PID control for intravenous depth of anesthesia

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***Abstract*—This paper focuses on automating the depth of anesthesia with the aim of ensuring patient safety and comfort during surgery. Using PKPD models to show the drug interaction with the body, a Single-Input (Propofol) Single-Output (Bispectral Index) model is developed. An important aspect of controlling the depth of anesthesia is inter- and intra-patient variability, given by the different dynamics of the PK models and the changes in Hill function parameters. To linearize the system, a parameter scheduling technique is used, specifically the inverse of the Hill curve. This study implements two PID control strategies: one based on frequency response and an internal model control (IMC). The performances of the two control strategies are evaluated, showing fast response and effective maintenance of the target BIS value and no significant undershoot or overshoot.**

***Index Terms*—anesthesia, inter- and intra-patient variability, drug administration, bispectral index, target control**

I. Introduction

The primary goal of general anaesthesia is to keep the unconsciousness of the patient undergoing surgery intervention. While under anaesthesia, individuals experience a state of insensitivity to pain and have no memory of painful stimuli associated with the surgery. Modern general anaesthesia is characterized by the triad of hypnosis, analgesia and muscle relaxation. Hypnosis achieves a state of unconsciousness, ensuring patients don't sense any painful stimuli during surgery. Analgesia represents the absence of pain, used for blocking the perception of painful sensations. Muscle relaxation is facilitated by neuromuscular blocking drugs, which interrupt the signal transmission between the nerves and skeletal muscles, preventing the muscle contraction during the surgery. A requisite balance among the three components of anaesthesia is essential during surgery. This balance ensures a consistent execution of the procedure, minimizing any potential harm to the patient [1].

Automating the anesthesia process can be seen as a challenge as it requires precise patient modelling and effective control strategies to optimize drug dosages while ensuring the patient's safety. In medical applications, this process rises difficulties beginning with the need of developing an appropriate mathematical model that can accurately capture patient dynamics during the intervention. Inter- and intra-patient variability results from the different dynamics in the PK model, as well as from changes in the Hill function parameters, which can lead to undesirable variations in the BIS value [2].

Implementing control in drug administration has come with several benefits, for instance lowering costs through reducing medication volume per intervention and faster recovery time with fewer postoperative side effects [3]. Despite these advantages, the anesthesiologist remains a key component in the control process. With a broader view than the controller, including access to information about the patient's vital signs (e.g. heart rate, blood pressure, breathing, body temperature), the anesthesiologist can intervene at any time if necessary to adapt decisions made by the controller [4].

From a control engineering perspective, several control strategies have been developed on hypnosis, including PID [5], IMC [6], fuzzy control [7] and MPC [8], [9]. These approaches show the efficiency of using closed-loop control in depth of hypnosis regulation. In this study, we consider a Single-Input (Propofol) Single-Output (Bispectral Index) system for depth of anesthesia control. The developed control strategies are PID, based on frequency response on Nicholis curve, and an internal model control (IMC) approach.

The paper is organized as follows. In Section II, basic concepts about hypnosis, PKPD models, PID and IMC control strategies are presented. Following, in Section III implementation of the controllers and closed-loop control results are discussed and the conclusions are in Section IV.

II. Theoretical Background

One of the most used drugs to induce hypnosis is propofol, due to its large absorption and rapid elimination by the body [10]. Monitoring the depth of anaesthesia is done through the observation of the BIS value (Bispectral Index), which is determined based on electroencephalogram waveforms. As it can be seen in Figure 1, the BIS value ranges from 0 to 100, where 0 indicates a flat line in the EEG and 100 indicates full awakeness. During surgery, it's important to maintain the BIS value within the range of 40 to 60 . If the BIS value is under 40, the risk of experiencing cardiovascular or respiratory collapse and postoperative delirium increases, as if it's above 60, the patient may recall and respond to commands, indicating awareness of the surgical intervention [6].

