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Fractional Order PID Control of Propofol Dosage and Optimization in Lean and Obese Patients

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Abstract: This paper outlines the design of a fractional-order proportional–integral–derivative controller for regulating the induction phase of Propofol infusion in lean and obese patients. The obtained controller is implemented within the pharmacokinetic-pharmacodynamic model and the nonlinear Hill function to conduct closed-loop simulations. The latter are employed using a dataset comprising 24 patients to obtain clinical evaluation results. The design of the controller relies on a generic second-order plus dead time approximation model, which characterizes interpatient variability in response to Propofol infusion within the studied population. The fractional-order proportional–integral–derivative is tuned to achieve sufficient robustness margins ie phase margin, cutoff frequency, and the consideration of the iso-damping properties. The results show no undershoot and a smooth convergence to the desired value of the bispectral index, which indicates the depth of hypnosis.

Keywords: Closed-Loop Control of Anesthesia, Obese Patients, Fractional-Order PID control

1. INTRODUCTION

General anesthesia is a medical state induced in a patient during surgery. It aims to ensure and maintain three states. Propofol is an intravenously administered hypnotic agent that aims to produce and maintain one of those states which is unconsciousness. Adequate dosing of this anesthetic drug is required to avoid awareness, maintain homeostasis, and reduce postoperative recovery time in the critical care unit (Ilyas et al. (2017)). In order to achieve this goal, continuous monitoring of the patient's anesthetic state is required, enabling the anaesthesiologist to adapt drug titration as needed. This ongoing decision-making process has prompted a great deal of study on closed-loop control systems for anesthetic drug dosing (Ionescu et al. (2014)). Indeed, the integration of an automated controller into a decision-making system, such as anesthesia and surgery not only alleviates the anesthesiologist of mundane and repetitive tasks but also ensures the perfect execution of reproducible actions (De Keyser et al. (2016)).

Despite an escalating number of clinical studies substantiating the advantages associated with automated controllers in anesthesia and surgery, the administration of anesthetic agents remains manual. Therefore, studies nowadays focus on developing advanced control strategies (Ghita et al. (2020)) and precise models to enhance anesthesia regulation.

To predict the optimal drug dosage for an intravenous administration, compartmental models are extensively used. These systems consist of a finite number of homogeneous, well-mixed subsystems, called compartments, which facilitate the exchange of material among them and with the environment. Among the myriad existing models, the Schnider model is widely used in anesthesia. It takes into consideration patient-specific variables such as age, weight, and sex, providing a refined understanding of Propofol's concentration-effect relationship. This model is used in guiding anesthesia practitioners in optimizing Propofol dosing for individual patients, thereby contributing to enhanced precision and safety in clinical settings (Ionescu

et al. (2008)). However, these models do not take into consideration anomalous diffusion that occurs in lean and obese patients who are considered more than half of modern society in Western Europe.
Anomalous diffusion constitutes a significant impediment in terms of controlling areas of variable diffusion coefficients and modified permeability due to the structure and properties of material cell composites (Sposini et al. (2022)). In practical terms, this necessitates a meticulous calibration of the controller to exhibit robustness in the face of such variations, while assuming homogeneous mixing and time-invariant dynamics irrespective of the patient's individualized patterns at hand. Within the contemporary landscape of personalized medicine and targeted drug therapy, there arises a compelling imperative to deviate from the homogeneity assumption. Instead, there is a discernible need to adopt tools that facilitate the polyvalent distribution of drug molecules within intricate and dynamic tissue environments.

