Depth of Anaesthesia Patient Models and Control

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Abstract - During surgery, the anaesthetist carefully controls the delivery of anaesthesia given to the patient in an effort to attain and maintain a consistent and adequate level of anaesthetic depth. The aim of this work is to design an internal model control (IMC) for anaesthesia depth, and to test it by simulation with clinical data. This study uses an internal model control structure for the adjustment of Bispectral Index (BIS). Performance of the two controllers has been studied for a step change in BIS, measured disturbances in the measured variables. In this study the simulation shows that the internal model control performed better than the PID controller.

Index Terms – Internal model control, depth of anaesthesia.

I. INTRODUCTION

During surgery the anaesthetist carefully controls the delivery of anaesthesia given to the patient in an effort to attain and maintain a consistent and adequate level of depth of anaesthesia, that is, adequate levels of hypnotic, analgesic, and paralytic [1]. The anaesthetist is acting as a manual feedback controller [2]. The monitoring and control of unconsciousness in operating theatre is a major challenge to both anaesthetist and machines [3].

Brain monitors like the BIS monitor can now be use to measure a patient brain response to anaesthesia this information helps clinicians to adjust amount the medication given to improve recovery from anaesthesia, also this information may help clinicians to reduce the risk of patient awareness. In clinical anaesthesia, automatic regulation, in a closed-loop control of infusion of drugs has been shown to provide more benefits when compared to manual administration. A well designed automatic control system can avoid both over-dosage and under-dosage of the drugs. Closed-loop control minimize the drug consumption, intra-operative awareness and recovery times, thereby decreasing the cost of the surgery and also the cost of the postoperative care. Overall, this is to improve the patient's safety and rehabilitation during and after the surgery [4].

The anaesthetist determines any subsequent alteration in the anaesthetic level by observing physical signs from the patient [5]. 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 [6]. However, they are not reliable indicators of changes in patient level of consciousness. Although an anaesthetist 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 [7].

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 [8]. Alson et al. (2008) presents a method for target control infusion for neuromuscular blockade level of patients. The estimates of the pharmacokinetic /pharmacodynamic (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 [9].

Closed loop administration of anaesthetics during surgery promises to supply a number of possible benefits, such as, minimizing the over all amount of drugs required for each person to reduced recovery time and costs, also allowing the anaesthetist to focus on more critical safety tasks [10]. However, in order to design and impalement feedback controls schemes, mathematical model of the patient and drug delivery system are required.

The proposed Internal Model Control (IMC) uses the approximate linear pharmacokinetic-pharmacodynamic (PK–PD) model in the controller design, which regulates patient's BIS by manipulating the infusion rate of isoflurane. An extensive simulation conducted to investigation the robustness of the proposed IMC controller, by considering parameters variations in the selected model to account for patient model mismatch. The proposed IMC scheme has also been evaluated for disturbance rejections. The main contributions of this study are to demonstrate the control of hypnosis using IMC, and to compare its performance with traditional PID controller.

The rest of the paper is presented as follows. Section II discusses patient mathematical modeling. The control design is introduced in section 3. Simulations and results are presented in section 4. The main outcome are summarizes in conclusion section.

II. PATIENT MATHEMATICAL MODELS

The human body is assumed to be divided into several compartments to drive the PK model [11]. A model based on a compartmental approach is used. According to this approach, the body is assumed to be divided into several compartments. In each compartment the drug concentration is homogeneous and there are exchanges between compartments. A three

compartments model is used, in which the main compartment represents intravascular blood (blood within arteries and veins) and highly irrigated organs (such as heart, brain, liver and kidney). The two other compartments represent muscles, fat and other organs or tissues. The PK consists of a 3-compartment model which is shown in Fig. 1, would be represented mathematically by the state equations

$$\dot{x}_1 = I + x_2k_{21} + x_3k_{31} - x_1k_{10} - x_1k_{12} - x_1k_{13}$$

$$\dot{x}_2 = x_1k_{12} - x_2k_{21} \quad (1)$$

$$\dot{x}_3 = x_1k_{13} - x_3k_{31}$$

where x_i is the amount of drug in the i th compartment, k_{ij} is the distribution transfer rate from the i thcompartment to the j thcompartment, k_{10} is the clearance transfer rate out of the central compartment, and I represents the anaesthetic infusion rate into the central compartment [12].

