

The Design and Investigation of Model Based Internal Model Control for the Regulation of Hypnosis

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Abstract—The manual control of anaesthesia is still the dominant practice during surgery. An increasing number of studies have been conducted to explore the possibility of automating this process. 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 differences in pharmacokinetics (PK), and pharmacodynamics (PD). This study develops patient dose-response models and provides 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 and compared with traditional PID controller. The performance is confirmed in our simulation.

I. INTRODUCTION

The monitoring and control of unconsciousness in operating theatre is a major challenge to both anaesthetist and machines [1]. Depth of Anaesthesia (DoA), can be defined as the lack of response and recall to noxious stimuli [2]. 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 [3]. 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 [4]. 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 [5]. 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 [6]. A commercial monitor is available to calculate the depth of anaesthesia in terms of the bispectral index (BIS). BIS is one of several systems used in anesthesiology to calculate the effects of specific anaesthetic drugs on the brain and to follow changes in the patient's level of sedation or hypnosis. In technical terms, the BIS itself is a complex mathematical algorithm that allows a computer inside an anaesthesia monitor to analyze data from a patient's electroencephalogram (EEG) during surgery. The BIS is an electroencephalogram (EEG) derived variable that quantifies the power and the phase couplings of the EEG at the different frequencies. BIS, which has been in use since 1997, is a sort of automated direct measurement of the patient's condition, and indirect assessments of sedation [7]. The BIS system displays both raw data from the EEG and a single number between 100 (indicating a conscious patient) and 0 (indicating the absence of brain activity) that represents the patient's degree of sedation. The target number for most anesthetized patients is between 50 and 60.

Model-based control has lead to enhanced control loop performance. One of the clearest model based technique is Internal Model Control (IMC). IMC has many advantages in control system design. The stability of the IMC is only depending on the controller and nominal plant. 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 control [8].

The proposed IMC uses the approximate linear PK– PD model in the controller design, which will regulate patient's

BIS by manipulating the infusion rate of isoflurane. Because of potential patient-model difference, a number of simulations are conducted to verify the robustness of the IMC controller. The proposed IMC scheme has also been tested for disturbance rejection and measurement signals. The performance obtained with the IMC controller is compared with the performances of the PID and MPC.

The rest of the paper is presented as follows. A synopsis of the pharmacokinetic and pharmacodynamic models used for prediction and for control is given in the next section. The depth of anaesthesia control is introduced in Section 3. Experiments and results are discussed in Section 4. The conclusion section summarizes the main outcome of this strategy.

II. DEPTH OF ANAESTHESIA AND MODELING

A. Patient model

The relationship between the drug effect and drug infusion rate can be described with PK and PD models. PK models illustrate the distribution of the drugs in the body and PD models describe the relationship between blood concentration of a drug and its systematic effect. These models can be identified for different kind of drugs by using a specific population of patients. The PK can be described by a three-compartment model as shown in Fig. 1.

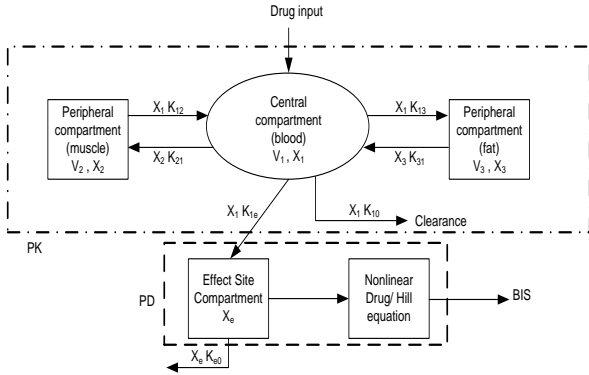


Figure 1. Patient model

B. Pharmacokinetic model

The human body is assumed to be divided into several compartments to drive the PK model [9]. In each compartment the drug concentration is homogeneous as shown in Fig. 2. The DoA model considers both propofol and remifentanyl since this last one has a non-negligible effect on the DoA level.

