35th Annual International Conference of the IEEE EMBS
Osaka, Japan, 3 - 7 July, 2013

High-Order Sliding-Mode Control for Anesthesia

Ana Gallardo Hernández, Jonathan Eslava Escobar, Ron Leder, Ana Luisa Hernández Pérez, Leonid Fridman, Jorge Dávila, Cristina Revilla Monsalve and Sergio Islas Andrade.

***Abstract*— Depth of anesthesia can be indirectly measured by Bispectral Index (BIS), therefore it is possible to administer propofol in a closed loop to maintain the optimal level of anesthesia while minimizing the dose to improve the postanesthesia recovery. High-Order Sliding-Mode control can be used to individualize drug dosing. In this study, the controller is tested with four *in silico* patients.**

I. Introduction

High-Order Sliding-Mode Control (HOSMC) has been used to automate the insulin infusion [1] [2]. HOSMC is insensitive to patient parameter variation, i.e. its design does not depend on the parameters of a nominal patient; therefore the same controller is used for all patients. The second advantage HOSMC presents with respect to other control techniques based on models, like Model Predictive Control (MPC), is that HOSMC is robust with respect to singular perturbations, such as unconsidered dynamics (bleeding, surgical stimuli, etc.) that may appear during anesthesia [3].

Propofol is an intravenous anesthetic drug used for surgery due to several advantages it presents over inhaled anesthesia. It produces less post-anesthetic nausea and vomiting and reduces the emergence agitation episodes [4]. The anesthesiologist calculates the necessary amount of drug according to dose regimes mostly based on the patient body weight, and during surgery physicians can adjust the dose based on observation of the patient behaviour and their clinical experience [5]. There is a large interpatient variability of the parameters of the pharmacokinetic models, thus propofol dosing is often uncertain, leading to possible under or over-dosing potentially responsible for prolonging delay of recovery or perioperative awareness [4].

There are several commercial systems to measure the depth of anesthesia based on the analysis of the electroencephalogram (EEG), like the Covidien's Vista Bis Monitor (Dublin, Ireland) [6], the CleveMed's NeuroSense Monitor (Cleveland, USA) [7], and the General Electric's Entropy Monitor. In this study we used Bispectral Index (BIS) due to is one of the most used monitors. In future studies other measurement technologies will be considered.

BIS is a processed EEG parameter that correlates with the patients' level of anesthesia, where 100=awake and 0=isoelectric EEG. BIS was designed to correlate with hypnotic clinical endpoints (sedation, lack of awareness, and memory) and to track changes in the effects of anesthetics on the brain [6]. The feedback obtained from the BIS has been used to make closed loop control like described in [8], [9] and [10].

Paper Contribution: this paper presents a closed loop propofol infusion system based on HOSMC simulated in four *in silico* patients to prove its insensitivity to parameter variations. The simulation represents a one hour surgical procedure including the induction, maintenance and emergence phases. Surgical stimuli are induced in the simulations to test the HOSMC perturbance rejection capability.

In section II a mathematical model describing the system's dynamic is presented. The design of a High Order Sliding Mode Control for automatic infusion of propofol is described in section III. In section IV the controller is tested by a simulation. Finally results and conclusions are presented.

II. Mathematical Model

The dynamic of a drug can be described by a pharmacokinetic-pharmacodynamic (PK-PD) model. The pharmacokinetic part describes the drug distribution in the body, and the pharmacodynamics part describes the effect the drug have with respect to its concentration in blood.

The pharmacokinetics of propofol can be described by Schnider three-compartment model (1). The pharmacodynamics are described in (2). The relationship of the propofol effect and BIS is shown in (3) [8].

$$\begin{aligned} \dot{x_1} &= -[k_{10}+k_{12}+k_{13}]x_1 + k_{21}x_2 + k_{31}x_3 + u(t) \\ \dot{x_2} &= k_{12}x_1 - k_{21}x_2 \\ \dot{x_3} &= k_{13}x_1 - k_{31}x_3 \end{aligned} \tag{1}$$

$$BIS(t) = E_0 - E_{max}\frac{C_e(t)^\gamma}{C_e(t)+C_{50}^\gamma} \tag{2}$$

$$\dot{C_e} = -0.456C_e + 0.1068x_1 \tag{3}$$

where

BIS Bispectral index is an electroencephalogram-derived measure of anesthetic depth. C_e is the *effect-site compartment concentration* and there are some commercial devices

