Proceedings of the 17th World Congress
The International Federation of Automatic Control
Seoul, Korea, July 6-11, 2008

Advanced Regulatory Controller for Automatic Control of Anesthesia ⋆

Sreenivas Yelneedi * **Lakshminarayanan S.** **
Rangaiah G.P. ***

* *National University of Singapore, Singapore 117576 (Tel: 65-93383549; e-mail: sreenivas@nus.edu.sg).*
** *National University of Singapore (e-mail: chels@nus.edu.sg)*
*** *National University of Singapore (e-mail: chegpr@nus.edu.sg)*

Abstract: Anesthesia process is to maintain a triad of hypnosis, analgesia and neuromuscular blockade by infusing several drugs which are specific for each state. This work focuses on controlling the hypnosis with RTDA (Robustness, Set-point tracking, Disturbance rejection, Aggressiveness) controller by regulation of propofol using Bispectral Index (BIS) as primary controlled variable. One of the main advantages of RTDA controller is its intuitive tuning parameters when compared to PID and MPC controllers. For the controller design, a fourth-order nonlinear pharmacokinetic - pharmacodynamic representation is used for the hypnosis dynamics of patients. Nominal values for pharmacokinetics and pharmacodynamics were taken from the literature. Then the performance of the RTDA controller is compared with the performances of the PID and MPC controllers. Robust performance of these controllers is tested for a selected range of patients by considering variability in parameters of the patient model. Also studied are the relative performances with respect to different set-points in BIS, and disturbances in BIS signal. Numerical simulations show that the RTDA controller provides better performance compared to the other two controllers.

Keywords: Automatic control; Hypnosis; RTDA; Bispectral index; propofol.

1. INTRODUCTION

During surgical process, anesthesiologists infuse several drugs by adjusting infusion devices to maintain an adequate level of anesthetic depth (a triad combination of hypnosis, analgesia and muscle relaxation). Measurement and control of hypnosis during surgery is one of the important problems in biomedical field (Bibian et al. [2005]). Hypnosis is related to unconsciousness and also to the inability of the patient to recall events (amnesia). An automatic controller that infuses drugs based on patient's anesthetic level provides more benefits, such as: (i) reduction of anesthetist's workload during the surgery and letting him/her to monitor and deal with other critical aspects of the surgery, (ii) more frequent sampling of the controlled variable results in frequent adjustment of the drug delivery rate and leads to better performance when compared to manual administration, (iii) the drug dosage is tailored to the patients' requirements and response characteristics leading to minimal drug consumption, intra-operative awareness and recovery times, decrease in the cost of surgery and postoperative care, and (iv) both over-dosage and under-dosage of the drugs are avoided. Overall, this improves the patient's rehabilitation and safety during and after the surgery (Bailey et al. [2005]).

However, in order to design a feedback controller for controlling hypnosis, a reliable mathematical model of the patient to represent hypnosis and also appropriate hardware devices to measure and monitor the level of hypnosis are required. In general, mammillary compartmental models are widely used to describe the pharmacokinetics (PK) and pharmacodynamics (PD) of inhalationally and intravenously administered drugs (Bibian et al. [2005]). The mathematical model employed in recent studies on hypnosis control is a series combination of a linear PK model and a nonlinear PD model. A theoretical effect compartment is also attached to the central compartment to represent the time-lag in the patient response to anesthesia. The values for parameters used in the PK and PD models are the population mean values and so the "patients" would have parameters that are different from the nominal values used in the controller design. Hence, the designed controller should be robust and result in stable responses for all the patients (Grieder et al. [2001]). A commercial monitor (approved by U.S. Food and Drug Administration (FDA)) from Aspect Medical systems (Newton, MA, USA), is available to measure the depth of hypnosis in terms of Bispectral Index (BIS). BIS is an Electroencephalogram (EEG) derived variable that quantifies the power and phase couplings of the EEG at different frequencies (Rampil [1998]).

