Design and implementation of PK-PD model based PID controller for closed loop anesthesia regulation

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Abstract. Anesthesia is a way to control pain during a surgery and also helps to maintain the patient blood pressure, blood flow, and heart rate etc., Regulating the depth of anesthesia is a difficult task, since anesthetists has to consider nonlinearity, inter and intra-patient variability, multivariable characteristics, variable time delays, dynamics dependent on the hypnotic agent, variability in model analysis. Automatic anesthesia regulation aims to automatically regulate the anesthesia levels by considering the several physiological measurements of patients. In this work we are study a safe and capable progress for hypnotic drug propofol delivery using closed loop control technology and Bispectral Index (BIS) have used to measure the depth of anesthesia. A control strategy that combines a bispectral index and pharmacokinetic/pharmacodynamics models Proportional, Integral, Derivative (PID) controller were investigated. The controller compares the calculated BIS value with its input reference for the path of the hypnotic drug propofol and then the controller manages the anesthetic of propofol entering the anesthetic process to attain the desired BIS value.

Keywords: Anesthesia, PK-PD Model, BIS, CO₂ Index, PID Controller

1. Introduction

A span control of anesthesia is an important phase of the patient care for surgery the same as intensive care[1]. Anesthesia plays a major role in many fields such as oral and maxillofacial surgery, major surgery and intensive care unit. The main goal of anesthesia is to allow patients to feel no pain during surgery and to stay them in an unconscious state. On the other hand, if an unusual amount of hypnotic drug is given, it is dangerous to patients. When any major operation is performed in the hospitals; the patient must be anesthetizing condition. The great challenge in anesthesia process is to identify the exact amount of dose required by a patient is because every person have a specific needs, and during surgery these demand can change. One critical matter that anesthetists often face in health check practice is how to accurately assess the amount of anesthesia in patients during major and minor operation, and also it was very important to monitor the amount of drug infused in order to maintain the depth of anesthesia. If the anesthetist fails to carry out the anesthesia to the patient at the particular time interval, it might cause some problems. In order to overcome these problems, the design of an automatic operation of an anesthesia machine based on some controller is important [8]. To maintain the anesthesia levels considering the patient's health, anesthetist should act as a multi task feedback controller to regulate and control the drug administration. The capability of closed-loop monitored anesthesia is that drug dosage is expected to decrease and post-operative recovery while increasing patient safety and falling the anesthesiologist's workload. [3].

There is no apparatus to accurately measures or monitors the patient's anesthetic state. Nearly every anesthetist actually manages anesthetic drugs manually using clinical symptoms and biological signals [6]. Patient symptoms representing anesthetic include speech response, eyelash reflex, grimacing and other expression, respiratory rhythm, lachrymation, and suddenness which
are relatively hard to measure online. Almost all mentioned patient signs indicate an excessively low anesthetic depth. The levels of heart beat rate, blood pressure, loss of blood oxygen, BIS and end-tidal $\text{CO}_2$ concentration are patient biological on-line measurable quantities reflecting the anesthetic state. These are monitored in every modern operating room.

In our work BIS is taken as the key measure to identify the hypnotic level of the patient and also developed a controller which independently controls the propofol infusion rates. Inter patient difference is sophisticated by the drug sensitivity, disturbances mainly caused by surgical stimulation and noise in the measurement. In this paper, a closed-loop controller using a proportional-integral-derivative algorithm that guides the administration of propofol through BIS monitoring during general anesthesia induction and maintenance. Patient models are known from clinical data to regulate the controllers and it can be developed by PK-PD models.

2. Monitoring Depth of Anesthesia

2.1 Clinical Signs
Clinical signs are necessary for anesthetists in clinical practice to monitor the DoA. Some of the clinical signs of anesthetic depth are blood pressure, heart rate, heart rate variability, sweating, lacrimation, movement and breathing behavior, and so on. However, medical signs could not be used to create standard measures of anesthetic depth. The efficiency of the clinical signs may change time to time, and for these anesthetics the clinical signs may inter connect with DoA and some may not. Some of the clinical signs such as heart rate, blood pressure, blood oxygen saturation, BIS, and end-tidal quantity of carbon dioxide may interfere with surgical stimulation.

