

First-Hand Design of a Fractional order PID for Controlling the Depth of Hypnosis during Induction

Marcian Mihai*, Isabela Birs**, Hegedus Erwin*, Dana Copot**, Martine Neckebroek***,
Robain De Keyser**, Clara M. Ionescu**, Cristina I. Muresan*

* Technical University of Cluj-Napoca, Department of Automation, Cluj-Napoca, Romania (e-mail: Cristina.Muresan@aut.utcluj.ro, Isabela.Birs@aut.utcluj.ro, Marcian.Mihai@aut.utcluj.ro, Erwin.Hegedus@aut.utcluj.ro).

** Ghent University, Department of Electromechanics, Systems and Metal Engineering, Research Group on Dynamical Systems and Control, Tech Lane Science Park 125, Gent 9052, Belgium, (e-mail: claramihaela.ionescu@ugent.be, robain.dekeyser@ugent.be, dana.copot@ugent.be)

*** Ghent University Hospital, Department of Anesthesia, C. Heymanslaan 10, 9000 Ghent, Belgium (e-mail: martine.neckebroek@ugent.be)

The integration of information technology and control engineering has significantly increased in the research field of clinical practice, including the management of medication dosing for general anesthesia. To achieve effective drug dosing, it is necessary to have appropriate controllers for closed loop control methods. A multitude of control mechanisms have been devised to manage hypnosis, with most of them based on pharmacokinetic-pharmacodynamic (PK-PD) models. This study presents a novel structure of a fractional order PID controller tuned for inducing hypnosis. The tuning algorithm uses a novel fractional order model instead of the classical PK-PD models. The main goal is to control the Bispectral Index by delivering Propofol during the hypnotic stage of anesthesia. Closed loop simulation results show that the proposed controller manages to ensure little undershoot and time to target for a nominal patient model. Robustness tests are also performed. The analysis shows that the proposed controller is suitable to maintain BIS signal within a safe operating range but fails to meet the time to target requirement for significant patient variability (greater than 2 orders of magnitude). Online adaptation rules are suggested as a solution.

Keywords: drug dosing, anesthesia, closed loop control of anesthesia, fractional-order models for hypnosis, fractional order control.

1. INTRODUCTION

To address the need for improved patient outcome in healthcare systems by aid of computerized management and engineering methods, closed loop control is a substantial candidate. In particular, it helped to develop ways to assist anesthesiologists to better ensure patient safety during surgeries by dosing the hypnotic drug Propofol appropriately, as hypnosis represents one of the main parts of total intravenous anesthesia (TIVA) (Vuyk, Sitsen, & Reekers, 2015), (Brown, Lydic, & Schiff, 2010).

Target controlled infusion devices have gained significant attention in recent years due to their widespread use in operating rooms. The study aims to optimize the hypnosis state for each patient, emphasizing the importance of precise Propofol dosage for optimal hypnosis state. Inter-patient variability is an important consideration when choosing an appropriate medication dosage. Personalized models and controllers are needed because of the human body's peculiar and unpredictable features. The depth of hypnosis is monitored through the Bispectral Index (BIS), which has to be maintained around a value of 50 to avoid unwanted side effects. From a control engineering perspective, the BIS signal represents the output, while the manipulated input is the Propofol progression rate. The Proportional-Integral-Derivative (PID) controller stands as the most preferred solution (Borase, Maghade, & Sondkar, 2020). However, the standard version

of the PID controller has its limitations (Shah & Agashe, 2016) and therefore a multitude of variations have been exploited.

This paper explores the potential application of the fractional order PID (FOPID) controller for TIVA systems. These controllers are versatile in their design formulation and, in some situations, outperform classical PIDs (Åström & Hägglund, 1995). The integrative component in a traditional PID controller removes steady-state error but reduces stability. The derivative component increases stability at the cost of increased noise sensitivity. To overcome these shortcomings, FOPIDs are investigated (Dabiri, Moghaddam, & Tenreiro Machado, 2018). FOPIDs have been developed for hypnosis control (Copot, Muresan, De Keyser, & Ionescu, 2017) and the majority of them use PK-PD models. The link between a drug's dose and plasmatic concentration is studied via pharmacokinetics. Models with compartments are used to illustrate this relationship. They are the following: the fast compartment, which contains the muscular tissues, the slow compartment, which contains the fat tissues, and the central compartment, which is the location of drug delivery (Ionescu, Neckebroek, Ghita, & Copot, 2021). The two sections of pharmacodynamics are separated. The first one is simulated with an extra compartment and links the plasma concentration inside the central compartment to the concentration inside the effect site. The second one connects the therapeutic action and the concentration at the effect site. A nonlinear gain is used to describe the Propofol-BIS relationship.