A. Gallardo Hernández, A. Hernández Pérez, C. Revilla-Monsalve and S. Islas-Andrade are with Unidad de Investigación en Enfermedades Metabólicas del Hospital de Cardiología, Centro Médico Nacional Siglo XXI (IMSS). Av. Cuauhtémoc 330 Col. Doctores C.P. 06725 México D.F.(e-mail: anagabygh@gmail.com, cristina_revilla@hotmail.com, sergioislas@prodigy.net.mx).

J. Eslava Escobar, L. Fridman R. Leder are with Universidad Nacional Autónoma de México (UNAM), Department of Control, Engineering Faculty. C.P. 04510. México D.F. (e-mail: lfridman@servidor.unam.mx, rleder@ieee.org).

J. Davila is with Instituto Politecnico Nacional, México D. F. (e-mail: jdavila@ieee.org)

This research is financially supported by the Mexican CONACyT (Consejo Nacional de Ciencia y Tecnología), grant no. 128251 and 132125 and the Programa de Apoyo a Proyectos de Investigación e Innovación Tecnológica (PAPIIT) UNAM, grant no. IN113613.

TABLE I

PARAMETER FOR THE SIMULATION OF THE *in silico* PATIENTS.

Patient	Gender	Age	Height	Weight	C_{50}	E_0	E_{max}	γ
1	F	40	163	54	6.33	98.8	94.1	2.24
2	F	36	163	50	6.76	98.6	86.0	4.29
3	F	28	164	52	8.44	91.2	80.7	4.1
4	F	50	163	83	6.44	95.9	102	2.18

used to estimate it. x_1 denotes the amount of drug in the central compartment (blood). x_2 represents the amount of drug in the well perfused peripheral tissues. x_3 is the amount of drug in the poorly perfused peripheral tissues. $u(t)$ is the infusion rate of the anesthetic drug (propofol).

The parameters for adults are calculated as follows:

$$\begin{aligned} V_1 &= 4.27L \quad V_3 = 238L \\ V_2 &= 18.9 - 0.391(age - 53)L \\ C_{l1} &= 1.89 + 0.0456(weight - 77) - 0.0681(lbm \\ &\quad -59) + 0.0264(height - 177) \\ C_{l2} &= 1.29 - 0.024(age - 53) \\ C_{l3} &= 0.836 \qquad (4) \\ lbm_{male} &= 1.1weight - 128\frac{weight^2}{height^2} \\ lbm_{female} &= 1.07weight - 148\frac{weight^2}{height^2} \\ k_{10} &= \frac{C_{l1}}{V_1} \quad k_{12} = \frac{C_{l2}}{V_1} \\ k_{13} &= \frac{C_{l3}}{V_1} \quad k_{21} = \frac{C_{l2}}{V_2} \quad k_{31} = \frac{C_{l3}}{V_3} \end{aligned}$$

where

V_1 is the central compartment's volume. k_{ji} with $j \neq i$ represent the drug amount transfer rate of drug from jth compartment to de ith compartment. k_{10} is the rate of drug metabolism. lbm is the lean body mass, and the sub-index indicates the gender of the patient. E_0 denotes the baseline (awake state). E_{max} is the maximum effect achieved by the drug infusion. C_{50} is the drug concentration at half maximal effect and represents the patients sensitivity to the drug.

III. HIGH ORDER SLIDING MODE CONTROLLER

The main parameter design for a HOSMC is the system's relative degree "r" [3]. It is defined as the order of the total time derivative of the system's output (BIS), where the input variable (u) explicitly appears for the first time. In this case the model's relative degree is $r = 2$, it means that the HOSMC u has to be of second order.

