Depth of Anesthesia Control using Internal Model Control Techniques

Shahab Anna and Peng Wen

***Abstract*— The major difficulty in the design of closed-loop control during anaesthesia is the inherent patient variability due to differences in demographic and drug tolerance. These discrepancies are translated into the pharmacokinetics (PK), and pharmacodynamics (PD). These uncertainties may affect the stability of the closed loop control system. This paper aims at developing predictive controllers using Internal Model Control technique. This study develops patient dose-response models and to provide an adequate drug administration regimen for the anaesthesia to avoid under or over dosing of the patients. The controllers are designed to compensate for patients inherent drug response variability, to achieve the best output disturbance rejection, and to maintain optimal set point response. The results are evaluated compared with traditional PID controller and the performance is confirmed in our simulation.**

I. Introduction

ANAESTHESIA comprises muscle relaxation, analgesia and unconsciousness, Depth of Anaesthesia (DoA), and can be defined as the lack of response and recall to noxious stimuli. The anaesthetic management of a surgical patient is a process that relies on the experience of an anaesthetist, since currently there are no direct means of assessing a patient level of consciousness during surgery. The decision for the initial anaesthetic level is generally made by using the recommended drug dosages based on different patient characteristics, such as age and weight. The anaesthetist determines any subsequent alteration in the anaesthetic level by observing physical signs from the patient [1]. These physical signs, the indirect indicators of the depth of anaesthesia, may include changes in blood pressures or heart rate, lacrimation (the production of tears in the eyes), facial grimacing, muscular movements, spontaneous breathing, diaphoresis (sweating, especially sweating induced for medical reasons), and other signs that may predicate awareness [2]. However, they are not reliable indicators of changes in patient level of consciousness. Although an anaesthesiologist can adjust recommended anaesthetic dosages based on individual patient characteristics, these adjustments cannot always account for variability in patient responses to anaesthesia or changes in anaesthetic requirements during the course of surgery [3].

In latest years, model-based control has lead to improved control loop performance. One of the clearest model based technique is Internal Model Control (IMC). IMC has many advantages in design control systems. The stability of the IMC is only depending on that the controller and nominal plant. In addition, even if the IMC system has control input saturation, satiability of Internal Model Control is only depending on that of the controller and the plant, too. Unlike many other developments of modern control theory, IMC was widely accepted by control engineering practitioners. It is therefore quite natural to attempt to extend IMC concepts to various classes of systems. It is thus here that we utilize IMC concepts to monitor depth of anaesthesia in order to explore the advantages it brings to their control [4].

A major gain of continuous intravenous drug infusion for general anaesthesia is the possibility of keeping something like constant value of the effect concentration of the drug in use. Alson et al. (2008) presents a method for target control infusion for neuromuscular blockade level of patients. The estimates of the PK/PD model parameters are computed from data collected in the first 10 minutes, after a bolus is applied to the patient in the induction phase of anaesthesia [5]. Ionescu et al. presents a single-input (propofol) single-output (bispectral index, BIS) model of a patient has been assumed for prediction as well as for simulation. The aim of the controller is to guarantee the model stability in a desired range. Absalom et al. produced a closed-loop control system of anaesthesia that uses the BIS as the control variable to automatically control the target blood concentration of propofol Target Controlled Infusion (TCI) system. The system was able to provide clinically sufficient anaesthesia in all patients, with enhanced accuracy of control. There was a tendency for more accurate control in those patients in whom the control algorithm incorporated effect-site steering [6]. A method and an algorithm are proposed for controlling the effect site concentration using a TCI method. The method limits the peak plasma concentration, thereby slowing the start of anaesthetic drug effect but potentially improving side effect.