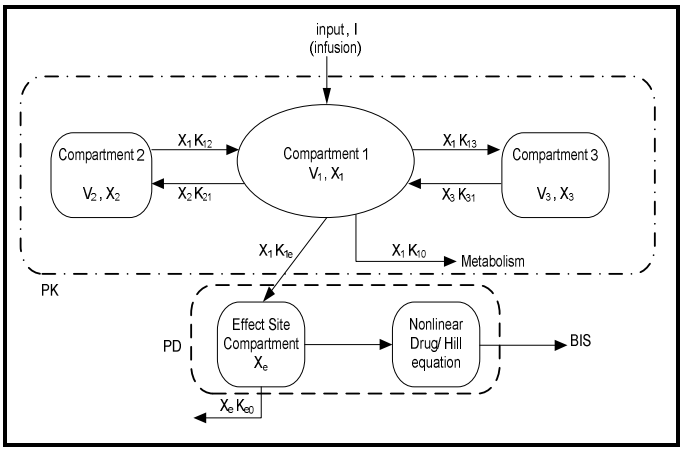

Fig. 1 Compartmental model of the patient.

The pharmacodynamics is characterized by a low-pass filter related to the central compartment concentration C_p in blood:

$$C_e = \dot{x}_e = -k_{e0}x_e + k_{1e}x_1 \quad (2)$$

where k_{e0} and k_{1e} are constants and x_e is the amount of drug in the effect compartment.

$$\dot{C}_e = k_{e0}(C_p - C_e) \quad (3)$$

Where C_e denotes the effect site compartemt concentration. C_p denotes plasma concentration.

The BIS varaible related to the drug effect concenration C_e by the empirical static non-linear relationship [13], that is called Sigmoid Hill Curve:

$$E(t) = E_o - E_{max}\frac{{C_e}^{\gamma}}{EC_{50}^{\gamma} + {C_e}^{\gamma}} \quad (4)$$

where E is the measured effect, E_0 represents the baseline value (conscious state without propofol), which is typically set to 100; E_{max} denotes the maximum effect achieved by the drug infusion; C_{50} is the drug concentration at half maximal effect and denotes the patient's sensitivity to the drug; and γ determines the steepness of the static nonlinearity.

III. The Control Structure

A. Internal Model Control

Internal model control relies on the internal model control 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 [14]. For example in an open loop control, the model of the process to be controlled is almost exactly known [15]. 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-modelled dynamics in the system usually affect system performance. In such cases IMC is found to be very useful [16].

Fig. 2, shows the IMC structure. Here $G_p(s) \in \mathcal{R}(s)$

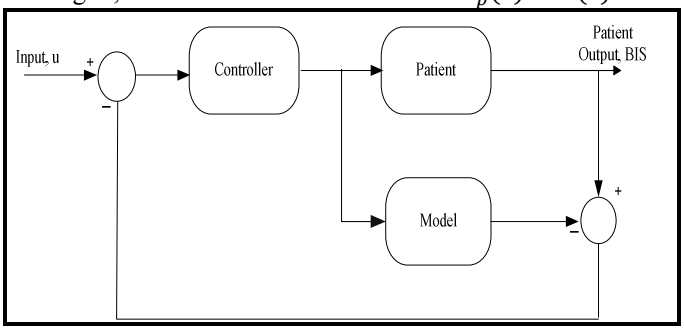

Fig. 2 Block diagram of IMC.

where $\mathcal{R}(s)$ is the space of all real-rational transfer function, r is the input, y is the output and u is the control input [15].

The transfer function from the input r to the error $e = r - y$ is given by

$$e = r - y = \big(1 - G_m(s)G_c(s)\big)r \quad (5)$$

$$\frac{e}{r} = 1 - G_m(s)G_c(s) \quad (6)$$

B. Internal Model Control for Depth of Anaesthesia

The structure of the IMC in depth of anaesthesia (DoA) is depicted in Fig 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 represented by $\widetilde{PK}$ and $\widetilde{PD}$ respectively together with linearization constant K.

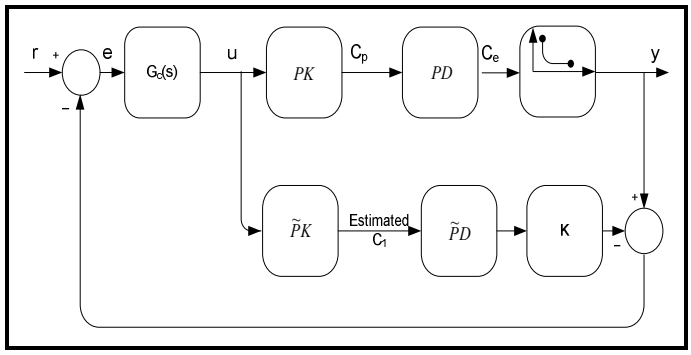

Fig. 3 Block diagram for the DoA control.