Let us denote the desired anesthetic-depth level as BIS_{target}. The sliding variable is defined as

$$\sigma = BIS_{target} - BIS(t) \qquad (5)$$

A second-order quasi-continuous high-order sliding-mode controller is proposed to bring to zero the sliding variable σ:

$$u = -\alpha \frac{\dot{\sigma} + \beta|\sigma|^{1/2} sign\, \sigma}{|\dot{\sigma}| + \beta|\sigma|^{1/2}} \qquad (6)$$

The 2nd order quasi-continuous controller (6) requires the availability of the first derivative of the sliding variable σ. In order to reconstruct such derivative exactly and in uniform finite-time, the uniform robust exact differentiator [11] can be used.

In the presence of bounded deterministic noise $|\nu(t)| \leq \nu^+$, the following equalities are ensured:

$$\begin{aligned} |\sigma| &\leq \eta_1 \nu^+ \\ |\dot{\sigma}| &\leq \eta_2 (\nu^+)^{1/2} \end{aligned}$$

Taking the second-order derivative of the system output we obtain:

$$\begin{aligned} &\ddot{y} = \phi(BIS, x_1, x_2, x_3, u) = -\left(0.456\mathrm{BIS} - 0.1068\mathrm{x_1}\right) \\ &\Big(\left(0.456\mathrm{BIS} - 0.1068\mathrm{x_1}\right)\Big(\tfrac{2\,\mathrm{E_{max}}\,\mathrm{BIS}^{\gamma}}{(\mathrm{BIS}+\mathrm{C_{50}}^{\gamma})^3} - \tfrac{2\,\mathrm{E_{max}}\,\gamma\,\mathrm{BIS}^{\gamma-1}}{(\mathrm{BIS}+\mathrm{C_{50}}^{\gamma})^2} \\ &+ \tfrac{\mathrm{E_{max}}\,\gamma\,\mathrm{BIS}^{\gamma-2}\,(\gamma-1)}{\mathrm{BIS}+\mathrm{C_{50}}^{\gamma}}\Big) - \tfrac{0.456\,\mathrm{E_{max}}\,\mathrm{BIS}^{\gamma}}{(\mathrm{BIS}+\mathrm{C_{50}}^{\gamma})^2} \\ &+ \tfrac{0.456\,\mathrm{E_{max}}\,\gamma\,\mathrm{BIS}^{\gamma-1}}{\mathrm{BIS}+125\,\mathrm{C_{50}}^{\gamma}}\Big) - 0.1068\mathrm{E_{max}}\,\mathrm{BIS}^{\gamma} \\ &\times (u - \mathrm{k_{10}\,x_1} - \mathrm{k_{12}\,x_1} - \mathrm{k_{13}\,x_1} + \mathrm{k_{21}\,x_2} + \mathrm{k_{31}\,x_3}) \\ &\times \tfrac{(\gamma\,\mathrm{BIS} - \mathrm{BIS} + \mathrm{C_{50}}^{\gamma}\,\gamma)}{\mathrm{BIS}\,(\mathrm{BIS}+\mathrm{C_{50}}^{\gamma})^2} \end{aligned}$$

Notice that, the control signal u appears explicitly in this derivative. As a consequence of the above obtained equality, it is clear that the control signal is applied to the system through the following function:

$$\varphi(BIS) = -0.1068\mathrm{E_{max}}\,\mathrm{BIS}^{\gamma}\,\frac{(\gamma\,\mathrm{BIS} - \mathrm{BIS} + \mathrm{C_{50}}^{\gamma}\,\gamma)}{\mathrm{BIS}\,(\mathrm{BIS} + \mathrm{C_{50}}^{\gamma})^2}$$

The nature of the process makes it impossible that BIS tends to infinity and, on the other hand, the proposed control avoids the possibility that $BIS = 0$. Then, it is possible to ensure that there exist constants C, K_m and K_M such that

$$\begin{aligned} \left|\frac{d^2(BIS_{target})}{dt^2} - \phi(BIS, x_1, x_2, x_3, 0)\right| &\leq C \\ K_m \leq |\varphi(BIS)| &\leq K_M \end{aligned}$$

Taking the second order derivative of the sliding variable σ, we obtain

$$\begin{aligned} \ddot{\sigma} &= \frac{d^2(BIS)}{dt^2} - \phi(BIS, x_1, x_2, x_3, u) \\ \ddot{\sigma} &= \frac{d^2(BIS_{target})}{dt^2} - \phi(BIS, x_1, x_2, x_3, 0) + \varphi(BIS)u \end{aligned}$$

Thus, the following differential inclusion (7) is satisfied

$$\ddot{\sigma} \in [-C \quad C] + [K_m \quad K_M]\, u \qquad (7)$$

The proof is in [12].

