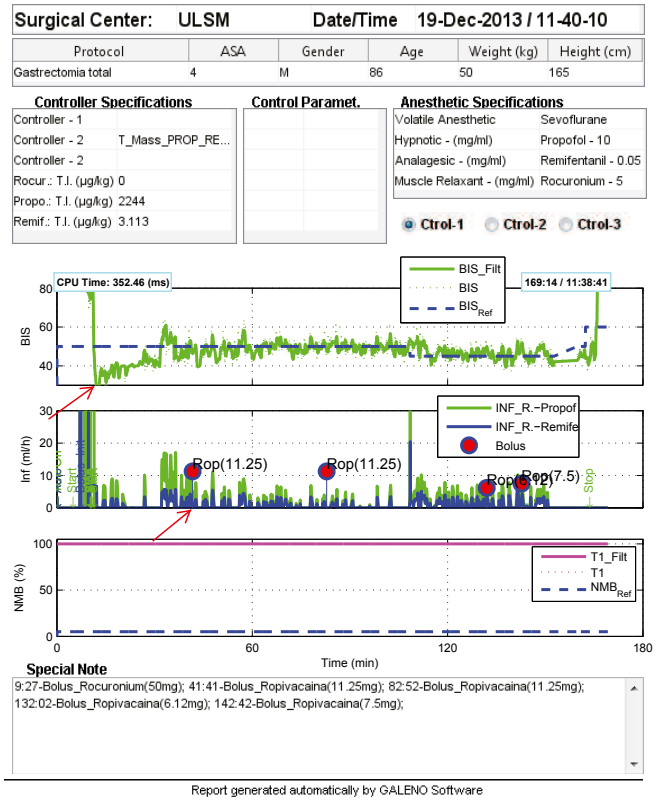

Fig. 1. Patient 1. The desired BIS level was initially set to be 50 and then was set to be 45 until the end of the surgery. Top red arrow marks the initialization of the automatic control and bottom red arrow marks a change of the proportions between the doses of drugs administered.

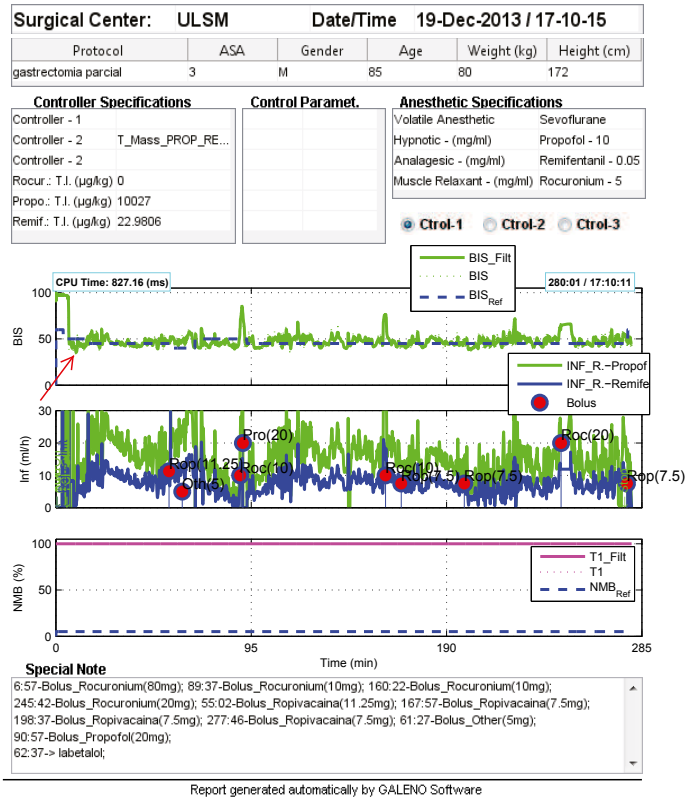

Fig. 2. Patient 2. The desired BIS level was initially set to be 50 and was changed along the surgery, due to clinical conditions. Top red arrow marks the initialization of the automatic control.

5. CONCLUSION

In this paper, a state observer was proposed in order to estimate the state of a patient BIS model by measuring the real BIS signal of the patient and the amount of drugs administered. This observer allows the use of the controller proposed previously by the authors for automatic control of the BIS of patients by means of the administration of propofol and of remifentanil. This control law was implemented, tested and evaluated in real patients during surgical procedures. The clinical results of this implementation showed that the control law performed in practice as theoretically expected leading to a good clinical performance under a variety of clinical situations, patients and surgery characteristics.

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Appendix A. DATABASE

This database was courteously provided by Galeno project (http://www2.fc.up.pt/galeno/).

The parameters presented in Table A.1 were identified in Mendonça et al. (2012).

Table A.1. PPM Parameters

	α	η	γ	μ
Patient 1	0.0667	0.3989	2.0321	4.3266
Patient 2	0.0874	0.0670	1.0133	4.3845
Patient 3	0.0693	0.0482	2.0196	3.3133
Patient 4	0.0590	0.0425	1.8930	4.2273
Patient 5	0.0489	0.1269	1.0702	3.9505
Patient 6	0.0677	0.3373	2.6169	4.3774
Patient 7	0.0737	0.2793	3.7297	4.1494
Patient 8	0.0860	0.0212	0.9172	1.0000
Patient 9	0.0701	0.2837	1.8645	3.8367
Patient 10	0.1041	0.1038	1.4517	3.7978
Patient 11	0.0343	3.5768	0.9334	4.4496
Patient 12	0.0467	0.1254	1.6649	4.2860
Patient 13	0.0687	4.5413	0.9882	3.8094
Patient 14	0.0774	0.0397	3.8213	3.2302
Patient 15	0.0995	0.0377	1.6771	3.4726
Patient 16	0.0929	0.1205	3.9302	3.9983
Patient 17	0.0811	0.1033	1.6096	4.2064
Patient 18	0.1336	0.2307	1.5613	4.2411