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# Advanced Model Based Control Strategy for Dynamic Dose of Propofol

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***Abstract :*** The main challenges in the control system for automatic infusion of anesthetic drugs are the patient drug tolerance variability due to differences in demographic. This paper describes the design and investigation of Internal Model Control based nonlinear fourth order compartmental mathematical model featuring pharmacokinetics and pharmacodynamics information. The main objectives of our paper are to calculate the robustness properties of the Internal Model Controller with respect to inherent drug response variability, to get the best output, disturbance elimination and to achieve optimal set point response. This control strategy has 8 different parameters that very from patient to patient depending upon patient's drug sensitivity. The control strategy is evaluated on a set of 10 patients models for the regulation of the hypnosis by EEG index (BIS - a surrogate measure of hypnosis derived from the electroencephalogram of the patient) using propofol as the administrated hypnotic agent. The simulations results show fast response, correctness of dose delivery and robustness to induce and maintain the desired BIS set point. The simulation results are evaluated and compared with PID controller. A large amount of improvement (13% to 60%) in performance error is achieved by the designed IMC controller

***Keywords :*** Current mode device; Anesthesia; Closed Loop Control; EEG index (BIS-bispectral index);Internal Model Controller; Hypnosis; Propofol; Integration of Absolute Error (IAE).

## 1. INTRODUCTION

Anesthesia automation with feedback control plays a key role during surgery and Intensive care unit (ICU) [1]. During surgery the role of anesthesia is to maintain balance effect of a combination of unconsciousness, antinociception and immobility. Adequate depth of anesthesia is desirable during surgical procedure [2]. Deep anesthesia, resulting in cardiovascular depression and prolonged awaking times and light anesthesia, resulting in frightening from the patients point of view. Manual feedback control based strategies do not calculate any measured variable in control system and even if they reach the desired level of anesthetic depth very fast, it can result in unsafe marginal BIS values (produce undershoot) [3]. The main contribution of our paper is to design and to investigate advance model based automation technique to reduce the anesthetist workload of some routine actions and therefore improve the safety of the patient.

Main challenges in automatic drug infusion control strategy for anesthesia are the variable characteristic of the patient body due to variances in drug tolerance, multivariable characteristics, changeable time delays, effect of hypnotic agent depends on patient body dynamics, model analysis variability, agent and stability issues [4]. A commercial BIS monitor analyze patient's electroencephalogram (EEG) data during complete surgery and evaluate the special effects of particular anesthetic drugs on the patient's brain response [5]. It is a numerical index, ranging from 100 (indicating a fully awake and alert patient) to 0 (EEG silence or absence of brain activity). An index value in the range 40-50 represents adequate anesthesia state. Major gain of automation scheme in continuous infusion of intravenous drug for general anesthesia is a popular method to maintain a single BIS value during maintenance phase

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of anesthesia [6]. Many patients' mathematical models proposed in latest research studies on hypnosis regulation. Patient model is a series combination of a linear pharmacokinetic (PK) model and a nonlinear pharmacodynamics (PD) model. Ioana Nascu *et al.* [7] have estimated PKPD model parameters from data gathered in the first 10 minutes, after a bolus dose is infused into the patient body during induction phase of anesthesia. Absalom *et al.* and G. Kenny *et al.* [5][8] proposed the design of PID control system based on BIS value to manipulate the propofol administration. Anesthesia automation techniques suggested by Absalom *et al.* and G. Kenny *et al.* were clinically accepted during general anesthesia. Dumont *et al.* [9] designed robust PID controller based on fractional calculus to maintain correct depth of anesthesia (DOA) intravenously. These traditional controllers have no prior knowledge about the anesthetics drug metabolism, these controllers cannot expect the reaction of the patient body and their output may not be optimal. PID tuning parameters are not continuously clear about how the process model of patient body affects the tuning design. To overcome it, designed IMC control scheme calculates the optimal control action considering parameters discrepancies in the selected model to account for patient model mismatch, constraints on the input, output and state variables. IMC is designed based on an assumption that closed loop performance of actual process and implemented model generate the model mismatch error. So we studied process model uncertainty (model plant mismatch) more cautiously and estimated its influence on the predictable result of the control system. Extensive simulations are conducted to examine the robustness, disturbance rejection and intraoperative set point changes during surgery. Main contribution of our study is to express the BIS based hypnosis control using IMC and compared robustness with traditional PID controller.