Propofol is a common intravenous anesthetic drug that is widely used for both induction and maintenance of general anesthesia during surgical operations. Its favorable pharmacokinetic profile and inhibition of postoperative nausea and vomiting makes it a popular anesthetic drug. Many

⋆ This work was supported by the National University of Singapore, Singapore in the form of a research scholarship to the first author.

closed-loop feedback systems for anesthesia control based on propofol infusion have been proposed in the literature. These works employ various surrogate measurements such as EEG as the measured variables (Struys et al. [2006]). Although the proposed closed-loop systems work well in clinical anesthesia, Struys et al. [2004] proposed a simulation methodology to test the performance of the two published controllers (Proportional-Integral-Derivative (PID) and model based controllers) under extreme conditions (sudden increase in BIS). They claimed that model based controller outperformed the conventional PID controller.

The contribution of this article is to demonstrate the application of a recently proposed regulatory controller, namely RTDA (Robustness, Set-point tracking, Disturbance rejection, Aggressiveness) controller for control of hypnosis. The RTDA controller (Ogunnaike et al. [2006]) is developed for SISO (single-input, single-output) processes and combines the simplicity of PID controller with the advantages of Model Predictive Controller (MPC). The RTDA controller is designed here to control hypnosis using BIS as the controlled variable by manipulating propofol infusion rate. We also compare the performance of RTDA controller with that of MPC (Morari et al. [1999], Furutani et al. [2005]) and PID controller. Acknowledging the presence of inevitable patient-model mismatch, simulations were conducted to check the robustness of all these controllers. The three controller schemes were also tested for set-point change, and disturbance rejection. These simulations show that RTDA and MPC controllers perform better than the PID controller; furthermore, RTDA controller shows relatively best performance.

2. MATHEMATICAL MODEL FOR BIS RESPONSE

The model developed for BIS response to propofol infusion consists of two interacting parts: a PK model for estimating the distribution of propofol in the internal organs, and a PD model to describe the effect of propofol on the measured physiological variable, *i.e.*, BIS. Figure 1 depicts a schematic of the system - comprising of propofol delivery circuit, the PK and PD models.

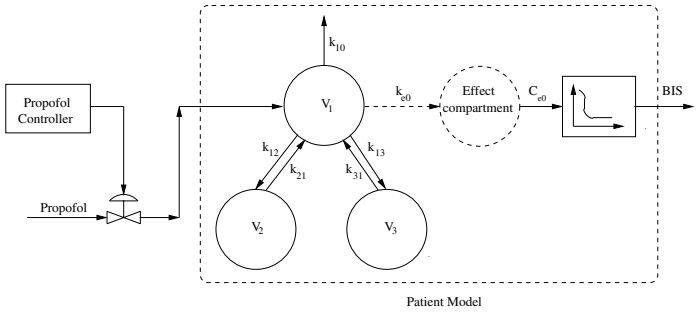

Fig. 1. Schematic representation of propofol delivery circuit with PK and PD models

For the distribution of propofol, a mammillary three compartmental PK model is adopted from literature (Marsh et al. [1991]). The model was assumed to be linear with three compartments and elimination from the central compartment, V_1. In this compartment (plasma compartment), the drug dissolves and is carried to the other two compartments. The second compartment is a shallow peripheral compartment, V_2, which is characterized by a very rapid movement of the drug from the plasma to this compartment. This is the characteristic of certain tissues which are well perfused (vessel-rich group). The third compartment is a deep peripheral compartment, V_3, which is characterized by a slow distribution of the drug from the central compartment to this compartment. This is because of the equilibration of the blood with tissues which are less well perfused.

Initially, the PK part assumes that all compartments (Figure 1) have a zero concentration of the drug (propofol). To achieve rapid target plasma drug concentration, (*i.e.*, concentration in V_1), sufficient drug must be given as a bolus dose. If the plasma drug concentration is to be kept constant, the amount of drug entering it and leaving it must be equal. Drug leaves the blood to pass into V_2 and V_3 at a gradually decreasing rate as the concentrations in these compartments increase. Drug also leaves the blood because it is metabolized (mainly in the liver). The PD part assumes some time delay between the infusion of propofol in the bloodstream and the dissolving of propofol in brain tissue thereby affecting the hypnosis level. This effect on hypnosis level is represented by a nonlinear equation relating the state variables and other system variables to BIS.