A method for an enhanced tuning of the PID controller parameters to the patient's individual dynamics is presented by Mendonca & Lago [7]. Auditory evoked potentials (AEP) have been reported to accomplish many requirements for measurement the level of anaesthesia. The AEP has been shown to provide good discrimination of the conversion from asleep to aware and vice versa. The development has

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Shahab Anna is with the Faculty of Engineering and Surveying, University of Southern Queensland, Toowoomba, QLD, 4350, Australia (phone: +61449150623; e-mail: Shahab.Abdulla@usq.edu.au).
Dr. Peng Wen is with the Faculty of Engineering and Surveying, University of Southern Queensland, Toowoomba, QLD, 4350, Australia, (e-mail: peng.wen@usq.edu.au).

been made to this system to obtain a single index which presents the morphology of the AEP and used this index as the input signal for closed-loop anaesthesia during surgery in patients who did not receive neuromuscular blocking drugs [8]. A robust control of depth of anaesthesia was developed by Dumont et al. to design both robust and PID controllers based on fractional calculus to control the hypnotic state of anaesthesia with intravenous management of propofol. The aim of the controllers is to supply an adequate drug administration treatment for propofol to evade under or over dosing of the patients. The objectives of these controllers are considered to compensate for the patients inherent drug response variability, to accomplish good output disturbance rejection, and to achieve good tracking to set point response [9].

A synopsis of the pharmacokinetic and pharmacodynamic patient's models used for prediction and for control is given in the next section. The depth of anaesthesia control is discussed in Section 3. Experiments and results are discussed in Section 4, while the conclusion section summarizes the main outcome of this strategy.

II. Depth of Anaesthesia and Modeling

A. Pharmaco-kinetic model

The human body is assumed to be divided into several compartments to drive the PK model [10]. In each compartment the drug concentration is homogeneous as shown in figure 1. The DoA model considers both propofol and remifentanil since this last one has a non-negligible effect on the DoA level.

Hereafter, c_e^{remi} (the remifentanil effect concentration) is assumed to be given and only the propofol chain is considered. The propofol infusion rate "r^{prop}" is called "u". where u is the manipulated variable. This yields the continuous linear state space model:

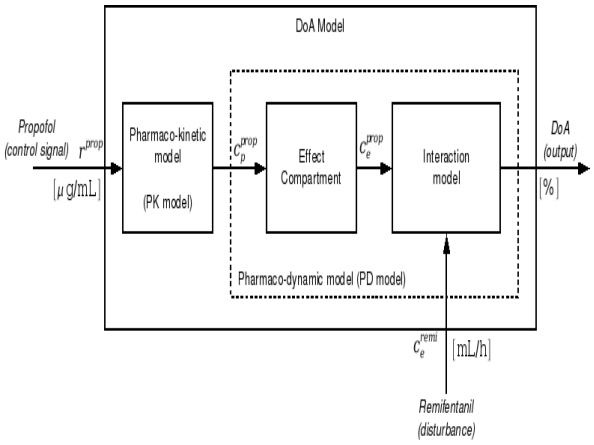

Fig. 1: DoA model

$$\begin{cases} \dot{x_1} &= A_1 x_1 + B_1 u \\ c_p^{prop} &= C_1 x_1 \end{cases} \quad (1)$$

With $A_1 = \begin{bmatrix} -k_{10}-k_{12}-k_{13} & k_{21} & k_{31} \\ k_{12} & -k_{21} & 0 \\ k_{13} & 0 & -k_{31} \end{bmatrix}$, $B_1 = \begin{bmatrix} \frac{10^4}{3600} \\ 0 \\ 0 \end{bmatrix}$, and $C_1 = \begin{bmatrix} \frac{1}{1000 \times v_1} & 0 & 0 \end{bmatrix}$

v_1 is measured with weight of the patient and coefficient v_c [L/kg] which represents the volume of compartment one per patient unit weight [kg]:

B. Pharmaco-dynamic model

A PD model presented as a low-pass filter is used to relate the propofol plasma concentration c_p^{prop} and the propofol effect concentration c_e^{prop}. This yields the following state space representation:

$$\begin{cases} \dot{x_2} &= A_2 x_2 + B_2 c_p^{prop} \\ c_e^{prop} &= C_2 x_2 \end{cases} \quad (2)$$

where $A_2 = -K_{e0}$, $B_2 = K_{e0}$ and $C_2 = 1$.

The effect-site concentration is related to DoA as (Hill equation) [11]:

$$E(t) = E_o - E_{max} \frac{{C_e}^{\gamma}}{EC_{50}^{\gamma} + {C_e}^{\gamma}} \quad (3)$$

where C_e is:

$$C_e(s) = \frac{k_{e0}}{s + k_{e0}} C_p(s) \quad (4)$$

where k_{e0} is the inverse of the effect-site compartment time constant and EC_{50} is the half-maximal effective concentration.