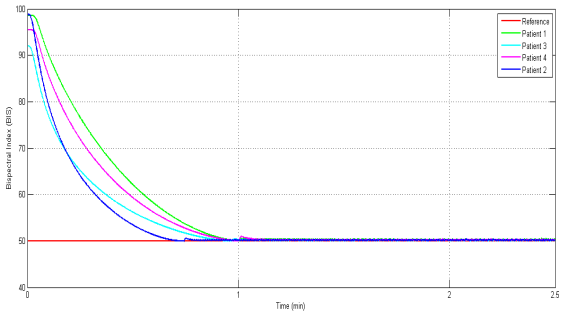

Fig. 1. BIS for the induction phase of the four *in silico* patients. It can be seen that there is no overdose.

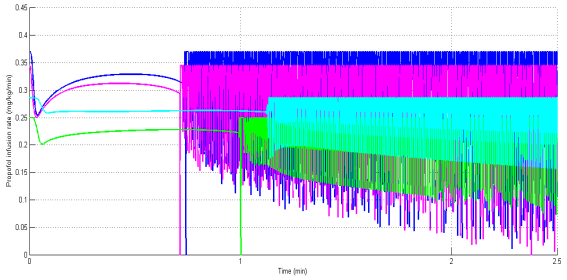

Fig. 2. Propofol infusion rate for the four *in silico* patients. As expected the same controler produces a differnt infusion rate for each patient. After the target $BIS = 50$ is reached the switching frequency is 1Hz, therefore it does not represent any danger for the infusion pump.

IV. *In silico* TRIAL

A. *Experiment 1:* ***Induction Phase***

In [13] the importance of a well controlled induction phase is stated, therefore the aim of the controller is to reach the ideal level for surgery $BIS_{target} = 50$, avoiding the overdose.

The inter-patient variability depends mostly on their age, weight and height, as it can be seen in (4), thus the *in silico* patients age for this study have mean $\overline{v}_{age} = 38.5 \pm 7.92$ years and the weight mean is $\overline{v}_{weight} = 59.75 \pm 13.49$. The parameters of the *in silico* patients can be seen in Table I, these values have been taken from [8].

The propofol infusion rate for surgery is 200 to500$\mu g/kg/min$. Usually the anesthesiologist fixes the rate at the maximum value and reduces the dose depending on the patient's response. In this study we use a maximum dose of $400\mu g/kg/min$.

In Figure 1 the output, BIS, of the four *in silico* patients is shown. It can be seen that all *in silico* patients reached the final target, $BIS_{target} = 50$, with no overdose. It is important to remark that the same HOSM controller (6) was used for all *in silico* patients. In Figure 2 propofol infusion rate (u) is shown. The dose of propofol is different for each *in silico* patient, however, that behaviour depends on the specific dynamic of each patient (see Table 1), it illustrates the insensibility of the HOSMC (6) to parameters variation. The controller (6) enforces the final target using discontinuous control, however the frequency of the switching is 1Hz, and this will not damage any infusion pump. This demonstrate that the same controller can produce the correct dose to achieve the BIS target even though patient's parameter were not used in the controller design.

B. *Experiment 2:* ***Surgical Stimuli***

Equally important to demonstrating the controller's insensitivity to inter-patient variability in the induction phase is to prove its robustness to perturbations during the surgery, such as surgical stimuli that can decreased the depth of anesthesia [14].

There are several surgical stimuli with different intensity in this study we considered two of them, incision that is

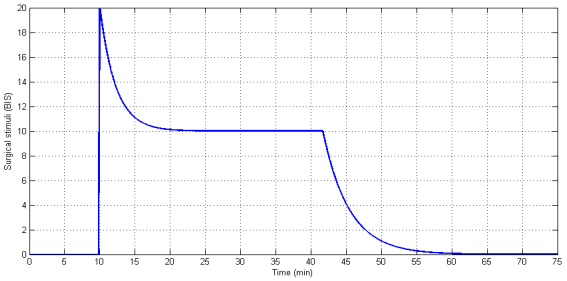

Fig. 3. Surgical stimuli considered in this study.

considered a high intensity stimulus, and surgical diathermy a medium intensity stimulus.