This paper is organized as follows: section II discusses, patient PKPD mathematical modeling. Section III presents the design steps of Internal Model Control (IMC) controller. The simulation results are presented and discusses for the hypnosis index regulation during induction and maintenance phase of surgery in Section IV. Section V summarizes the outcomes of the paper.

## 2. MODEL OF HYPNOSIS TO MANIPULATE DRUG INFUSION

The design of a controller for intravenous infusion of anesthetics requires reliable PKPD mathematical models of the patient to represent the depth of anesthesia [11]. Schematic representation of PKPD model is shown in Figure 1. We construct our study based on The Schüttler–Ihmsen fourth-order model for bolus and continuous infusion of propofol, proposed by Sawaguchi *et al*. [12]. Equations are given by (1)

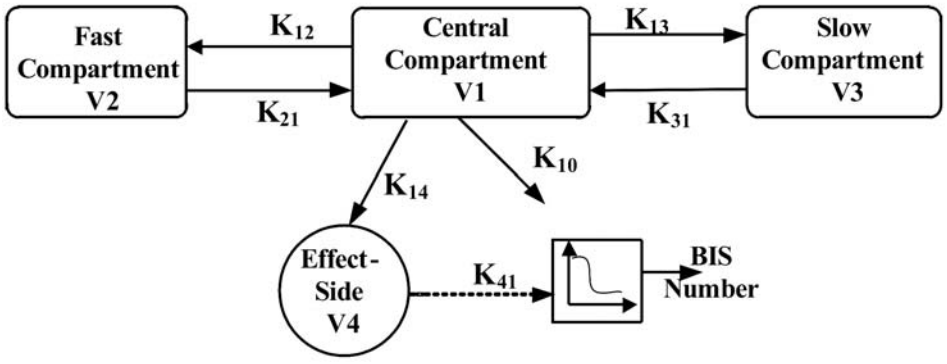


**Figure 1: 4th Compartmental PKPD model of the patient**

$$\dot{C}_1 = -\left[(K_{10}+K_{12}+K_{13}+K_{14})/V_1\right]C_1(t)+\frac{K_{21}}{V_1}C_2(t)+\frac{K_{31}}{V_1}C_3(t)+\frac{K_{41}}{V_1}C_e(t)+U(t)\frac{1}{V_1}$$

$$\dot{C}_2 = \frac{K_{12}}{V_2}C_1(t)-\frac{K_{21}}{V_2}C_{2(t)}$$

$$\dot{C}_3 = \frac{K_{13}}{V_3}C_1(t)-\frac{K_{31}}{V_3}C_{3(t)}$$

$$\dot{C}_4 = \frac{K_{14}}{V_4} C_1(t) - \frac{K_{41}}{V_4} C_{4(t)}$$

Here $C_i$ ($i$ = 1, 2, 3, $e$) are the central, other two peripheral and brain compartment concentration of propofol (ug/ml). Respectively: $V_i$ ($i$ = 1, 2, 3, 4) are the respective volumes (L) of compartments. $K_{ij}$ ($i, j$ = 1, 2, 3, 4) are distributive micro rates in (min-1) between central compartment and others peripherals compartments. And U($t$) is an administration rate of propofol in (mg/kg/$h$). $K_{10}$ is an elimination rate of drug from body through kidney and liver organ's. The volume of the brain $V_4$ is one hundredth of the central compartment. Value of $V_4$ equal to $V_1$/100. Many studies have ignored the volume of effect side compartment because this volume is negligible. That assumption may be irrelevant for hypnotic agents. Value of $K_4$ was taken to 0.12 L/min to create the median peak time [12]. Here, one assumption is $K_{14} = K_{41}$. The parameters of $K_{ij}$ and $i \neq j$, these PK model parameters depends on age and weight of the patient. We can calculate the constants using the following equations:

$$\begin{aligned}
Cl_1 &= 1.44(BW/70)^{0.75} \quad \text{If age} \leq 60 \\
V_1 &= 9.3(BW/70)^{0.71} \,.\, (age/30)^{-0.39}[l] \\
Cl_1 &= 1.44(BW/70)^{0.75} \quad -(age - 60).\, 0.045 \\
V_2 &= 44.2(BW/70)^{0.61}[l] \quad \text{If age} \geq 60 \\
Cl_2 &= 2.25(BW/70)^{0.62} \\
V_3 &= 266[l] \\
K_{12} &= K_{21} = \frac{Cl_2}{V_2}[\text{min}]^{-1} \\
K_{10} &= \frac{Cl_1}{V_1}[\text{min}]^{-1} \\
Cl_3 &= 0.92(BW/70)^{0.55} \\
V_4 &= \frac{V_1}{100}[l] \\
K_{13} &= K_{31} = \frac{Cl_3}{V_3}[\text{min}]^{-1} \\
K_4 &= 0.12[\text{min}]^{-1}
\end{aligned}$$

State space representation of PK parameter is given as equation (2),

$$\begin{bmatrix} \dot{C}_1 \\ \dot{C}_2 \\ \dot{C}_3 \\ \dot{C}_4 \end{bmatrix}(t) = \begin{bmatrix} -\frac{(K_{10}+K_{12}+K_{13}+K_{14})}{V_1} & \frac{K_{21}}{V_1} & \frac{K_{31}}{V_1} & \frac{K_{14}}{V_1} \\ \frac{K_{12}}{V_2} & -\frac{K_{21}}{V_2} & 0 & 0 \\ \frac{K_{13}}{V_3} & 0 & -\frac{K_{31}}{V_3} & 0 \\ \frac{K_{14}}{V_4} & 0 & 0 & -\frac{K_{41}}{V_4} \end{bmatrix} \times \begin{bmatrix} C_1 \\ C_2 \\ C_3 \\ C_4 \end{bmatrix}(t) + \begin{bmatrix} \frac{1}{V_1} \\ 0 \\ 0 \\ 0 \end{bmatrix} \times u(t)$$

$$Y(t) = \begin{bmatrix} 0 & 0 & 0 & 1 \end{bmatrix} \times \begin{bmatrix} C_1 \\ C_2 \\ C_3 \\ C_4 \end{bmatrix} \tag{2}$$

where, C($t$) is a state vector of the compartments concentration, $u(t)$ is infusion rate of propofol into the blood compartment and Y($t$) is drug concentration in brain. PD model denotes the transition time between the distribution of drug and subsequent effect on BIS value which is calculated by the static nonlinear relationship (Hill equation) [13].

$$\mathrm{BIS}(t) = \Delta \mathrm{BIS}_{\mathrm{MAX}} \frac{(\mathrm{C}e)^{\lambda}}{(\mathrm{EC}_{50})^{\lambda} + (\mathrm{C}e)^{\lambda}} \tag{3}$$

$\mathrm{EC}_{50}$ is the half maximum concentration of administration drug and denotes the patient's sensitivity to the infused drug, and λ is a dimensionless parameter that defines the degree of nonlinearity or steepness of the curve.