The transfer function for the PK in Fig. 3, can be expressed by:

$$C_p(t) = Ae^{-p_1 t} + Be^{-p_2 t} + Ce^{-p_3 t} \left[\frac{\mu g}{ml}\right] \quad (7)$$

where $C_p(t)$ is the drug concentration expressed in microgram per milliliter (propofol), p_1 and p_2 in the above formula would refer to the rate constant of the distribution phase , and p_3 is the rate constant of the elimination phase. In many cases, a tri-exponential model will capture significantly better the kinetic of the drug 2 :

$$PK(s) = \frac{C_p(s)}{u(s)} = A\frac{1}{s+p_1} + B\frac{1}{s+p_2} + C\frac{1}{s+p_3} \quad (8)$$

A major advantage of exponential models as in (7) is that they can be easily derived using graphical means. The identification can be carried out directly by using either bolus data and analyzing the decaying blood plasma characteristic , or by using infusion data and analyzing how the plasma concentration increases over time.

$$PD(s) = \frac{k_{e0}}{s+k_{e0}} + \frac{\gamma}{4EC_{50}} \quad (9)$$

IV. Simulation and Results

The data from Hospitals are collected into a Matlab spreadsheet program. In case of hardcopy form, the data is entered manually on the Matlab spreadsheet. These data are collected and analysed to establish the relative importance of each independent variable in the prediction. The data analysis results are integrated for model development. The models are developed and designed based on these data analysis and initial results presented. Testing is scheduled to the final stage of model development. In this study, however, the IMC used to generate and provide a much easier framework for design of robust control systems.

The nonlinear DoA model is shown in the block diagram in Fig. 4. To perform these simulations, Matlab program is developed to compute parameters for both linear and nonlinear Simulink models. The Matlab programs is developed to evaluate the influence of several parameters (Υ, k_{e0}, and C_p) on the nonlinear model. 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.

This section provides the simulation results of the IMC controller for the control of BIS by manipulating Propofol as shown in Fig. 5. In Figure 5, the controller regulates the BIS by adjusting infusion rate of propofol based on the error between set-point and the difference between actual and predicted BIS. The IMC performance is considered in this work and compared with the PID controller the complete close loop system is presented in Fig. 6.

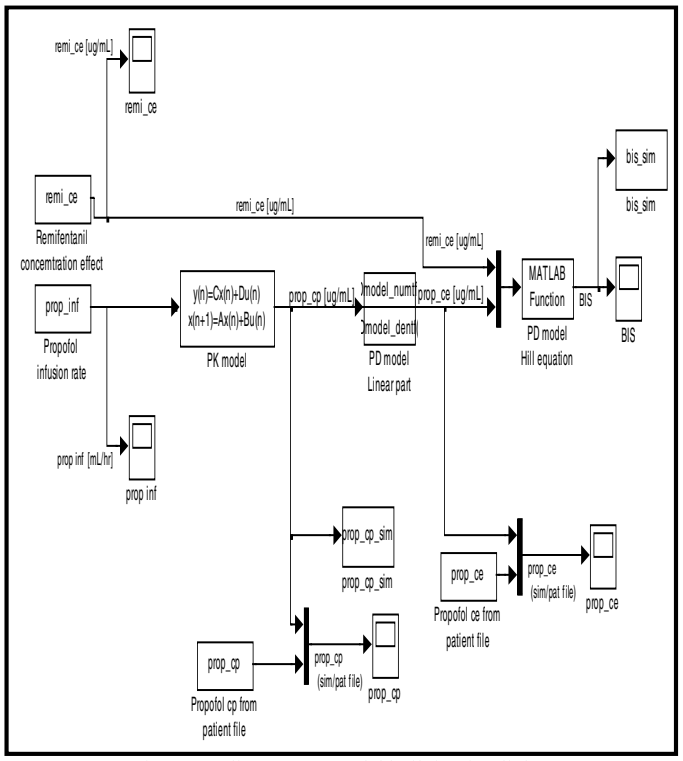

Fig. 4 Non linear DoA model built in Simulink.