The novelty of this research lies in the structure and tuning of the FOPID and in the patient models used for designing the controllers. The patients are modelled not by using the classical PK-PD approach, but using fractional order time delay transfer functions that mimic the BIS variation as a function of the Propofol progression rate. A novel structure for the FOPID is proposed in this manuscript, compared to previous research (Copot, Muresan, De Keyser, & Ionescu, 2017), (Hegedus, Birs, Ghita, & Muresan, 2022) and the tuning of the parameters is done using the novel fractional order models. The controller was tested on 22 patients' models. They correspond to a database of patients previously reported in (Ionescu C. , et al., 2024). The controller was designed for one nominal patient. To analyse the robustness of the proposed controller, all remaining models were tested in closed-loop simulation together with the designed FOPID.

The paper is structured as follows. Section 2 explains the fractional order models, while Section 3 details the novel FOPID tuning algorithm. Simulation results are included in Section 4, while the last section contains the and proposes prospective routes for further study in the field.

2. FRACTIONAL ORDER MODEL FOR THE DEPTH OF HYPNOSIS

A fractional order (FO) model that mathematically describes the effect of Propofol upon BIS has been developed. Previous research has shown that the BIS signal gradually decreases from a state of fully awake (corresponding to 100) to a state of hypnosis, corresponding to a BIS signal around 40-60. The dynamics suggests a stable and all-pole transfer function with time delay:

$$H_{DOH}(s) = \frac{BIS(s)}{PROP(s)} = \frac{k}{a_2 s^{\alpha_2} + a_1 s^{\alpha_1} + 1} e^{-\tau_m s} \quad (1)$$

where $BIS(s)$ and $PROP(s)$ are the Laplace transforms of the BIS signal and Propofol progression rate. The time delay is denoted as τ_m , a_2 and a_1 are coefficients and α_1 and α_2 are the fractional orders. An optimization routine was implemented to estimate the parameters in (1). The standard Levenberg-Marquart algorithm (Zhang, Wang, & Liu, 2023) produces good estimations of the parameters in the FO transfer function (1) by minimizing the sum of squared errors between the actual measured BIS output and the computed BIS signal. To evaluate the fit of the models, first the mean value \overline{BIS} of the measured BIS signal is computed according to:

$$\overline{BIS} = \frac{1}{n} \sum_{k=1}^n BIS_k \quad (2)$$

where n is the maximum number of samples considered in the estimation of the model parameters and BIS_k denotes the measured BIS output at each sample k . The fit of the FO model is computed based on R^2 , the coefficient of determination, as indicated in the equations (3) and (4):

$$fit = 100 \cdot R^2 \quad (\%) \quad (3)$$

$$R^2 = 1 - \frac{SS_{res}}{SS_{tot}} \quad (4)$$

where SS_{res} is the residual sum of squares and SS_{tot} is the total sum of squares. These are estimated according to (5) and (6):

$$SS_{res} = \sum_{k=1}^n (BIS_k - BIS_k^{est})^2 \quad (5)$$

$$SS_{tot} = \sum_{k=1}^n (BIS_k - \overline{BIS})^2 \quad (6)$$

where BIS_k^{est} is the estimated value of the BIS signal computed using (1) and the estimated parameters at each sample k . A database of 22 patients with measured input/output signals has been used. (Mihai, et al., 2024, under review). The estimated parameters of the FO model for each of the 22 patients is given in Table 1, along with the resulting fit exceeding 20% in almost all cases, except for patient P70. In all the studied cases, the patient received a bolus of Propofol of approximately 140 mcg/kg/min for a short period of time which produced the onset of hypnosis (induction phase), followed by a lower drug rate to maintain the BIS signal in the range 40-60. The administered drug for patient 21 is indicated in Fig. 1a), while Fig. 1b) includes the corresponding evolution of the BIS signal for the same patient.