Hereafter, c_e^{remi} (the remifentanyl 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:

$$\begin{cases} \dot{x}_1 = A_1 x_1 + B_1 u \\ c_p^{\text{prop}} = C_1 x_1 \end{cases} \quad (1)$$

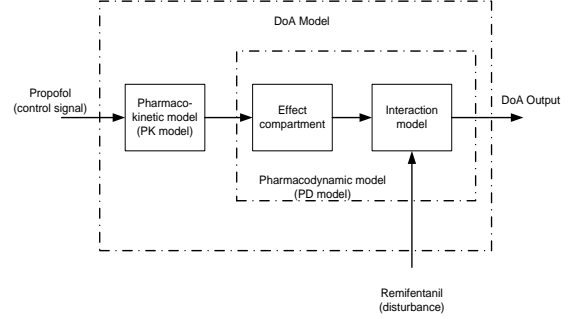


Figure 2. DoA model

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

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].

$$v_1 = \text{weight} \times v_c \quad (2)$$

C. Pharmacodynamic 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:

$$\begin{cases} \dot{x}_2 = A_2 x_2 + B_2 c_p^{\text{prop}} \\ c_e^{\text{prop}} = C_2 x_2 \end{cases} \quad (3)$$

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

The effect-site concentration is related to DoA as (Hill equation) [10]:

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

where C_e is:

$$C_e(s) = \frac{k_{e0}}{s + k_{e0}} C_p(s) \quad (5)$$

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

III. DEPTH OF ANAESTHESIA CONTROL

The IMC is a technique that is extensively used in chemical and process industries where uncertain models are quite common [11]. The internal model control philosophy relies on the Internal Model Principle, which states that control can be achieved only if the control system encapsulates, either implicitly or explicitly, some representation of the process to be controlled [12]. 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 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. It is noted that the system model is explicitly used in the IMC structure unlike the classical controller structure [13].

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. The block diagram of IMC is shown in Fig. 3.

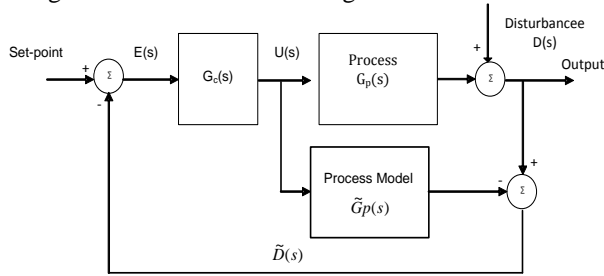


Figure 3. Block diagram of IMC

$G_c(s)$ is the controller. Assume $\widetilde{G}_p(s)$ is a model of $G_p(s)$. The inverse of the model of the process is equal $G_c(s)$,

$$G_c(s) = \widetilde{G}_p(s)^{-1} \quad (5)$$

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. The process-model mismatch is common; that means the 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 is not 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 Fig. 3. The disturbance affecting the system is $D(s)$ in Fig. 3. The desired input $U(s)$ is introduced to both the model and the process [14]. 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:

$$\widetilde{D}(s) = \{G_p(s) - \widetilde{G}_p(s)\}U(s) + D(s) \quad (6)$$

From equation (6), if $D(s)$ is equal to zero, then $\widetilde{D}(s)$ is the difference between the process and its model. Also if $G_p(s) = \widetilde{G}_p(s)$, then $\widetilde{D}(s)$ is equal to the unknown disturbance. Thus $\widetilde{D}(s)$ 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 be write as,

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

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

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

From 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 means 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 still be realized provided $G_c(s) = \widetilde{G}_p(s)^{-1}$. Furthermore, to enhance 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 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. 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 shown in Fig. 4. 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.

A linear IMC requires an internal linear time- invariant model as step response model to estimate the future output via past values of the inputs.

The dynamic system for the process's model is a combination of PK and PD models, which are mathematically represented as a sequences connection from input setting to concentration at the effect-compartment in series with the BIS amount as shown in Fig. 4. The above mathematical system can be represented mathematically as a sequences cascade of two linear time-invariant systems followed by nonlinear systems. The linear time-invariant systems lead to single input single output models (SISO), where the anaesthetic drug concentration U and plasma concentration C_1 are the input and output of the PK model, and the plasma concentration C_1 and effect-compartment concentration C_e are the input and output

the model parameters (inter- and intra-patient variability). The details are shown in table I.

TABLE I. VALUES OF THE PARAMETERS FOR THE 15 PATIENT

Parameter								
Patient no.	k_{10}	k_{12}	k_{21}	k_{13}	k_{31}	k_{e0}	EC_{50}	γ
1	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	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

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 show that changes in volumes of the compartments (V_1 , V_2 , and V_3) has very small 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 (3.21) 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 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. 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.