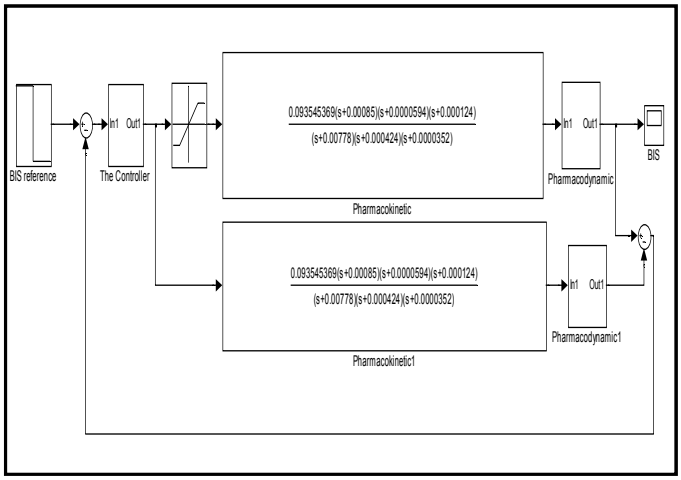

Fig. 5 Schematic representation of IMC.

With the PID controller, the settings were $K_c = -0.088, \tau_I = 30.476$, and $\tau_D = 3.331$.

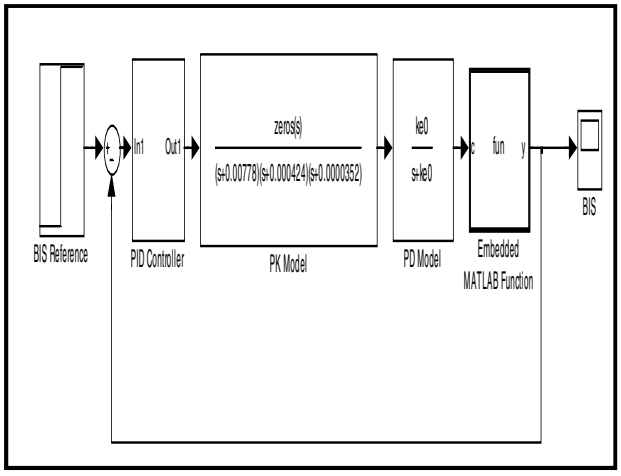

Fig. 6 Schematic representation of PID Controller.

The proposed algorithm is simulated using the parameters in Table I, for all 12 patient models.

TABLE I
THE 12 PATIENT PHARMACODYNAMIC MODELS USED IN THIS STUDY

Patient	Age	Length	Weight	Gender	C_{50}	E_0	E_{max}	γ
1	40	163	54	F	6.33	98.80	94.10	2.24
2	36	163	50	F	6.76	98.60	86.00	4.29
3	28	164	52	F	8.44	91.20	80.70	4.1
4	50	163	83	F	6.44	95.90	102.00	2.18
5	28	164	60	M	4.93	94.70	85.30	2.46
6	43	163	59	F	12.10	90.20	147.00	2.42
7	37	187	75	M	8.02	92.00	104.00	2.10
8	38	174	80	F	6.56	95.50	76.40	4.12
9	41	170	70	F	6.15	89.20	63.80	6.89
10	37	167	58	F	13.70	83.10	151.00	1.65
11	42	179	78	M	4.82	91.80	77.90	1.85
12	34	172	58	F	4.95	96.20	90.80	1.84

Changes in volumes of the compartments (V_1, V_2, and V_3) has very small effect on the performance. In the PD parameters, higher $EC_{50}(3.7)$ indicates the need for further drug to get the same DoA level, higher $\Upsilon(3.21)$ represents higher nonlinearity and lower k_{e0} (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 $\Upsilon(2)$ 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. To come to the point, two parameters (λ, n) for IMC, and three parameters (K_c, τ_I, τ_D) for PID are used for modifying the controller.

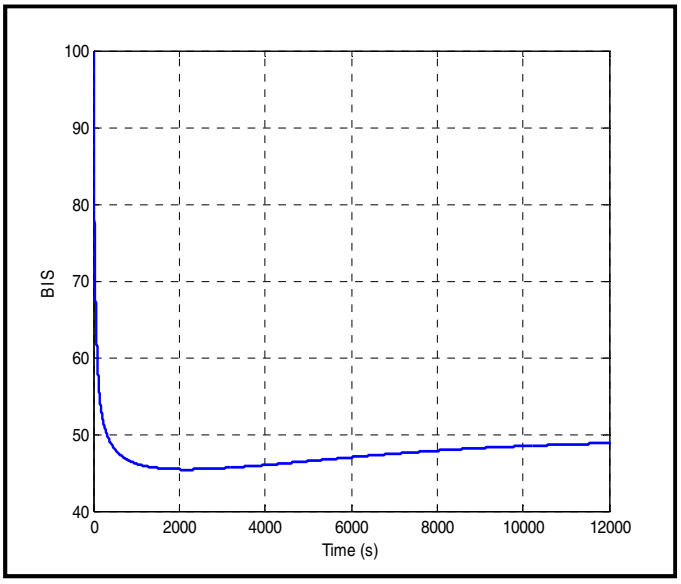

Fig. 7 BIS vs time for the IMC.