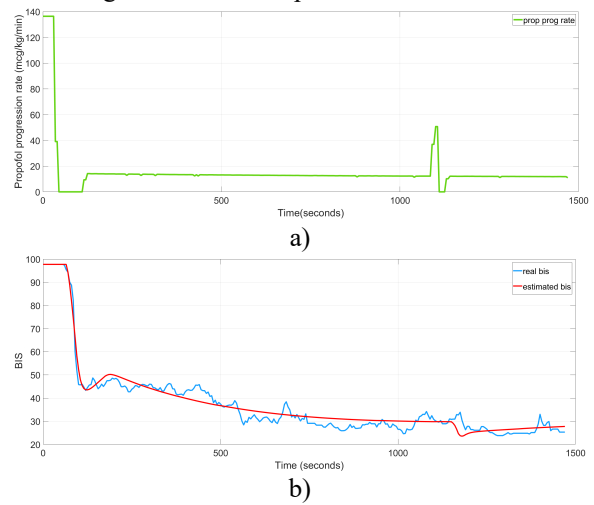


Fig. 1 a) Propofol drug rate administered to patient 21 (experimental data, green line) b) Measured BIS signal (experimental data, blue line) and estimated BIS signal (red line)

Notice that the signal is rather noisy, but the trend suggests dynamics that are suitably represented by the transfer function in (1). The accuracy in estimating the parameters of the FO model for patient 21 is 82.8%. The estimated value of the BIS signal, as resulting from the model in (1) is also represented in Fig. 1b). Notice that the two signals overlap.

A statistical analysis based on Table 1 suggests that the mean value for the gain is $k_{mean}=3.62$, while for the denominator coefficients $a_{2mean}=24916.1$ and $a_{1mean}=627.46$. The fractional order mean values are $\alpha_{1mean} = 1.03$ and $\alpha_{2mean} = 2.21$. The mean value of the time delay is estimated as: $\tau_m=61.1$. This results in a gain variation of -90% up to 145%, coefficient variations ranging from -100% to 270% for a_2 and 530% for a_1 . The fractional order varies from their nominal values from approximately -25% up to 62%, while the time delay varies in a range from -60% to 162%. A robust controller needs to be designed to tackle all these large parameter uncertainties. The solution developed in this manuscript consists in a FOPID controller as indicated in Section 3. The design of the controller is not complicated by using a noncommensurate

fractional order model, since the frequency response can be easily evaluated analytically.

Table 1. Estimated parameters of the fractional order models for depth of hypnosis for 22 patients

P. No.	k	a ₂	a ₁	α ₂	α ₁	τ _m	Fit%
P3	5.04	2500	179.43	1.81	0.76	45	82.2
P8	1.53	24100	16.81	1.93	0.89	55	82.5
P9	4.70	41700	950.00	2.86	1.19	65	86.4
P10	1.89	29700	342.12	1.86	0.94	60	85.0
P14	2.55	0.89	396.58	1.93	0.89	45	85.8
P21	5.71	3480	375.18	1.96	0.96	60	82.8
P25	0.56	2550	100.58	1.69	1.67	85	82.7
P33	4.62	43900	1614.8	2.15	1.15	50	85.5
P35	4.29	0.37	1233.1	2.13	1.08	65	82.7
P36	8.22	34900	3988.9	2.24	1.06	160	82.1
P38	1.87	4500	82.18	1.72	0.86	35	83.9
P39	2.55	69300	294.23	2.05	0.98	140	86.2
P40	8.85	22300	459.67	2.00	0.79	45	82.0
P41	2.31	60300	418.18	2.14	0.95	30	86.6
P48	2.19	44700	769.42	2.21	1.13	50	85.3
P54	1.66	8830	112.88	1.87	0.91	35	86.2
P56	0.77	16700	216.09	2.36	1.20	65	87.1
P59	5.24	3290	1440.4	2.52	1.19	45	86.0
P63	1.01	39800	271.30	3.58	1.03	90	86.3
P64	6.93	22.90	340.70	3.25	0.84	60	86.2
P66	0.46	3880	51.83	2.31	0.99	35	87.9
P70	6.66	91700	149.7	2.05	1.04	25	79.7