2.1 Pharmacokinetic model of Propofol

Figure 1 shows the PK model for distribution of drug and is described by a mass balance between the two compartments which are attached to the central compartment. The main assumptions here are that the central compartment is a well mixed tank with the plasma propofol concentration being uniform everywhere and the distribution of propofol is not affected by the presence of other drugs. Hence, the resulting mass balance for propofol in the central compartment is given by (1).

$$\frac{dC_1}{dt} = \sum_{j=2}^{3} \left(k_{j1} C_j \frac{V_j}{V_1} - k_{1j} C_1 \right) - k_{10} C_1 + \frac{\rho}{\bar{k} V_1} U \quad (1)$$

where C_1, C_2, and C_3 are concentrations of propofol (μg/ml) in the first (central), second and third compartments respectively; V_1, V_2, and V_3 are the respective volumes (ℓ); k_{12}, k_{13}, k_{21}, and k_{31} are the mammillary rate constants (min^{-1}) of the respective compartments, k_{10} is the hepatic metabolism rate constant to represent the elimination rate of propofol from the patient (min^{-1}); ρ = 10 (mg/ml) is the available propofol concentration; $\bar{k}$ = 60 (min/hr) is a normalization constant; and U is the infusion rate of propofol (ml/hr). To convert U in ml/hr to u in $mg/kg/hr$ (normalized propofol infusion rate with respect to patient weight), it is multiplied by ρ/w, where w is the weight of the patient in kg. Similarly for the second and third compartments, the corresponding mass balance is

$$\frac{dC_j}{dt} = k_{1j} C_1 \frac{V_1}{V_j} - k_{j1} C_j, \qquad j = 2, 3 \quad (2)$$

With the availability of different sets of PK parameters reported by various research groups, it is difficult to select a specific PK parameter set from all the available sets. Usually with all the PK sets, there is a difference

between predicted and actual concentrations. This is not so important provided the actual concentrations are within the desired therapeutic window. The usefulness of target-controlled infusion lies in the ability to dose more accurately, to maintain stable drug concentrations (and therefore stable effects) and to make proportional changes to the concentrations. Coetzee et al. [1995] worked with several PK parameter sets and concluded that the parameters provided by Marsh et al. [1991] are the most accurate ones. Values of these parameters in (1) and (2) for the Marsh model are summarized in Table 1.

Table 1. Parameters of the PK model for 34 year old and 66 kg subject (Marsh et al. [1991])

Parameter	Value
$k_{10}(min^{-1})$	0.119
$k_{12}(min^{-1})$	0.112
$k_{21}(min^{-1})$	0.055
$k_{13}(min^{-1})$	0.0419
$k_{31}(min^{-1})$	0.0033
V_1 (ℓ)	15.05
V_2 (ℓ)	30.6
V_3 (ℓ)	191.1

2.2 Pharmacodynamic model of Propofol

The above PK model is limited to the representation of distribution kinetics of propofol into different compartments. A PD model is required to measure the effect of drug on the anesthetic level. The PD model consists of an effect-site compartment model which represents the time-lag between the distribution of drug and its effect on BIS which is given by the nonlinear Hill equation. The effect-site compartment accounts for the equilibration time between plasma drug concentration and central nervous system (brain) concentration. The effect-site concentration, C_e and plasma drug concentration, C_1 are related by a first-order lag given by

$$\frac{dC_e}{dt} = k_{e0}(C_1 - C_e) \tag{3}$$

where k_{e0} is the time course of equilibration between the plasma and the effect-site. The effect-site concentration is related to BIS as (Hill equation):

$$\triangle \text{BIS} = \triangle \text{BIS}_{\text{MAX}} \frac{C_e^{\gamma}}{C_e^{\gamma} + EC_{50}^{\gamma}} \tag{4}$$

where, $\triangle \text{BIS} = \text{BIS} - \text{BIS}_0$

and $\triangle \text{BIS}_{\text{MAX}} = \text{BIS}_{\text{MAX}} - \text{BIS}_0$

and EC_{50} is the concentration of drug at half maximal effect and represents the patient's sensitivity to the drug, and γ is a dimensionless parameter that determines the degree of nonlinearity. BIS has the range 0 to 100, where $\text{BIS}_0 = 100$ denotes a fully conscious state and $\text{BIS}_{\text{MAX}} = 0$ denotes nil cerebral electrical activity, *i.e.*, deep coma. With this information, (4) can be written as:

$$\text{BIS} = 100 - 100 \frac{C_e^{\gamma}}{C_e^{\gamma} + EC_{50}^{\gamma}} \tag{5}$$

The parameters $k_{e0} = 0.349\ min^{-1}$, $EC_{50} = 2.65$ μg/ml and $\gamma = 2.561$ were the nominal values obtained from the pooled analysis (Schnider et al. [1999]).