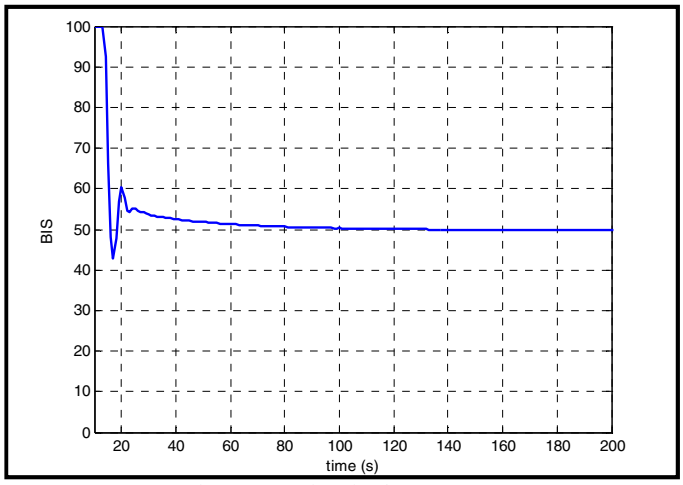

Fig. 8 BIS vs time for the PID.

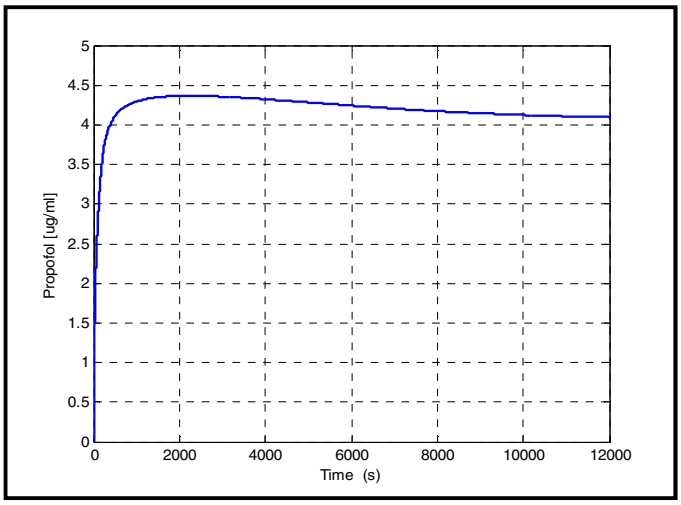

Fig. 9 Propofol infusion rate in IMC.

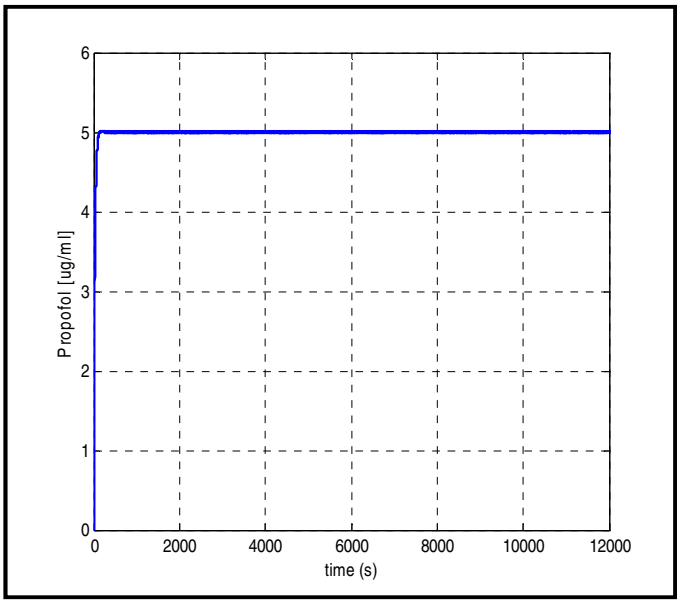

Fig. 10 Propofol infusion rate in PID controller.

V. Conclusions

In this paper, an internal model control, for regulation of anaesthesia using BIS as the controlled variable have been developed and evaluated thoroughly. The performance of this controller is considered along with the performance of the traditional PID controller. In comparison with traditional PID controller, the proposed internal model control is found to be robust to intra- and inter-patient variability, and better at handling disturbances and measurement noise. In system performance, the settling time has been shortened (≅4.5 min) and the performance with no undershoot in the IMC, also undershoot was higher with PID controller. The performance of the IMC controller is found to perform the best and hence recommended for DoA control. The proposed IMC strategy was also found to be more robust to intra- and inter-patient variability.

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