3. TUNING OF THE NOVEL FRACTIONAL ORDER CONTROLLER

Patient 21 is selected as the nominal patient. The tuning of the fractional order controller is performed based on the fractional order model of patient 21, estimated to be:

$$H_{21}(s) = \frac{5.71}{3480s^{1.96} + 375.18s^{0.96} + 1} e^{-60s} \quad (7)$$

To tune the fractional order controller, the modulus (M_{21}), phase (P_{21}) and derivative of the phase ($\frac{dP_{21}(j\omega)}{d\omega}$) of (7) are firstly computed as functions of the real (Re) and imaginary (Im) parts of the denominator as follows:

$$\begin{aligned} Re(j\omega) &= a_2\omega^{\alpha_2} \cos\frac{\pi\alpha_2}{2} + a_1\omega^{\alpha_1} \cos\frac{\pi\alpha_1}{2} + 1 \\ Im(j\omega) &= a_2\omega^{\alpha_2} \sin\frac{\pi\alpha_2}{2} + a_1\omega^{\alpha_1} \sin\frac{\pi\alpha_1}{2} \\ M_{21}(j\omega) &= \frac{|k|}{\sqrt{(Re(j\omega))^2 + (Im(j\omega))^2}} \end{aligned} \quad (8)$$

$$P_{21}(j\omega) = -\tan^{-1} \frac{Im(j\omega)}{Re(j\omega)} - \omega\tau_m \quad (9)$$

$$\begin{aligned} \frac{dP_{21}(j\omega)}{d\omega} &= -\left(\frac{(a_2\alpha_2\omega^{\alpha_2-1} \sin\frac{\pi\alpha_2}{2} + a_1\alpha_1\omega^{\alpha_1-1} \sin\frac{\pi\alpha_1}{2}) Re(j\omega)}{(Im(j\omega))^2 + (Re(j\omega))^2} - \right. \\ &\left. \frac{Im(j\omega)(a_2\alpha_2\omega^{\alpha_2-1} \cos\frac{\pi\alpha_2}{2} + a_1\alpha_1\omega^{\alpha_1-1} \cos\frac{\pi\alpha_1}{2})}{(Im(j\omega))^2 + (Re(j\omega))^2} \right) - \tau_m \end{aligned} \quad (10)$$

The following fractional order controller is designed:

$$C_{FOPID}(s) = k_p(1 + k_i s^{-\lambda}) \frac{T_1 s + 1}{T_2 s + 1} \quad (11)$$

where k_p and k_i are the proportional and integral gains, $\lambda \in (0, 2)$ is the fractional order of integration and T_1 and T_2 are the time constants of the lead controller. It is well known that this lead element brings an extra overshoot with itself, overshoot which is directly proportional with the ratio of the two-time constants. Since this controller is designed for drug dosing, the overshoot has to be kept as small as possible

because any excess of medication can have severe effects on the human body. Any increase in the ratio T_1/T_2 will reduce the Time-to-target (TT), however it will also increase the overshoot. A compromise has to be made in order to obtain a small enough TT and also to keep the overshoot close to 0, the second condition being the more essential of the two. Another aspect to be resolved is that the lead element is non-zero steady-state error, and this error has to be removed by the integrator. In case of $\lambda < 1$ (partial integrator) this error will not be eliminated fast, and the system will reach steady state slower. Considering all the above constraints, the natural conclusion would be to have similar T_1 and T_2 values. Another observation is that both values need to be related to the gain crossover frequency, ω_c , which means they will be computed as a ratio between a constant value and ω_c .

To tune the controller in (11), a set of frequency domain performance specifications is imposed that refers to a certain phase margin (to ensure stability and a lower undershoot of the BIS signal), a gain crossover frequency (to ensure a certain settling time), constraints on the sensitivity and complementary sensitivity to tackle any load disturbances or noise and robustness to gain variations.