3. CONTROLLER DESIGN

RTDA controller uses a First-Order Plus Time-Delay (FOPTD) approximation of the process - essentially the same information used to design and tune a PID controller. The main advantage of the RTDA controller is that it has independent parameters θ_R, θ_T, θ_D and θ_A that permits the user to directly and independently alter the robustness, set-point tracking, disturbance rejection and aggressiveness of the controller. Furthermore, these tuning parameters are normalized to lie between 0 and 1 (Mukati et al. [2004]). The main features and the governing equations of the RTDA controller as described in (Mukati et al. [2004]) are given below for the benefit of the readers.

The FOPTD model can be written as:

$$y(s) = \frac{Ke^{-\alpha s}}{\tau s + 1} u(s) \tag{6}$$

where y, u, K, α, and τ respectively represents process output, input, gain, time delay, and time constant. Since RTDA controller is designed in digital form, the discretised form of (6) is given by:

$$\hat{y}(k+1) = a\hat{y}(k) + bu(k-m); \qquad k = 0, 1, 2, \ldots \tag{7}$$

where, $a = e^{\frac{-\Delta t}{\tau}}$; $b = K\left(1 - e^{\frac{-\Delta t}{\tau}}\right)$; $m = \text{round}\left(\frac{\alpha}{\Delta t}\right)$ and Δt is the sampling time.

In the derivation of the control law, it is assumed that at each time instant k, the current control move $u(k)$ is held constant over the prediction horizon N beyond the delay period, m. The control move $u(k)$ is chosen so as to bring the predicted process output as close as possible to the reference trajectory. Based on this strategy, predicted process output is given by:

$$\hat{y}(k+m+i) = a^{m+i}\hat{y}(k) + a^{i-1}b\mu(k,m) + b\eta_i u(k) \tag{8}$$

$1 \le i \le N$, with $\mu(k,m) = \sum_{i=1}^{m} a^i u(k-i)$, and $n_i = \frac{1-a^i}{1-a}$.

The use of a FOPTD model in place of the *true* model, results in modeling error between the actual process output and the model predicted output, $e(k) = y(k) - \hat{y}(k)$. The modeling error, $e(k)$ can be grouped into two types of estimates $e_m(k)$ and $e_D(k)$ as given by:

$$e(k) = e_m(k) + e_D(k) \tag{9}$$

where $e_m(k)$ represents the inherent modeling uncertainties and $e_D(k)$ represents the effects of unmeasured disturbances. By using Bayesian estimation procedure, $e_D(k)$ can be estimated as:

$$\hat{e}_D(k) = \theta_R \hat{e}_D(k-1) + (1 - \theta_R) e(k) \tag{10}$$

where θ_R $(0 < \theta_R < 1)$ serves as the tuning parameter for robustness of the controller. With the current error estimate, the future error is then estimated to update the model prediction. This can be written as:

$$\hat{e}_D(k+j\,|k) = \hat{e}_D(k) + \frac{(1-\theta_D)}{\theta_D}\left[1 - (1-\theta_D)^j\right] \nabla \hat{e}_D(k) \tag{11}$$

for $m+1 \le j \le m+N$, where,

$$\nabla e_D(k) = e_D(k) - e_D(k-1) \tag{12}$$

and θ_D $(0 < \theta_D < 1)$ serves as the tuning parameter for disturbance rejection. Using the above outlined error estimation, the future prediction of $y(k+m+i)$ over the N-step prediction horizon is given by updating the model prediction in (8) with (11) is represented as:

$$\tilde{y}(k+m+i) = \hat{y}(k+m+i) + \hat{e}_D(k+m+i\,|k) \quad (13)$$

For the purpose of set-point (y_d) tracking, a desired set-point trajectory (y^*) needs to be defined. The control action is computed based on at each instant k, the single control move, $u(k)$, is determined to minimize the error between predicted output from the desired set-point trajectory, y^*, over the next N discrete steps in the future. The desired set-point trajectory for the set-point, y_d, is given by:

$$y^*(k+j) = \theta_T^j y^*(k) + \left(1-\theta_T^j\right) y_d(k); \quad 1 \le j \le \infty \quad (14)$$

with θ_T $(0 < \theta_T < 1)$ serves as the tuning parameter for set-point tracking.