Well-tuned Proportional–Integral–Derivative (PID) controllers have demonstrated sufficient robustness, performance, and safety within clinical environments (Reboso et al. (2019)). The PID controller stands out for its straightforward structure and minimal parameter count. This makes synthesis, implementation, and verification more accessible. Various design methods have been published for tuning the parameters of the proportional-integral-derivative controllers, and more advanced controllers have undergone clinical evaluation (Naşcu et al. (2015)). However, the lack of objective comparisons between different controller structures leaves uncertainty regarding whether advanced controller types in closed-loop anesthesia could enhance performance while maintaining safety. Indeed, discrepancies in patient cohorts, surgical procedures, administered drugs, and the practical application of the controller can introduce biases in the comparison. Additionally, the sets of patient models employed for controller synthesis differ among research groups, as do the dynamics upon which the acquired controllers are assessed. While studies in the literature typically scrutinize the performance of a specific controller, they offer limited insights into whether this performance is primarily constrained by the controller type or by other factors, such as the variability in the patient model set used for synthesis. For fat and lean patients PharmacoKinetic-PharmacoDynamic (PK-PD) model, the clearance rate is slower than in the regular models leading to post-anesthesia side effects.

This study aims to apply and verify the feasibility of Fractional-Order PID (FO-PID) control of the induction phase of Propofol infusion in higher-order Linear Time-Invariant (LTI) structures / state-space representation of lean and obese patients using the Bispectral index (BIS) as a measure of the clinical effect; then to discuss the achievable performance of this controller for the regulation of the depth of hypnosis in anesthesia. The robustness of this controller is then tested on 24 patient's database to demonstrate that a well-tuned PID can accommodate the large inter-patient variability. The paper is organized as follows: Section 2 introduces the PK-PD model with the augmented fat trap compartments model. Section 3 gives the mathematical background for designing the FO-PID controller. Section 4 shows the simulation results with

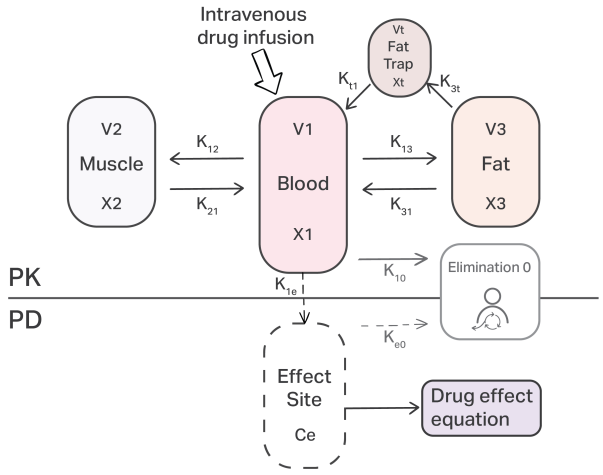

Fig. 1. Augmented compartmental model with the additional volume of fat cells

an emphasis on evaluating the control performance that was achieved, pinpointing the limitations of the proposed design. A conclusion section summarizes the results and outlines future research and improvement opportunities from a control engineering perspective.

2. MATERIALS AND METHODS

This section delineates the PK-PD model with its parameters. Next, it introduces the proposed Fat trap compartment model, offering a comprehensive overview of its conceptual framework and it outlines the patients database used for simulation.

2.1 Pharmacokinetic - Pharmacodynamic model

Pharmacokinetics (PK) is the movement of drugs through the body, whereas pharmacodynamics (PD) is the body's biological response to drugs. In general, the PK model of Propofol is represented by a three-compartmental model: Blood, muscles, and fat, as shown in Figure 1. The ordinary differential equation (ODE) of this model is defined in (Neckebroek et al. (2019)).

The PK model parameters for Propofol in Figure 1 are from the Schnider model (Merigo et al., 2017) and are calculated using the set of equations:

$$\begin{aligned} V_1 &= 4.27 \\ V_2 &= 18.9 - 0.391 \cdot (age - 53) \\ V_3 &= 238 \\ C_{l1} &= 1.89 + 0.0456 \cdot (weight - 77) \\ &\quad -0.0681 \cdot (LBM - 59) \\ &\quad +0.0264 \cdot (height - 177) \\ C_{l2} &= 1.29 - 0.024 \cdot (age - 53) \\ C_{l3} &= 0.836 \end{aligned} \tag{1}$$