Phase margin (PM) is a crucial and often utilized performance criterion that is associated with the closed loop's stability and directly impacts the predicted overshoot and undershoot. Typically, a large value is used, indicating a reduced overrun. The mathematical formula that addresses the overshoot requirement is:

$$\angle H_{OL}(j\omega_c) = -\pi + PM \quad (12)$$

The gain crossover frequency indirectly addresses the settling time requirements. Smaller settling times are associated with larger values of ω_c . Mathematically, this is specified using the magnitude equation:

$$|H_{OL}(j\omega_c)| = 1 \quad (13)$$

where $H_{OL}(j\omega) = H_{21}(j\omega)C_{FOPID}(j\omega)$ is the open loop transfer function. A robustness requirement is combined with (12) and (13) to handle potential gain errors resulting from patient variability:

$$\left. \frac{d\angle H_{OL}(j\omega)}{d\omega} \right|_{\omega=\omega_c} = 0 \quad (14)$$

In this paper, it is crucial that both the control signal and the output do not exhibit oscillatory behavior. The administration of medicine carries significant hazards, and a substantial overshoot can potentially injure the patient. Hence, the PM value is selected such that a maximum undershoot is obtained as follows:

$$\sigma \leq 5\% \quad (15)$$

As previously mentioned, the TT performance indicator should be as small as possible, usually between 3 to 5 minutes. This condition is in opposition to (15) since a faster TT usually implies a greater overshoot. Therefore, the gain crossover

frequency was chosen such that TT satisfies the following requirement:

$$TT \leq 4 \text{ minutes} \quad (16)$$

A safe operating range must be maintained for all patient signals that need to be managed. It is mandatory that the BIS signal remains in a 40 to 60 range. Thus, the minimization of the error signal is attached as a tuning constraint to the previous requirements:

$$IAE = \int_0^{\infty} |e(t)| dt \quad (17)$$

where $e(t) = r(t) - y(t)$ with $r(t)$ the reference value and $y(t)$ the measured patient BIS signal. The closed loop results are evaluated according to the most widely used performance measures in closed loop control of anesthesia, as indicated in Section 4.

4. SIMULATION RESULTS

For patient 21 taken as the nominal patient, the parameters of the FOPID controller in (11) are computed using an optimization routine that minimizes (17) with constraints as specified in (12)-(16).

Based on clinical practice, performance indicators for the tuning of the FOPID controller in (11) are imposed, such as:

- Time-to-target (TT), defined as the time required for the controller to bring the BIS signal to 50. This should not exceed more than 4 minutes. (Pawlowski, Schiavo, Latronico, Paltenghi, & Visioli) (2023 a)
- The smallest (BIS-NADIRs) and largest amplitudes (BIS-NADIRI) of the BIS signal. This should not be lower than 40 or larger than 60.
- Propofol rate should remain within 5-200 mcg/kg/min (Bataille, et al., 2018)

The controller parameters are obtained using optimization routines, such as "fmincon" from Matlab. This involves identifying the minimum error while considering the specified equations (8-10) as the algorithmic conditions. The performance indicators mentioned above are translated into specific frequency domain performance criteria as follows: $\omega_c = 0.0076 \text{ rad/s}$, $PM=50^\circ$, $\sigma \leq 4\%$, $TT \leq 230 \text{ seconds}$. The resulting FOPID controller is:

$$C_{\text{FOPID}}(s) = 0.5093(1 + 0.0045s^{-0.9250}) \frac{142.8571s+1}{114.2857s+1} \quad (18)$$

The fractional order is implemented using an efficient and simple approximation method (De Keyser, Muresan, & Ionescu, 2018). To test the efficiency of the proposed control strategy, Fig. 2a) presents the simulation results for patient 21. The BIS signal decreases from 100 to 50 in 3.73 minutes. The minimum amplitude of the BIS signal is 48.3, which indicates a small undershoot. The BIS signal is kept within the safe range [40-60] and depth of hypnosis is achieved within less

than 5 minutes, as required by clinical practice (Pawlowski, Schiavo, Latronico, Paltenghi, & Visioli) (2023 b). The corresponding Propofol rate is indicated in Fig. 2b) and remains within normal drug rates required in clinical protocols (Hounscome, et al., 2016).