A very important advantage of continuous drug infusion for general anaesthesia is the opportunity of keeping nearly constant rate of the effect concentration of the drug in use. The advances of the pharmacologic and the amount to the improvement of adequate drugs, plus the technological circumstances such as computer control devices (controlled syringes); automatic drug management in the proper doses require knowledge of the corresponding PK/PD models. There are two corresponding ways to implement the control strategy.

- *Closed-loop control of drug dosage.*
- *Open-loop control.*

Close-loop control of anaesthesia has been a goal of many researchers, so closed-loop control has the main

advantage of rendering the control action not sensitive to model uncertainty [12]. Open-loop control is a type of dual feedback, allows a response rapid to the required value [13]. On the other hand, system errors will propagate without decrease to the tracking error. From a clinical point of view, a perfect controller would lead the induction of anaesthesia in order to achieve the goal as fast as possible without initial overshoot. After that, the controller would simply keep up the desired target as well as possible. For that reason, the Internal Model Control (IMC) plays an important role in this area.

III. Depth of Anaesthesia Control

A. The Internal Model Control

The IMC is one such technique that is extensively used in chemical and process industries where uncertain models are quite common [14]. Internal model control relies on the internal model principle, which states that a plant or a process can be controlled only if the control system incorporates or encapsulates, either implicitly or explicitly, some representation of the process [15]. For example in an open loop control, the model of the process to be controlled is almost exactly known. Hence an inverse model is used for the controlling the plant in this case. However, an exact model of the plant is not known in almost all practical cases and process-model mismatch is very common. These uncertainties and un-modeled dynamics in the system usually affect system performance. In such cases Internal Model Control (IMC) is found to be very useful. The general structure of an internal model control methodology compared to the classical controller structure like PID. It is noted that the system model is explicitly used in the IMC structure unlike the classical controller structure [16].

The disadvantage of the linear IMC controller is that it cannot handle open-loop unstable systems and nonlinear models should be linearized for designing the controller.

$G_c(s)$ is the controller; it is used to control the process, $G_p(s)$. Assume $\widetilde{G_p}(s)$ is a model of $G_p(s)$. The inverse of the model of the process is equal $G_c(s)$,

$$G_c(s) = \widetilde{G_p}(s)^{-1} \tag{5}$$

And if $G_p(s) = \widetilde{G_p}(s)$, that is mean the model is an exact representation of the process. Then it is obvious that the setpoint and the output will always be equal. It is clear that this ideal control performance is accomplished in open loop without feedback. That is mean we have complete knowledge about the process under control with perfect achievement control. Also that mean, the feedback control is necessary only when information about the process is incomplete and imprecise. The process-model mismatch is common; that is mean invertible of the process model may not be easy and the system is often affected by noises and unknown disturbances. Thus the open-loop control will not be able to keep output at setpoint. However, it forms the basis for the improvement of a control strategy that has the potential to accomplish ideal control. This method, IMC has the general structure shown in Figure 2. The disturbance affecting the system is D(s) in Figure 2. The planning input U(s) is introduced to together the model and the process [17]. The difference between the process output, Y(s), and with the output of the model is the signal $\widetilde{D}(s)$. The $\widetilde{D}(s)$ can be found as:

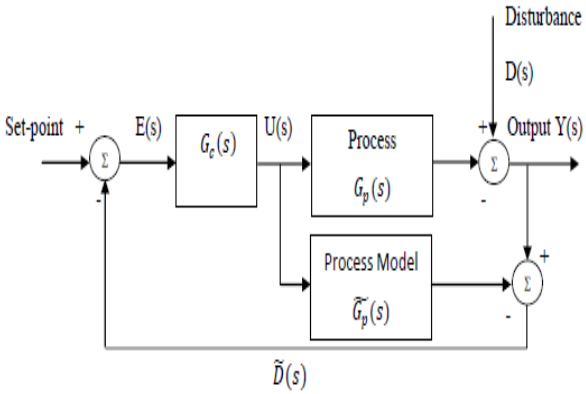

Fig. 2: Block diagram of the IMC

$$\widetilde{D}(s) = \{G_p(s) - \widetilde{G_p}(s)\}U(s) + D(s) \tag{6}$$

From equation 6, if D(s) is equal zero, then $\widetilde{D}(s)$ is measure of the difference in behaviour between the process and its model. Also if $G_p(s) = \widetilde{G_p}(s)$, that mean $\widetilde{G_p}(s)$ is equal to the unknown disturbance or noise. As a result $\widetilde{D}(s)$ regarded as the information that is missing in the model, $\widetilde{G_p}(s)$, and can be used to improve control. The control signal can write by,