## 3. DESIGN OF INTERNAL MODEL CONTROL

IMC control technique is designed based on cancellation of pole zero methods for perfect set point response and disturbance rejection. The IMC controller is a robust controller, has been presented by Morari [14]. The IMC control technique attitude obeys to this robustness, allowing for all process model errors as bounded and stable. The design concept of IMC is "control can be achieved only if the control system encapsulates, either implicitly or explicitly, some representation of the process to be controlled". The IMC technique design to regulate BIS is shown in Figure 2. Here, series combination of PKPD model represents Single Input-Single Output (SISO) linear time invariant system. IMC controller demands linearized model of patient, thus, corresponding PKPD model and linearization constant Km are connected in parallel model [10]. IMC method will perform as a system inverter that makes the unity transfer function of system in which it assurances the output to track the input instantly. If process model is not perfectly represent the actual model, the difference signal d(s) affected by both disturbance and process model mismatch on the output variable. Perfect design of IMC controller assure stability, with one condition process is stable itself.

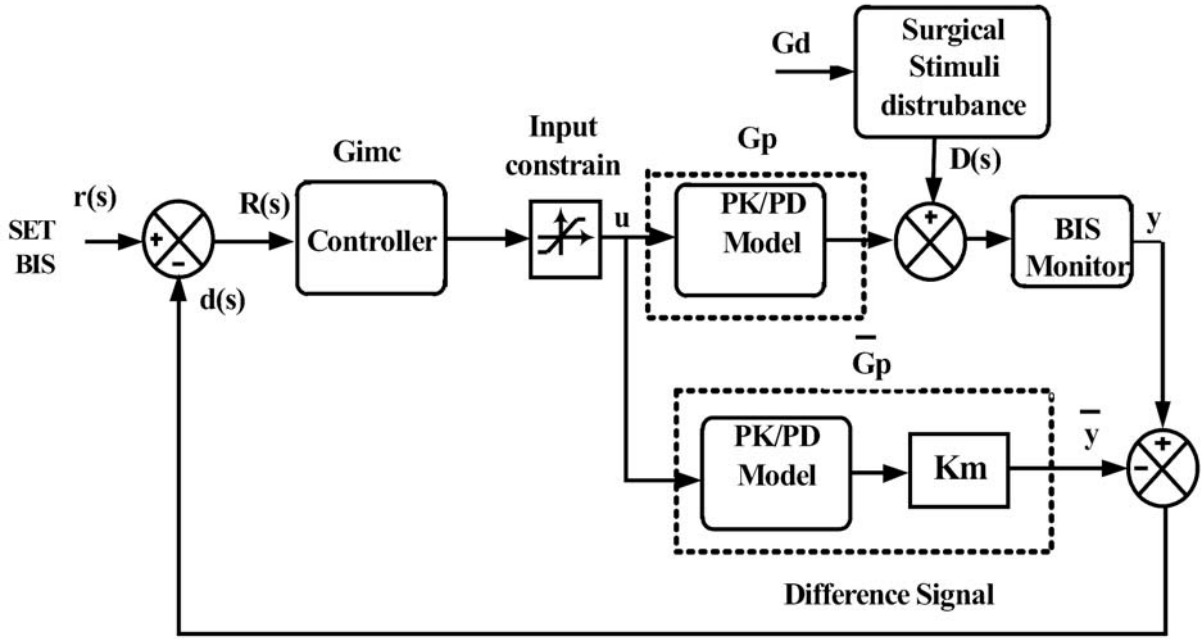


**Fig. 2. The Internal Model Control structure for hypnosis.**

### A. Design steps of IMC for hypnosis control:

**Step 1:** Factor of the Gp($s$) into invertible part $\mathrm{Gp}(s)_{+}$ and non-invertible part $\mathrm{Gp}(s)_{-}$ contain time delay and RHP zero) elements. This factorization is mandatory for stable IMC controller design.

$$\overline{\mathrm{Gp}}(s) = \overline{\mathrm{Gp}}_{+}(s)\overline{\mathrm{Gp}}_{-}(s) \tag{4}$$