The tuning parameter for overall controller aggressiveness, θ_A, depends on the value of N and which is given by:

$$\theta_A = 1 - e^{-\left(\frac{(N-1)\Delta t}{\tau}\right)} \quad (15)$$

Having defined a reference trajectory and derived the model prediction with error correction, the current *optimal* control action $u(k)$ may be obtained analytically as:

$$u(k) = \frac{1}{b}\frac{\sum_{i=1}^{N}\eta_i\psi_i(k)}{\sum_{i=1}^{N}\eta_i^2} \quad (16)$$

where

$$\psi_i(k) = y^*(k+i) - a^{m+i}\hat{y}(k) - a^{i-1}b\mu(k,m) - \hat{e}_D(k+m+i\,|k)$$

4. RESULTS AND DISCUSSION

This section provides a comparison between the performances of RTDA, MPC and PID controllers. Because, FOPTD model is used to design and tune RTDA and PID controllers, the four state, nonlinear patient model is approximated to FOPTD model through process reaction curve method. Figure 2 depicts the degree of approximation obtained.

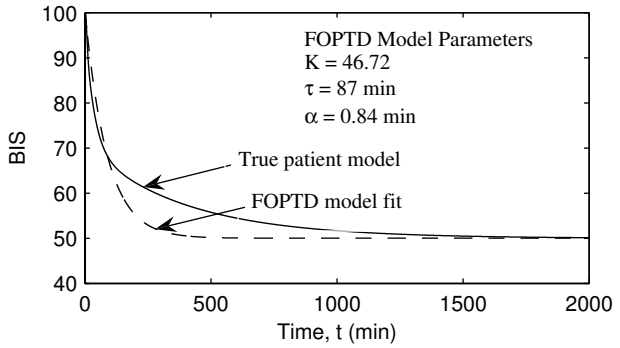

Fig. 2. FOPTD model fit to true patient model response

The four parameters of this controller are tuned for the best performance *i.e.*, minimum Integral of the Absolute Error (IAE) value (Seborg et al. [2004]) based on set-point changes to BIS from 100 to 50 (the BIS value recommended during surgery). Figure 3 depicts the performance of the RTDA controller for different values of θ_T and based on the performance, a value of 0.044 is selected. These settings ($\theta_R = 0.037$, $\theta_D = 0.937$, $\theta_A = 0.812$, and $\theta_T = 0.044$) will be used for further performance comparisons. The sampling time of all the controllers is set to 0.0833 *min* which is equal to the sampling time of BIS.

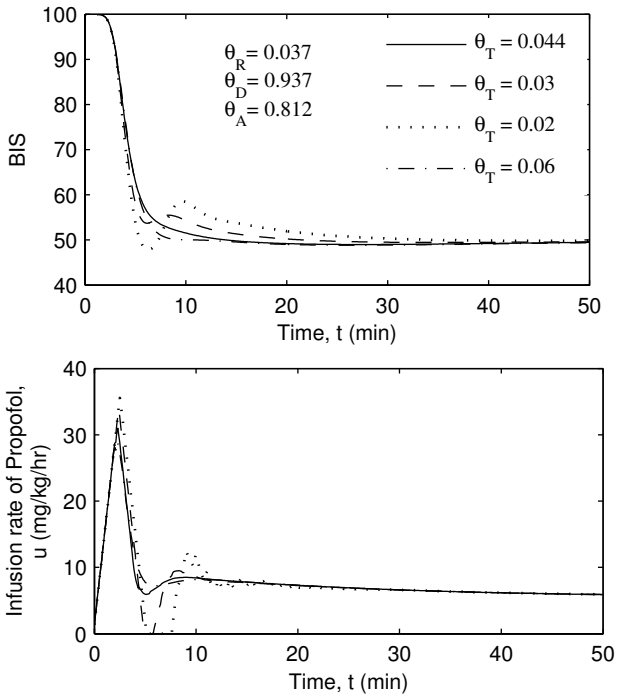

Fig. 3. Performance of the RTDA controller for different values of θ_T

The tuning parameters for the PID controller are proportional gain (K_c), integral time (τ_I), and derivative time (τ_D) - the values set for these parameters respectively are 0.053, 0.0041, and 0.1506. The tuning parameters for the MPC controller are prediction horizon, control horizon, weights (penalty) on incremental control moves and weight on output which are respectively taken to be 12, 2, 1 and 50.