where $V_i (i = 1, 2, 3)$ denotes the volume of the i-th compartment, in $[l]$, with their respective clearance rates C_{li}, in $[l/min]$. The model coefficients $k_{ij}, i \neq j$, in $[min^{-1}]$, are constants that represents the drug transfer rate from the j^{th} compartment to the i^{th} compartment, and are calculated as follows:

$$\begin{aligned} k_{10} &= \tfrac{C_{l1}}{V_1}, & k_{12} &= \tfrac{C_{l2}}{V_1} \\ k_{13} &= \tfrac{C_{l3}}{V_1}, & k_{21} &= \tfrac{C_{l2}}{V_2} \\ k_{31} &= \tfrac{C_{l3}}{V_3}, & k_{e0} &= 0.456 \end{aligned} \tag{2}$$

The LBM is Lean Body Mass which differs according to the patient's gender. For male patients, it is calculated as:

$$LBM = 1.1 \cdot weight - 128 \cdot (weight/height)^2 \tag{3}$$

The PD model represents the relation between the effect site concentration C_e and the clinical effect. The effect site concentration is used as input to calculate the BIS, which is the hypnosis index, described as the Hill function:

$$BIS(t) = E_0 - E_{max}\left(\frac{C_e^{\gamma}(t)}{C_e^{\gamma}(t) + C_{50}^{\gamma}}\right) \tag{4}$$

where C_{50} is the concentration at half effect (50%), C_e is the effect site concentration, γ describes the steepness of the concentration–effect relationship, E_0 is baseline effect and E_{max} is maximum possible effect.

2.2 Augmented Pharmacokinetic Model for Trap fat volume

Adipose tissue is composed of various types of cells, contingent upon the type of fat it makes and the period of time the fat has been formed. This concept can be analogous to distinct geological materials such as clay, sand, gravel, and stones. In this case, adipose tissue exhibits varying degrees of porosity and permeability to water across these substrates (Palombo et al. (2022)). The proposed augmented compartment to the PK model of general anesthesia is represented with the ODE:

$$\dot{x}_t(t) = k_{3t}x_3(t) - k_{t1}x_t(t) \tag{5}$$

where:

$$\begin{aligned} k_{3t} &= C_{l1t}/V_t, & k_{t1} &= C_{lt}/V_1 \\ V_t &= BMI \cdot V_3/100, & C_{lt} &= C_{l3}/R \end{aligned}$$

Here, k_{3t} and k_{t3} represent the constants of the drug transfer rate from the fat compartment to the fat trap compartment and vice versa. V_t denotes the volume of the fat trap compartment with its clearance rate C_{lt}. Moreover, the BMI is the Body Mass Index which represents a numerical value of a person's weight in relation to their height.

$$BMI = weight/(height)^2 \tag{6}$$

R may be considered as the amount of risk for trapping, hence the higher R values (as the BMI increases), the slower the clearance from the trap volume. Consequently, the molecules stay longer times in the fat-trap tissue.
The relation between the porosity of fat tissue and the evolution of the body mass is nonlinearly correlated to the relation between the porosity of fat tissue and the permeability of drug molecules. This nonlinear correlation gives the relative ratio between porosity and permeability that is used against BMI to find the relationship between the relative ratio of porosity to permeability against BMI from normal to morbidly obese. This latter represents R and is calculated as a 4th-order regression polynomial:

$$\begin{aligned} R = &-0.000436 \cdot BMI^4 + 0.0489 \cdot BMI^3 \\ &-2.012 \cdot BMI^2 + 34.01 \cdot BMI - 236 \end{aligned} \tag{7}$$