**Step 2:** Design of ideal IMC control consist only invertible elements of process model

$$\text{Gimc}(s) = \overline{\text{Gp}}_{-}(s)$$

**Step 3:** Low pass filter transfer function is mostly connected in series with Gimc(*s*) transfer function. The process-model mismatches usually produce a high frequency response of the system. Also to make IMC controller transfer function proper, this means polynomial of denominator greater or equal to numerator [1][14].

$$\text{Gimc}(s) = \overline{\text{Gp}}(s)\text{G}f(s) = \overline{\text{Gp}}_{-}(s)\text{G}f(s) \tag{6}$$

Low pass filter with steady state gain one. Mostly preferred transfer function of filter is given in equation (17).

$$\text{G}f(s) = \frac{1}{(\tau s+1)^n} \tag{7}$$

Here, *n* represent order of low pass filter and τ is a tuning parameter of low pass filter. Largest value of τ produces sluggish response in output. We construct our simulation based on $n = 2$ and $\tau = 1.7$ to achieve best output response BIS.

Transfer function of IMC structure is:

$$\text{Y}(s) = \frac{\{\text{Gimc}(s) \times \text{Gp}(s) \times \text{R}(s) + [1 - \text{Gimc}(s) \times \overline{\text{Gp}}(s)] \times \text{D}(s)\}}{\{1 + [\text{Gp}(s) - \overline{\text{Gp}}(s)] \times \text{Gimc}(s)\}} \tag{8}$$

Final Gimc(*s*) is a combination of G*f*(*s*), $\overline{\text{Gp}}(s)^{-1}$ with linearization constant Km. Linearization constant is obtained by equation (3) [14]. Km = –24.16

## 4. SIMULATION RESULTS AND DISCUSSION

The Internal Model Control technique is applied and tested in simulation using Simulink. In this section we have compared model based controller IMC and PID controller for regulating hypnosis based on IAE value for the comparison, IMC performance is tested on a 10 patient's data given by Ionescu *et al.* [7]. Patients' data are given in table I. Patients profile P7 is more insensitive (due to higher $EC_{50}$) compared to the other and patients profile P6 is insensitive (oscillatory), due to the higher λ value. Patients profile P9 is sensitive compared to normal patients P2 due to smaller value of λ. Performance of closed loop IMC hypnosis index control and propofol drug flow rate, for a set-point equal to 50 is shown in Figure 3(*a*) and (*b*).

**Table 1**

**Patient profile parameters set for regulating hypnosis**

| *Patient Profile* | *Age* | *Weight(Kg)* | *E0* | *EC50* | *Emax* | λ |
|---|---|---|---|---|---|---|
| P1 | 50 | 83 | 95.9 | 6.44 | 102 | 2.18 |
| P2 | 28 | 60 | 94.7 | 4.93 | 85.3 | 2.46 |
| P3 | 43 | 59 | 90.2 | 12.1 | 147 | 2.42 |
| P4 | 37 | 75 | 92 | 8.02 | 104 | 2.1 |
| P5 | 38 | 80 | 95.5 | 6.56 | 76.4 | 4.12 |
| P6 | 41 | 70 | 89.2 | 6.15 | 63.8 | 6.89 |
| P7 | 37 | 58 | 85.1 | 13.7 | 151 | 1.65 |
| P8 | 42 | 78 | 91.8 | 4.82 | 77.9 | 1.85 |
| P9 | 34 | 58 | 96.2 | 4.95 | 90.8 | 1.84 |
| P10 | 38 | 65 | 93.1 | 7.42 | 96.58 | 3 |