2.2 Drug Concentration
One of the ways to find out the extent of anesthesia is to determine the anesthetic level of the blood samples from the patient. Upon intravenous management, the drug is agreed through blood circulation to the rest of human body and only part of the drug reaches its peak of effects such as change in blood pressure, heart rate, oxygen level in blood etc., Pharmacokinetics build the relationship between the quantity of drug administered and the concentration of drug in plasma, while pharmacodynamics establishes the relationship between the concentration of drugs in plasma and the concentration of drugs at the site of contact. The concentration of drugs at the insertion site, however, is only a measure of the pharmacological effect and the strength of anesthesia is a measure of the effect of drugs. A sigmoid model is available to compute the drug effect from the concentration of the treatment site [4].

| BIS VALUE | ANESTHETIC STATE                  |
|-----------|-----------------------------------|
| 0         | Depressed EEG                     |
| 20        | Burst suppression                 |
| 40        | Deep hypnotic level               |
| 60        | Moderate hypnotic level           |
| 80        | Sedated                           |
| 100       | Awake                             |

2.3 Human Electroencephalogram (EEG) Signal
Such electrical activity is physiologically straight relevant to anesthesia time. The level of EEG activity is correlated with cerebral blood flow and cerebral metabolism. EEG is a valuable tool because it represents cerebral physiology and is a continuous and invasive measure; its pattern changes markedly in anesthetic drug administration and neuromuscular blockers also do not affect it. EEG usually switches from small amplitude, high frequency signals when awake to broad amplitude,
low frequency signals while deeply anesthetized. The EEG signal has been used as an objective measure of anesthesia concentration.

2.4 Bispectral Index
One of several technologies used to monitor anesthesia depth is the Bispectral Index (BIS). The BIS screen provides a single size less number ranging from 0 to 100. As indicated by the anesthesiologist, a BIS value between 40 and 60 suggests an appropriate level of general anesthesia. BIS monitor approved as a possible tool by the FDA in 1996 to decrease perception of intraoperative. Table 1 shows the hypnotic level of patient for the corresponding BIS value.

3. Mathematical Model of Closed Loop Anesthesia
The relationship between Propofol infusion stage and its impact can be defined using the model of pharmacokinetic (PK) and pharmacodynamics (PD). PK and PD modeling is the method of creating a mathematical model for the length of dose to concentration (pharmacokinetics) and impact concentration (pharmacodynamics) (Minto & Schnider, 2008). PK model describes the body's propofol distribution and PD model describes the relationship between the concentration of propofol blood and its clinical impact.

3.1 Pharmacokinetics Model
Pharmacokinetics is defined as drug absorption, distribution, metabolism and excretion (ADME) kinetics and their relationship to human pharmacological, therapeutic or toxicological response. Also it can be defined in terms of the “what the body does to the drug”. A pharmacokinetic model is a mathematical model that is used after a drug infusion to predict a particular drug's blood concentration profile. These are derived from experimental studies in which arterial or venous drug concentrations are measured in a group of patients or volunteers after a bolus or infusion and subject to standardized statistical approaches and software.

The most commonly used PK-PD models for Propofol are the 4th order compartmental model that Schnider et al. introduced in 1999 presented in Figure 1. The concentration of drugs is homogeneous in each part of these compartments.

![Existing Four Compartmental PK-PD Model](image)

**Figure 1.** Existing Four Compartmental PK-PD Model.

From Fig.1, The drug insertion compartment is called the central compartment C1 and may also be called the initial distribution volume. The second C2 compartment is called the shallow peripheral compartment, the fast redistribution compartment. Drug distribution from C2 and C1 is rapid. The third compartment C3 is called the deep peripheral compartment in which the drug distribution is slow between C1 and C3. Drug metabolism and distribution levels are defined by constants of the
level or clearances a constant rate is the percentage of the drug in a compartment that undergoes a process during a time unit and is represented as units per minute or units per hour.

The heart rate, blood pressure and BIS are the patient biological on-line measurable quantities reflecting the anesthetic state of the patient which can be considered in the 4th order PK-PD compartmental model introduced by Schnider et al., 1999. Figure 2 shows the proposed 4th order PK-PD compartmental will include the carbon dioxide index. The carbon dioxide level of the patient is measured by capnography and the \( \text{CO}_2 \) range of the patient during the operation is to be from 30-40 mmHg. By including this parameter, the output result of the controller with respect to the patient will provide better performance.