The incision stimulus ss_{in} was modeled as

$$ss_{in} = 10e^{(-1/135(t-250))} + 10 \tag{8}$$

where t is the time in seconds. And the surgical diathermy stimulus,ss_{dt} is

$$ss_{dt} = ss_{in}e^{-1/225(t-2500)} \tag{9}$$

The signal of the total perturbation ($ss_{in}+ss_{dt}$) considered can be seen in figure 3.

The simulation includes the induction phase, the perturbation of surgical stimuli during the maintenance phase and the emergence phase.

After the infusion phase, where there is no overshoot, a 1 hour surgery is considered when the surgical stimuli showed in Fig. 3 is perturbing the patients. It can be seen in minute 25 the notorious influence of the surgical stimuli, that is rapidly compensated by the controller. In the minute 60 the emergence phase begins. In Fig. 5 a zoom of the time when the surgical stimuli begins. In this figure, it can be seen that in less than 15 seconds the HOSMC (6) compensates the perturbation, and every patient is under 60 BIS, that is considered a good lever to perform a surgery. All the *in silico* patients have 50 BIS that is de optimal level with no overshoot in less than 1.5 minutes.

V. RESULTS

The HOSMC is a well suited algorithm to perform individual drug delivery because the parameter of the patients are

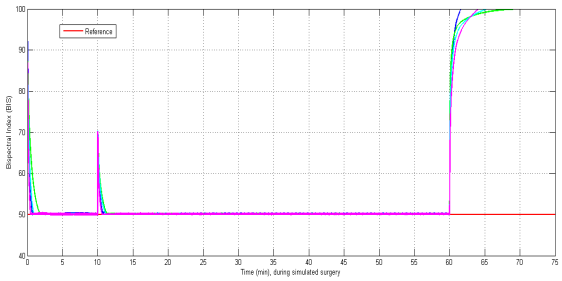

Fig. 4. BIS (output).

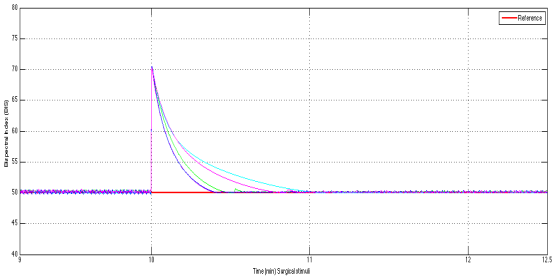

Fig. 5. BIS during the start of surgical stimuli.

not used in the design process. The performance of the controller was tested with the performance error in percentage (10), the bias of the error, or median performance error, (11). The median absolute performance error that represents the inaccuracy (12). Wobble (13) measures the controller ability to achieve a stable depth of anesthesia [7]. The results of the statistical analysis of controller's performance is shown in Table II.

$$PE = 100\frac{BIS(t)_{ij} - Bis_{target}}{Bis_{target}} \tag{10}$$

$$MDPE = median\{PE_{ij}, j = 1, \dots N\} \tag{11}$$

$$MDAPE = median\{|PE_{ij}|, j = 1, \dots N\} \tag{12}$$

$$Wobble = median\{|PE_{ij} - MDPE_i|, j = 1, \dots N\} \tag{13}$$

where i is the patient number, and j is the sample number.

TABLE II

STATISTICAL DATA EVERY *in silico* PATIENTS.

	P1	P2	P3	P4
PE	0.75	1.05	1.5	0.62
MDPE	0.305	0.447	0.337	0.318
MDAPE	0.305	0.447	0.337	0.318
Wobble	0.164	0.183	0.086	0.188

VI. CONCLUSIONS

The HOSMC designed was able to deal not only with the inter-patient variability, but it was also robust with respect to surgical stimuli, the patients were no more than 15 seconds outside the usual surgical range of BIS that is between 40 and 60, and this does not represent any danger for the patients. There was no propofol overdose for any patient. The fact that the controller is not model oriented makes it suitable to use for any patient even in emergency situations. The discontinuous control signal applied has a 1Hz frequency, therefore it does not represent any electro-mechanical danger for the infusion pump. In our on going will analyse signal noise and other types of depth of anesthesia metrics.