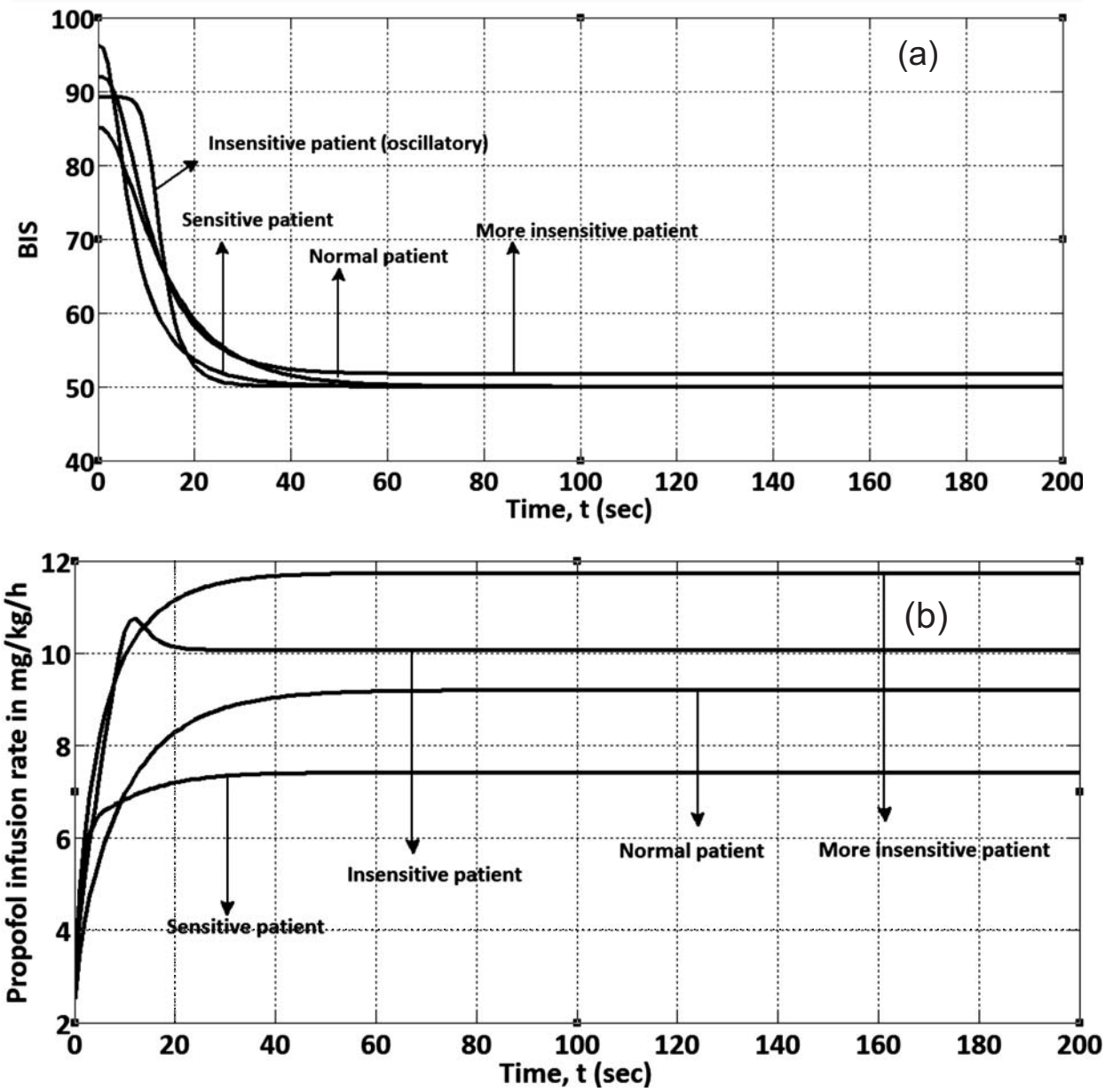


**Figure 3: IMC based hypnosis Control of BIS and propofol infusion rate**

Figure 4(*a*) also shows the sluggish BIS response with higher settling time for the more insensitive patient (IAE = 569) and insensitive patient has slightly faster BIS response compared to more insensitive patient (IAE = 560). Faster BIS response and lesser settling time of the sensitive patient (IAE = 437) as compare to normal patient (IAE = 445). More insensitive patient has required large drug dose and higher settling time as compare to others.