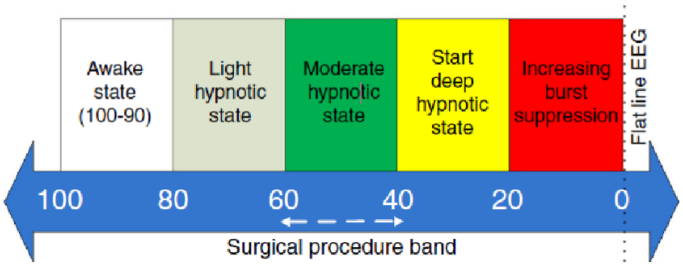

Fig. 1: BIS index range and patient's state. Source: [2]

The hypnosis process can be divided into three stages: induction phase, maintenance phase and emergence phase. The induction phase usually lasts about 4-5 minutes, during which the BIS value is drawn from 100 to 50. In the maintenance phase, the BIS value must be ensured within the 40-60 range as aforementioned. During the emergence phase, administration of propofol is stopped, starting the patient's awakening [6].

The most used model to capture patients variability and to describe how the drugs interact with the body is the PKPD model, which is based on the principle "what the body does to the drug" versus "what the drug does to the body". The PK model addresses "what the body does to the drug", involving modelling drug diffusion through body tissues and the drug flow in the blood. Contrastingly, the PD model captures "what the drug does to the body", describing the relationship between drug concentration and observed clinical effects, such as patient vital signs [12].

A. Patient Model

1) PK model: Pharmacokinetics is generally defined as the interaction between a drug and the body, describing drug distribution, its elimination and effect-site concentration after its administration. These models are often multi-compartmental, especially for intravenously administrated drugs, such as propofol.

The structure of a three-compartmental model with effect-site compartment can be seen in the figure below.

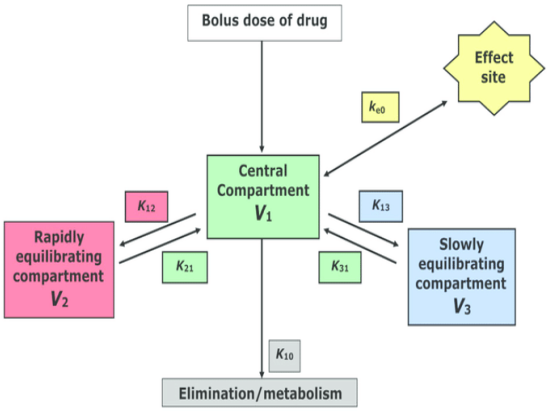

Fig. 2: Pharmacokinetic three-compartment model. Source: [11]

Typically, the central compartment represents the fast-acting compartment (blood), while the other two represent slow-acting compartments (muscle and fat). The effect-site compartment is hypothetical compartment that shows the transport dynamics of the drug to the effect location [13].

The PK model is expressed by the next set of equations:

$$\begin{aligned}\frac{dV_1}{dt} &= -[k_{10}+k_{12}+k_{13}]C_1 + k_{21}C_2 + k_{31}C_3 + \frac{u(t)}{V1}\\ \frac{dV_2}{dt} &= k_{12}C_1(t) - k_{21}C_2(t)\\ \frac{dV_3}{dt} &= k_{13}C_1(t) - k_{31}C_3(t)\end{aligned} \tag{1}$$

- V1 - concentration in the fast compartment
- V2, V3 - concentrations in the slow compartments
- k_{ij}, $i = 1{:}3$, $i \neq j$ - rate constants for distribution between compartments (they depend on age, gender, height and weight)
- u_t - bolus dose of drug

The parameters k_{ij}, $i = 1{:}3$, $i \neq j$ for propofol have been developed for widely differing patient categories, but further we will be using the Schnider model that is described by the following model equations: [15]