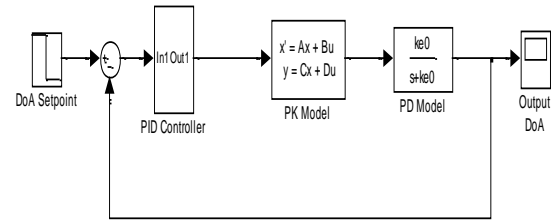


Figure 8. PID controller

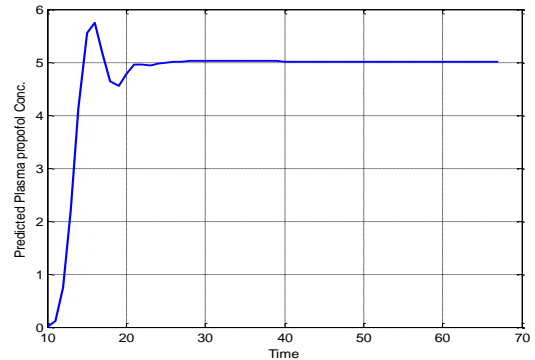


Figure 9. Performance of PID controller

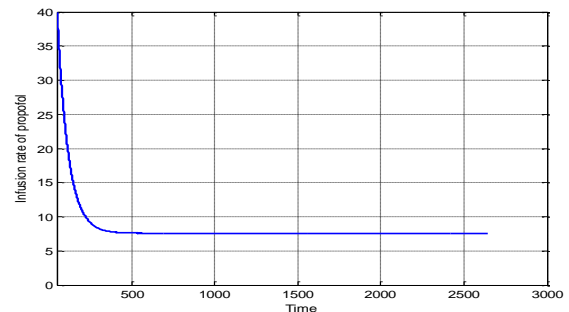


Figure 10. Infusion rate of propofol (IMC)

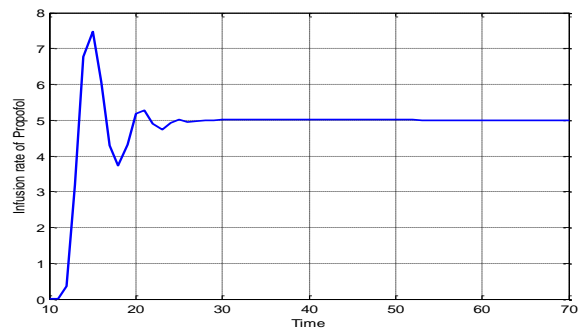


Figure 11. Infusion rate of propofol (PID)

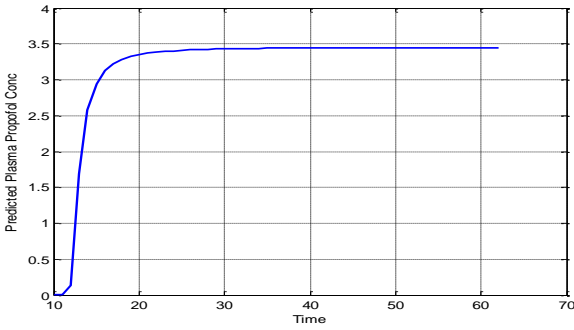


Figure 12. Predictive plasma propofol concentration (IMC)

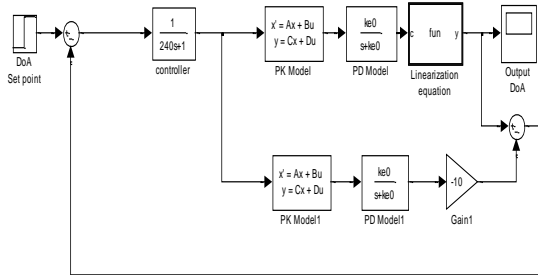


Figure 13. IMC system

V. CONCLUSIONS

In this study, the regulation of anaesthesia using BIS as the controlled variable has been investigated. A robust controller is designed to compensate for patient inherent drug response variability. The performance of this controller is evaluated and compared with the performance of the conventional PID controller. The IMC controllers are found to be robust to intra- and inter-patient variability, and better at handling disturbances and measurement noise.

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