4.1 Performance comparison for a step change in BIS during surgery

The anesthesiologist can anticipate periods that involve high surgical stimulation (requires higher sedation) and periods during which light sedation is sufficient during the surgery. For example, if surgical stimulation is severe at any time during the surgical process, the patient needs to be more unconscious and hence the BIS value should be decreased to some lower value (*e.g.* 40). Afterwards, towards the end of the surgery, the patient needs to be less unconscious and the BIS set-point may be increased from 40 to 60. The three controllers are now tested for different step changes in BIS value on the nominal patient. Figure 4 depicts the performance of the three controllers for a step change in BIS from 50 to 40 at $t = 50$ *min* and from 40 to 60 at $t = 100$ *min*. Better transition of the BIS is obtained with RTDA and MPC controllers when compared to PID

controller. Also, the PID controller has a relatively longer settling time.

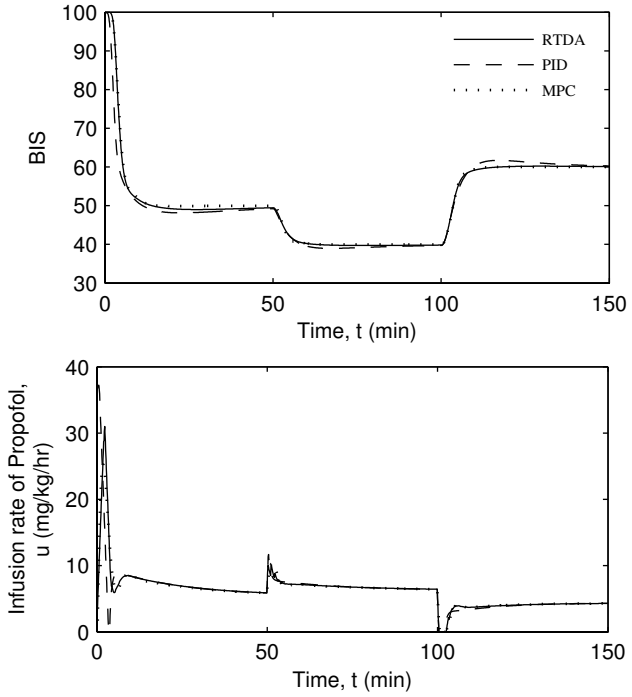

Fig. 4. Performance of the three controllers for different set-point changes during the surgery

4.2 Robustness comparison

This section discusses the robustness of the three controllers based on the IAE values. We would like to test if all of these three controllers can meet the performance specifications (BIS between 40 to 60) despite significant and reasonable variation in the model parameters (inter- and intra-patient variability). Here, we assume that variability is in both the PK and PD model parameters. There is a variation of 25 % in PK model parameters (Schnider et al. [1998]) and the possible range of PD parameters has been assumed (Schnider et al. [1999]). After a sensitivity test of the parameters, 17 patients (representing the *population* of patients) are selected and used for comparing the robustness of the three controllers.

Figure 5 depicts the closed-loop performance of the RTDA controller with 17 patient sets. The top subplot shows the tracking performance with respect to BIS set-point 50. With all these sets, the BIS value reached the set-point with some undershoot and time delay based on the patient's sensitivity to the drug. Insensitive patient (IAE = 324) has sluggish response whereas sensitive patient (IAE = 141) has faster response when compared to the response of the nominal patient (IAE = 217). The bottom subplot of Figure 5 represents the propofol infusion rate, u. In line with the above observations, more drug is injected to the insensitive patient and less drug is infused into the sensitive patient as compared to the nominal patient.