$$\begin{aligned} U(s) &= [R(s) - D(s)]\, G_c(s) \\ &= \{R(s) - [G_p(s) - \widetilde{G_p}(s)]U(s) \\ &\quad - D(s)\}\, G_c(s) \end{aligned} \tag{7}$$

Because $Y(s) = G_p(s)U(s) + D(s)$then the closed loop transfer function for IMC is equal to:

$$Y(s) = \frac{[R(s)-D(s)]\, G_c(s)G_p(s)}{1+[G_p(s)-\widetilde{G_p}(s)]G_c(s)} + D(s) \tag{8}$$

Form the equation 8, we can see that if $G_c(s) = \widetilde{G_p}(s)^{-1}$, and if $G_p(s) = \widetilde{G_p}(s)$, that is mean perfect setpoint tracking and disturbance rejection is accomplished. Also can notice that, theoretically, if $G_p(s) \neq \widetilde{G_p}(s)$, perfect disturbance rejection can be still be realised

provided $G_c(s) = \widetilde{G_p}(s)^{-1}$. Furthermore, to advance robustness, the process model mismatch and its effects should be minimised. Because a distinct difference and failure to match between process and model performance usually occur at that the high frequency end of the system's frequency response, a low pass filter $G_f(s)$ is usually added to attenuate the effects of process and model discrepancies [18]. As a result, the internal model controller is usually designed as the inverse of the process model in series with a low-pass filter. The structure of the IMC in DoA is depicted in Figure 3. The blocks PK and PD together with the nonlinear equation represent the patient's pharmacokinetics and pharmacodynamics, respectively. Both PK and PD are single-input single-output linear time invariant systems. The equivalent parallel models for the pharmacokinetics and pharmacodynamics are respectively $\widetilde{PK}$ and $\widetilde{PD}$ together with linearization constant K.

Where $K = -\frac{BIS_0\gamma}{4EC_{50}} = -24.16$

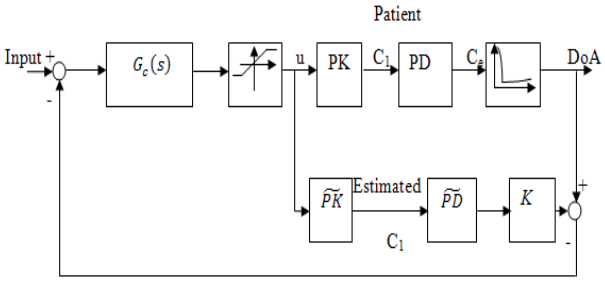

Fig. 3: IMC in DoA

IV. Experiments and Results

This section provides the application and evaluation of the IMC control strategy, and also compares their performances with the PID controller.

The data from Hospitals is recorded into a Matlab spreadsheet. In case of hardcopy form, the data is manually entered on the Matlab spreadsheet. These data are collected and analyzed to establish the relative importance of each independent variable in the prediction. The data analysis results are integrated for model development. The model are developed and designed based on these data analysis and initial results presented. Then simulations are carried out to study the feasibility and reliability. Testing is scheduled to the final stage of model development. The implementation arrangements will be specified and user's feedback will be incorporated to finalize the model. In this study, however, a the IMC used to generate and provides a much easier framework for design of robust control systems.

Simulink model is developed for DoA. The nonlinear DoA model as shown in the block diagram in Figure 4. To perform these actions, Matlab program is developed to compute parameters for both linear and nonlinear Simulink models. We also compare data from our simulation with real data from patients file. The Matlab programs is developed to evaluate the influence of several parameters (Υ, K_{eo}, and c_e^{prop}) on the nonlinear model. The simulations evaluate the influence of drugs in steady state on the Hill equation.