## A. Performance comparison of IMC and PID for a step change and sudden disturbance in BIS signal during surgery

The anesthesiologist can anticipate phase that involves high surgical stimulation as a disturbance (require higher sedation) during surgery and reverse anesthesia phase, which light sedation is sufficient during the last 10 min of surgery. We have compared the results of PID and IMC controller for a set-point changes in BIS value, from 85 to 50 in induction phase at $t$ = 30 sec, 50 to 40 in maintenance phase at $t$ = 30 min and 40 to 70 in last phase of surgery at $t$ = 40 min. Simulation results for BIS and drug flow rate are shown in Figure 4. PID gain values K$c$, K$i$, and K$d$ – set for these parameters respectively are –0.08, –0.0069, and –0.0024.

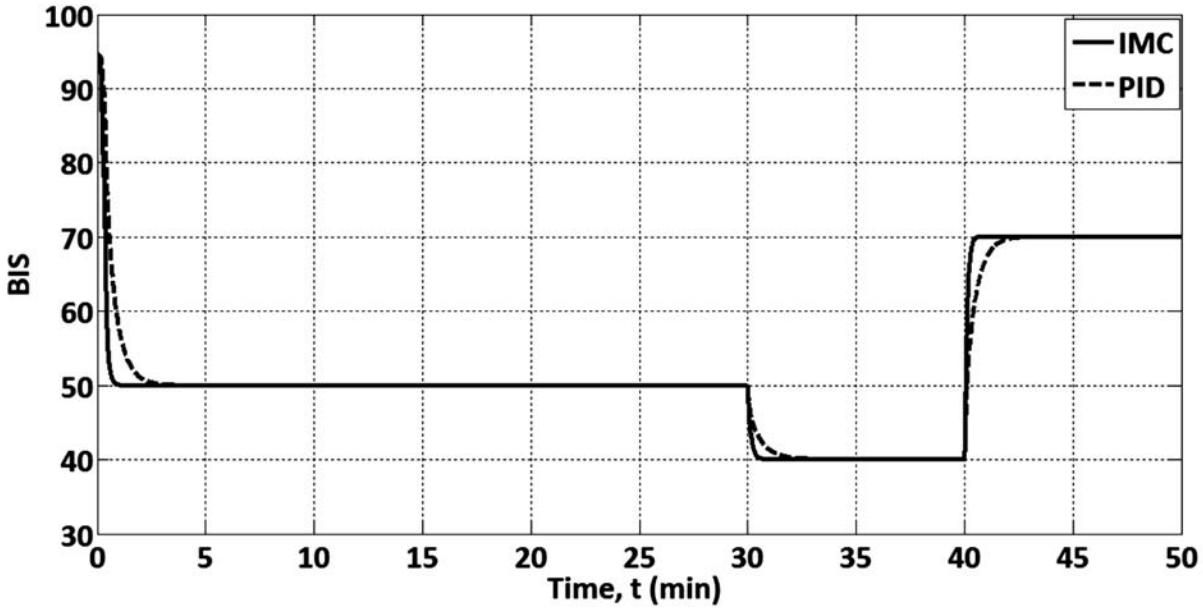


**Figure 4: IMC and PID result for series of intra operative set-points during surgery**

BIS signal of patient may be despoiled by artifacts likes, noise or a sudden disturbance in BIS signal due to some excitement in body. For better result, noise and disturbance in the BIS must be controlled correctly. If not, the inappropriate and unpredictable values of the BIS signals infused incorrect drug dosage into the patient body. Here, simulation results are evaluated for adding a disturbance pulse of strength + 20 at $t$ = 30 min and – 10 at $t$ = 40 min in BIS. Figure 5 represents the performance evaluation of IMC and PID controller with sudden disturbance in BIS for nominal patient.