The PK model described previously is then augmented by adding a 4^{th} compartment represented by the equation (5). The state-space representation of the final PK-PD model is represented by (8)

$$\begin{bmatrix} \dot{x}_1 \\ \dot{x}_2 \\ \dot{x}_3 \\ \dot{x}_t \\ \dot{C}_e \end{bmatrix} = \begin{bmatrix} -(k_{10}+k_{12}+k_{13}) & k_{21} & k_{31} & k_{t1} & 0 \\ k_{12} & -k_{21} & 0 & 0 & 0 \\ k_{13} & 0 & -k_{31} & 0 & 0 \\ 0 & 0 & k_{3t} & -k_{t1} & 0 \\ k_{1e} & 0 & 0 & 0 & -k_{e0} \end{bmatrix} \cdot \begin{bmatrix} x_1 \\ x_2 \\ x_3 \\ x_t \\ C_e \end{bmatrix} + \begin{bmatrix} 1/V_1 \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix} u(t); \quad y = [0\ 0\ 0\ 0\ 1] \begin{bmatrix} x_1 \\ x_2 \\ x_3 \\ x_t \\ C_e \end{bmatrix} \tag{8}$$

where states x_i, $i = (1, 2, 3, t)$, represent the concentration in volume of compartments. The input $u(t)[mg/min]$ denotes the drug infusion rate.
The output $y(t) = C_e[mg/l]$ is the effect-site concentration.

To illustrate the effects taking place in the new compartment, 24 patient database described in Table 1 is useed (Ionescu et al. (2021)). This database gives the biometric and the Hill function parameters for a set of representative datasets of patients. Moreover, the average patient is added to the database as 25th patient. These parameters will be used to obtain nominal transfer function.

Table 1. Representative Patient Database (24 patients, all males) with PK model biometric values and PD model sensitivity values. 25th Patient is the average

ID -	Age (yrs)	Height (cm)	Weight (kg)	BMI (kg/m^2)	LBM -	C_{50} (μ/ml)	γ -
1	74	164	88	32.7	60	2.5	3
2	67	161	69	26.6	53	4.6	2
3	75	176	101	32.6	69	5.0	1.6
4	69	173	97	32.4	67	1.8	2.5
5	45	171	64	21.9	52	6.8	1.78
6	57	182	80	24.2	62	2.7	2.8
7	74	155	55	22.9	44	1.7	3. 5
8	71	172	78	26.4	60	7.8	2.9
9	65	176	77	24.9	60	2.9	1.88
10	72	192	73	19.8	62	3.9	3.1
11	69	168	84	29.8	60	2.3	3.1
12	60	190	92	25.5	71	4.8	2.1
13	61	177	81	25.9	62	2.5	3
14	54	173	86	28.1	62	2.5	3
15	71	172	83	28.1	62	4.3	1.9
16	53	186	114	33	77	2.7	1.6
17	72	161	87	33.2	59	4.5	2.9
18	61	182	93	28.1	69	2.7	1.78
19	70	167	77	27.6	58	6.8	3.1
20	69	168	82	29.1	60	9.8	1.6
21	69	158	81	32.4	55	3.2	2.1
22	60	165	85	31.2	60	5.1	2.51
23	70	173	69	23.1	56	3.67	3.1
24	56	186	99	28.6	73	5.8	2.3
25	65	173	83	27.8	61	4.2	2.5

3. CONTROL DESIGN

A rudimentary closed-loop system is characterized by including a controller that monitors and adjusts the output variable of a given system to maintain it at a predetermined set value. In the context of anesthesia, the role of the controller is taken by the anesthesiologist, the system under consideration is the patient, and the monitored output variables are clinical parameters. The anesthesiologist diligently observes and scrutinizes these output data, so that customized interventions can be administered to the patient. In practical application, the entirety of our actions adheres to the prescribed closed-loop definition. The distinctiveness of this paradigm lies in the fact that the controller is a human being, which introduces limitations associated with intermittent surveillance and actions.

In this study, an FO-PID controller will substitute the role of the anesthesiologist to control the Depth of Hypnosis (DoH) regulation. In order to achieve this goal, diverse studies suggested that the segregation of the control strategy into two distinctive phases is significantly more advantageous and specific: Induction phase where a strong synergistic effect caused by the combination of the opioid and anesthetic drug needs to be unified for all patients. Maintenance phase where the controller has to keep the hypnotic state of the patient (BIS) between the range 50%±10% and reject the surgical stimuli as fast as possible (Hegedus et al. (2022)).