The BIS and the infusion rate in typical cases of automatic control are shown.

Figure 5 shows the closed loop simulation for controlled output (BIS) for the IMC. The controller performance over the family of the patients is affected due to inter-patient variability, when using a nominal model for IMC strategy. Notice that the IMC strategy includes an identification of the patient specific parameters, and therefore, it takes into account the patient variability to obtain a better control performance.

During the induction phase, the time-to-target for the IMC strategy has rather high performance. The IMC controller brings the BIS variable to the reference interval. The results in this study can be attributed to the fact that the IMC controller is more cautious controller, making an exchange between small time-to-target, small undershoot and robustness against patient variability as shown in figure 6.

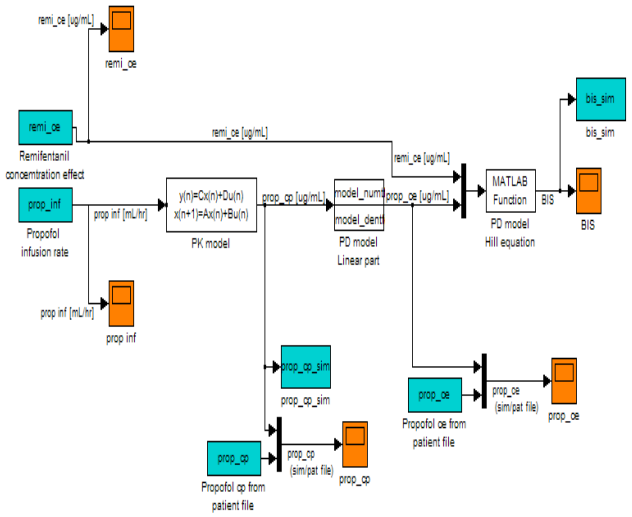

Fig. 4: Non linear DoA model built in Simulink

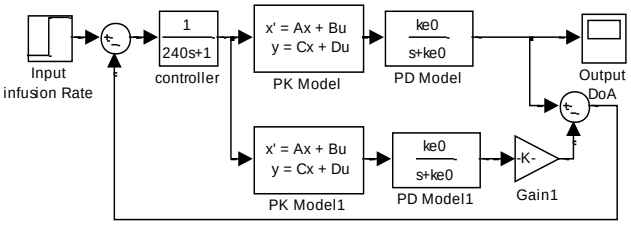

Fig. 5: Simulink diagram for IMC system

The closed loop performance of the IMC will be present here. Because plasma propofol concentration measurement is unavailable, it is estimated through the nominal PK model. BIS is measured online. The controller has maintained BIS between 40 and 60 during the surgery. Firstly, it is assumed that the patient is in a fully awake state (BIS≈100) and then

the controller is turned on the set-point is changed from 100 to 50. This condition brings the patient to the surgical operating range (40 ≤ BIS ≤60) which must be maintained for the period of the surgery. The predicted plasma propofol concentration must be among 1 μg/mL and 5 μg/mL. The lower bound guarantees a lowest amount delivery of anaesthetic, whereas the upper bound prevents overdosing of the drug for an average subject. The manipulated variable (propofol infusion rate) u is constrained between 0 and 40 mg/kg/h. The higher bound is needed because higher propofol infusion leads to more rapidly increase of propofol concentration in the subject's body and this may lead to hypnotic crisis, cardiac arrhythmia, or even cardiac arrest. The lowest amount bound on u reflects the impossibility of administering negative concentrations of propofol.

We start on by discussing the design of IMC. Because the safe regulation of DoA level is very crucial during the surgery, the constraints imposed on the inputs will be hard constraints, that is, at any time the controller should not violate these limits. The modification parameters for the IMC controller are the filter time constant λ which is put at 1.7 and order of the filter n which is set at 2. Here also, the value of K used is -24.16. With the PID controller, the settings were $K_c = -0.0598, \tau_I = 28.476$, and $\tau_D = 2.368$.