REFERENCES

[1] Y. Shtessel and P. Kaveh, "Blood glucose regulation using higher-order sliding mode control," *Int. J. of Robust and Nonlinear Control*, vol. 18, pp. 557–569, 2008.

[2] A. Gallardo Hernandez, L. Fridman, A. Levant, Y. Shtessel, R. Leder, C. Revilla Monsalve, and S. Islas Andrade, "High-order sliding-mode control for blood glucose: Practical relative degree approach," *Control Engineering Practice*, 2013. [Online]. Available: http://www.sciencedirect.com/science/article/pii/S0967066112002547

[3] A. Levant, *Sliding Modes after the First Decade of the 21st Century State of the Art*. Springer Verlag, 2011, vol. 412, ch. Finite-Time Stability and High Relative Degrees in Sliding-Mode Control.

[4] A. Rigouzzo, L. Girault, N. Louvet, F. Servin, T. De-Smet, V. Piat, R. Seeman, I. Murat, and I. Constant, "The relationship between bispectral index and propofol during target-controlled infusion anesthesia: A comparative study between children and young adults," *Anesthesia and Analgesia*, vol. 106, no. 4, pp. 1109–1116, April 2008.

[5] O. Simanski, A. Schubert, R. Kaehler, M. Jandat, J. Bajoratt, R. Hofmockel, and B. Lampe, "Automatic drug delivery in anesthesia: From the beginning until now," in *Control & Automation, 2007. MED'07. Mediterranean Conference on*. IEEE, 2007, pp. 1–6.

[6] S. Aspect Medical System, *BIS VISTA^{TM} Monitoring System, Operating Manual*, 2008.

[7] G. Dumont, A. Martinez, and J. Ansermino, "Robust control of depth of anesthesia," *International Journal of Adaptive Control and Signal Processing*, vol. 23, no. 5, pp. 435–454, 2009.

[8] C. Ionescu, R. De Keyser, B. Torrico, T. De Smet, M. Struys, and J. Normey-Rico, "Robust predictive control strategy applied for propofol dosing using bis as a controlled variable during anesthesia," *Biomedical Engineering, IEEE Transactions on*, vol. 55, no. 9, pp. 2161–2170, 2008.

[9] H. Ihmsen, K. Naguib, G. Schneider, H. Schwilden, J. Schüttler, and E. Kochs, "Teletherapeutic drug administration by long distance closed-loop control of propofol," *British journal of anaesthesia*, vol. 98, no. 2, p. 189, 2007.

[10] M. Struys, T. De Smet, L. Versichelen, S. Van de Velde, R. Van den Broecke, and E. Mortier, "Comparison of closed-loop controlled administration of propofol using bispectral index as the controlled variable versus standard practice controlled administration," *Anesthesiology*, vol. 95, no. 1, p. 6, 2001.

[11] E. Cruz-Zavala, J. Moreno, and L. Fridman, "Uniform robust exact differentiator," in *Decision and Control (CDC), 2010 49th IEEE Conference on*. IEEE, 2010, pp. 102–107.

[12] A. Levant, "Quasi-continuous high-order sliding-mode controllers," *IEEE Transaction on Automatic Control*, vol. 50, no. 11, pp. 1812–1816, 2005.

[13] N. Liu, T. Chazot, A. Genty, A. Landais, A. Restoux, K. McGee, P. Laloë, B. Trillat, L. Barvais, and M. Fischler, "Titration of propofol for anesthetic induction and maintenance guided by the bispectral index: closed-loop versus manual control: a prospective, randomized, multicenter study," *Anesthesiology*, vol. 104, no. 4, p. 686, 2006.

[14] C. Nunes, M. Mahfouf, D. Linkens, and J. Peacock, "Fuzzy logic to model the effect of surgical stimulus on the patient vital signs," in *Control & Automation, 2011. MED'11. Mediterranean Conference on*.