3.1 Fractional-Order PID

The general function of the FO-PID is represented by the equation

$$H_c(s) = k_p(1 + \frac{k_i}{s^\lambda} + k_d s^\mu) \tag{9}$$

where k_p, k_i and k_d are the proportional, integral and derivative gains respectively and λ, μ are the integral and derivative orders.
For the induction phase, three specifications need to be satisfied which are the minimization of the intra- and interpatient variability, the respect of the time-to-target, and the rejection of oscillations and excessive undershoot. In order to do so, an imposed phase margin, cutoff frequency, and the consideration of the iso-damping properties, that are presented in (10), lead to the definition of the nonlinear equations (12) where $P(j\omega_c)$ is the process transfer function at the imposed gain crossover frequency (ω_c).

$$\begin{aligned} &i) \quad |H_{ol}(j\omega_c)| = 1 \\ &ii) \quad \angle H_{ol}(j\omega_c) = -\pi + \varphi_m \\ &iii) \quad \left.\frac{d(\angle H_{ol}(j\omega_c))}{d\omega}\right|_{\omega=\omega_c} = 0 \end{aligned} \tag{10}$$

where

$$H_{ol}(j\omega_c) = Hc(j\omega_c) \cdot P(j\omega_c) \tag{11}$$

For the maintenance phase, which will be considered in a future study, the patient's depth of hypnosis needs to be maintained in the recommended range of 40% to 60% of BIS. This means that the controller's speed, the attenuation of the potential disturbances, and the sustention of the patients' variability to the minimal are prioritized.

4. RESULTS AND DISCUSSION

The design of the controller involved the generation of a nominal state space representation (8) using Table 1. This latter is calculated as the mean of the 24-patient PK-PD state-space model. After that, a corresponding nominal transfer function was subsequently made (13).

$$\frac{0.1075s^3 + 0.1127s^2 + 0.03108s + 0.001677}{s^5 + 2.84s^4 + 2.693s^3 + 1.072s^2 + 0.1687s + 0.006467} \tag{13}$$

The output of the nominal transfer function (13) was used as an input to the nonlinear Hill equation (BIS) (4), this latter is calculated using patient 25. The simulation of both systems has been used with a sampling time of 1 second, as shown in Fig 2, to approximate the process to a second order transfer function plus dead time (14) using the identification toolbox in Matlab. This later facilitates the design of the FO-PID controller and has 91.66% accuracy.

$$P(s) = \frac{1.637}{s^2 + 2.86s + 0.9686} e^{-0.3s} \tag{14}$$

In this study, the imposed specifications of $\omega_c = 1 rad/s$, which is gain crossover frequency, and $\varphi_m = 80$, which is the phase margin, are taken from (Yumuk et al. (2019)) to design FO-PID controller given in (9). Using the possess approximation (14), the control performances are calculated using an optimization-solver algorithm (Hegedus et al. (2022); Birs et al. (2019)). The resulting controller is:

$$H_{induction}(s) = 1.5320(1 + \frac{0.5126}{s^{0.9198}} + 0.667 s^{0.9373}) \tag{15}$$

This PID satisfies all imposed specifications as shown in Fig 3.

The simulation was made in the Matlab/Simulink ® environment. To test the robustness of the designed FO-PID controller (15), it was applied to all patients individually. For each patient, the coefficients of the PK-PD model (8) and the nonlinear Hill function (4) were calculated using the Table 1. Figures 4, 5, and 6 illustrate the BIS outputs, effect-site concentrations, and infusion rates of Propofol for each patient, respectively.