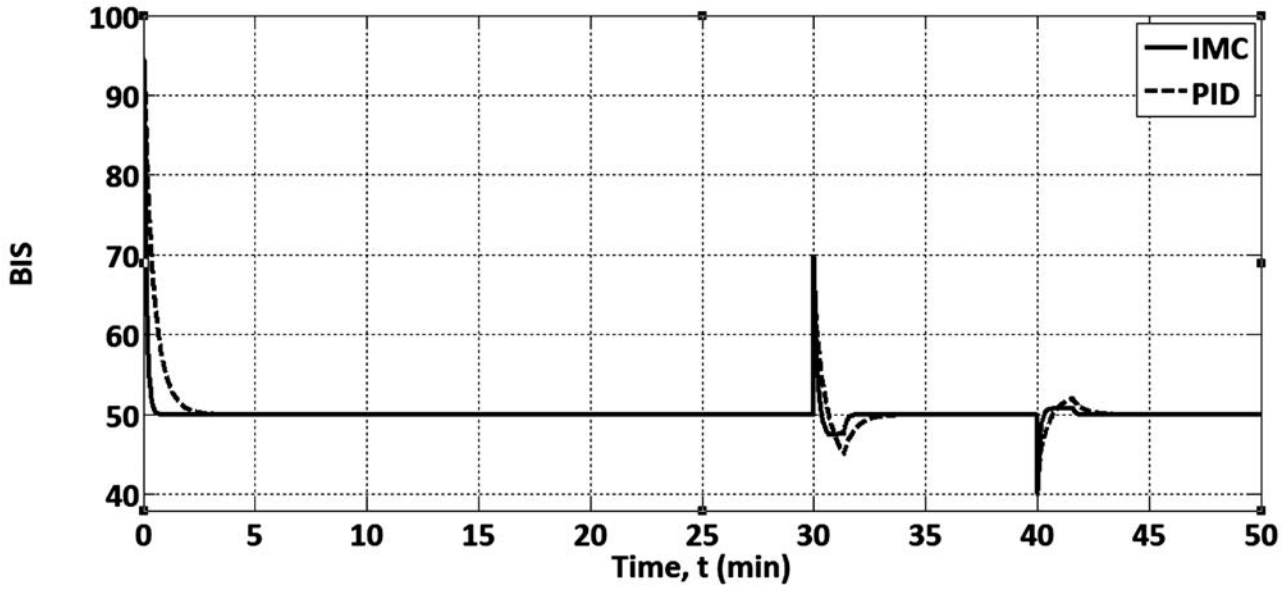


**Figure 5: Results of IMC and PID for sudden disturbance in BIS signal during surgery**

The performance result of IMC control scheme (IAE = 880) is superior to PID (IAE = 1945). Large IAE value indicates more sluggish and less desirable responses [15].

## 5. CONCLUSION

Internal Model Control based nonlinear fourth order compartmental mathematical model featuring pharmacokinetics and pharmacodynamics information was designed and investigated for proposed

anesthesia automation. We have applied and evaluated IMC controller performance based on EEG index (BIS) as a feedback to measure the clinical effect of propofol and manipulate propofol administration rates to the individual patient. This work shows the applicability of IMC controller for hypnosis control. The control strategy is evaluated on a set of 10 patients models for the regulation of the hypnosis by EEG index using propofol as the administrated hypnotic agent. The simulations results reveal fast response, correctness of dose delivery and robustness to induce and maintain the desired BIS set point. The simulation results are evaluated and compared with PID controller. Designed IMC based system is found to be effective compared to the PID controller as formal leads to less settling time and less IAE. A large amount of improvement (13% to 60%) in performance error is achieved by the designed IMC controller. In view of above IMC based robust system may be recommended for the dynamic dose of anesthesia when physical parameters of the patient are changing with the operational and other conditions.

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