$$\begin{aligned}V_1 &= 4.27\,[\mathrm{L}]\\ V_2 &= 18.9 + (-0.391 \times (Age - 53))\,[\mathrm{L}]\\ V_3 &= 238\,[\mathrm{L}]\\ CL_1 &= 1.89 + 0.0456 \times (TBM - 77) - 0.0681 \times (LBM - 59)\\ &\quad + 0.0264 \times (HT - 177)[\mathrm{L/min^{-1}}]\\ CL_2 &= 1.29 - 0.024 \times (Age - 53)[\mathrm{L/min^{-1}}]\\ CL_3 &= 0.836\,[\mathrm{L/min^{-1}}]\\ k_{10} &= \frac{CL_1}{V_1}\ [\mathrm{min^{-1}}]\\ k_{12} &= \frac{CL_2}{V_1}\ [\mathrm{min^{-1}}]\\ k_{13} &= \frac{CL_3}{V_1}\ [\mathrm{min^{-1}}]\\ k_{21} &= \frac{CL_2}{V_2}\ [\mathrm{min^{-1}}]\\ k_{31} &= \frac{CL_3}{V_3}\ [\mathrm{min^{-1}}]\\ k_{e0} &= 0.456\ [\mathrm{min^{-1}}]\\ k_{1e} &= k_{e0}\ [\mathrm{min^{-1}}]\end{aligned}$$

2) PD models: The PD model represents the dose-effect response, given by the Hill equation. This static nonlinear function represents the relationship between drug concentration, C, and drug effect E [13].

$$E = E_0 - E_{max} \cdot \frac{C_e(t)^\gamma}{C_e(t)^\gamma + C_{50}^\gamma} \tag{2}$$

- E_0 - the effect when the drug concentration equals 0
- E_{max} - maximum possible effect

- C_{50} - drug concentration for which 50
- γ - Hill coefficient of sigmoidicity

To compensate the nonlinearity introduced by the Hill function within the pharmacodynamic model, a parameter scheduling technique is used, respectively the inverse of Hill function [14]. This parameter transforms the measured BIS values into a Ce value, used as feedback for the controller. Afterwards, the controller determines the appropriate drug infusion rate by comparing the estimated Ce value from the inverse function with the reference value. Similarly, the reference BIS value is converted into a corresponding Ce value using the inverse Hill function to provide a suitable reference for the controller. The inverse of the Hill curve is defined as follows:

$$C_e(t) = EC50 \left(\frac{E_0 - BIS(t)}{E_{\max} - E_0 + BIS(t)} \right)^{\frac{1}{\gamma}} \tag{3}$$

B. Control methods

The PID controller minimizes the error given by the difference between the measured output and the setpoint value. It contains three parameters: proportional, integrative and derivative. The proportional term determines the ratio of the output response to the error signal, the integral term sums the error over time in order to eliminate the steady-state error, and the derivative term reacts to the rate of change of the process variable. The mathematical form of a PID controller is:

$$c(t) = K_p e(t) + K_i \int_0^t e(\tau)\, d\tau + K_d \frac{de(t)}{dt} \tag{4}$$

- $c(t)$ - control signal
- $e(t)$ - error signal
- K_p, K_i, K_d - coefficients for the proportional, integrative and derivative terms

By tuning the parameters of a PID, specifically setting the optimal gains for P, I and D, we can achieve an ideal response from the control system.

1) PID tuning with FRTool: The first PID implemented in this paper was done using FRTool (Frequency Response Tool for Computer Aided Control System Design in Matlab) which works with Nicholis diagram. This tool converts design specifications, such as overshoot and settling time, into graphical constraints, simplifying the tuning process. After importing the model's transfer function into the FRTool and defining the design specifications, the interface will appear as in Figure 3.

The design specifications are met if the Nicholis curve does not intersect the overshoot constraint and if the bandwidth frequency is above the -3dB green line.