The results of this simulation show that the FO-PID control of Propofol infusion in lean and obese patients, using the BIS as a measure of the clinical effect, is feasible and can accommodate the inter-patient variability in this patient database. The hypnotic state is reached in the range of 10 to 15 minutes and stabilized around 20 minutes (BIS Value of ±50%): In lean and obese patients, the trap compartments (which represent fat) imprison the drugs for a longer period. In other words, it takes time for the drugs to get in and out of the fat. This phenomenon causes an extended time to reach the effect site concentration as shown in Fig 5. This later explains why obese patients may require a longer preparation time before surgery and a longer recovery time after. The controller gives a slow and smooth convergence of the BIS. The Time to Target (TT) is between 13min - 18.22min which is considered relatively long for surgery considering that the average is around 3-4 minutes. This matter can be fixed by redesigning a

$$\begin{cases} k_p\sqrt{k_d\omega^{\mu}(sin\frac{\mu\pi}{2}+cos\frac{\mu\pi}{2})+(\omega^{-\lambda}k_i cos\frac{\lambda\pi}{2}+1)^2-(\omega^{-\lambda}k_i sin\frac{\lambda\pi}{2})^2}-\frac{1}{|P(j\omega_c)|}=0 \\ \frac{k_d\omega^{\mu}sin\frac{\mu\pi}{2}-k_i\omega^{-\lambda}sin\frac{\lambda\pi}{2}}{1+k_i\omega^{-\lambda}cos\frac{\lambda\pi}{2}+k_d\omega^{-\mu}cos\frac{\mu\pi}{2}}-tan(-90^\circ+\varphi_m-\angle P(j\omega_c))=0 \\ \frac{\omega^{\lambda-1}(k_i\lambda sin\frac{\pi\lambda}{2}+k_d\mu\omega^{\lambda+\mu}sin\frac{\pi\mu}{2}+k_dk_i\omega^{\mu}(\lambda sin\frac{\pi(\lambda+\mu)}{2}+\mu sin\frac{\pi(\lambda+\mu)}{2}))}{\omega^{2\lambda}+k_i^2+k_d^2\omega^{2(\lambda+\mu)}+2k_i\omega^{\lambda}cos\frac{\pi\lambda}{2}+2k_d\omega^{2(\lambda+\mu)}cos\frac{\pi\mu}{2}+2k_dk_i\omega^{\lambda+\mu}cos\frac{\pi(\lambda+\mu)}{2}}+\frac{\angle P(j\omega_c)}{d\omega}\Big|_{\omega=\omega_c}=0 \end{cases} \tag{12}$$