Figure 6 shows the comparison of the performance (IAE values) of all the three controllers for BIS set-point 50 for these 17 patient models. In this plot, the average IAE value

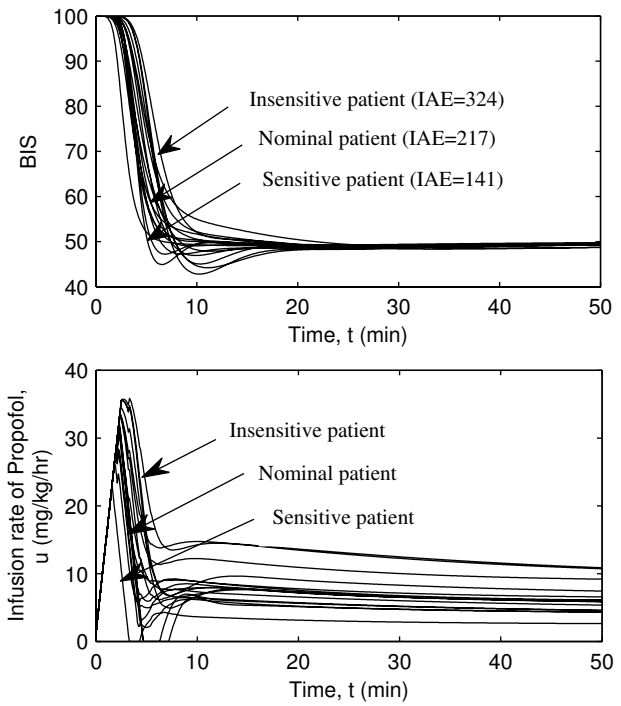

Fig. 5. Robust performance of the RTDA controller for different sets of patient model parameters

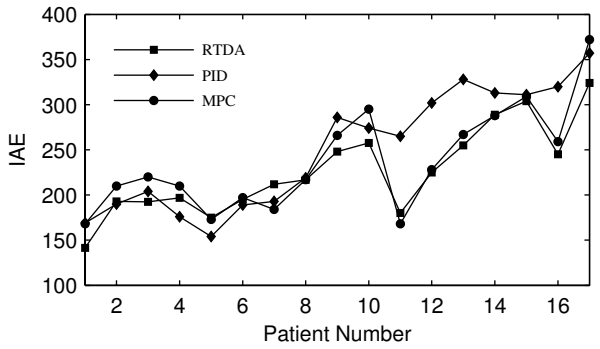

Fig. 6. IAE for all the 17 patient models for BIS set-point 50

is lower for the RTDA controller (IAE = 226) and highest for the PID controller (IAE = 250). The IAE value for the MPC controller is 237 - this is slightly higher than that obtained for the RTDA controller.

4.3 Performance comparison for a sudden disturbance in BIS signal

Faults can occur with any of the equipment or variables during surgery. BIS signal may be corrupted by artifacts such as measurement noise or a disturbance in BIS signal which causes arousal reflex. For better control performance, noise and disturbance in the BIS signal must be handled appropriately (*e.g.* filtering for noise removal). If not, the incorrect and unreliable values of the measured signals can result in wrong drug dosage delivered to the patient. Here, simulations are carried out by adding a disturbance pulse of strength 20 in the BIS signal (Struys et al. [2004]) from $t = 50$ to 80 *min.*