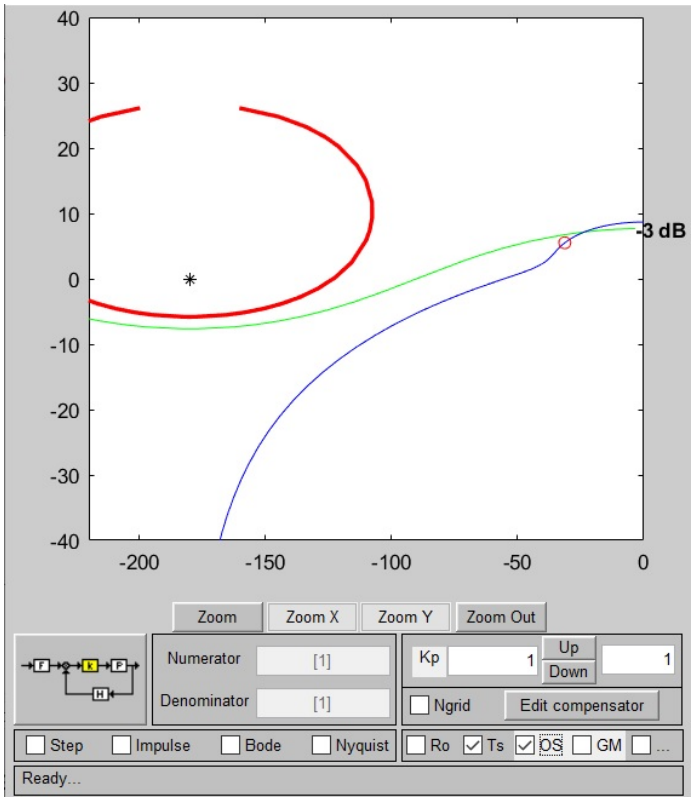

Fig. 3: FRTool interface before designing the controller

2) IMC tuning: The IMC principle is based on the acknowledging that, in reality, we have an approximation of the actual process, requiring us to consider an imperfect model in the controller design. The block diagram of the internal model structure can be seen in the figure below.

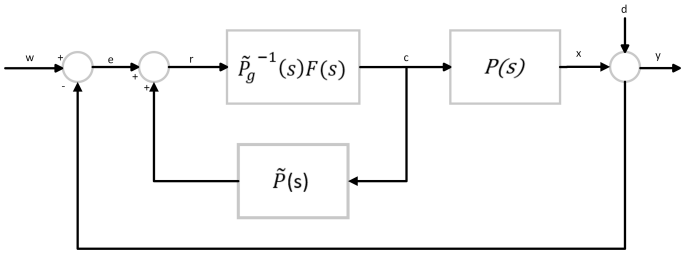

Fig. 4: Internal Model Control Structure

The first step involves writing the approximated process as follows: $\tilde{P}(s) = \tilde{P}_g(s)\tilde{P}_b(s)$, where $\tilde{P}_g(s)$ represents the invertible part of the process transfer function, while $\tilde{P}_b(s)$ contains the non-invertible part, such as time-delay and RHP zeros. The approximation of time-delay is usually done through first-order Pade approximation: $e^{-\tau_m s} = \frac{1-\frac{\tau_m}{2}}{1+\frac{\tau_m}{2}}$. Additionally, the controller contains a filter of the form $\frac{1}{(\lambda s+1)^n}$, where n is chosen such that the controller transfer function becomes proper and λ is a tuning parameter, with an effect on settling time.

III. Implementation and Results

Simulations were performed using Simulink Matlab on a set of 12 patients, with an additional one representing the nominal patient. The controller should take the BIS value from 100 to 50 within 4-5 minutes and maintain it within the range of 40-60. The control scheme used in this paper is shown in Figure 5.

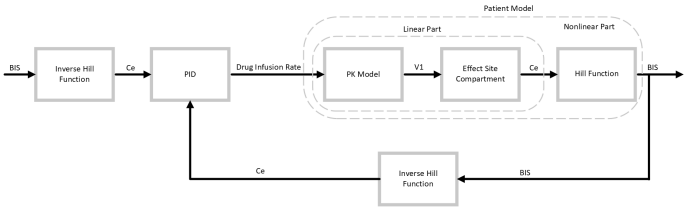

Fig. 5: Control scheme

To begin with, an open-loop simulation was performed in order to highlight patients sensitivity to the drug. As it can be seen, patient 12 and patient 8 show the most sensitivity: for patient 12, the BIS value drops under 40, which can lead to burst suppression associated with coma, as for patient 8 the BIS value exceeded 60, causing potential awareness during surgery.