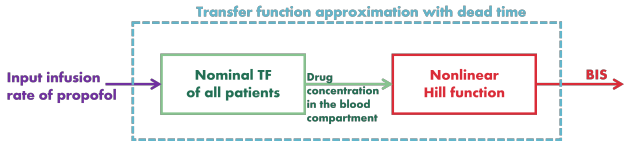

Fig. 2. Approximation of the overall process

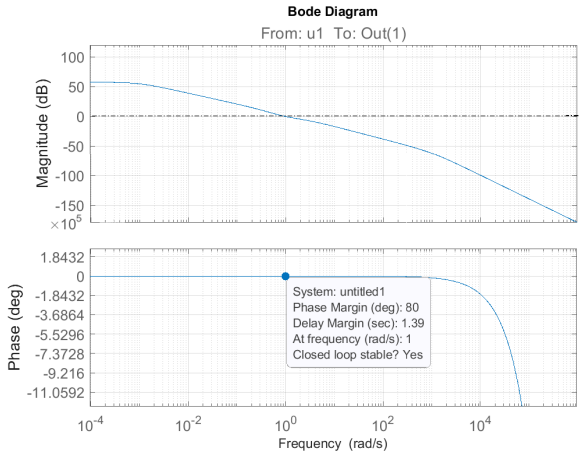

Fig. 3. Bode diagram of the open loop transfer function $H_{ol}(s)$

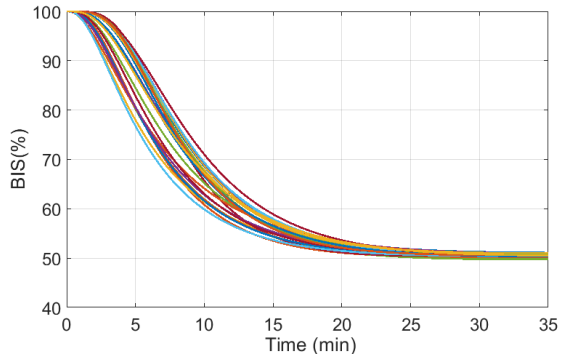

Fig. 4. BIS outputs obtained using the designed FO-PID for all 24 patients.

faster controller. However, doing a change in the controller implies having a bigger undershoot. The current BIS-NADIR, which is the lowest observed BIS value, is 49.8 % which is considered less than 1% undershoot. A faster controller will certainly change the transient phase to an oscillatory behavior.

Ensuring robustness margins is crucial for the closed-loop control of Propofol in anesthesia to prevent scenarios

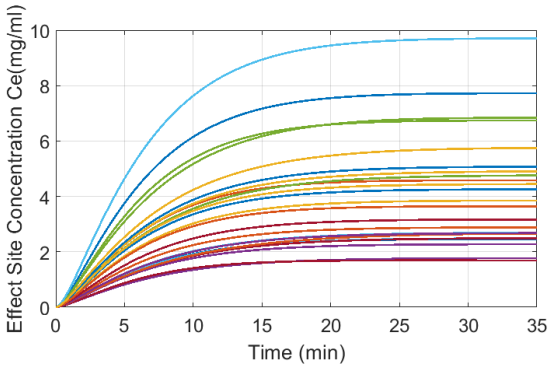

Fig. 5. The outputs of the effect-site concentration for all 24 patients

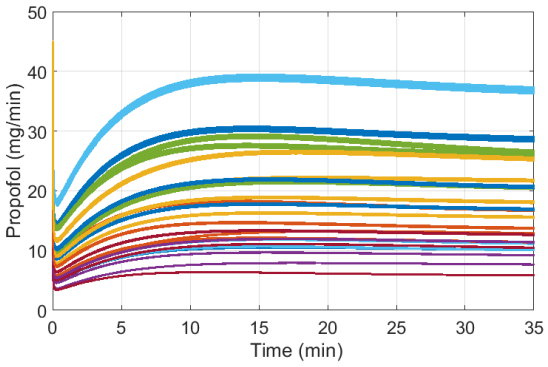

Fig. 6. The infusion rates of the propofol for all 24 patients.

such as overdosing. In this simulation, the absence of undershoot and oscillatory behavior upon induction of the drug observed in the clinical evaluation confirms the predicted robustness margins.

In this study, several specifications were considered in elaborating the final result, namely the strict imposed time in driving every patient from a fully awake state to a moderate hypnotic state (20 seconds), avoiding an undershoot, and preventing overdosing by optimizing the controller performances. However, all those specifications concerned only the induction phase controller. Indeed, the maintenance phase controller that ensures a stable anesthetic state during the surgical stimuli was not considered, which opens a door for further investigations.

The maintenance phase presents other challenges such as the rejection of nociceptive surgical stimuli and handling them is significantly more complex. In addition, having a pain signal that transcribes the nociceptive stimuli is still a research matter. Ongoing studies continue to investigate

the development of a universally applicable pain sensor that accurately captures nociceptor stimuli (Ionescu et al., 2024). As a future perspective, the development of a fractional order controller for the maintenance phase that can reject this perturbation and maintain a hypnotic state can be considered.

5. CONCLUSION

This paper introduced the control of the Propofol dosage using a novel compartment in the PK model. The challenge was the fact that the novel fat trap compartment presented slower drug transfer. Despite the severe limiting factors, the FO-PID controller specifically tuned for induction phase specifications, has been successfully validated on all patients with satisfactory performances.

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