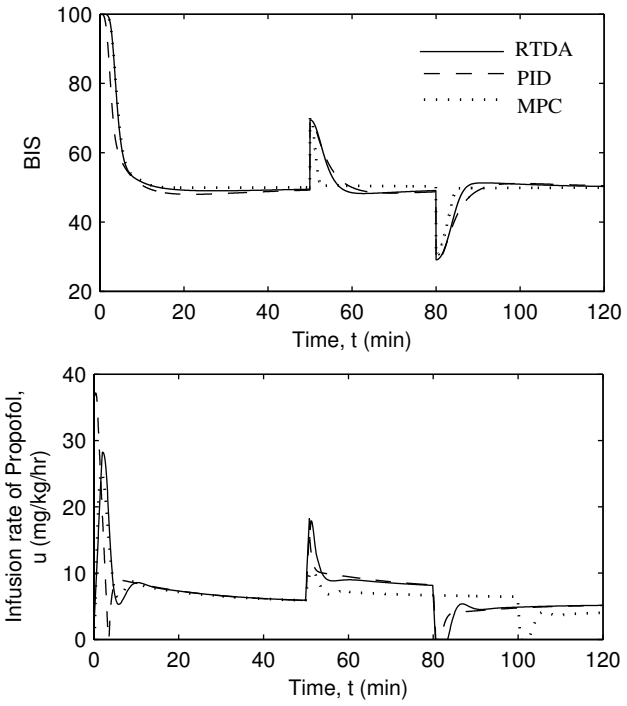

Fig. 7. Performance of the three controllers for disturbance during the surgery

Figure 7 depicts the performance of all the controllers with disturbance in the BIS signal for the nominal patient. The top subplot shows the BIS signal (BIS set-point = 50) and the bottom subplot shows the propofol infusion rate profile. Here also, the performance of RTDA controller (IAE = 403) is slightly better than MPC (IAE = 407) performance. The PID controller performs poorly (IAE = 450) compared to RTDA and MPC.

5. CONCLUSION

This work illustrates the applicability of the novel RTDA controller for controlling hypnosis. The RTDA controller performs significantly better than the PID controller and does slightly better than the MPC controller in regulating hypnosis when tested on patient models. The RTDA controller also appears to be robust in the context of variation in patient parameters.

REFERENCES

J.M. Bailey, and W.M. Haddad. Drug dosing control in clinical pharmacology. *IEEE Control Systems Magazine*, 25:35–51, 2005.

S. Bibian, C.R. Ries, M. Huzmezan, and G.A. Dumont. Introduction to automated drug delivery in clinical anesthesia. *European Journal of Control*, 11:535–557, 2005.

J.F. Coetzee, J.B. Glen, C.A. Wium, and L. Boshoff. Pharmacokinetic model selection for target controlled infusions of propofol: assessment of three parameter sets. *Anesthesiology*, 82:1328–1345, 1995.

E. Furutani, and M. Araki. Computer control of physiological states of patients under and after surgical operation. *Annual Reviews in Control*, 29:229–236, 2005.

P. Grieder, A. Gentilini, M. Morari, and T.W. Schnider. Robust adaptive control of hypnosis during anesthesia. *Proceedings of the 23rd Annual International Conference of the IEEE Engineering in Medicine and Biology Society*, pages 2055-2058, 2001.

B. Marsh, M. White, N. Morton, and G.N. Kenny. Pharmacokinetic model driven infusion of propofol in children. *British Journal of Anaesthesia*, 67:41–48, 1991.

M. Morari, and J.H. Lee. Model predictive control: past, present and future. *Computers & Chemical Engineering*, 23:667–682, 1999.

K. Mukati, and B. Ogunnaike. Stability analysis and tuning strategies for a novel next generation regulatory controller. *Proceedings of the American Control Conference*, pages 4034–4039, 2004.

B.A. Ogunnaike, and K. Mukati. An alternative structure for next generation regulatory controllers - Part I: Basic theroy for design, development and implementation. *Journal of Process Control*, 16:499–509, 2006.

I.J. Rampil. A primer for EEG signal processing in anesthesia. *Anesthesiology*, 89:980–1002, 1998.

T.W. Schnider, C.F. Minto, P.L. Gambus, C. Andresen, D.B. Goodale, S.L. Shafer, and E.J. Youngs. The influence of method of administration and covariates on the pharmacokinetics of propofol in adult volunteers. *Anesthesiology*, 88:1170–1182, 1998.

T.W. Schnider, C.F. Minto, S.L. Shafer, P.L. Gambus, C. Andresen, D.B. Goodale, and E.J. Youngs. The influence of age on propofol pharmacodynamics. *Anesthesiology*, 90:1502–1516, 1999.

D.E. Seborg, T.F. Edgar, and D.A. Mellichamp. *Process Dynamics and Control*. pages 297–330. John Wiley & Sons, New York, 2nd edition, 2004.

M.M.R.F. Struys, T. De Smet, S. Greenwald, A.R. Absalom, S. Bing, and E.P. Mortier. Performance evaluation of two published closed-loop control systems using bispectral index monitoring: a simulation study. *Anesthesiology*, 100:640–647, 2004.

M.M.R.F. Struys, E.P. Mortier, and T. De Smet. Closed loops in anaesthesia. *Best Practice & Research Clinical Anaesthesiology*, 20:211–220, 2006.