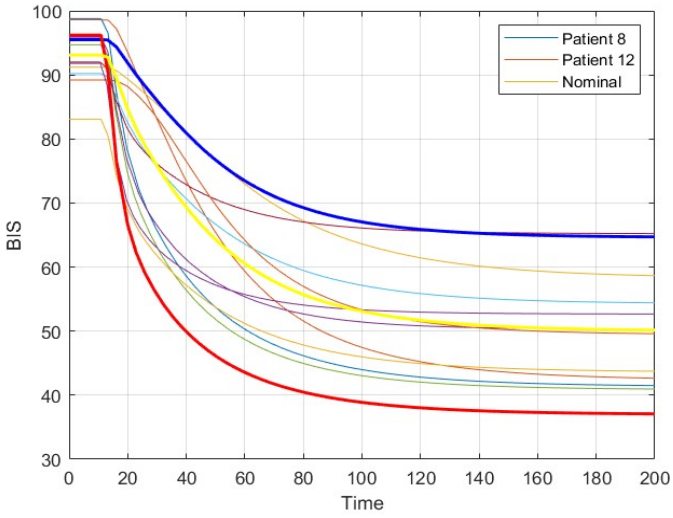

Fig. 6: Open Loop Simulation Results

The controllers were designed using the nominal patient's transfer function:

$$H_{\text{nominal}} = \frac{0.456(s+0.3513)(s+0.06663)}{(s+1.071)(s+0.456)(s+0.2666)(s+0.03014)} \tag{5}$$

A. FR controller

The initial step in designing the controller involves specifying the desired performances. Given that the drug induction must be performed in 4-5 minutes, a settling time of 180 seconds was imposed. Also, to maintain the BIS value within the recommended range, an overshoot of 10% was imposed.

The designed controller introduces one pole at zero from the integrator, one zero in -0.03989 and one zero in -2.86:

$$PID(s) = 0.29\left(1 + \frac{0.0393}{s} + 0.3448s\right) \tag{6}$$

As it can be observed from Figure 7, the settling time constraint increases for certain patients due to high inter- and intra-patient variability, along with a small undershoot.

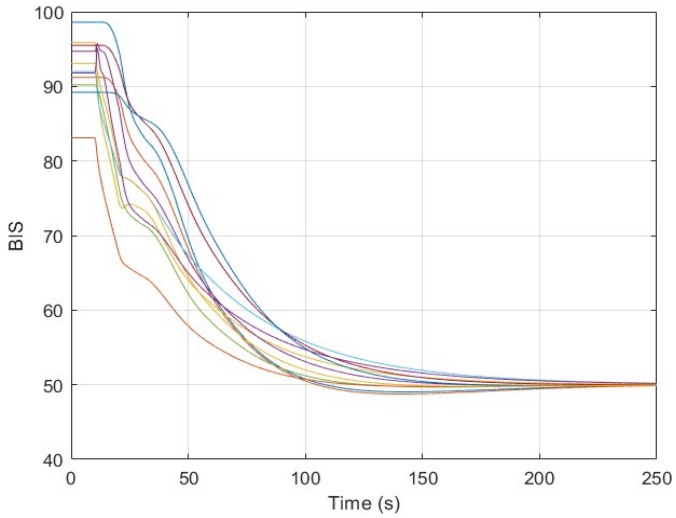

Fig. 7: Frequency response control of all patients

B. IMC controller

The IMC controller was tuned as presented in II-B2. Regarding the filter, a second-order configuration was chosen (n=2), and the tuning parameter λ was set to 23 to satisfy the settling time specification.