![Figure 2. Proposed Four Compartmental PK-PD Model.](image)

A state space representation of three compartment PK model with effect site compartment is described by equation (1),

\[
\begin{align*}
\dot{x}(t) &= Ax(t) + Bu(t) \quad (1a) \\
y(t) &= Cx(t) \quad (1b)
\end{align*}
\]

Where \( x(t) \) is a concentration vector of the drug, \( U(t) \) is the level of infusion of drugs, \( y(t) \) is the concentration of drugs corresponding to the compartment of the impact site. A, B and C are the system, input and output matrix respectively. The Pharmacokinetic Parameters given as,

\[
A = \begin{bmatrix}
-\left( k_1 + k_2 + k_3 + k_4 \right)/v_1 & k_2 & k_3 & k_4 \\
\frac{k_2}{v_1} & -k_2/v_2 & 0 & 0 \\
\frac{k_3}{v_3} & 0 & -k_3/v_3 & 0 \frac{k_4}{v_4} \\
\frac{k_4}{v_4} & 0 & 0 & v_4
\end{bmatrix}
\]

\[
B = \begin{bmatrix}
\frac{1}{v_1} \\
0 \\
0 \\
0
\end{bmatrix} \quad C = \begin{bmatrix} 0 & 0 & 0 & 1 \end{bmatrix}
\]
where subscribers 1, 2, 3 and 4 denote, respectively, the central, shallow peripheral, deeper peripheral and impact-site compartment (Sawaguchi et al. 2008).

Table 2 Pharmacokinetic parameter values given as a function of patient’s AGE (years) and BW (Kg) (Sawaguchi et al. 2008).

| PARAMETERS | VALUES |
|------------|--------|
| \( K_1 \)  | \( 0.0595BW^{0.75} \), If AGE \( \leq 60 \) \( 0.0595BW^{0.75} - 0.45AGE + 2.7 \), If AGE > 60 |
| \( K_2 \)  | 0.0969BW^{0.82} |
| \( K_3 \)  | 0.0889BW^{0.55} |
| \( K_4 \)  | 0.12 |
| \( V_1 \)  | 1.72BW^{0.71} \* AGE^{-3.9} |
| \( V_2 \)  | 3.32BW^{0.61} |
| \( V_3 \)  | 266 |
| \( V_4 \)  | 0.01V_1 |

The parameters \( K \) and \( V \) are the clearance and volume provide as age (AGE) and weight (BW) functions as shown in Table 2 in each compartment.

3.2 Pharmacodynamics Model

The model of pharmacodynamics (PD) explains what the drug is doing to the body; how the health effect is correlated with the impact site concentration of the drug. The general definition is that the PD defines the relationship between the concentration of blood plasma drug \( Cp \) and clinical impact. A sigmoid model is used in pharmacology to show this relationship of concentration-effect and the mathematical expression of this relationship. The Hill equation is an equation used to describe the biochemistry [9].

Figure 3. PD Model.

The pharmacodynamics model usually explains the nonlinear dynamics of BIS, MAP and HR to the concentration of impact site \( y(t) \) where the PD model is used in shown in Fig 2. Hill's sigmoid model (Sawaguchi et al, 2008) is the commonly used nonlinear function in PD modeling. In 1900, Hill proposed a non-linear equation describing the relationship between two unusual factors to describe the quantitative balance between the oxygen tension and the percentage saturation of hemoglobin with oxygen in dissimilar salts Equation 2 shows the dose effect modeling equation Hill, which Wagner first proposed in 1968. Hill equation is based on the receptor-occupancy theory, “Intensity of response to a drug is proportional to the number of receptors occupied by that drug”. The formula of Hill consists of a static model with one (or two) input and one (DoA) output which was given by equation 2,

\[
E(t) = E_0 - E_{max} \frac{C_e \dot{y}}{C_e \dot{y} + e_{50}}
\]

Where
\( C_e = \) effect site drug concentration
6

$E_{o}$ = baseline effect

$E_{max}$ = maximum drug effect,

$C_{50}$ = steady-state drug concentration when 50% of drug effect has been achieved

$\gamma$ = steepness of the relationship curve

BIS is taken as the key measure of DoA (controller reference) in this paper, whereas MAP, HR and CO$_2$ are used during surgery to observe the corresponding blood pressure and heart rate.