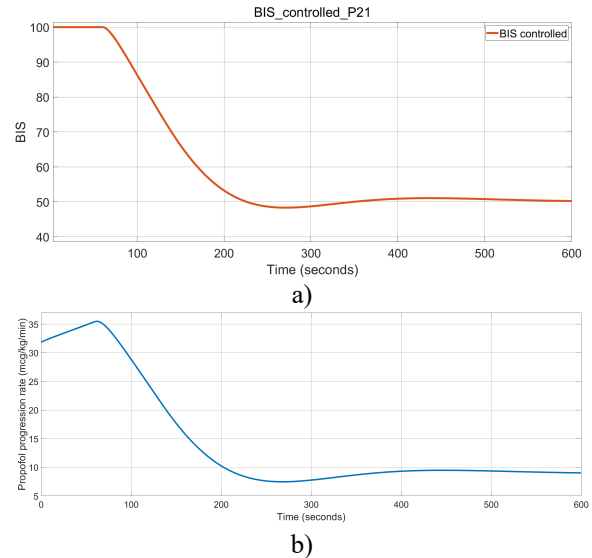


Fig. 2. Closed loop results for patient 21 a) BIS signal (red line) b) Propofol (blue line)

To test the robustness of the designed controller, the FOPID in (18) is applied successively to each of the patient models in Table 1. The closed loop simulation results are included in Fig. 3a) for the BIS signal and Fig. 3b) for the corresponding Propofol rate. Notice that for 10 out of the 22 patients, the maximum and minimum amplitude of the BIS signal remains within acceptable ranges. The Propofol rate corresponds to acceptable clinical ranges. The quantitative results that correspond to the simulations in Fig. 3 are included in Table 2. In some cases, there is a large variation in the TT. This is due to large variability in the a_1 and a_2 model coefficients, which is insufficiently tackled by the FOPID in (18). The two red lines in Fig. 3 emphasise the intra-patient variability. The controller maintains the BIS signal between the desired limits of 40 to 60, however it fails to deliver the expected TT. This happens because of the large difference in parameters of the FO models, as seen in Table 1. The dead time, τ_m , differs from -58% up to +166% from the nominal model, P21. The denominator coefficients differ as follows: a_2 from -99% to +2535% and a_1 from -95% to 963%.

Table 2. Performance measures for the developed FOPID control; bolded line indicates choice for nominal patient response used for controller tuning.

Patient no	TT (s)	BIS-NADIRI	BIS-NADIRs
3	832	48.9	50
9	218	40.2	53.8
14	1100	48.5	50
21	225	48.3	51.1
33	386	40.5	51.8
35	494	43.6	50.9
39	385	44.8	55.4
48	424	51.4	53.6

59	282	43.8	51.5
64	169	46.3	50.1

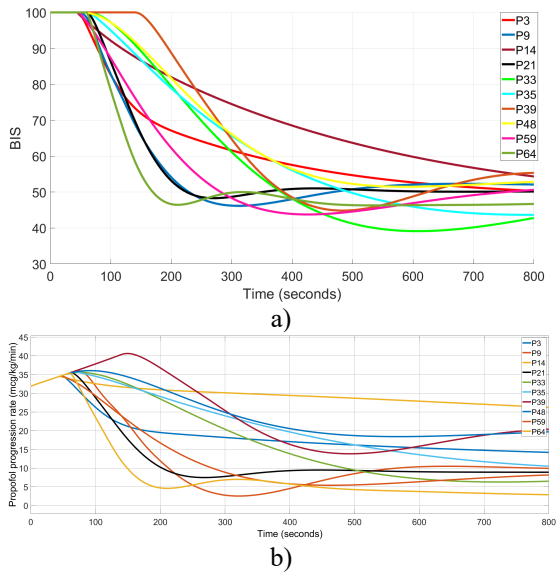


Fig. 3. Closed loop robustness results a) BIS signal b) Propofol

In some situations, the controller in (18) is no longer able to maintain the BIS signal in the 40 to 60 range. Such an example is indicated in Fig. 4, for patient 40, with the corresponding fractional order model given by:

$$H_{40}(s) = \frac{8.85}{2.3300s^2 + 459.67s^{0.79} + 1} e^{-30s} \quad (19)$$

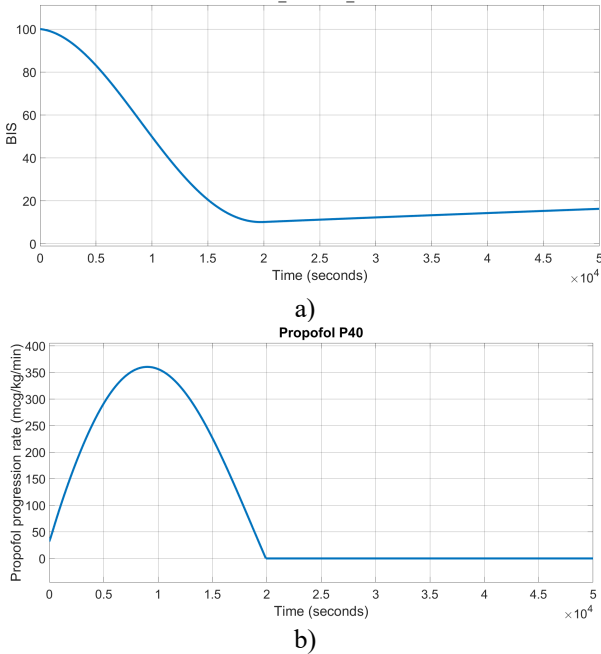


Fig. 4. Closed loop results for patient 40 a) BIS signal b) Propofol

Notice, the significant variation of the fractional order model parameters of patient 40 in (19), with the coefficient a_2 being 6.7 orders of magnitude larger compared to that of the nominal model in (7). Additionally, a 100% variation of the time delay is also present. The closed loop simulation results in Fig. 4

show that in this case the FOPID controller is unable to meet the requirements related to TT, neither to maintain the BIS signal within the [40-60] range. The Propofol drug rate also exceeds normal values.

This research is neither the first nor the only study to examine the use of a FOPID controller in the context of hypnosis treatments for managing the Bispectral Index (BIS). A comparative examination can be performed (Hegedus, Birs, Ghita, & Muresan, 2022). The observed overshoot values in both instances are extremely similar, with a deviation of less than 5%, especially ranging from 3% to 4%.

However, differences emerge when analyzing the time to target. Our research reveals that the obtained TT falls between 200 and 300 seconds, however in (Hegedus, Birs, Ghita, & Muresan, 2022) the values fall within the range of 150 to 200 seconds. It is important to emphasize that, while our controller may appear to have worse performance compared to others, taking into account the peculiarities of the model shows a critical element. More precisely, the models used in this study had an average time delay of 50 seconds and great variability in the parameters (more than 2 orders of magnitude in the a_1 and a_2 coefficients). The results in (Hegedus, Birs, Ghita, & Muresan, 2022) are more appealing, but the models used have less variation in the parameters, with small time delays close to 20 seconds, which remains the same for all studied patients. From this point of view, the models used in this study are more realistic.

Within the field of medicine, intra-patient variability is a significant difficulty, especially when it comes to patient-specific treatments and therapies. Despite their effectiveness in a variety of applications, offline FOPID controllers frequently fail to sustain optimal performance when physiological responses are dynamic and patient specific.

Intra-patient variability is the term used to describe the distinct and dynamic variations in a patient's physiological characteristics that occur throughout time. These discrepancies may result from variables including shifting illness conditions, oscillations in metabolism, or even individual differences in how each person responds to different treatment regimens. The need for real-time control strategy adaptation arises from the need for healthcare providers to provide precise and tailored care.

PID controllers with tuning and online adaptation features can improve accuracy and responsiveness by learning from patient physiological variables. However, the proposed fractional order controller struggles with significant parameter variations. An online adaptation routine for the FOPID could improve flexibility and responsiveness, especially in situations where robustness is crucial (Ionescu & Copot, 2019).

5. CONCLUSIONS

The study demonstrates the use of a FOPID controller to regulate hypnosis depth during induction. This innovative approach differs from traditional PK-PD models and uses

fractional order models for the design of the controller. The results show that the FOPID controller was successful, especially for the nominal patient, with an undershoot of only 3.8% and a good time to target of 225 seconds. Moreover, the results' acceptability for 10 out of 22 patients highlights the suggested controller's resilience and demonstrates its capacity to handle the inherent unpredictability across a varied patient population. Its robustness and ability to handle unpredictability across a diverse patient population were highlighted. The study also points out that significant variations in the fractional order models due to patient variability greatly affect the closed loop performance. Further research is needed to improve model accuracy and explore online controller tuning for flexibility and promptness in changing patient situations.

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