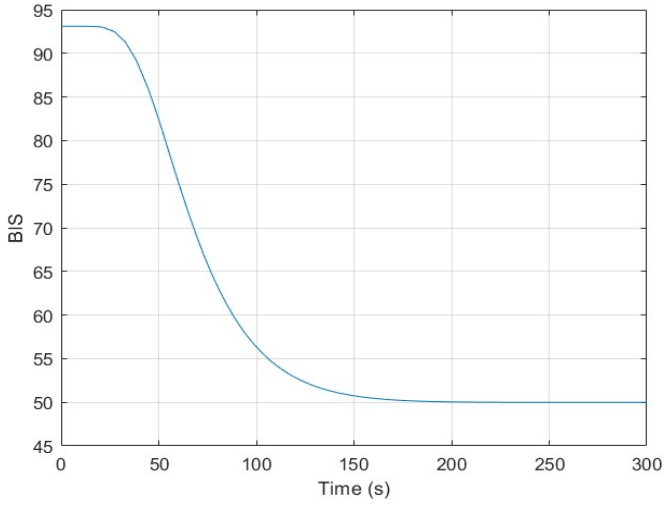

Fig. 8: IMC control response of nominal patient

Figure 8 illustrates the closed-loop response of the nominal patient, while Figure 9 shows the responses for all patients. In the nominal patient's case, the settling time requirement is fulfilled, without any overshoot or undershoot. When the controller is tested on all patients, a 2% undershoot is present for two of the patients. The settling time remains within the 4-5 minutes range, exhibiting the 180 seconds constraint desired for the nominal patient. In Figure 10, the IMC control action can be observed, specifically how the bolus of propofol is administrated by the controller during surgery.

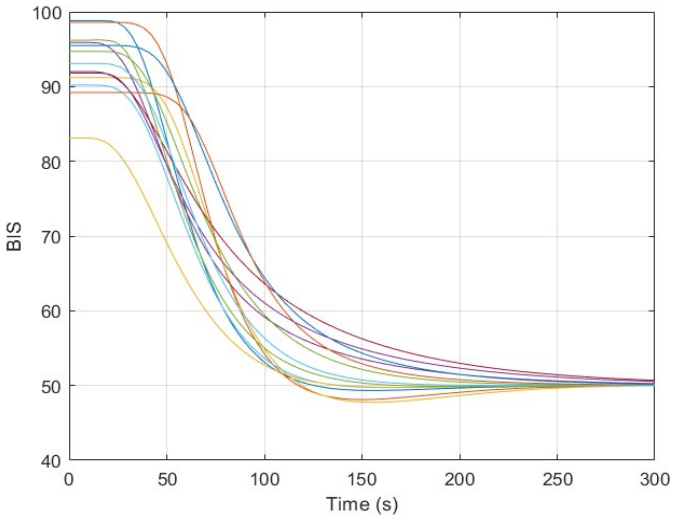

Fig. 9: IMC control response of all patients

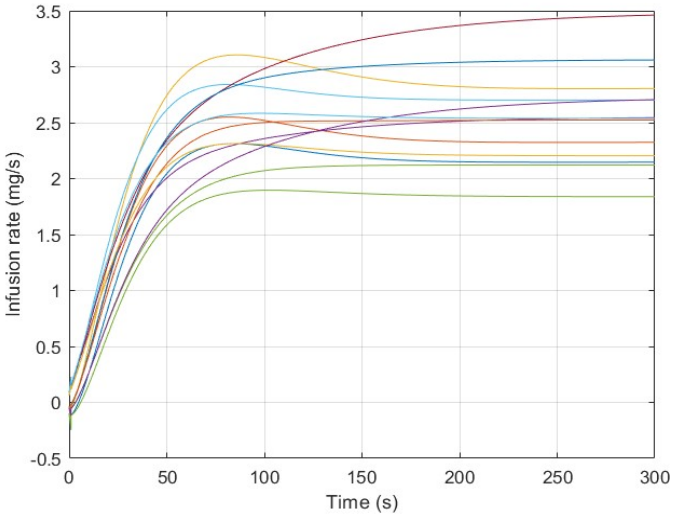

Fig. 10: Control signal of the IMC

IV. Conclusions

Depth of anesthesia control presents a manifold of challenges, beginning with patient modelling. Effective modelling is essential for capturing the patient's dynamics, including inter- and intra-patient variability given by the dynamics in the PK models and variations in Hill function parameters. These aspects are necessary when developing the control strategy in order to achieve the goal of maintaining the desired BIS values.

This paper focuses on the design and implementation of two PID tuning methods, a FR controller and an IMC. The performances were tested on a set of 12 patients in order to evaluate how these controllers deal with patient variability and maintain the desired clinical specifications during surgery. The goal is to simplifying the anesthesia process, while comforting the patients and ensuring their safety.

Both control strategies presented are capable of maintaining the process at the target value, in comparison with the open-loop simulation. The implemented controllers show good performances, meeting the settling time constraints and showing minimal undershoot or overshoot. Moreover, the simulations indicate that these controllers handle the patient variability effectively, successfully meeting the specified constraints.

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