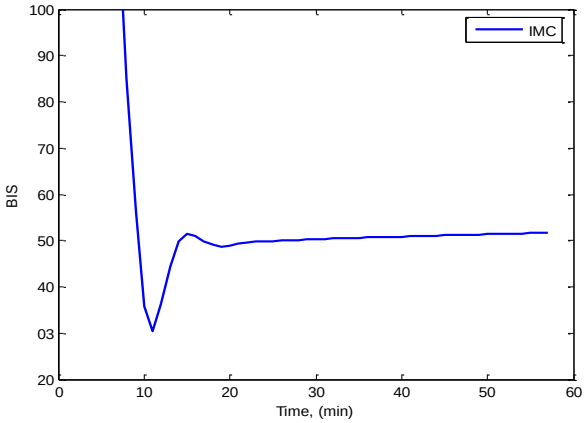

Fig.6. Performance of the IMC

The comparison of closed-loop performance of the two controllers is discussed next. The response is faster with PID controller than with the IMC controller, a small offset persists throughout the simulation time. Figure 8 shows the predicted plasma propofol concentration, where it is seen that all the controllers result in overshoot (higher with PID controller) but are still maintained within the constraints.

We would like to test if the two controllers are able to meet performance specifications despite significant and reasonable variation in the model parameters (inter- and intra-patient variability) as shown in table 1. At this point, we assume that variability is in both the PK and PD (based on patient's sensitivity to the drug) model parameters. Our control simulations showed that the variability in PD parameters have more impact on BIS than the variability in PK parameters. First, each PK parameter (k_{10}, k_{12}, k_{21}, k_{13}, k_{31}, V_1, V_2, and V_3) is assumed to vary over three levels (minimum, average, maximum).Simulations showed that changes in volumes of the compartments (V_1, V_2, and V_3) has very a smaller amount effect on the performance. For the insensitive patient, depletion rate constants of the central compartment (k_{10}, k_{12}, and k_{13}) are high (0.1488, 0.139, and 0.05211, respectively) and generating rate constants (k_{21}, k_{31}) are low (0.041, and 0.0021, respectively). In the PD parameters, higher EC_{50} (3.7) indicates the need for further drug to get the same DoA level, higher γ (3.12) represents higher nonlinearity and lower ke0 (0.2388) indicates sluggishness in response. For the sensitive patient k_{10}, k_{12}, and k_{13} are low (0.089, 0.084, and 0.031, respectively) and k_{21}, k_{31}, are high (0.0691, and 0.0039, respectively). In the PD parameters, lower EC_{50} (1.6) indicates the need of a smaller amount drug to get the same DoA level, lower γ (2) represents lower nonlinearity, and higher k_{e0} (0.459) indicates more rapidly response. Also, since k_{e0} represents the process gain, higher k_{e0} (higher gain) represents faster response and lower k_{e0} (lower gain) represents slower response of the process.

TABLE I
VALUES OF THE PARAMETERS FOR THE 15 PATIENT SETS ARRANGED IN THE DECREASING ORDER OF THEIR BIS SENSITIVITY TO PROPOFOL INFUSION

Parameter								
Patient no.	k_{10}	k_{12}	k_{21}	k_{13}	k_{31}	k_{e0}	EC_{50}	γ
1 (sensitive)	0.08925	0.084	0.06875	0.031425	0.004125	0.459	1.6	2
2	0.14875	0.14	0.04125	0.052375	0.004125	0.239	1.6	2
3	0.14875	0.112	0.04125	0.0419	0.004125	0.239	1.6	3.122
4	0.14875	0.14	0.04125	0.052375	0.004125	0.239	1.6	3.122
5	0.08925	0.084	0.04125	0.052375	0.002475	0.459	2.65	2.561
6 0.	08925	0.084	0.06875	0.031425	0.002475	0.349	2.65	2.561
7	0.14875	0.112	0.06875	0.031425	0.002475	0.459	2.65	2.561
8 (nominal)	0.119	0.112	0.055	0.0419	0.0033	0.349	2.65	2.561
9	0.119	0.112	0.055	0.0419	0.0033	0.239	2.65	2
10	0.119	0.112	0.055	0.0419	0.0033	0.239	2.65	2.561
11	0.08925	0.084	0.06875	0.031425	0.002475	0.459	3.7	2
12	0.14875	0.112	0.06875	0.031425	0.002475	0.349	3.7	2.561
13	0.08925	0.084	0.06875	0.031425	0.002475	0.239	3.7	2.561
14	0.08925	0.084	0.06875	0.031425	0.002475	0.239	3.7	3.122
15	0.08925	0.084	0.04125	0.052375	0.002475	0.239	3.7	3.122