Equation 3 for the BIS index gives the Hill Sigmoid $E_{max}$ model,

$$\text{BIS}(t) = \text{BIS}_0 - \text{BIS}_{max} \frac{C_{e}}{C_{e} + C_{st}}$$

Where

$\text{BIS}_0$ = Base value at no drug is given to patient a

$\text{BIS}_{max}$ = Max change of concentration to input drug

From that data, the pharmacokinetic parameters are defined by,

$$A = \begin{bmatrix}
-0.3952 & 0.1393 & 0.0951 & 0.0126 \\
0.0304 & -0.0304 & 0 & 0 \\
0.0304 & 0 & -0.0304 & 0 \\
1.2613 & 0 & 0 & -1.2613
\end{bmatrix}$$

$$B = \begin{bmatrix}
0.1051 \\
0 \\
0
\end{bmatrix}$$

$$c = [0 \quad 0 \quad 0 \quad 1]$$

4. Controller Design

In order to achieve the desired worth of system control, it is essential to choose the appropriate control strategy and design the exact controller. In industry, various control strategies have been used, and many other areas, including medicine, there is no such control strategy that is the best for all control issues. The control strategies vary from conventional control (e.g. control of PID), plan reference control, optimal control, stochastic control, control of the neural network, and control of the fuzzy logic. All control strategies may be adaptive in full, adaptive in part or non-adaptive. Due to its simplicity and consistency, PID control could be the most efficient control strategy used in control engineering. If the plant dynamics are undecided or partly unstated, it is particularly useful. Better control output from other control strategies can be obtained; however, PID control usually provides sufficient power. In this paper, for the closed-loop control of anesthesia regulation, PK-PD model based proportional integral derivative (PID) controller is presented.

5. Results and Discussions

The data investigation in Table 2 presented a mathematical model of a 27-year-old patient with a body weight of 68 kilograms. The model must be considerably improved with the insertion of age and weight. Adjusting PK for each person should improve the accuracy of the target-controlled infusion and may help to extend the range of induction and maintenance of the target-controlled infusion Propofol of DOA.

5.1 Open Loop Control

Here the propofol (ml) is given as input to the patient model and BIS is taken as output. The propofol given to the patient is from the range of 1ml to 10ml. The open loop response is taken for that given range of input and BIS settling time is to be taken. In open loop system, the BIS value is settled at different values in different times at corresponding propofol input. Table 3 shows the settling rate of BIS at different propofol input.
Table 3. Propofol vs. BIS in Open Loop system

| Propofol (ml) | 1   | 2   | 3   | 4   | 5   | 6   | 7   | 8   | 9   | 10  |
|--------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| BIS          | 92  | 86  | 78  | 70  | 61  | 54  | 47  | 42  | 36  | 32  |

Figure 4 shows that BIS settling value for the propofol input from 1-10ml. Initially the BIS value starts from 90-100 which shows the awake state of the patient. In order to maintain the patient hypnotic level during surgery, the BIS value should be from the range of 60-100. Hence it is need to maintain the BIS value at the set point of 50. For that purpose we use the PK-PD model based PID controller in closed loop anesthesia regulation surgery by using the PK-PD model based PID controller.

5.2 Closed Loop Control

The PK-PD model based PID controller is developed for the closed loop anesthesia regulation. Here the BIS value is given as input to the controller and PID controller used in that closed loop anesthesia process is developed by trial and error. For the closed loop anesthesia regulation, PID controller is auto tuned to get the $k_p$, $k_i$, and $k_d$ values. The Figure 4 shows the simulation result shows that the BIS value reach the required hypnotic level of 50-60 at the 2nd minute after the patient takes the propofol. The BIS quality was set at 8 minutes in 50. Therefore the required BIS value is controlled and regulated for patient during the surgery by using the PK-PD model based PID controller.

Figure 4. Simulation Results for Open loop and Closed Loop System.

6. Conclusions

This paper is set out to investigate the simulation results for closed loop anesthesia regulation by using the PID controller. The mathematical model for the patient is developed by using the pharmacokinetics and pharmacodynamics models. Based on the PK-PD model, the PID controller is designed and developed. In open loop system, the BIS value cannot be stable at 50-60. It could be vary for the different input amount of propofol. Hence the PK-PD model based PID controller is designed by trial and error and simulated for closed loop system of anesthesia regulation process.
7. Future Work

For the closed loop anesthesia regulation, the controller requires fast response for the corresponding patient variability. After the simulation is to be done, a prototype setup is to be developed. Here we have to see how the PID controller responds to the patient variability when the propofol is given and also to achieve the required output of BIS at 50. Also for a closed-loop anaesthesia regulation, PK-PD model based model predictive controller is to be developed in future.

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