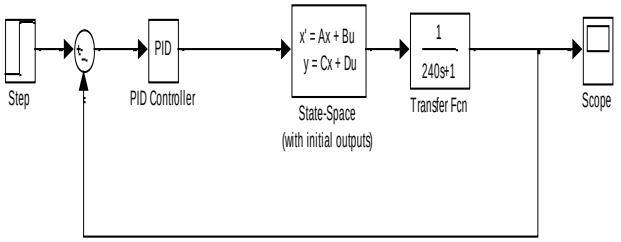

Fig7: PID controller

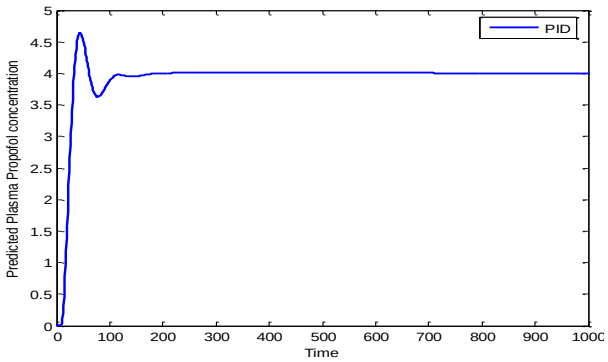

Fig. 8: Performance of PID controller

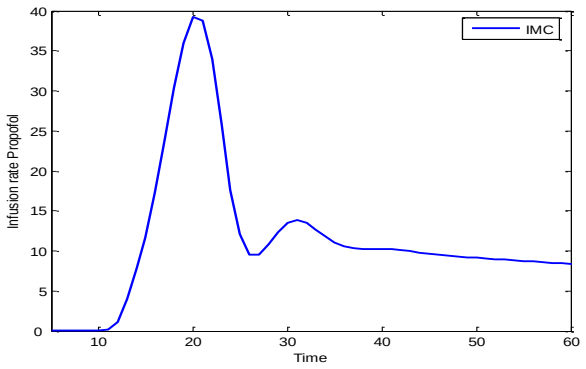

Fig. 9: Infusion rate of propofol (IMC)

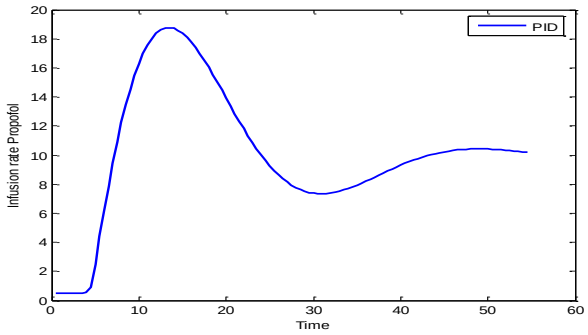

Fig. 10: Infusion rate of propofol (PID)

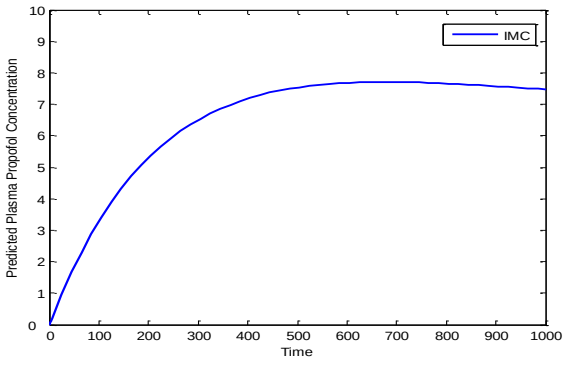

Fig. 11: Predictive plasma propofol concentration (IMC)

V. CONCLUSIONS

In this study, internal model control, for regulation of anaesthesia using BIS as the controlled variable have been evaluated thoroughly. The performance of this controller is considered along with the performance of the conventional PID controller. In comparison with conventional PID controller, the advanced, model-based controllers are found to be robust to intra- and inter-patient variability, and better at handling disturbances and measurement noise. The performance of the IMC controller is found to perform the best and hence recommended for DoA control.

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